
Captopril Renography in Two Kidney and One Kidney Goldblatt Hypertension in Dogs

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In order to improve on the technique of noninvasive detection of renal artery stenosis, we studied the effects of angiotensin converting enzyme inhibition with captopril on individual kidney hemodynamics and function as assessed by technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc]DTPA) renal flow studies and iodine-131 orthoiodohippurate (^{131}I]hippuran) renography in experimental Goldblatt's hypertension. In two-kidney, one-clip (renin-dependent) hypertension, captopril (1.5 mg/kg bolus with 1.5 mg/min infusion) reduced mean arterial pressure (MAP) and ipsilateral glomerular filtration rate (GFR) without changes in the contralateral kidney. Captopril infusion resulted in alterations in both the ^{99m}Tc]DTPA and ^{131}I]hippuran studies, which were most evident in the 15-min ^{99m}Tc]DTPA renal flow studies. In one-kidney, one-clip (volume-dependent) hypertension, captopril reduced MAP but did not alter GFR, renal plasma flow, or the radionuclide studies. These studies suggest that the ^{99m}Tc]DTPA renal flow study coupled with captopril challenge may unmask intrarenal angiotensin II-dependent functional and hemodynamic changes of the stenotic kidney, and offers promise in the detection of renin-dependent hypertension.

J Nucl Med 28:1171-1179, 1987

Development of pharmacologic inhibitors of the renin angiotensin system has provided new insights on the pathophysiology and diagnosis of renal vascular hypertension (RVHT). The purpose of this study is to evaluate the effect of angiotensin converting enzyme inhibition (CEI) with captopril on individual kidney glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), as assessed by technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc]DTPA) and iodine-131 orthoiodohippurate [^{131}I]hippuran renography. The effect of CEI on the renal vascular bed was studied for several reasons. First, angiotensin CEI drugs have been reported to result in acute deterioration of renal function in selected patients with either bilateral renal artery stenosis or renal artery stenosis of a solitary kidney (1,2). It is postulated that this decrease in glomerular filtration rate results from removal of post-glomerular arteriolar vasoconstriction mediated by angiotensin II (3). Converting enzyme inhibition with captopril also has been reported to enhance the diagnostic accuracy of plasma renin activity and renal vein

renin determinations in evaluating hypertensive patients for RVHT (4,5). More recently, several investigators (6-15) have reported that CEI with either captopril or enalapril induces changes in radionuclide studies of the renal vascular bed, which are believed to enhance our ability to diagnose RVHT noninvasively.

We had previously reported the development of computer-assisted 90-sec and 15-min ^{99m}Tc]DTPA renal flow studies without CEI, which appeared superior to conventional [^{131}I]hippuran renography in the diagnosis of moderate-to-severe unilateral renal artery stenosis (16). During the course of those studies, there was a subset of hypertensive animals with less severe stenosis that did not consistently exhibit diagnostic changes of the radionuclide studies. Consequently, the effect of CEI with captopril was examined in animals with two-kidney, one-clip hypertension of a less severe degree. Captopril infusion resulted in a significant decrease in the GFR of the stenotic kidney and induced striking alterations in the ^{99m}Tc]DTPA time-activity curves of that stenotic kidney (12). The present studies were designed to observe the effect of CEI in two canine models: (a) in two-kidney, one-clip hypertension (2K1C), a renin-dependent form of hypertension, and (b) one-kidney, one-clip (1K1C) hypertension, presumed to be a form of volume-dependent hypertension.

Received June 26, 1986; revision accepted Dec. 23, 1986.

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MATERIALS AND METHODS

Experimental Protocol

Studies were performed on female mongrel dogs ($n = 16$), which were known to have single normal renal arteries from previous angiography. Throughout the studies, the animals were sodium replete as they were permitted free access to food and water. In Group 1 with 2K1C hypertension ($n = 9$), the animals were anesthetized with pentobarbital (30 mg/kg) during the control period and conventional clearance studies with paraaminohippurate (PAH) and inulin were performed via a bladder catheter as markers of ERPF and GFR, respectively (17,18). Mean arterial pressure (MAP) determinations via a femoral artery catheter were also performed.* In Group 2 with 1K1C hypertension ($n = 7$), a right nephrectomy was performed 1 wk before the control clearance studies. For both groups, the anesthetized animals were hydrated with 0.9% normal saline intravenously to assure a urine output of >2.0 cc/min, and underwent control [^{99m}Tc]DTPA renal flow studies and conventional [^{131}I]hippuran renography (see Nuclear Studies section).

For the renal artery stenosis phase of the experiment, the dogs were anesthetized and the left renal artery was approached anteriorly. A nonocclusive electromagnetic flow probe (EMFP)[†] was placed and measurements of unilateral renal flow were taken after a stabilization period. A metallic vascular clip was positioned proximal to the EMFP to approximate a 50% reduction in renal blood flow, which was observed during a postclip period ranging from 30 to 60 min. Subsequent protocols for Groups 1 and 2 follows.

Group 1. On the day following stenosis, the well-hydrated animals again underwent the [^{99m}Tc]DTPA and [^{131}I]hippuran studies. On the second postoperative day the animals were hydrated intravenously and captopril was administered at a dose of 1.5 mg/kg i.v. followed by an infusion of 1.5 mg/min for 60 min.[‡] The [^{99m}Tc]DTPA and [^{131}I]hippuran studies were then performed during the captopril infusion. The following day recovery scans (REC) without captopril were performed. In six animals, MAP was similarly lowered using the vasodilator nitroprusside to assess if changes observed in the radionuclide studies during CEI were related to reduced renal perfusion pressure or were specific for captopril. Blood pressure determinations and split function clearance studies of PAH and inulin via individual ureteral catheters prior to and during the identical captopril infusion were performed in sodium-replete animals on the final day of the experiment ($n = 6$).

Group 2. These uninephrectomized, well-hydrated animals began the [^{99m}Tc]DTPA and [^{131}I]hippuran renography protocol on the fourth postoperative day in order to allow renin secretion to return toward normal. The radionuclide studies without and with captopril, as well as clearances of PAH and inulin, were subsequently performed in an identical fashion to the Group 1 animals.

Nuclear Studies

For the [^{99m}Tc]DTPA study, 5 mCi were injected rapidly by way of the cephalic vein with the animal lying supine and the anatomy viewed posteriorly by a large field-of-view gamma camera[§] using a medium energy collimator. Data were acquired by a PDP 11/34 computer[¶] using a predefined study routine operating under gamma-11 and RT-11 software. Data

acquisition was formulated into a 64×64 pixel matrix. The dynamics of the [^{99m}Tc]DTPA study was specified by a collection time of 1 sec/frame for 90 sec, then 10 sec/frame for 13.5 min, for a total of a 15-min study.

The regions of interest were selected to include the aorta, left and right kidneys, and corresponding background areas to be subtracted. The time-activity curves that were generated served as input for our analysis programs. A separate time-activity curve for the aortic region was plotted in order to assess the quality of bolus at the main renal arteries. A poor, staggered aortic curve was a potential criterion for rejecting the study. The time-activity curve for the left and right kidneys were plotted on the same set of axes, with the activity scale normalized, to the higher kidney's peak activity (Fig. 1A,B). This display format facilitates direct bilateral comparison. For the Group 2 animals with only one kidney, a single time-activity curve was plotted.

Eight computer-isolated curve parameters were analyzed from the 90-sec [^{99m}Tc]DTPA renal flow study as described previously (16). The pairs of time-activity curves from the 90-sec and 15-min [^{99m}Tc]DTPA renal flow studies were also visually analyzed for configuration, slope, and symmetry, and judged to be either normal or diagnostic of RAS according to previously defined criteria (16). The curve parameters for an individual kidney were compared before and after the creation of RAS, as well as during the captopril infusion, recovery studies, and nitroprusside infusion.

In addition to the visual analysis of the [^{99m}Tc]DTPA time-activity curves, the 90-sec and 15-min [^{99m}Tc]DTPA time-activity curves were also analyzed by integrating the area under the curve (expressed as counts-seconds) as well as the ratio (stenotic kidney/contralateral kidney) of the area under the curve using in-house software. For the 90-sec study, the area under the curve was computed over 30 sec using the initial 10% upslope point as the point of origin (Fig. 2a). For the 15-min DTPA study, the area under the curve was computed for the first 5 min of the study with 10% initial upslope as the point of origin (Fig. 2b).

The 30-min [^{131}I]hippuran renograms were completed using the same gamma camera and collimator as described for the [^{99m}Tc]DTPA studies. The regions of interest were selected for each kidney and the bladder with background regions for subtraction. The [^{131}I]hippuran dose was selected to be 40 μCi i.v. for these experimental dog studies, such that this activity provided count rates comparable with our human studies and resulted in target-to-background ratios exceeding 5:1 for adequate statistical analysis. The time-activity curves were analyzed in the conventional manner with respect to time to maximum activity, time to return from maximum to 75% maximum activity, upslope, backslope, and the differential (stenotic/contralateral) maximum activity ratios. These curves were also subjected to visual analysis and interpretation as either normal or diagnostic of RAS, as previously defined (16). The time-activity curves of the [^{131}I]hippuran study were also analyzed utilizing similar area under the curve parameters and ratio (stenotic/contralateral) of areas under the curves as detailed above. For the hippuran studies, the area under the curve was computed for the first 5 min of the study using the initial upslope as the point of origin. Results are expressed as the mean \pm s.e.m. Statistical analysis was accomplished by use of Student's paired t-test.

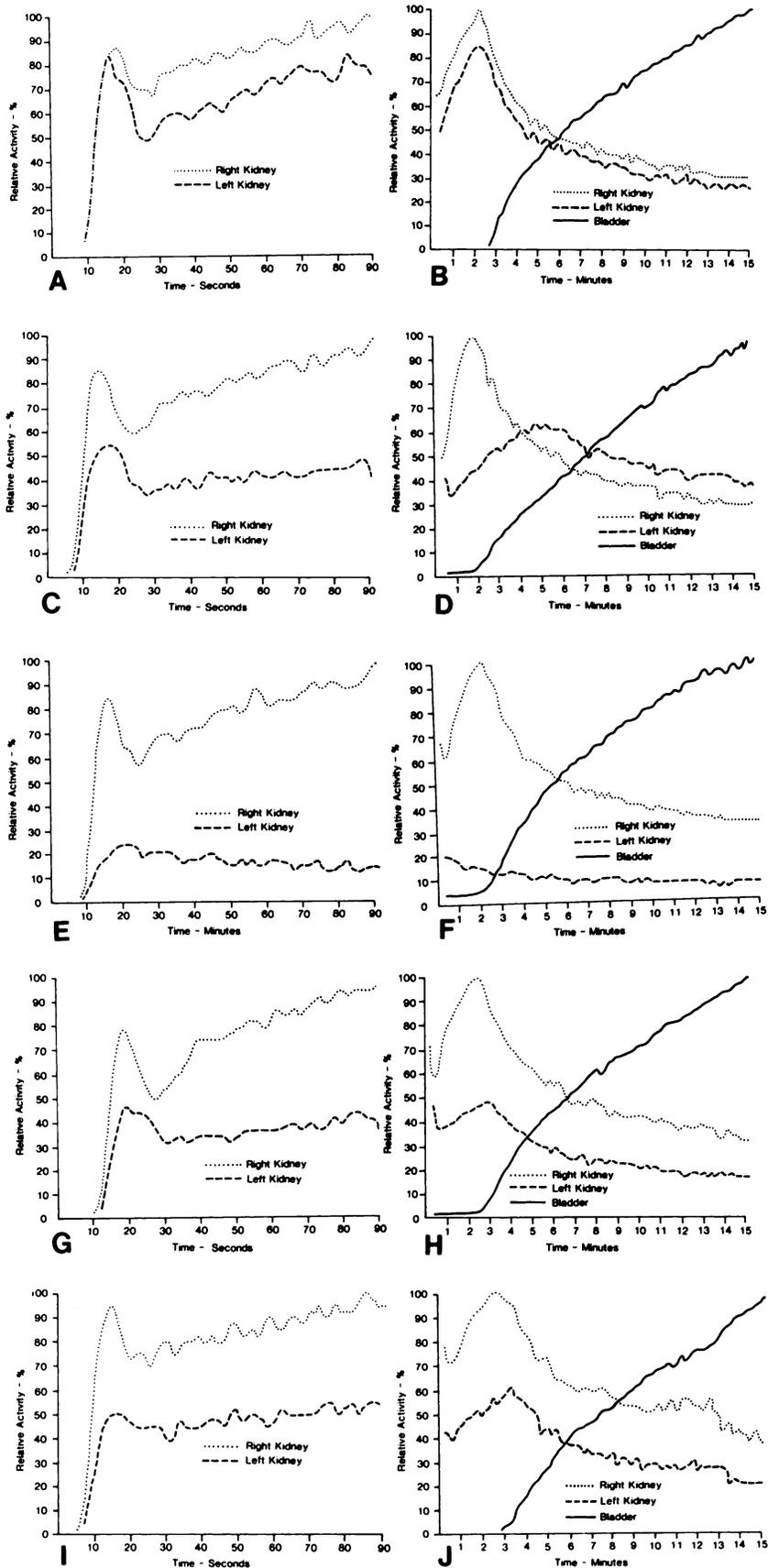


FIGURE 1

A-J: This panel of figures depicts the 90-sec and 15-min [^{99m}Tc]DTPA studies during control (Fig. 1A,B), after stenosis of the left renal artery without captopril (Fig. 1C,D), renal artery stenosis during captopril infusion (Fig. 1E,F), during the recovery study (Fig. 1G,H), and during nitroprusside infusion (Fig. 1I,J). See text for details (Reproduced with permission from Ref. 12.)

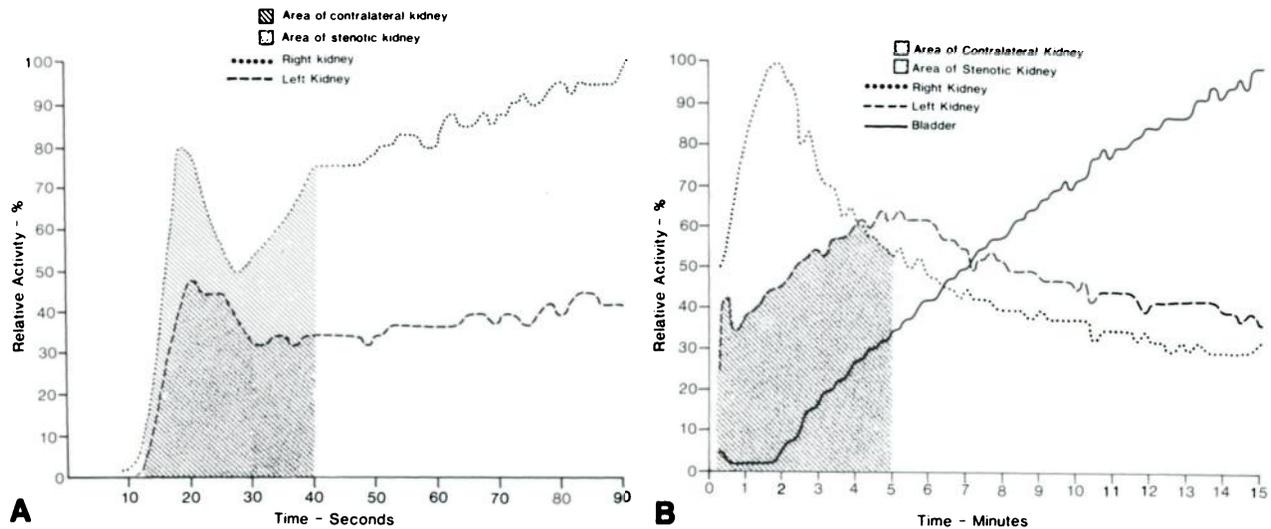


FIGURE 2
Area under the curves for the 90-sec (A) and 15-min (B) [^{99m}Tc]DTPA study in 2K,1C hypertension.

RESULTS

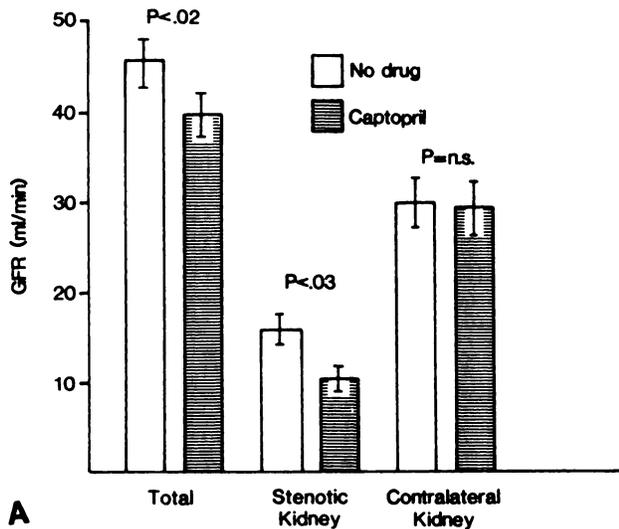
In Group 1, creation of unilateral renal artery stenosis resulted in $47.3 \pm 7\%$ decrease in ipsilateral clearance of PAH with an increase in MAP from 128 ± 4 to 140 ± 4 mmHg ($p < 0.02$). The results of the visual analysis of the radionuclide studies (Table 1) demonstrated that the 90-sec and 15-min [^{99m}Tc]DTPA renal flow studies without captopril were considered to be diagnostic of renal artery stenosis in five of nine and seven of nine cases, respectively. The nondiagnostic studies occurred in the four hypertensive animals with milder stenosis, in which the reduction in ipsilateral ERPF averaged approximately 30% as assessed by PAH clearances (20%, 28%, 33%, 47%). Analysis of the parameters of the 90-sec [^{99m}Tc]DTPA time-activity curves demonstrated only a significant reduction in differential (stenotic/contralateral) maximum activity ratios (1.03 ± 0.05 versus 0.64 ± 0.05 , $p < 0.02$). The 15-min Tc-DTPA curves that were considered diagnostic of renal artery stenosis demonstrated a depressed peak activity value compared with the contralateral kidney, yet it is important to note that all 15-min [^{99m}Tc]DTPA curves exhibited an uptake/accumulation of the radionuclide followed by an excretory phase (Fig. 1D). For the [¹³¹I] hippuran time-activity curves, five of the nine studies

were diagnostic of renal artery stenosis although the patterns of change were quite variable, ranging from marked depression of peak activity to prolonged accumulation of the radionuclide.

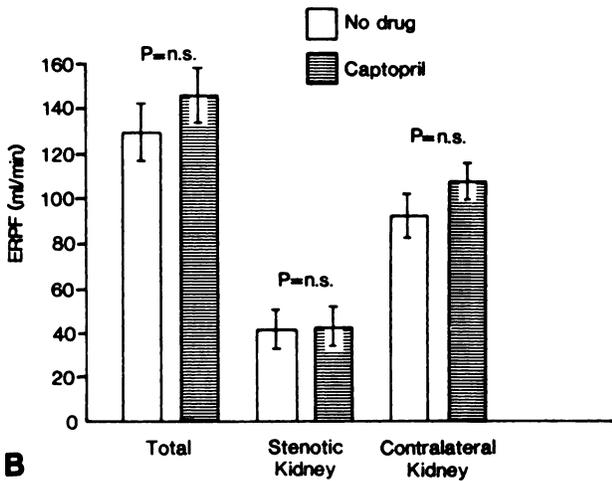
Infusion of captopril reduced MAP from 140 ± 4 to 106 ± 4 mmHg ($p < 0.02$), which was maintained throughout the radionuclide studies. The effect of captopril in the 2K1C model can be best appreciated by briefly reviewing representative [^{99m}Tc]DTPA curves from Dog 12, an animal with moderately severe left renal artery stenosis (Figs 1A–J). In the control studies (Fig. 1A and B), note the symmetry of curve, slope, and configuration of both the 90-sec (a) and the 15-min (b) time-activity curves. Following renal artery stenosis on the left, there are changes in both the 90-sec and 15-min studies, which were considered diagnostic of stenosis, noting differences in curve height, slope, and differential activity ratios (Fig. 1C and D). Although the 15-min time-activity curve of the stenotic kidney is diminished, note the definite uptake/accumulation and excretory phases of the renogram (Fig. 1D). With the administration of captopril, there was a marked change in all the 15-min [^{99m}Tc]DTPA studies in which the time-activity curve of the stenotic kidney approximates a blood disappearance curve without the significant uptake/accumulation or excretory phases (Fig. 1F). These changes were reversible off captopril with return of the uptake/accumulation and excretory phases of the recovery studies (Fig. 1H). In the animals scanned during the nitroprusside infusion, the studies demonstrated persistence of the uptake/accumulation and excretory phases despite drug-induced hypotension (Fig. 1J). In summary, this animal with moderate stenosis had diagnostic changes of unilateral renal artery stenosis in the [^{99m}Tc]DTPA study without captopril, which was enhanced by administration of the CEI.

TABLE 1
Visual Analysis of the Radionuclide Studies in 2K1C

	90-sec [^{99m} Tc]DTPA	15-min [^{99m} Tc]DTPA	30-min [¹³¹ I]Hippuran
Control	0/9	0/9	0/9
RAS alone	5/9	7/9	5/9
RAS + captopril	7/9	9/9	7/9



A



B

FIGURE 3

The effect of captopril upon (A) glomerular filtration rate (GFR) as measured by inulin clearance and (B) effective renal plasma flow (ERPF) as measured by PAH clearance in 2K,1C hypertension. (Reproduced with permission from Ref. 12).

To correlate the changes in radionuclide studies seen during captopril with renal hemodynamic and functional changes, split function clearances of inulin and PAH were performed in the 2K1C group (Figs. 3A and

B). There was a significant 31% fall in GFR of the stenotic kidney (16.0 ± 3.1 versus 11.0 ± 2.5 ml/min, $p < 0.03$) with a nonsignificant fall in GFR of the contralateral kidney (32.4 ± 2.6 versus 28.4 ± 2.8 ml/min, $p = \text{N.S.}$) (Fig. 3A). The fall of total GFR (48.4 ± 4 to 39.4 ± 3 ml/min, $p < 0.02$) resulted mostly from the marked decrement in GFR from the stenotic kidney and emphasizes the importance of assessing individual kidney function when evaluating the effect of converting enzyme inhibitor drugs in RVHT. There was no significant change in effective renal plasma flow in either kidney (Fig. 3B), although there was a 22% increase seen in the contralateral kidney at a time when blood pressure had been lowered by 20%, suggesting a decrease in renal vascular resistance with renal vasodilatation.

Converting enzyme inhibition with captopril in the 2K1C model resulted in an increased sensitivity in detecting renal artery stenosis with the radionuclide studies (Table 1). As noted earlier, the 90-sec and 15-min [^{99m}Tc]DTPA studies and the [^{131}I]hippuran renogram did not detect milder reductions in renal plasma flow following stenosis. Captopril infusion increased the sensitivity for stenosis in all three studies with the 15-min [^{99m}Tc]DTPA study being the most sensitive index as well as having the most consistent, striking alterations of the time-activity curves with loss of its uptake/accumulation and excretory phases. More objective data analysis of the area under the curve parameters for the radionuclide studies also supported these subjective observations. Figure 2 illustrates the area under the curves for the 90-sec (a) and 15-min (b) [^{99m}Tc]DTPA studies in Dog 12 with RAS alone. Table 2 shows the results of the ratios of the area under the curves (stenotic/contralateral) for the [^{99m}Tc]DTPA and [^{131}I]hippuran studies. The ratio for the 90-sec [^{99m}Tc]DTPA studies fell significantly from control to RAS alone ($p < 0.05$). This ratio fell further to 0.37 ± 0.05 during the captopril infusion and was highly significant ($p < 0.001$) compared with control. However, this decrease in the ratio during captopril infusion did not reach statistical significance when compared with the value of RAS without captopril. The previously defined

TABLE 2
Ratios of the Areas Under the Curves (Stenotic/Contralateral) in 2K1C

	90-sec [^{99m}Tc]DTPA	15-min [^{99m}Tc]DTPA	30-min [^{131}I]Hippuran
Control	0.90 ± 0.08	0.91 ± 0.07	0.88 ± 0.06
RAS alone	0.56 ± 0.08	0.66 ± 0.07	0.81 ± 0.13
RAS + captopril	0.37 ± 0.05	0.28 ± 0.07	0.46 ± 0.08

* $p < 0.05$ versus control.

** $p < 0.001$ versus control.

† $p < 0.005$ versus RAS alone.

†† $p < 0.03$ versus RAS alone.

parameters of the 90-sec [^{99m}Tc]DTPA study also did not change further with captopril. Additional data for the area under the curve ratio (stenotic/contralateral) for the 15-min [^{99m}Tc]DTPA study is reported in Table 2. There was a significant fall in the ratio following stenosis compared with control ($p < 0.05$). During captopril infusion, the ratio decreased markedly to 0.28 ± 0.07 , which was highly significant compared with control ($p < 0.001$) and RAS alone ($p < 0.005$). During the recovery study, the ratio significantly increased (0.67 ± 0.05 , $p < 0.001$) compared with RAS and captopril. The significant changes in these objective parameters agree with the subjective visual analysis data in Table 1. Table 2 also lists these curve parameters for the [^{131}I]hippuran studies. Without captopril, the studies did not differ significantly after the creation of RAS alone. However, captopril infusion did result in a significant reduction in the ratio (0.81 ± 13 versus 0.46 ± 0.08 , $p < 0.03$) for the [^{131}I]hippuran studies. This reduction of the ratio actually resulted from an increase in the contralateral kidney without a significant change in the stenotic kidney following captopril, which is in agreement with the ERPF measurements seen in Figure 3B. Overall, the 15-min [^{99m}Tc]DTPA studies exhibited the greatest degree of sensitivity in the detection of RAS compared with the 90-sec [^{99m}Tc]DTPA or [^{131}I]hippuran studies.

In Group 2, creation of renal artery stenosis of the solitary kidney resulted in a significant increase of MAP from 117 ± 4 to 146 ± 2 mmHg ($p < 0.03$). This degree of hypertension superimposed on mild to moderate surgically-induced renal artery stenosis in the one kidney model resulted in only minor alterations of the [^{99m}Tc]DTPA and [^{131}I]hippuran time-activity curves, such that definitive diagnosis of RAS could not be made with confidence (Fig. 4A). Converting enzyme inhibition with captopril did significantly reduce MAP from 146 ± 5 to 111 ± 5 mmHg ($p < 0.001$). In contrast

with Group 1 studies, the effect of captopril in the sodium replete 1K1C model was not evidenced in the radionuclide studies (Fig. 4B). There were minimal changes in the [^{99m}Tc]DTPA and [^{131}I]hippuran studies that were not considered definitively diagnostic in any case. More specifically, there was uptake/accumulation and excretory phases in every 15-min [^{99m}Tc]DTPA time-activity curve performed during captopril infusion (Fig. 4A and B). There were no significant changes in the area under the curve parameters for the 90-sec and 15-min DTPA studies or in the [^{131}I]hippuran study prior to or during captopril infusion. There was no change in renal uptake (60–180 sec) expressed as a percentage of the injected dose pre- and postcaptopril (6% versus 6%, = N.S). Figure 5 shows the changes in MAP, GFR, and ERPF with RAS alone and with RAS plus captopril infusion. Despite a significant reduction in MAP with CEI in 1K1C hypertension, there were no significant changes in GFR (29.2 ± 4 versus 25.6 ± 3 ml/min) or in ERPF (83.9 ± 11 versus 96.5 ± 14 ml/min). Because of the small decrement in GFR with a simultaneous increase in ERPF, there was a significant decrease in the filtration fraction with captopril (0.35 ± 0.02 versus 0.27 ± 0.02 , $p < 0.05$). In summary, captopril significantly reduced MAP but did not alter GFR, ERPF, or the radionuclide studies. These observations, coupled with those made during nitroprusside infusion in the 2K1C model, suggest that it is changes in GFR, and not renal perfusion pressure, that are important in assessing the effect of converting enzyme inhibition on the radionuclide studies.

DISCUSSION

In renin-dependent hypertension, angiotensin CEI effects changes in radionuclide studies of the renal vascular bed and offers promise in enhancing the sen-

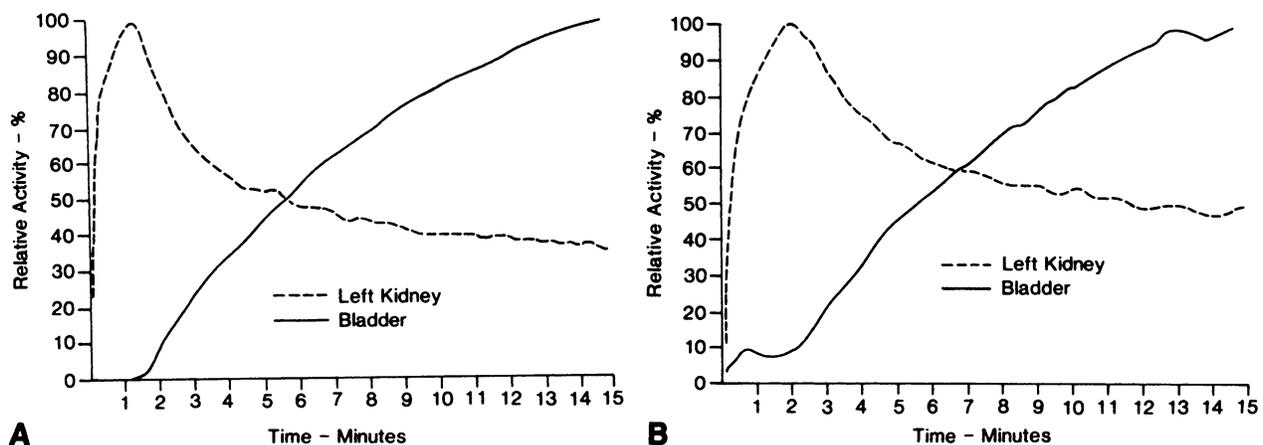


FIGURE 4
The 15-min [^{99m}Tc]DTPA time-activity curve prior to (A) and during (B) captopril infusion in 1K,1C hypertension.

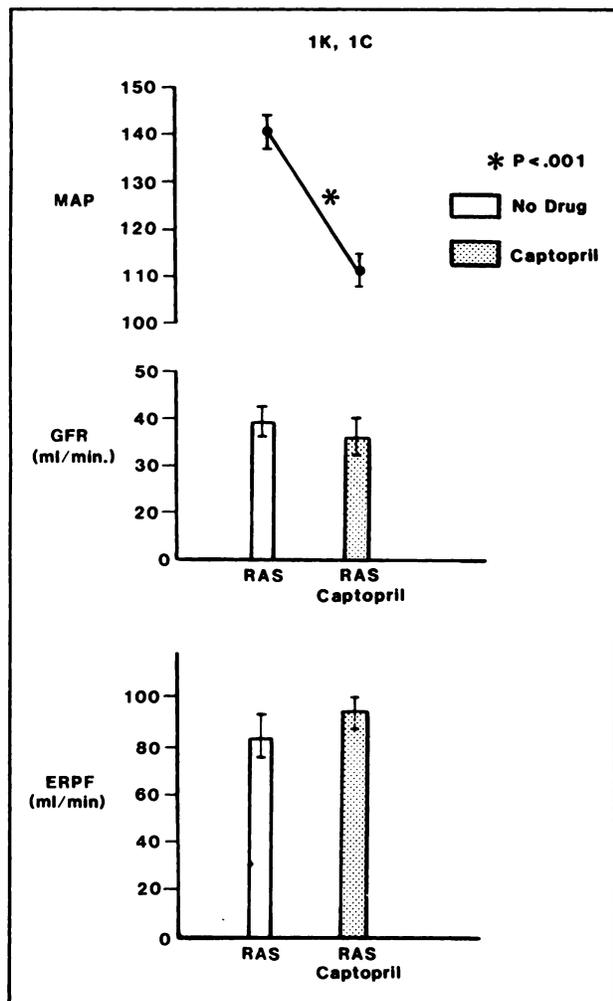


FIGURE 5
The effect of captopril upon mean arterial pressure (MAP), glomerular filtration rate (GFR), and effective renal plasma flow (ERPF) in 1K,1C hypertension.

sitivity of noninvasive radionuclide studies in the diagnosis of RVHT. In our canine model of two-kidney, one-clip hypertension, CEI with captopril lowered MAP and significantly reduced the GFR of the affected stenotic kidney. These physiologic changes with CEI resulted in alterations of the time-activity curves with both the [^{99m}Tc]DTPA and [^{131}I]hippuran studies, but were best appreciated with the 15-min [^{99m}Tc]DTPA renal flow study in which all curves of the stenotic kidney were altered markedly with loss of their uptake/accumulation and excretory phases. The changes were reversible and appeared specific for captopril, because they were not seen when MAP was lowered to a similar degree with the vasodilator sodium nitroprusside. The changes in the 15-min [^{99m}Tc]DTPA study with captopril correlated with a significant 31% decrease in the GFR of the stenotic kidney with no change in the contralateral kidney or in the ERPF of either kidney. These observations are consistent with the hypothesis

that maintenance of intrarenal resistance and GFR are mediated via angiotensin II-dependent, efferent arteriolar vasoconstriction when renal perfusion pressure is diminished as seen with preglomerular stenosis (3).

The observations made in this study confirm earlier reports in human and experimental models by several investigators (6-15) that CEI with either captopril or enalapril is capable of altering renal perfusion and function as assessed by radionuclide studies so as to potentially enhance the diagnostic accuracy of these studies in evaluating patients for renovascular hypertension. In patients with unilateral renal artery stenosis and preserved renal function, Oei et al. (7,8) recently reported that captopril 25 mg p.o. 1 hr before the radionuclide studies resulted in a blood disappearance curve of the DTPA renogram on the stenotic side, as well as effecting slower excretion (yet persistent upslope) on the stenotic side with the orthoiodohippurate renogram. Of their 38 hypertensive patients with either essential hypertension or RVHT, captopril-stimulated renography was reported to have a 94% sensitivity and 100% specificity in identifying those patients with correctable RVHT (7). While studying individual kidney hemodynamics and function with radionuclide studies in patients with unilateral renal artery stenosis, Bender et al. (6) found a significant decrease in GFR 4 hr after CEI with enalapril, which returned toward control values after 4 days in their patients with unilateral renal artery stenosis. In contrast, those patients with bilateral renal artery stenosis were found to have a significant decrease in renal function at 4 hr, which persisted when restudied after 4 days. Unfortunately, the studies by Bender et al. (6) only reported total GFR and did not quantitate individual kidney function after CEI. The observations by Oei et al. suggest that changes induced by CEI in unilateral renal artery stenosis have their pronounced effect with decrement in the GFR such that agents like [^{99m}Tc]DTPA, which are excreted via glomerular filtration, may be the preferred radionuclide for detecting these physiologic changes by noninvasive techniques. However, other investigators have reported success with captopril renography using either [^{131}I]hippuran (13) or [^{99m}Tc] 2, 3-dimercaptosuccinic acid (DSMA) (15).

In contrast to our positive results with CEI in two-kidney, one-clip hypertension, CEI with captopril reduced MAP but did not significantly reduce GFR or alter the radionuclide studies in one-kidney, one-clip hypertension. In the chronic stages of the 1K1C model, systemic hypertension is no longer believed to be renin-dependent but volume-dependent (19). When sodium replete, autoregulation of GFR in 1K1C is only slightly impaired by angiotensin-II blockade, even though a marked decrease in efferent arteriolar resistance occurs when systemic pressure is lowered (20). However, sodium depletion in this model may modulate autoregu-

lation of the GFR and result in a decrease in GFR in response to CEI (20). Our observations in sodium replete animals are at variance with the studies in the rat model of one kidney Goldblatt hypertension recently reported by Blaufox and Lee (10). In their model, when MAP was reduced by 11% with CEI there was a concomitant 39% decrease in GFR of the solitary clipped kidney. The discrepant findings in these two models may result from the variability in the degree and duration of renal artery stenosis. Additionally, the state of sodium balance may play a pivotal role in the response of the systemic vasculature and renal vasculature to CEI. Our animals were intentionally sodium replete during the course of these studies. Perhaps sodium depletion (with or without diuretics) would be required to stimulate the renin-angiotensin-aldosterone system in these 1K1C animals, such that a decrease in GFR would be seen in response to CEI.

These experimental observations in the 1K1C model, indeed, may have clinical implications in the interpretation of changes in renal function and/or radionuclide studies of the kidney in response to CEI. There are two clinical observations regarding patients with renal artery stenosis of a solitary kidney which appear relevant. First, it is in this subset of patients with stenosis of a solitary kidney or severe bilateral RAS that acute reversible renal insufficiency was first noted when the patients were given oral CEI drugs (1,2). Renal insufficiency secondary to CEI may have occurred in this model of presumed volume-dependent hypertension because of diuretic-induced stimulation of the renin-angiotensin-aldosterone system, such that maintenance of GFR was angiotensin-II dependent. Secondly, Dubovsky et al. (9) reported that hypertensive renal transplant recipients with renal artery stenosis experienced a significant fall in ERPF of the transplant kidney after CEI compared with those hypertensive transplant patients whose hypertension was due to other causes such as their native kidneys, chronic rejection, or nephrotoxicity induced by cyclosporine A. However, the state of sodium balance and use of diuretics in those renal transplant patients was not stated. Additional radionuclide studies with CEI may be required in patients with renal artery stenosis of a solitary kidney or severe bilateral renal artery stenosis in both the sodium replete and sodium deplete states to further address these concerns.

In summary, captopril renography appears to offer promise in identifying the renin-dependent forms of hypertension. Based on our observations in our experimental model of 2K1C hypertension, it is suggested that an agent like [^{99m}Tc]DTPA, which is excreted by glomerular filtration, may be the radionuclide of choice in assessing the response to CEI in patients with unilateral renal artery stenosis and preserved renal function. The [^{99m}Tc]DTPA renal flow study, coupled with the

challenge of CEI, may unmask intrarenal angiotensin II-dependent functional and hemodynamic changes of the stenotic kidney and offers promise in the detection of renin-dependent hypertension. In contrast with the 2K1C studies, there were no significant changes in the radionuclide studies, GFR, or ERPF during CEI in the sodium replete 1K1C model of hypertension. It is suggested that patients with the analogous form of renal vascular hypertension—either stenosis of a solitary kidney or marked bilateral stenosis—be evaluated in more detail using radionuclide studies with CEI, with special attention to their state of sodium balance. Preliminary investigations utilizing radionuclide studies with CEI of the renal vascular bed has been encouraging in hypertensive patients. It appears that a prospective, multicenter study is warranted to investigate the sensitivity and specificity of captopril renography as a noninvasive technique to identify patients with potentially correctable renovascular hypertension.

NOTES

- * Hewlett-Packard 321 recorder, Waltham, MA.
- † Micron Instruments, Los Angeles, CA.
- ‡ E.R. Squibb Co., Princeton, NJ.
- § Maxicamera II, General Electric, Milwaukee, WI.
- ¶ Digital Equipment Corp, Maynard, MA.

ACKNOWLEDGMENTS

This work was presented in part at the *Radionuclides In Nephro-Urology* international symposium in Lausanne, Switzerland, May 1986 and at the *Society of Nuclear Medicine* in Washington, DC, June 1986.

This work was supported by NIH Grant AM/HL 35467 and a Biomedical Research Support grant from the Medical College of Ohio.

The authors thank Bernice Haefner for her secretarial assistance.

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