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Effects of unclipping and converting enzyme inhibition on bilateral renal function in Goldblatt hypertensive rats

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Effects of unclipping and converting enzyme inhibition on bilateral renal function in Goldblatt hypertensive rats. Previous studies have demonstrated that blockade of the renin-angiotensin system in two-kidney, one clip Goldblatt hypertensive rats induced arterial pressure associated reductions in the function of the renin rich, clipped kidney even though the renin-depleted, contralateral kidney exhibited enhanced renal hemodynamics and excretory function. This study was performed to evaluate the influence of inhibition of the activity of the renin-angiotensin system on the function of each kidney following the unclipping of the clipped kidney. Renin-angiotensin system blockade was accomplished by intravenous infusion of converting enzyme inhibitor (CEI, SQ 20881, 3 mg/hr · kg), either before (group 1, $N = 15$) or after (group 2, $N = 16$) removal of the clip. CEI infusion before unclipping decreased arterial blood pressure (BP), from 157 ± 3 to 124 ± 3 mm Hg and led to increases in renal blood flow (RBF), GFR, urinary volume and sodium excretion in the nonclipped kidney. When the clip was still in place, renal function decreased in the clipped kidney during CEI infusion. Upon removal of the clip, there were immediate increases in RBF and GFR, and pronounced diuresis; natriuresis and kaliuresis ensued despite a further reduction of BP from 124 ± 3 to 110 ± 3 mm Hg. In group 2, unclipping of the clipped kidney prior to administration of CEI reduced BP from 161 ± 4 to 118 ± 3 mm Hg within 2 hr. Nevertheless, RBF, GFR, urine flow, and sodium and potassium excretion rates increased in this newly unclipped kidney. Subsequent infusion of CEI decreased BP further, but RBF, GFR, and urinary excretion rates of both kidneys increased significantly. These results suggest that hemodynamic and excretory function of both the nonclipped and clipped kidneys are influenced substantially by the renin-angiotensin system; however, this influence on the clipped kidney can be unmasked only after the clip has been removed.

Effets de l'ablation du clip et de l'inhibition de l'enzyme de conversion sur la fonction rénale bilatérale chez des rats hypertendus selon Goldblatt. Les études antérieures ont démontré que le blocage du système rénine-angiotensine chez des rats hypertendus selon Goldblatt à deux reins et un clip entrainait des réductions de la fonction du rein riche en rénine clippé, en rapport avec la pression artérielle, bien que le rein contralatéral, déplété en rénine, ait une augmentation de l'hémodynamique et de la fonction excrétoire rénales. Cette étude a été entreprise afin d'évaluer l'influence de l'inhibition de l'activité du système rénine-angiotensine sur la fonction de chaque rein après ablation du clip du rein clippé. Le blocage du système rénine-angiotensine a été effectué par perfusion intra-veineuse de l'inhibiteur de l'enzyme de conversion (CEI, SQ 20881, 3 mg/hr · kg) soit avant (groupe 1, $N = 15$) soit après (groupe 2, $N = 16$) ablation du clip. La perfusion de CEI avant l'ablation du clip a abaissé la pression artérielle (BP) de 157 ± 3 à 124 ± 3 mm Hg, et a augmenté le flux sanguin (RBF), le GFR, le volume urinaires et l'excrétion sodée du rein non clippé. Lorsque le clip était encore en place, la fonction rénale diminuait du côté du rein clippé pendant la perfusion de CEI. Lors de l'ablation du clip, il y avait des augmentations immédiates du RBF et de GFR et une diurèse; une natriurèse et une kaliurèse prononcées se produisaient malgré une réduction supplémentaire de la BP de 124 ± 3 à 110 ± 3 mm Hg. Dans le groupe 2, l'ablation du clip avant l'administration de CEI a réduit la BP du rein clippé de 161 ± 4 à 118 ± 3 mm Hg en 2 hr. Cependant, le RBF, le GFR, le débit urinaire, et l'excrétion de sodium et de potassium se sont élevés dans ce rein dont le clip a été récemment enlevé. La perfusion ultérieure de CEI diminuait BP plus mais RBF, GFR, et les excrétions urinaires des deux reins ont augmenté significativement. Ces résultats suggèrent que les fonctions hémodynamique et excrétoire des reins clippés et non-clippés sont substantiellement influencées par le système rénine-angiotensine; cependant, cette influence sur le rein clippé ne peut être démasquée qu'après ablation du clip.

One of the characteristic features of the two-kidney, one clip Goldblatt hypertensive rat (GHR) is that the clipped kidney contains high tissue renin and is exposed to a near normal perfusion pressure, while the contralateral kidney is renin-depleted and faces a high blood pressure [1–3]. Clearance and micropuncture studies have demonstrated that there are differences in renal vascular resistance and tubular function between the clipped and nonclipped kidneys [2–8]. In recent studies [2, 9], we have shown that acute infusion of converting enzyme inhibitor (CEI, SQ 20881) and an angiotensin II competitive analogue (Saralasin) increased RBF, GFR, and excretory function in the nonclipped kidney. In contrast, the clipped kidney exhibited reductions in renal function in response to the blockade of the renin-angiotensin system.

Since it has been suggested that the amount of angiotensin II generated locally is reflected by the endogenous renin levels [10–13], it was anticipated that the renin-rich, clipped kidney would be under substantial influence of angiotensin. Therefore, the finding that renal function in the clipped kidney decreased following angiotensin blockade was surprising. Because the clip produces a pressure difference between the systemic blood pressure and the actual pressure perfusing the clipped kidney, it was speculated that the hypotension following renin-angiotensin blockade might have lowered renal perfusion pressure of the clipped kidney to such an extent that the effects due to inhibition of the actions of angiotensin could not be manifested. To evaluate this possibility, experiments were conducted exploring the responses of the clipped kidney to removal of the clip under conditions of angiotensin II blockade imposed by

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converting enzyme inhibition. In another series of experiments, the clip was removed prior to the administration of CEI.

Methods

Two-kidney, one clip Goldblatt hypertensive rats were prepared by placing a 0.25-mm silver clip on the left renal artery of 80 to 110 g Sprague-Dawley male rats (Charles River Breeding Laboratories, Wilmington, Maryland). The clipping procedure was performed under pentobarbitol anesthesia (5.0 mg/100 g, i.p.) 3 to 4 weeks prior to the experiments. All rats were fed with commercial rat chow (Wayne Lab Blox, Chicago, Illinois) containing 0.5 mEq sodium per gram of chow and were given tap water ad libitum.

The acute experiments were carried out within week 4 postclipping at which time the hypertensive rats weighed 200 to 290 g. Rats were anesthetized with sodium pentobarbitol (5.0 mg/100 g, i.p.). The surgical preparations were similar to those described previously [2]. Briefly, rats were prepared for clearance experiments on a heated table and body temperature was maintained at 37°C by a thermostatic system monitoring the rectal temperature. The trachea was cannulated and an external jugular vein catheter was inserted for infusion of solutions and drugs. The left femoral artery was catheterized for blood sampling and measurement of blood pressure using a Statham P23Dc transducer (Gould-Statham Instruments Inc., Hato Rey, Puerto Rico) and a P7 Grass polygraph (Grass Instrument Co., Quincy, Massachusetts). Through a lateral approach, the left (clipped) kidney was exposed and placed in a cup (Lucite®). The left ureter and the urinary bladder were catheterized for sequential collection of urine from both kidneys. The fibrous tissue surrounding the silver clip on the left renal artery was carefully dissected free without damaging the renal artery or causing bleeding. This approach allowed the clip to be removed easily later in the experiment.

During the surgical operation, rats were infused with isotonic saline at a rate of 0.02 ml/min. Upon completing the surgery, a priming dose of a mixed solution of polyfructosan (Inutest®, 10 g/dl, Laevosan-Gesellschaft, Linz, Austria) and para-aminohippurate (PAH, 2 g/dl, Merck Sharp and Dohme, West Point, Pennsylvania) was administered and followed by a sustaining infusion at a rate of 0.01 ml/min. To maintain the total volume infusion rate constant, the saline infusion rate was decreased to 0.01 ml/min. Rats were allowed to reach a steady state for 30 min, and then urine samples were collected using 30-min clearance periods. Blood samples were taken at the midpoint of each period. Plasma was separated and blood cells were returned to the animals.

Experiments were performed on two groups of hypertensive rats. In group 1 ($N = 15$), CEI was infused prior to unclipping. After two control periods, converting enzyme inhibitor (CEI; SQ 20881, 2 mg/ml, E. R. Squibb and Sons, Princeton, New Jersey) was administered at an initial dose of 0.5 mg followed by a constant infusion of 3 mg $kg^{-1}hr^{-1}$. The effectiveness of CEI in blocking the angiotensin II formation has been demonstrated in a previous study [2] in which 85% of the vasopressor response to 100 ng of exogenous angiotensin I was blocked during CEI infusion. Thirty minutes were allowed to elapse before commencing the next urine collection. After four consecutive clearance periods, the clip on the left kidney was removed. After a 10-min waiting period to allow the dead space in the ureter and urinary bladder catheters to wash out, three subsequent clearance collections were taken. In group 2 ($N = 16$), the unclipping procedure was carried out before CEI infusion. After two initial control periods, the clip on the left kidney was removed carefully. Ten minutes were allowed to elapse before proceeding with the four subsequent 30-min clearance collections. CEI was then administered as described for group 1, and two additional clearance periods were followed.

Plasma and urine polyfructosan concentrations were measured with an anthrone colorimetric method and PAH concentrations in plasma and urine were analyzed with a colorimetric technique as described previously [9]. Plasma sodium and potassium concentrations were determined with a flame photometer (Model 443, Instrumentation Laboratory, Lexington, Massachusetts). Hematocrits were measured with an autocrit centrifuge (Autocrit II, Clay Adams, Inc., Parsippany, New York). Because of the technical difficulty in sequential sampling of renal venous blood, PAH clearance (C_{PAH}) was used as a measure of renal plasma flow without correction for extraction; the filtration fraction (FF) was calculated as the ratio of GFR to PAH clearance. Total renal vascular resistance (RVR) of the nonclipped kidney was computed from calculated renal blood flow and systemic arterial pressure, but RVR calculations for the left (clipped) kidney were not made because the true renal perfusion pressure was not known. The results are expressed as mean ± SEM. The data were analyzed using both paired and unpaired analysis where applicable; a probability less than 5% was accepted as being statistically significant.

Results

Group 1 experiments. The average body weight of the rats in group 1 was 277 ± 16 g; the left clipped kidney weighed 1.1 ± 0.06 g and was significantly smaller than the contralateral nonclipped kidney (1.3 ± 0.06 g). The effects of CEI infusion and subsequent unclipping on blood pressure and renal hemodynamics are depicted in Figure 1. The mean arterial blood pressure fell from 157 ± 3 to 139 ± 4 mm Hg following 30 min of CEI infusion and then decreased progressively to 124 ± 3 mm Hg after 2.5 hr of CEI infusion. Unclipping in the presence of CEI caused a further significant decrease in blood pressure to 110 ± 3 mm Hg during the first clearance period and to 107 ± 2 mm Hg by the end of the experiment.

During the period of CEI infusion, a significant renal vasodilatation was observed in the nonclipped kidney. PAH clearance significantly increased from 3.3 ± 0.3 to 4.8 ± 0.4 ml/min after 30 min and averaged 5.3 ± 0.6 ml/min by the end of 2 hr of CEI infusion. Estimated renal blood flow increased from 6.6 ± 0.7 to 9.1 ± 0.9 ml/min and to 9.7 ± 1.3 ml/min over the corresponding time course. Right kidney renal vascular resistance decreased significantly from 25.8 ± 2.9 to 16.0 ± 1.2 (mm Hg · min)/ml by the first clearance period and to 14.0 ± 1.2 (mm Hg · min)/ml prior to unclipping. In the clipped kidney, there were significant decreases in both renal plasma and blood flow. PAH clearance was reduced from 2.4 ± 0.3 to 1.7 ± 0.3 ml/min following 30 min of CEI and then maintained at similar levels over the three additional clearance periods. Estimated renal blood flow also decreased from 4.7 ± 0.6 to 3.2 ± 0.3 ml/min. Removal of the clip led to pronounced increases in PAH clearance and calculated RBF in the previously clipped kidney, although the non-

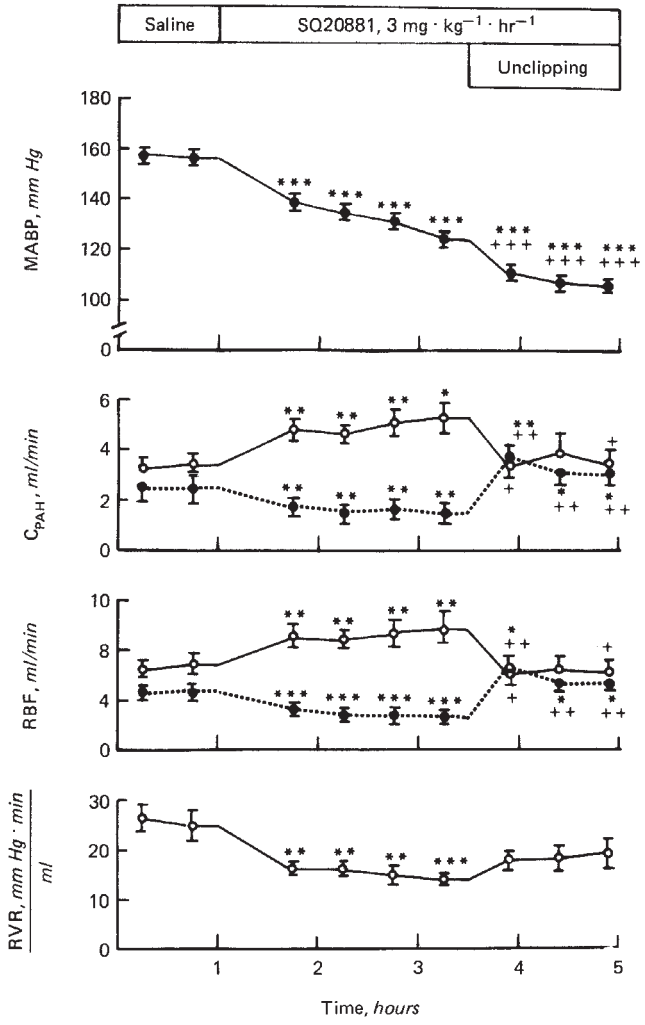

Fig. 1. *Responses of mean arterial blood pressure* (MABP), *PAH clearance* (C_{PAH}), *renal blood flow* (RBF), *and total renal vascular resistance* (RVR) *of the clipped kidney* (●---●) *and the nonclipped kidney* (○—○) *during infusion of CEI and the following period of unclipping*. Data *points* are plotted at the midpoint of each clearance period. Symbols are: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ when compared to control period; + $P < 0.05$; ++ $P < 0.01$; +++ $P < 0.001$ when compared to the last period of CEI infusion alone.

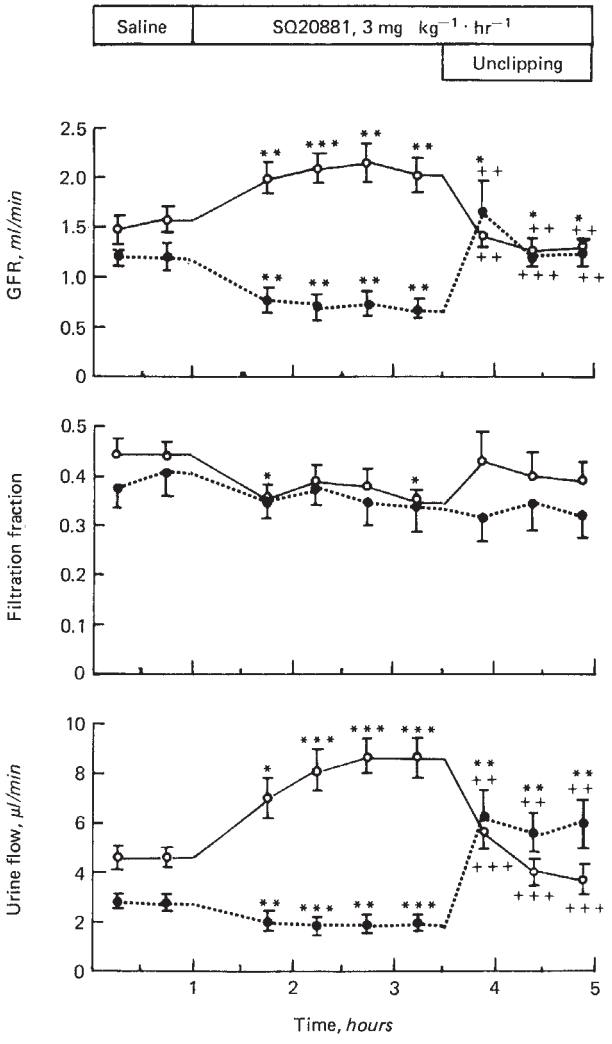

Fig. 2. *Responses of GFR, filtration fraction, and urine flow of the clipped kidney* (●---●) *and the nonclipped kidney* (○—○) *during CEI infusion and subsequent unclipping*. Statistical notations are identical to that shown in Figure 1.

clipped kidney exhibited decreases in these values. PAH clearance and estimated RBF were similar in both kidneys following the removal of the clip.

Figure 2 shows the GFR, filtration fraction, and urine flow in response to CEI and unclipping. CEI infusion increased GFR of the nonclipped kidney significantly from 1.53 ± 0.13 to 1.99 ± 0.16 ml/min; filtration fraction decreased from 0.44 ± 0.03 to 0.35 ± 0.03; and urine flow increased from 4.6 ± 0.4 to 7.0 ± 0.8 µl/min following the first 30 min. With continuous CEI infusion, GFR and urine flow increased further despite progressive reductions in arterial blood pressure. The filtration fraction varied slightly during this period, but still remained at a level lower than that of the control period. In the clipped kidney, there were significant decreases in GFR and urine flow in response to CEI. The slight decrease in filtration fraction was not significant. The subsequent removal of the clip from the left kidney elicited marked increases in GFR and urine flow in this kidney. The augmented GFR then receded slightly to a level comparable to that observed in the contralateral kidney 1 hr after unclipping; however, the diuretic response persisted. The filtration fraction was not altered significantly. There were significant reductions in GFR and urine flow in the nonclipped, contralateral kidney following removal of the clip.

The sodium and potassium excretion responses to CEI and subsequent unclipping are shown in Figure 3. CEI caused natriuretic and kaliuretic responses in the nonclipped kidney. Both the absolute excretion rates and the fractional excretion rates of sodium and potassium increased significantly. The maximum increases were sixfold for total sodium excretion (from 0.16 ± 0.03 to 0.93 ± 0.23 µEq/min) and fivefold for fractional excretion of sodium (0.08 ± 0.02 to 0.36 ± 0.08%) following 2.5 hr of CEI infusion. The corresponding maximum increases in potassium excretion were only two- to threefold (from 0.87 ± 0.15 to 2.21 ± 0.30 µEq/min and from 16 ± 2 to 38 ± 5%, respectively). Sodium excretion from the clipped kidney

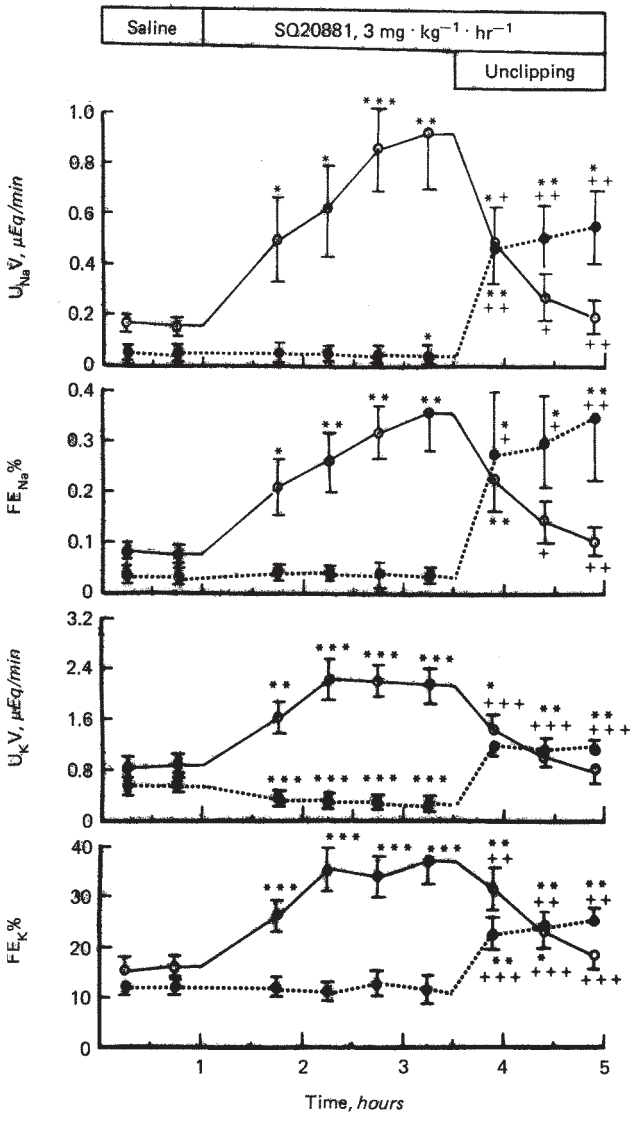

Fig. 3. *Responses of absolute sodium excretion* ($U_{Na}V$), *fractional sodium excretion* (FE_{Na}), *absolute potassium excretion* (U_KV), *and fractional potassium excretion* (FE_K) *of the clipped kidney* (●---●) *and the nonclipped kidney* (○—○) *during CEI infusion and subsequent unclipping.* Statistical notations are in Figure 1.

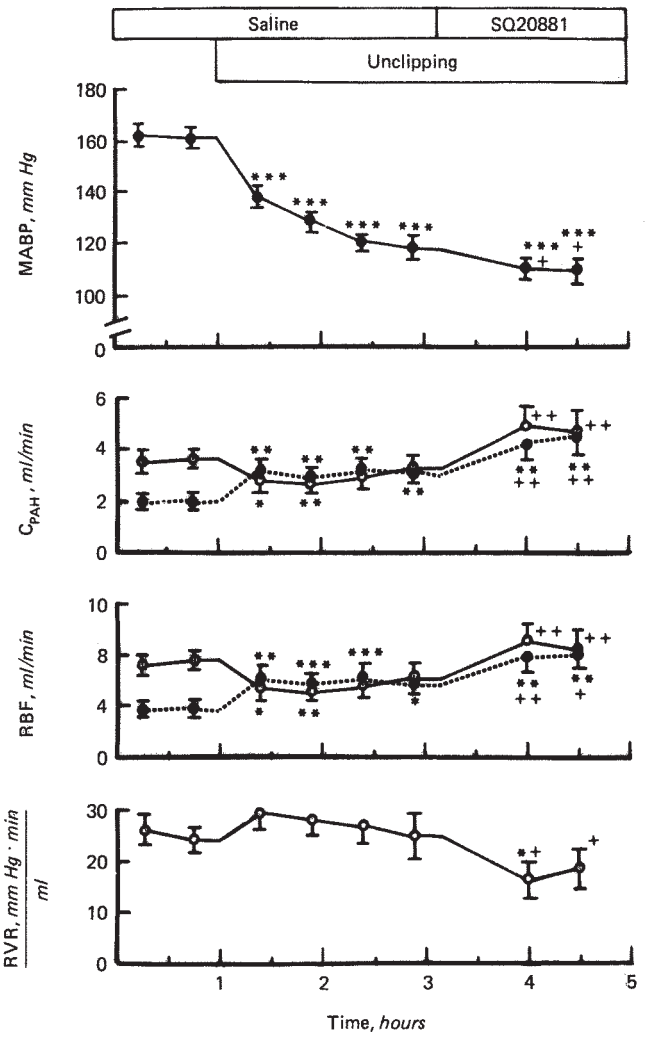

Fig. 4. *Responses of mean arterial blood pressure and renal hemodynamics of the clipped kidney* (●---●) *and the nonclipped kidney* (○—○) *following unclipping and superimposed infusion of CEI.* Statistical notations are identical to those shown in Figure 1 except that the *plus sign* indicates significant differences between the last period of unclipping and the superimposed CEI period.

did not change significantly except during the last clearance period. Absolute potassium excretion decreased significantly during CEI infusion. Unclipping induced an abrupt increase in absolute and fractional sodium output from the previously clipped kidney (from 0.04 ± 0.01 to 0.47 ± 0.14 μEq/min and 0.03 ± 0.01 to 0.28 ± 0.14%, respectively). The natriuresis continued and was even accentuated although there were further decreases in arterial blood pressure. A concomitant increase in potassium excretion was noted, but the response was relatively less than that of sodium excretion and did not increase further with time. Sodium and potassium excretion from the nonclipped kidney diminished significantly and the early augmented saluretic response resulting from CEI infusion was partially reversed.

Group 2 experiments. In this group, body weight was 240 ± 11 g; the left (clipped) kidney weighed 1.06 ± 0.07 g, a value significantly less than that of the nonclipped contralateral kidney (1.32 ± 0.08 g). The responses of blood pressure and renal hemodynamics in the group of rats subjected to unclipping first followed by CEI infusion are shown in Figure 4. Removal of the clip from the clipped kidney rapidly decreased the arterial blood pressure from 161 ± 4 to 138 ± 4 mm Hg during the first clearance period. Arterial pressure declined further and reached 118 ± 3 mm Hg within 1.5 hr. The reversal of arterial blood pressure resulting from unclipping alone was faster and greater than that observed with CEI administration; furthermore, subsequent infusion of CEI induced only a slight additional decrease in blood pressure (118 ± 3 to 111 ± 4 mm Hg).

The estimated renal plasma flow, renal blood flow, and GFR in the nonclipped kidney decreased slightly during the first hour of unclipping and subsequently returned to the control levels (Figs. 4 and 5). A slight but insignificant increase in renal

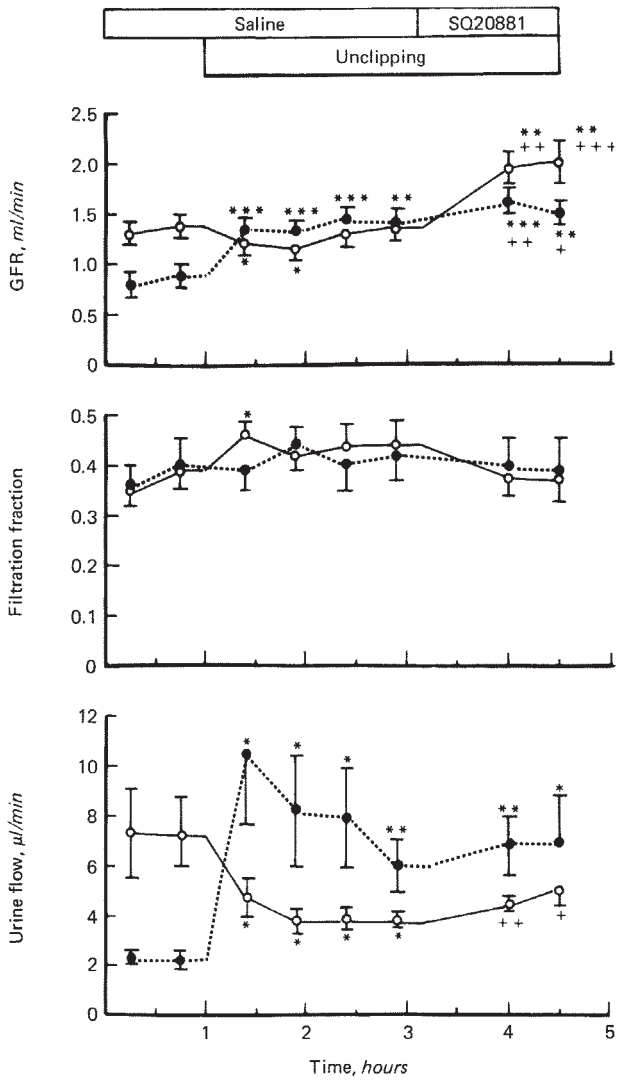

Fig. 5. *Responses of GFR, filtration fraction, and urine flow of the clipped kidney (●---●) and the nonclipped kidney (○—○) during unclipping and the superimposed infusion of CEI.*

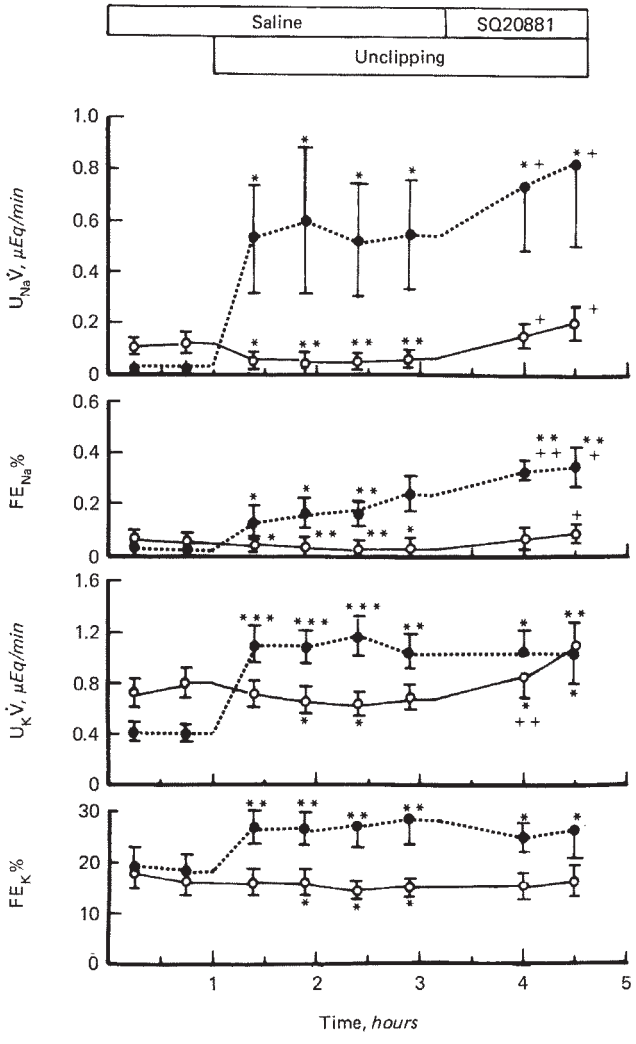

Fig. 6. *Responses of absolute and fractional excretion rates of sodium and potassium of the clipped kidney (●---●) and the nonclipped kidney (○—○) during unclipping and the superimposed infusion of CEI.*

vascular resistance was noted at the early period of unclipping but then fell to the pre-unclipping level. In contrast, the removal of the clip induced significant increases in renal blood flow and GFR of the ipsilateral kidney which were sustained. Infusion of CEI resulted in increases in renal plasma flow, renal blood flow and GFR in both kidneys. Filtration fraction increased significantly in the first clearance period following unclipping in the nonclipped kidney; otherwise, filtration fractions remained unaltered in these experiments.

There were significant reductions in urine flow (Fig. 5) and sodium and potassium excretion (Fig. 6) from the nonclipped kidney following unclipping. Upon administration of CEI, there were increases in urine flow and sodium excretion so that these excretion rates did not differ significantly from those existing prior to removal of the clip. The unclipping procedure resulted in a marked and rapid diuresis, natriuresis, and kaliuresis by the previously clipped kidney. The diuretic response tended to subside but the sodium excretion rate remained elevated. The subsequent infusion of CEI elicited even further increases in absolute and fractional sodium excretion rates in both kidneys with the absolute magnitudes being slightly greater in the previously clipped kidney. Sodium excretion increased by an average of 0.28 μEq/min during the second CEI period compared to the fourth unclipping period. The corresponding increase was only 0.13 μEq/min in the nonclipped kidney. However, as shown on Figure 6, the absolute sodium excretion rates from the previously clipped kidney were much higher than in the nonclipped kidney despite the similar values for renal plasma flow and GFR.

Although comparisons of the responses of the unclipped kidney to removal of the clip between groups 1 and 2 are difficult due to the different levels of arterial pressure, the relative responses might provide further appreciation of the influence exerted by CEI. In response to unclipping alone (group 2), PAH clearance increased by 55% while GFR increased by an average of 61% during the first period following removal of the clip (Figs. 4 and 5). These relative responses

were less than those observed during CEI infusion (group 1) where PAH clearance increased by 147% and GFR increased by 155% during the first period after the unclipping (Figs. 1 and 2). Fractional sodium excretion responses to unclipping in the presence of CEI increased by 7.5 to eightfold while these increased by four- to fivefold in the rats not infused with CEI.

Discussion

As demonstrated previously [2], CEI infusion to two-kidney, one clip hypertensive rats resulted in arterial pressure associated decreases in the function of the clipped kidney and increased function of the nonclipped kidney. In this study, the removal of the renal clip in the presence of CEI not only reversed the depressed kidney function but led to immediate diuretic, natriuretic and kaliuretic responses by the previously clipped kidney. Of interest is the finding that urine flow and the sodium excretion rate from this kidney were even greater than those from the nonclipped, contralateral kidney (Figs. 2 and 3). For example, in the third period following unclipping, sodium excretion of the previously clipped kidney was 0.56 ± 0.16 μEq/min and significantly greater than the 0.20 ± 0.06 μEq/min of the nonclipped kidney (Fig. 3). These differences were apparently not due to differences in the hemodynamic status of the two kidneys since GFR and PAH clearance data were similar in both kidneys following unclipping. These CEI observations are consistent with the hypothesis that the elevated endogenous renin and presumably angiotensin II levels [1, 2, 7, 12] were exerting an influence on renal function which was not unmasked by CEI administration until an adequate renal perfusion pressure was provided.

The increases in RBF, GFR, and excretory function of the nonclipped, contralateral kidney in response to CEI were similar to those observed previously [2]. However, the removal of the clip during continuous CEI infusion led to reductions in the renal hemodynamic and excretory function of the nonclipped, contralateral kidney. The mechanism for these responses is unclear; however, it has been shown that the nonclipped kidney requires a higher arterial blood pressure for the maintenance of normal renal function [7, 13]. Thus, it is possible that the additional fall of blood pressure in response to unclipping was responsible for the decreases in the function of the contralateral kidney.

In group 2, the unclipping procedure was performed prior to CEI administration. The fall in arterial pressure appeared to be faster and greater and contralateral kidney function decreased in association with these marked reductions in arterial pressure. The later recovery of renal blood flow and GFR in the nonclipped kidneys in this group suggests that delayed factors, perhaps reductions in circulating angiotensin allowed a slow restoration of RBF and GFR in the contralateral kidney. As expected, hemodynamic function and urinary excretion rates from the clipped kidney increased substantially following the removal of the silver clip. On a relative basis, however, the hemodynamic responses of the clipped kidney to removal of the clip were less in the rats not infused with CEI. Infusion of CEI subsequent to the unclipping procedure increased renal function in both kidneys in this group.

A particularly interesting finding was that both absolute and fractional sodium excretion rates remained substantially higher in the previously clipped kidney than in the contralateral kidney. These differences in sodium excretion suggest that the renin-rich clipped kidney was under a greater influence of angiotensin II than the renin-depleted nonclipped kidney. Alternatively, it is possible that an additional factor capable of stimulating sodium excretion is highly active in the previously clipped kidney and becomes dominant when the counteracting antinatriuretic influences of a low perfusion pressure and high angiotensin levels are reduced or blocked. Several clearance studies performed on normal animals have demonstrated that angiotensin II has a direct intrarenal effect on tubular reabsorption [14–16]. Evidence suggesting that angiotensin II stimulates tubular reabsorption of sodium has also been obtained in microperfusion and micropuncture studies. Harris [17] showed that microperfusion of low concentrations of angiotensin II into the peritubular capillary surrounding the proximal tubule directly enhanced proximal tubular sodium reabsorption in normal rat kidneys. Recently, we observed that inhibition of angiotensin II formation by SQ 20881 elicited a significant fall of proximal tubular reabsorption of chloride, fluid and total solute in the two-kidney, one clip hypertensive rat [18]. A similar observation was obtained by Steiner, Tucker, and Blantz [19] in sodium-depleted rats using saralasin to antagonize the actions of angiotensin II. Collectively, these data support the notion that the increased sodium excretion rates were due, in part, to blockade of angiotensin-mediated effects on tubular reabsorption following CEI. This study shows that the effects occurred in both the nonclipped and the previously clipped kidney.

The rapid reduction in arterial blood pressure after unclipping observed in this study is consistent with other studies performed on unanesthetized animals [20–23]. The major portion of the arterial blood pressure decrease occurred within the first hour after removal of the clip. Interestingly, the magnitude of the decrease in arterial blood pressure induced by CEI was less than that which occurred following unclipping. A similar difference in hypotensive responses has been reported previously [23–25]. These results suggest that the reduction of angiotensin II levels is not the sole factor responsible for the decrease in arterial blood pressure following unclipping. Dietz et al [22] found that there was not a correlation between the reduction of plasma angiotensin II concentration and the change in blood pressure after unclipping. In other studies [26], it was shown that the early elevated plasma renin activity was reduced to control levels after 2 hr of unclipping. However, Gulati et al [27] reported that renin infusion during unclipping of the clipped kidney prevented the reversal of blood pressure. In this study, we observed further and significant reductions in arterial blood pressure after unclipping during continuous CEI administration. This additional fall in blood pressure was not simply time-related since it did not occur in our previous study where CEI was infused continuously for 3.5 hr [2]. Also, it apparently was not just due to continued loss of sodium and water occurring concurrently with the unclipping procedure since total urinary sodium and volume losses from both kidneys were at least as great during continued CEI infusion without unclipping [2]. Thus, the nonangiotensin-mediated mechanism responsible for this additional fall remains unclear. The vasodepressor response is apparently not related to alterations in the status of the prostaglandin system or the kallikrein-kinin system [28]. Other recent studies [29–31] support the concept that a vaso-

depressor system, probably of medullary origin [29], is activated following removal of this clip.

Acknowledgments

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