Renal Functional Response to Captopril During Diuretic Therapy

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Antihypertensive agents may modify the renal effects of angiotensin converting enzyme inhibition (ACEI). This potential interaction, which is important in the diagnosis of renovascular hypertension was studied in two rat models with and without diuretic treatment prior to ACEI. Acute intravenous administration of furosemide or hydrochlorothiazide in one-kidney, one-clamp animals (1K1C) did not change glomerular filtration rate (GFR) or effective renal plasma flow (ERPF). ACEI administration after furosemide and hydrochlorothiazide decreased GFR ($p < 0.001$, $p < 0.01$) but not ERPF. Chlorothiazide administered to 1K1C prior to ACEI, decreased GFR ($p < 0.02$) but not ERPF captopril administration to 1K1C which received hydrochlorothiazide intraperitoneally for 7–10 days decreased GFR ($p < 0.007$) and ERPF ($p < 0.02$), while two-kidney, one-clamp animals (2K1C) decreased GFR only in the clamped kidney ($p < 0.005$). ERPF in 2K1C increased only in the contralateral kidney ($p < 0.01$). Without diuretic 1K1C animals decreased GFR and ERPF after ACEI ($p < 0.005$, $P < 0.001$). In the clamped kidney of 2K1C rats, GFR and ERPF decreased significantly ($p < 0.0005$, $p < 0.004$) and contralateral kidney ERPF increased ($p < 0.001$), but GFR did not. The consequences of ACEI on GFR are similar with or without diuretic. These data suggest that diuretic therapy may not significantly interfere with ACEI evaluation of renovascular hypertension.

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The increasing utilization of captopril renography has raised concerns about possible factors which may alter the results of this test. Antihypertensive agents may affect the renal function changes induced by angiotensin converting enzyme inhibition (ACEI) in the differential diagnosis of renovascular hypertension (RVH). Although it is well established that the combined use of a diuretic agent and captopril may induce renal insufficiency (*1,2*), the additive effects of captopril on diuretic agents in RVH have not been studied extensively. Experimental RVH due to the constriction of the renal artery is angiotensin-dependent and has different hemodynamic consequences depending on the model. In the two-kidney, one-clamp (2K1C) RVH model, plasma-renin activity increases, but the one-kidney one-clamp (1K1C) model does not increase plasma-renin activity (*3*). Sodium depletion caused by diuretics may contribute to the reduction of GFR in the presence of renal artery stenosis (RAS) (*4*).

Chlorothiazide and hydrochlorothiazide act primarily at the cortical diluting site and they can cause the loss of 5%–8% of filtered sodium (*5*) by increasing urine volume and sodium excretion. Their action is quite different from furosemide, which acts at the loop of Henle. Therefore, it is reasonable to expect that the effect of diuretic therapy on the results of ACEI may depend on the specific diuretic used.

Normal animals develop acute sodium diuresis during the first day of diuretic treatment and return to normal after long-term treatment (*6*). The diuretic effect on the kidney with RAS is not well characterized. A few studies suggest that acute administration of furosemide increases glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and urinary sodium excretion rate both in kidneys with and without RAS in rats and in patients (*7–8*). Sodium excretion and plasma volume depletion following diuretic treatment in RVH may influence the renin angiotensin system and may affect the diagnostic sensitivity of ACEI-induced renal insufficiency test (*9,10*).

The elevated angiotensin II level in the clamped kidney contributes to the alteration of renal hemodynamics and tubular function (*8*), while the renal hemodynamics remain relatively unchanged in the contralateral kidney. In 1K1C RVH, the renin level increases for a week and then gradually decreases to normal, but the blood pressure remains high (*11*).

In diuretic-treated unilateral RVH, the diuretic alone may affect renal function and reduce the sensitivity of the captopril-induced renal insufficiency test. Alternatively, depleted plasma volume caused by diuretic treatment may sensitize the captopril-induced renal insufficiency test.

This study was designed to observe the acute and chronic effect of diuretic treatment on captopril-induced functional changes in 2K1C and 1K1C rats in an effort to define the influence of diuretic therapy on the interpretation of a captopril challenge in the differential diagnosis of RVH.

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METHODS

Male Sprague Dawley rats weighing 280–300 g were studied 1–2 wk after the left renal artery was clamped. Renal artery stenosis was produced by clamping the left renal artery with polyethylene tubing (PE 50). Two millimeter lengths of tubing were cut longitudinally and placed over the main renal artery. The rats were maintained on a normal diet with laboratory purina chow and provided with water ad libitum. At the time of the renal clearance study, catheters were placed in the left and right ureter (PE 10 silastic tubing), femoral vein and artery (PE 50). Blood pressure was recorded on a Hewlett Packard 78205D recorder using a femoral artery catheter. The mean of three measurements during each time period was used for the analysis. The interventions used are summarized in Table 1.

Acute Studies

Control renal clearance was determined 1 wk after operation using continuous infusion in the animals that received furosemide or hydrochlorothiazide (HCTZ). Animals treated with chlorothiazide did not acutely have control clearances performed. Following three control periods, rats with 1K1C received furosemide intravenously, 0.15 mg (Group 1, n = 10) or HCTZ 1.5 mg (Group 2, n = 9) 15 min prior to ACEI. Chlorothiazide (CTZ) was administered as 1.0 mg in 10 ml of drinking water overnight (Group 3, n = 8). Captopril (1.3–1.7 mg per 100 g BWT) was injected intravenously and blood pressure was measured. When blood pressure was stabilized, three post-captopril clearances were done.

Chronic Studies

For the chronic experiment, 1K1C (Group 4, n = 11) and 2K1C (Group 5, n = 10) rats received 4 mg HCTZ by peritoneal injection daily for 7–10 days prior to ACEI.

GFR and ERPF Measurement

After the rats were awake, normal saline was infused into the femoral vein at a rate of 1.5 ml/hr for 2K1C or 1.0 ml/hr for 1K1C rats using a SAGE automatic infusion pump. GFR and ERPF were measured when urine flow was stable. Technetium-99m-DTPA (50 μCi) and [^{131}I]orthoiodohippurate (OIH) (30 μCi) mixed in 10 ml of saline were infused with a SAGE constant infusion pump at the same flow rate as the saline. Once steady-state blood levels of ^{99m}Tc-DTPA and [^{131}I]OIH were reached, urine was collected using 10-min collection periods for each clearance. Blood from the femoral artery was obtained at the midpoint of each clearance period using two heparinized capillary tubes. Plasma samples of 0.05 ml and 0.1 ml urine samples diluted to 3 ml with water were counted in a well counter with cross-talk correction for ^{99m}Tc and ^{131}I. The samples were recounted for ^{131}I after ^{99m}Tc had been allowed to decay to background. Clearance values were calculated by the standard UV/P relationship. The blood pressure was measured for each clearance period before the blood sample collection.

The mean values of all three GFR and ERPF values for the control and experimental periods were used for the analysis. Statistical analysis was performed by Student's paired t-test for each group, and two p values less than or equal to 0.05 were considered to be significant. Regressions were calculated using one-way analysis of variance. Significance of correlations was determined from Pearson's rank order coefficients.

TABLE 1
Study Design

Acute Studies	
Model	1K1C
Procedure	Control followed by i.v. furosemide (Gp1)
	Control followed by HCTZ (Gp2)
	CTZ without control (Gp3)
	Each of the above followed by i.v. captopril
Chronic studies	
Model	1K1C
	HCTZ 7–10 day peritoneal injection followed by i.v. captopril (Gp4)
	2K1C
	HCTZ 7–10 day peritoneal injection followed by i.v. captopril (Gp5)
Control Studies	
Model	1K1C
	Control followed by i.v. captopril (Gp6)
	2K1C
	Control followed by i.v. captopril (Gp6)

RESULTS

Acute Diuretic Effects on GFR and ERPF

Acute intravenous injection of furosemide or HCTZ alone in the 1K1C model did not significantly change GFR or ERPF. The control and post-furosemide treated GFRs were 0.34 ml/min/100 g BWT ± 0.03 (s.e.) and 0.30 ± 0.02 (ns), respectively. The GFR of control and HCTZ-treated animals were 0.38 ± 0.05 and 0.38 ± 0.05 (ns), respectively. The control and furosemide-treated ERPFs were 1.25 ± 0.10 and 1.06 ± 0.06 (ns), and the HCTZ-treated group ERPFs were 1.17 ± 0.13 and 1.15 ± 0.13 (ns), respectively. Significant changes in renal function were observed in both groups after acute administration of captopril following furosemide or HCTZ treatment. The GFR of the furosemide-treated group fell to 0.23 ± 0.02, ($p < 0.001$) and that of the HCTZ-treated group fell to 0.27 ± 0.04 ($p < 0.01$). In the group of animals receiving CTZ in drinking water overnight, the GFR fell from 0.39 ± 0.02 to 0.25 ± 0.06 ($p < 0.02$) after captopril treatment. ACEI after diuretic treatment did not significantly affect ERPF in any of the three groups (Fig. 1).

1K1C animals that did not receive diuretics prior to captopril had a control GFR and ERPF of 0.36 ± 0.02 and 1.17 ± 0.06, respectively. After captopril administration, GFR and ERPF were 0.27 ± 0.03 ($p < 0.0005$) and 1.05 ± 0.09 ($p < 0.0001$), respectively (Fig. 1). The percent decrease in GFR and ERPF-induced by captopril in the group of animals treated with diuretic and in the group without diuretic (prior to captopril administration) was not significantly different.

Chronic Diuretic Effect on GFR and ERPF

In the 1K1C group, GFR after 1 wk of peritoneal injection of HCTZ was 0.33 ± 0.03 (s.e.). Captopril ad-

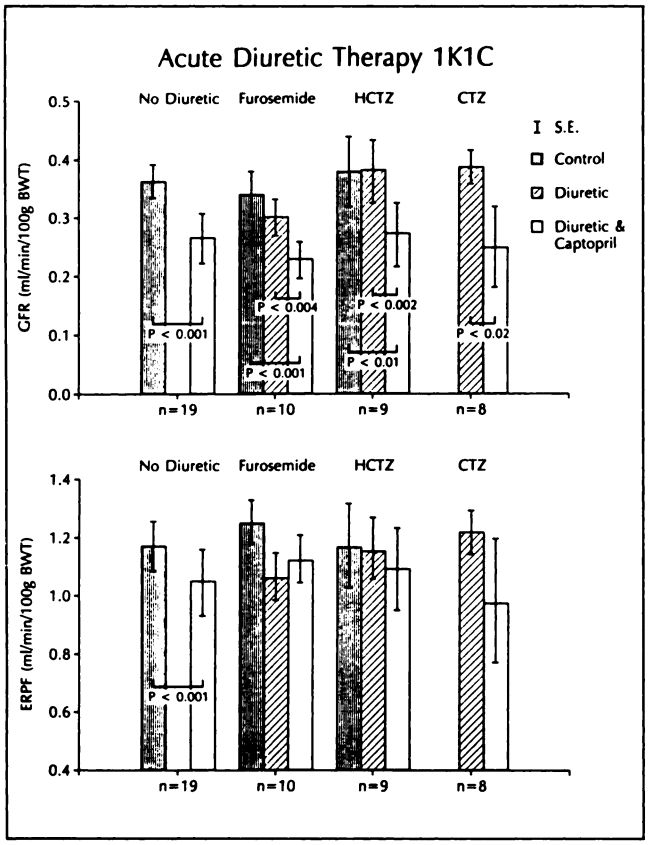

FIGURE 1. GFR and ERPF response to acute diuretic therapy and captopril is illustrated for the 1K1C rat. The responses of GFR and ERPF to acute diuretic therapy alone were not significant. The addition of captopril decreased GFR significantly when compared with baseline and with diuretic therapy alone.

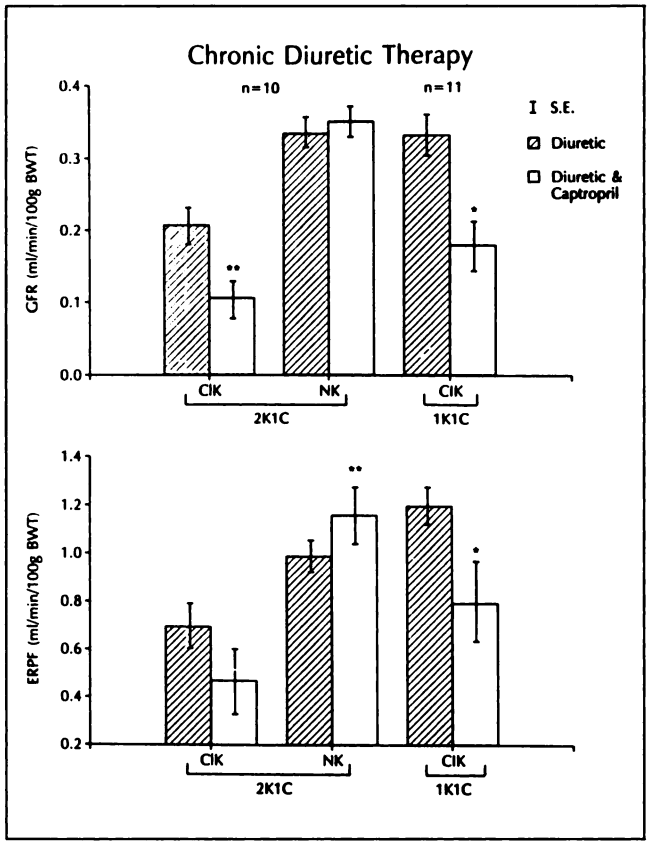

FIGURE 2. GFR and ERPF response to chronic diuretic therapy followed by captopril in the 1K1C and 2K1C rats is shown. GFR responses in the 1K1C and in the clamped kidney of 2K1C were significant, but not in the normal kidney. ERPF in the 1K1C decreased significantly, but not in the clamped kidney of 2K1C. ERPF in the normal kidney of 2K1C increased significantly. Single asterisk indicates $2p < 0.05$ and double asterisk indicates $2p < 0.01$.

ministration decreased GFR to 0.18 ± 0.04 ($p < 0.007$). ERPF decreased from 1.20 ± 0.07d to 0.79 ± 0.16 ($p < 0.02$) (Fig. 2).

After 1 wk of peritoneal injection of HCTZ, the clamped kidney in the 2K1C animals decreased GFR from 0.21 ± 0.03 to 0.11 ± 0.03 ($p < 0.005$). The ERPF fell from 0.70 ± 0.07 to 0.47 ± 0.13 (ns). The GFR in the contralateral kidney prior to captopril administration was 0.34 ± 0.02 and after captopril it was 0.35 ± 0.02 (ns). The ERPF increased significantly from 0.99 ± 0.05 to 1.16 ± 0.09 ($p < 0.01$) (Fig. 2).

In the 2K1C control group of animals, control GFR in the clamped kidney was 0.20 ± 0.02 (n = 19) and ERPF was 0.61 ± 0.06. After captopril treatment, GFR (0.10 ± 0.02, $p < 0.0005$) and ERPF (0.37 ± 0.07, $p < 0.00004$) decreased significantly. Captopril did not affect contralateral kidney GFR significantly but was associated with an increase in ERPF that was significant ($p < 0.001$). The percentage decrease of GFR and ERPF caused by captopril in the group of animals treated with diuretics prior to captopril was not significantly different from the changes in animals that did not receive diuretic treatment. The changes observed in renal function in all of these groups of animals are summarized in Table 2.

Blood Pressure

Blood pressure response in each group is shown in Figures 3 and 4. The acute diuretic-treated 1K1C animals did not decrease blood pressure significantly, but blood pressure decreased significantly after ACEI (Fig. 3). Chronic diuretic treatment decreased blood pressure significantly in both the 1K1C and 2K1C groups (Fig. 4). In the group of animals not receiving diuretics prior to captopril, blood pressure (mmHg) reduction after captopril between the 2K1C and 1K1C groups were significantly different. Blood pressure in the 2K1C group decreased by −27.8 ± 3.5 (s.e.) mmHg, and in the 1K1C group, it decreased by −15.5 ± 21.2. After chronic diuretic treatment, the blood pressure in 2K1C and 1K1C rats were not significantly different.

DISCUSSION

Since diuretic therapy is used widely in hypertensive patients, its potential influence on captopril renography is of great importance. The use of a diuretic in addition to captopril may play a role in the development of captopril-

TABLE 2
Effects of Diuretics and Captopril Renal Clearance

		2K1C				1K1C	
		GFR		ERPF		GFR	ERPF
Group	Rx	NK	C1K	NK	C1K	C1K	C1K
1	Control					0.34 ± 0.03	1.25 ± 1.0
	Acute Furo					0.30 ± 0.02	1.06 ± 0.06
	Furo + ACEI					0.23 ± 0.02†	1.21 ± 0.06
2	Control					0.38 ± 0.05	1.17 ± 0.13
	HCTZ					0.38 ± 0.05	1.15 ± 0.13
	HCTZ + ACEI					0.27 ± 0.04†	1.09 ± 0.14
3	CTZ, Acute					0.39 ± 0.02	1.22 ± 0.05
	CTZ + ACEI					0.25 ± 0.06*	0.97 ± 0.02
4	HCTZ, Chronic					0.33 ± 0.03	1.20 ± 0.07
	HCTZ + ACEI					0.18 ± 0.04*	0.79 ± 0.16*
5	HCTZ, Chronic	0.34 ± 0.02	0.21 ± 0.03	0.99 ± 0.05	0.70 ± 0.07		
	HCTZ + ACEI	0.35 ± 0.02	0.11 ± 0.03*	1.16 ± 0.09	0.47 ± 0.13		
6	Control	0.38 ± 0.02	0.20 ± 0.02	0.95 ± 0.05	0.61 ± 0.06	0.36 ± 0.02	1.17 ± 0.06
	Cont + ACEI	0.37 ± 0.02	0.10 ± 0.02†	1.12 ± 0.06*	0.37 ± 0.07†	0.27 ± 0.03†	1.05 ± 0.09*

* $2p < 0.05$.
† $2p < 0.01$.
The statistical significance shown compares the value for the kidney indicated in the column against the baseline value in that group.

induced renal failure (*1,2*) and it may enhance the diagnosis of RVH. However, it is also possible that the changes expected to occur with ACEI in patients with RVH may be obscured by concomitant antihypertensive therapy. Some investigators report that patients developed renal failure only after diuretic was added to captopril treatment (*1,12*). The combination of diuretic and ACEI treatment has been shown to control blood pressure in patients with RVH with previously resistant hypertension (*13*). However, a substantial proportion of failure of antihypertensive action after combination of diuretic and captopril treatment also has been reported (*14*). These conflicting observations are difficult to interpret and study in humans. Therefore, an animal model was chosen in this study to try to clarify the effects of diuretics on ACEI.

Acute administration of a low dose diuretic alone in this study did not alter either GFR or ERPF in the 1K1C rat. Other investigators have reported that high doses of Furosemide in 2K1C rats also did not alter GFR and ERPF in either the stenotic kidney or the contralateral kidney (*9*). ACEI in 1K1C rats after acute diuretic treatment decreased GFR significantly in all groups. The ERPF did not significantly change in any of the groups of 1K1C animals. Although these results are similar to high-dose furosemide-treated 2K1C rats with RVH (*7*), other studies indicate that the effect of diuretics on renal blood flow depends on the experimental conditions, including the dose and the speed of diuretic administration (*10*).

When captopril was given to patients with RAS without diuretic treatment, it induced changes in sodium balance

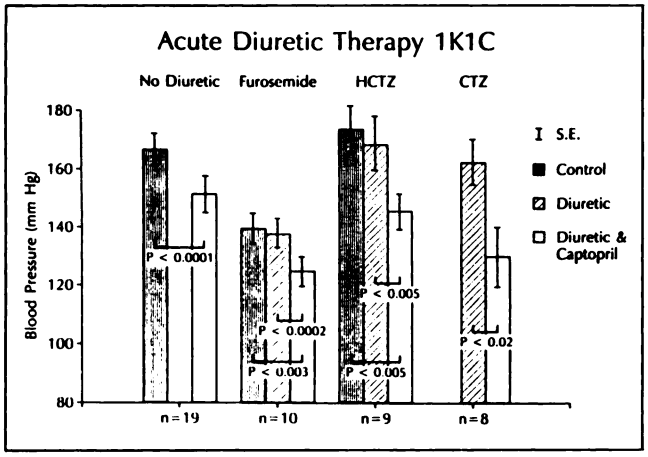

FIGURE 3. Response of mean BP after acute treatment with diuretics (furosemide, HCTZ and CTZ) and with combinations of one diuretic and captopril.

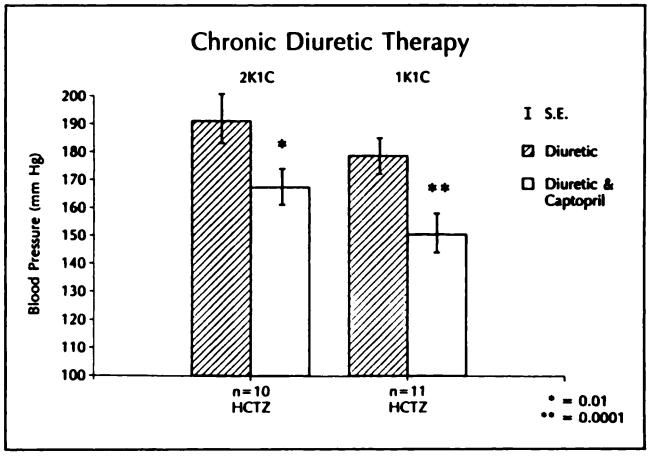

FIGURE 4. Response of mean BP after treatment with 4 mg of HCTZ by peritoneal injection for 7–10 days and treatment with captopril followed by HCTZ in 2K1C and 1K1C rats.

in all patients except patients with low renin (*12*). Some patients with RAS developed positive sodium balance, while others developed negative sodium balance, although all patients experienced blood pressure reduction (*4,12*).

In 1K1C and 2K1C rats with RVH, captopril increases urinary sodium excretion and plasma-renin levels and results in decreased blood pressure (*15,16*). The dependency of autoregulation of GFR on the renin angiotensin system in these animals is most marked during sodium depletion (*7*). Under conditions of sodium depletion and increased renin, inhibition of ACE is expected to disturb autoregulation. When the renin angiotensin system is blocked, sodium and water retention may play a role in the pathogenesis of 1K1C hypertension but not in that of 2K1C (*17*).

The kidneys with RAS in both 1K1C and 2K1C animals have a low perfusion pressure, therefore they tend to retain sodium. However, in 1K1C animals, hypertension was associated with a progressive positive sodium balance, while 2K1C animals developed a progressive negative sodium balance, probably due to the sodium excretion from the contralateral kidney (*17*). In 1K1C animals, sodium retention continues until regulating mechanisms develop a new equilibrium of sodium balance. The rise in central arterial pressure is an important factor in the equilibrium, since it tends to raise the pressure in the renal artery distal to the stenosis. The dependency of autoregulation of GFR on the RAS is most marked during sodium depletion (*7*). The GFR is usually maintained in the sodium replete state, but mild sodium and water depletion can impair renal function.

In patients with severe bilateral RAS, renal function deteriorates (*1,18*) during the combination of captopril and diuretic treatment but not with captopril alone. The dependency of autoregulation of GFR on the RAS is more marked during a combination of captopril and diuretic treatment.

In the present study, the acute intravenous administration of furosemide or HCTZ in 1K1C rats did not change GFR or ERPF significantly. ACEI administered after the diuretic decreased GFR significantly, while captopril given to animals administered CTZ in drinking water overnight prior to ACEI decreased GFR significantly but not ERPF. Captopril administration to rats receiving HCTZ intraperitoneally for 7–10 days decreased both GFR and ERPF in 1K1C rats, while in 2K1C rats it decreased GFR in the clamped kidney but not in the contralateral kidney. ERPF in the 2K1C group did not change in the clamped kidney but increased significantly in the contralateral kidney after ACEI. For control 1K1C rats that did not receive diuretics prior to ACEI, there was a decrease in both GFR and ERPF after ACEI. Both GFR and ERPF decreased significantly after ACEI in the clamped kidney in the control 2K1C rats. In the contralateral kidney in these animals, GFR did not change and ERPF increased significantly. The effects of diuretics on renal function in animals with RAS are variable. The consequences of ACEI on GFR are similar with or without diuretics. These data suggest that diuretic therapy may not significantly interfere with ACEI evaluation of RVH.

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