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ASSESSMENT OF THE CONTRIBUTION OF THE RENIN-ANGIOTENSIN SYSTEM TO ALTERED RENAL HEMODYNAMIC AND TUBULAR FUNCTION IN 2-KIDNEY, 1 CLIP GOLDBLATT HYPERTENSION

by

WANN-CHU HUANG

A DISSERTATION

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ABSTRACT OF DISSERTATION

GRADUATE SCHOOL, UNIVERSITY OF ALABAMA IN BIRMINGHAM

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Title Assessment of the contribution of the renin-angiotensin system to altered renal hemodynamic and tubular function in 2-kidney, 1 clip Goldblatt hypertension.

The influence of the renin-angiotensin system (RAS) on individual kidney function of 2-kidney, 1 clip Goldblatt hypertensive rats was evaluated by intravenous infusion of a converting enzyme inhibitor (CEI, SQ20881) or an angiotensin II antagonist (saralasin). Rats were made hypertensive 3 to 4 weeks prior to the experiment. Both hypertensive and normotensive control rats were prepared to allow urine collections from both kidneys.

Both CEI and saralasin produced reductions in arterial pressure in hypertensive rats. Despite the fall in arterial pressure, the nonclipped kidney with reduced renal renin activity exhibited significant increases in renal blood flow (RBF), glomerular filtration rate (GFR) and excretory function and a decrease in renal vascular resistance. In the clipped kidney, significant arterial pressure-associated decreases in RBF, GFR and excretory function were observed during RAS blockade. In control rats, CEI and saralasin infusion produced a mild hypotensive effect. Changes in

GFR and excretory function were smaller in magnitude than those observed in the nonclipped kidneys of hypertensive rats.

The segmental nephron reabsorption of the nonclipped kidney was assessed by recollection micropuncture technique before and during CEI infusion. There were significant decreases in absolute and fractional reabsorptions of fluid, chloride and total solute by the proximal tubule, while the single nephron GFR (SNGFR) increased significantly. A significant increase in absolute and a decrease in fractional reabsorption were observed in the nephron segment between the late proximal and early distal tubules. The proximal and distal tubule hydrostatic pressures increased significantly, while the peritubular capillary pressure decreased slightly. The reductions of the proximal tubule reabsorption and increases in SNGFR in response to CEI were also observed when the decrease in arterial pressure produced by CEI was eliminated by mechanically reducing aortic pressure prior to the control collection.

These results indicate that the elevated circulating angiotensin II in 2-kidney, 1 clip Goldblatt hypertensive rats substantially influences the function of the renin-depleted, nonclipped kidney, leading to an elevated renal vascular resistance and enhanced tubular reabsorptions of fluid, chloride and total solute. These could play an important role in the pathogenesis of hypertension in this model.

Abstract Approved by: Committee Chairman Luis Gabriel Navar

Program Director

Date 12/4/81 Dean of Graduate School

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LIST OF ABBREVIATIONS

AV3V	=	anterior ventral portion of the third ventricle
BP	=	blood pressure
CEI	=	converting enzyme inhibitor
FE	=	fractional excretion
FR	=	fractional reabsorption
GFR	=	glomerular filtration rate
PAH	=	para-aminohippurate
PRA	=	plasma renin activity
RAS	=	renin-angiotensin system
SNGFR	=	single nephron glomerular filtration rate
VMH-ME	=	ventromedial hypothalamus-median eminence

INTRODUCTION

Constriction of one renal artery without contralateral nephrectomy produces what has been referred to as 2-kidney, 1 clip Goldblatt hypertension. This hypertensive model has been extensively used in investigating the role of the renin-angiotensin system (RAS) in the initiation and maintenance of hypertension. Accumulated observations obtained through the administration of angiotensin I converting enzyme inhibitors and angiotensin II receptor antagonists have strongly suggested that the elevated RAS is the triggering factor for the initiation of high blood pressure in this hypertensive model. The basis for this conclusion is that prior administration of RAS blockers prevents the development of hypertension due to constriction of renal artery, and that blockade of RAS results in a significant reduction in blood pressure during the early phase when plasma renin activity is high. When hypertension is established, factors including RAS, sodium retention and the nervous system may participate in the maintenance of high blood pressure. In addition, there are some observations suggesting that alterations in the renal vasodepressor system might be involved in the development of hypertension.

It has been hypothesized that altered excretory function of the kidney might contribute to the pathogenesis of hypertension

(110). In Goldblatt hypertension, the elevated RAS resulting from the stenosis of one renal artery may influence the contralateral kidney so that it fails to respond to an elevated blood pressure with pressure natriuresis which, under normal condition, could restore the blood pressure to a normal level. The loss of excretory antihypertensive action of the kidney may reflect some derangements in renal function.

The 2-kidney, 1 clip Goldblatt hypertensive rats are characterized by a renin-depleted, nonclipped kidney subjected to high blood pressure and a renin-rich, clipped kidney protected from hypertension. Both kidneys are exposed to elevated circulating renin and angiotensin for several weeks. This unique feature allows the evaluation of the function of the nonclipped kidney as it responds and adapts to the progressive elevation in blood pressure and plasma renin activity (PRA).

Previous studies have shown that there were differences in the renal hemodynamics and excretory function between the clipped and the nonclipped kidneys. An angiotensin-mediated increase in renal vascular resistance has also been found in the nonclipped kidney. However, there is no direct evaluation of both renal hemodynamics and excretory function and single nephron function during blockade of RAS. Thus the present study was designed to explore the role of RAS on individual kidney function by means of converting enzyme inhibition and angiotensin receptor blockade. A direct assessment of the segmental nephron reabsorption function of the nonclipped kidney was also made. These observations provide some insight into

the contribution of RAS to the altered renal function. This is of significance in determining the role of altered kidney function in the pathogenesis of hypertension in this model.

I. Review of Literature

Historical background of Goldblatt hypertension, renin-angiotensin system and its pharmacological blockers

Kidney involvement in hypertension was first described in the early 1830's by Richard Bright, who observed that albuminous urine was associated with dropsy and cardiac hypertrophy (32). He postulated that either the altered physicochemical properties of blood or the affected minute arteries and capillaries led to a greater action necessary to force the blood through the distant vessels and thereby produced cardiac hypertrophy. The discovery of this so called Bright's disease aroused great interest and has stimulated further study since then (243). Clinicians often noted that thickened arterioles and capillaries were associated with contracted kidneys and a hypertrophied heart (243). In 1898, Tigerstedt and Bergman (308) demonstrated that the crude saline extract of rabbit kidney raised blood pressure when injected into anesthetized dogs and concluded that a pressor substance which they named renin existed in the extract.

Before 1934, studies designed to elucidate the relation between hypertension and renal disease usually employed such methods

as damage of the kidney by coagulation, partial excision, irradiation, and occlusion of renal artery, renal vein or ureter to produce hypertension (104). However, most of the procedures either did not produce hypertension or only produced slight and temporary hypertension. These inconsistent observations made in experimental hypertension were mainly attributed to the different techniques used for producing high blood pressure and for measuring blood pressure. In the early 1930's, Goldblatt and his co-workers thought that the renal vascular abnormality might be the cause rather than the result of hypertension since it was observed clinically that renal arteriosclerosis always accompanied high blood pressure. They wished to limit the renal circulation without causing significant damage to the kidney and renal excretory function. Thus they designed clips to constrict the renal artery and successfully induced sustained hypertension in dogs by this method in 1934 (105). This entirely new and efficient technique of producing sustained hypertension was quickly adopted and applied to rats and other animals (243).

The search for mechanisms of hypertension started even before Goldblatt's experimental model of hypertension. The idea that a renal pressor substance is the cause of hypertension was then repeatedly postulated, reported and denied. The introduction of the Goldblatt method of producing a sustained hypertension in animals gave an impetus to study the elusive pressor substance. In 1937, Harrison et al. (119) and Prinzmetal and Friedman (248) reported that a saline extract of the ischemic kidney elicited a greater

pressor effect than that from normal kidneys. In 1938, Fasciolo et al. (77) showed that grafting the ischemic kidney of a hypertensive dog into the neck of a nephrectomized recipient raised the blood pressure of the recipient, but kidneys from normal donor dogs usually did not. In the same year, Kohstaedt et al. (146) attempted to purify renin and proposed that renin was an enzyme-like substance which was activated by a plasma protein, renin activator. In 1939, Braun-Menendez et al. (31) found that the pressor substance in the renal venous blood coming from acutely ischemic kidney was soluble in 75% acetone, dialyzable, thermostable and produced a vasopressor action lasting for 3 to 4 minutes. They concluded that it was distinguishable from renin and named it hypertensin. The same year, Goormaghtigh (106), who had previously described two groups of cells in the vascular pole region of the glomerulus (now known as juxtaglomerular cells and macula densa), noted increased granulation of juxtaglomerular cells in the ischemic (clipped) kidney. He then proposed that the granular cells were secretory and that the substance secreted was renin. In 1940, Page and Helmer (232) showed that renin acted on a plasma substrate to produce a pressor substance which was named angiotonin. Since hypertensin and angiotonin were the same substance, Page and Braun-Menendez agreed to unify the nomenclature and gave a new name angiotensin for this pressor substance in 1958 (76).

In 1954, Skeggs et al. (278,279) obtained pure angiotensin I from the action of pig renin on horse angiotensinogen. They found that the pressor product of renin action existed in two forms,

hypertensin (angiotensin) I and hypertensin (angiotensin) II. In 1956, Peart et al. (238) isolated a pure angiotensin II from the reaction of rabbit renin and bovine plasma. Bumpus et al. (39) sequenced and synthesized hog angiotensin II and Rittel et al. (254) synthesized an analogue of bovine angiotensin II in 1957. In addition, Ng and Vane (220) found that the conversion of inactive angiotensin I to active angiotensin II occurred in the lung.

In 1965, Ferreira (81) isolated a bradykinin potentiating factor, a mixture of small peptides, from the venom of the Brazilian viper, Bothrops jararaca. Bakhle (14) reported in 1968 that bradykinin potentiating factor was also a potent inhibitor of pulmonary angiotensin converting enzyme. Two years later, Yang et al. (324) showed that angiotensin I converting enzyme and kinanse II were the same protein kininase. In 1970, Ferreira et al. (82) purified 9 bardykinin potentiating factors, determined their amino acid sequences, synthesized the simplest one (Glu-Lys-Trp-Ala-Pro) and demonstrated its activity in vivo as a bradykinin potentiator and an inhibitor of angiotensin I conversion. In 1971, Ondetti et al. (227) isolated and synthesized 6 peptides from the same venom used by Ferreira et al. (82). Five of them had amino acid compositions identical to those described by Ferreira et al. (82). Teprotide (SQ 20881, Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) is one of them. The same year, similar peptides from other snake venom (Agkistrodon halys blomhoffii) were characterized and synthesized by Kato and Suzuki (140) in Japan. These peptides have not been studied extensively, however.

In other studies, great efforts to study the importance of each animo acid of angiotensin II for pressor and myotropic activity continued. These efforts finally led Khairallah et al. (141) to develop a competitive analogue which could block the action of angiotensin II in 1970. Thereafter a series of antagonists of angiotensin II was developed, including saralasin (P113) which as been extensively studied both clinically and experimentally.

Although teprotide is a potent antihypertensive drug, it is effective only when administered parenterally. An interest in using converting enzyme inhibitors as antihypertensive agents led to an intensive search for orally effective inhibitors of angiotensin I converting enzyme. In 1977, Ondetti et al. (226) reported synthesis of a new, orally effective converting enzyme inhibitor, captopril (SQ 14225, D-3-mercapto-2-methylpropanoyl-L-proline). Since then, other converting enzyme inhibitors have been developed. MK 421, N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-Ala-L-Pro, is one of these compounds which has been shown to have a longer duration but a slower onset of action compared to captopril (237).

The RAS, as presently known, is a system consisting of at least 5 components. Activation of RAS starts with renin being secreted from the juxtaglomerular cell of the kidney. This proteolytic enzyme acts on a globulin (renin substrate or angiotensinogen which is synthesized in the liver) to release a decapeptide called angiotensin I. Angiotensin I has been generally considered to be a prohormone devoid of vasoactive effect. In the presence of converting enzyme, which is mainly located on the luminal surface

lining the endothelial cell of pulmonary vascular bed, angiotensin I is rapidly and extensively hydrolyzed to yield the octapeptide angiotensin II and the dipeptide, His-Leu (228). Angiotensin II is the predominant active component of the system. It is the most potent vasoconstrictor and can stimulate aldosterone secretion, act on the central nervous system to produce a pressor response and alter renal hemodynamics and tubular function. It has also been shown that angiotensin II can modulate the peripheral adrenergic system and interact with the renal kallikrenin-kinin system and prostaglandins (69,168,299,329,332). Angiotensin II has a short half-life of 16-20 seconds (4,83) and is rapidly hydrolyzed by an amino peptidase to form (des-Asp^1) angiotensin II (angiotensin III) and by a variety of other peptidases to form inactive peptide fragments. Additionally, it has been reported that tonin, a protease existing in the circulation and some tissues, can directly hydrolyze renin substrate and angiotensin I to form angiotensin II.

The converting enzyme inhibitors compete with native substrate for binding to the active site of angiotensin I converting enzyme (52,227). Both teprotide and captopril effectively block the generation of angiotensin II in vivo and in vitro (72,226,227,259) and lead to increases in plasma renin and angiotensin I levels. The elevated plasma renin and angiotensin I levels following CEI could be due to the release of negative feedback inhibition of renin release by angiotensin II. In hypertensive animals, the reduction in blood pressure caused by CEI might also contribute to

the elevation in plasma renin through a reflex increase in sympathetic nerve activity to the kidney.

The potency of captopril is greater than that of teprotide in terms of angiotensin I converting enzyme inhibition or bradykinin potentiation. In 'in vitro' studies with guinea pig ileum, the dose ratios of 50% angiotensin I conversion inhibition to 50% bradykinin potentiation were 30-40 for teprotide and 7 for captopril (52,226). Thus captopril is 5 times as potent as teprotide. The half time for recovery of blood pressure after intravenous infusion of angiotensin I at a rate of 2.5 mg/Kg per minute for 10 minutes was 101 minutes in normal rats and 127 minutes in 2-kidney, 1 clip Goldblatt hypertensive rats (72). The half time of angiotensin I pressor response recovery after single intravenous dose of captopril at 0.01-1.00 mg/Kg in unanesthetized rats was 8-55 minutes (259).

The hypotensive action of converting enzyme inhibitor has been a subject of controversy because of the dual action of converting enzyme (kininase II) in degrading bradykinin as well as converting angiotensin I to angiotensin II. Inhibition of converting enzyme might accumulate and potentiate the bradykinin effect or indirectly stimulate prostaglandin release (70,178,184,186,302). The lack of specificity of converting enzyme inhibitor has led to the suggestion that part of the hypotensive response results from non-angiotensin mediated effects (178,290,302). Favoring this proposal, CEI has produced hypotensive effect in anephric humans and animals,

in low renin hypertension, and in hypertensive animals pretreated with angiotensin II antagonists (178,303,321). There are several lines of evidence indicating that factors other than inhibition of angiotensin II formation play minor roles in the hypotensive response. Erdos and Yang (73) indicated that there were at least 5 circulating enzymes involved in bradykinin metabolism. Textor et al. (298) demonstrated that captopril did not affect the blood pressure of conscious rats with moderate hypertension produced by infusion of angiotensin.

There are additional studies demonstrating that administration of catopril and saralasin produced similar blood pressure reductions in hypertensive rats or rats with activated renin angiotensin activity due to sodium depletion (127,196). In addition, direct measurement of circulating kinins or prostaglandins and urinary kallikrein activity after converting enzyme inhibition did not show a consistent change (135,183,212,322). As mentioned earlier, the dose ratio of angiotensin I inhibition to bradykinin potentiation for teprotide is 5 times greater than that for captopril, indicating that angiotensin conversion and bradykinin potentiation are not linked quantitatively (52,112,226). Inhibition of prostaglandin synthesis by indomethacin did not block renal vasodilation induced by captopril (322). Also, the renal venous prostaglandin E_2 did not increase after teprotide and captopril administration in dogs and rabbits (130,322). These observations suggest that renal prostaglandins are not involved in the response of the renal vasculature to converting enzyme inhibition.

Saralasin competes with angiotensin II at its various receptor sites (141,235). It is an analogue of angiotensin II in which the aspartic acid is replaced by the unusual amino acid, sarcosine. This replacement in amino acid position 1 enhances the vasoactive activity of the peptide in vivo is due to increased binding affinity to the receptor and a decreased rate of degradation (115). The pharmacological half-life of saralasin when given intravenously has been found to be 4-6 minutes in normal rats (4,241) and 8 minutes in hypertensive patients with high renin levels (241). Saralasin has been used extensively in clinical and experimental hypertension. Unfortunately, this compound and other angiotensin analogues have been found to possess both agonist and antagonist effects on the peripheral vasculature and perhaps on renal function (60,198, 235). Thus, the physiological effect of angiotensin II could be masked or underestimated if saralasin were used as a sole blocker of RAS.

Pathogenesis of Goldblatt Hypertension

The pathogenesis of renovascular hypertension is not fully understood. Different forms of renovascular hypertension may involve different etiological factors. In this literature review, attention will be focused on experimentally induced 2-kidney, 1 clip Goldblatt hypertension.

A. Renin-antiogensin system

The etiological role of the RAS in the 2-kidney, 1 clip model of Goldblatt hypertension has been extensively studied. It is generally accepted that increased activity of the RAS is the trigger for the initiation of hypertension in this model. In the first few days following unilateral renal artery constriction with the contralateral kidney left in place, plasma renin activity consistently rises in rats (55,65,79,122,157,222,258,290), dogs (24,93, 180,317), rabbits (164,257) and sheep (27). The elevated plasma renin activity persists for 4-7 days in dogs (24,317), several weeks in rabbits and sheep (27,257), and from several weeks to months in rats (122,157,194,222,258). Increased granularity of juxtaglomerular cells of the clipped kidney has been shown early in the course of the hypertension (311). The initial increase in plasma renin activity following constriction of the renal artery is believed to contribute directly to the rise in arterial pressure. This notion is supported by observation that administration of either converting enzyme inhibitors or angiotensin antagonists prevents or reverses the hypertension (7,36,40,72,167,180,204,235, 253,267,323) without causing changes in plasma volume or cardiac output (272,289). Although the level of blood pressure in this model is not correlated with the level of plasma renin activity, the magnitude of the reduction in blood pressure following blockade of the RAS has been found to be correlated with the pretreatment level of plasma renin activity (45,164,180,231). Renal venous

renin activity in the clipped kidney has been shown to be correlated with blood pressure (157).

In the natural history of 2-kidney, 1 clip Goldblatt hypertension, the initial increase in plasma renin activity returns to normal levels despite continued high blood pressure (24,45,148,180, 317). This observation has led some investigators to conclude that the RAS may play no role in the maintenance of the late phase of 2-kidney, 1 clip Goldblatt hypertension (99,180,293). This hypothesis is supported by the observation that administration of RAS blockers fails to alter blood pressure at this stage (45,79,99, 180,293). Other experimental observations tend to refute this explanation. Atkinson et al. (12) showed a left shift in angiotensin II dose-response curve in the 2-kidney, 1-clip Goldblatt hypertensive rat. He also showed that a similar shift could be produced in normal animals by infusing a low dose of angiogensin II. Increased vascular sensitivity to angiotensin II, but not to norepinephrine, has also been demonstrated in other studies (97,280,297). Thus the RAS could still be responsible for maintenance of high blood pressure though the plasma renin activity has returned to normal level in the later phase.

It is not known whether or not the vascular hypersensitivity is due to increased numbers of vascular angiotensin II receptors. It has been shown that numbers and affinity of adrenal and uterine angiotensin II receptors were not altered in 2-kidney, 1 clip Goldblatt hypertensive rats clipped for 4 weeks (62). However, Aguilera and Catt (1) demonstrated that the angiotensin II receptor

concentrations in mesenteric artery and urinary bladder were reduced in response to increased angiotensin II levels due to sodium restriction or 2-day angiotensin II infusion. This reduction in numbers of angiotensin II receptors may account for the attenuated vascular reactivity to exogenous angiotensin II during sodium depletion. It is unclear whether or not the different findings of changes in angiotensin II receptors of smooth muscle in these studies are due to different duration of elevated angiotensin II levels, different smooth muscles or other factors.

In addition to the increased vascular reactivity to angiotensin II that may contribute to the continued high blood pressure, there are several other possible mechanisms by which angiotensin II might stimulate the rise in blood pressure. These include modulation of sympathetic nerve activity (329,330,332) and altered secretion of other hormones which influence sodium balance (111,275). Some studies have indicated that the arterial renin concentration in chronic Goldblatt hypertensive rats was increased at a time when plasma renin activity was normal (98,302,303,306). Angiotensin II generated locally in arterial wall might be more important than circulating angiotensin II with regard to the reduction of arterial pressure in response to RAS blockade (272,303).

B. Neural mechanisms

The renin-angiotensin system has been found in the brain (86). Intracranial injection of angiotensin II can act on the central nervous system to increase blood pressure and vasopressin secretion

and to produce a dipsogenic effect, suggesting that this central renin-angiotensin system is involved in the control of cardiovascular function (25,64,80,132). At least 4 areas within the central nervous system have been proposed as targets for central angiotensin II action: the subnucleus medialis of midbrain, the area postrema, the anterior ventral portion of the third ventricle (AV3V) and the subfornical organ. The area postrema and the midbrain have been shown to be the primary central sites of angiotensin action in dogs, cats, and rabbits, while the AV3V area is the dominant area in mediating the central action of angiotensin II in rats (38,121). In the rat, destruction of AV3V resulted in an acute adipsic syndrome with persisting thirst deficit (37), reduced vasopressin secretion and temporary hypertension for about one week (37). Lesions of AV3V and the area of ventromedial hypothalamus-median eminence (VMH-ME) attenuated pressor and thirst responses to central angiotensin and osmotic stimuli (38,131). A lesion in the subfornical organ also reduced the pressor effect of systemic angiotensin II injection (171). Selective central blockade of angiotensin II by cerebroventricular injections of angiotensin II antagonist or CEI reduced blood pressure in 2-kidney, 1 clip Goldblatt hypertension and in hypertension produced by aortic coarctation (223,293). Ablations in AV3V or VMH-ME reduced blood pressure in 2-kidney, 1 clip Goldblatt hypertension. Lesions in these areas also prevented or reversed DOCA-salt hypertension (induced in unilaterally nephrectomized animals by administration of deoxycorticosterone acetate combined with 1% NaCl solution to

drink) and 1-kidney Goldblatt hypertension (induced by removal of one kidney and clamping the other) (85).

It has been suggested that the mechanism of the cardiovascular response to central angiotensin II is mediated by increased sympathetic outflow from the central nervous system (64,80). It has been demonstrated that 2-kidney, 1 clip Goldblatt hypertension in rabbits is potentiated by electrical stimulation of hypothalamus, suggesting that activation of sympathetic outflow may synergistically enhance the activity of the RAS to produce hypertension (313). Direct electrical stimulation of AV3V and VMH-ME produced a rapid, frequency-dependent increase in renal and mesenteric vascular resistance and a mild increase in blood pressure (34,85). Surgical denervation or ganglionic blockade, but not adrenalectomy, abolished all responses (34,85). The efficiency of the VMH-ME lesion in reducing the blood pressure of hypertensive rats raises the possibility that the neurophypophysial axis might be involved in the response. Johnson and Schwob (131) proposed that the antihypertensive effects of AV3V and VMH-ME lesions may be due to altered vasopressin secretion. However, some studies demonstrated that posterior or complete hypophysectomy neither prevented the development of hypertension (224) nor normalized blood pressure in established hypertension (224,234). It seems that disruption of a neurogenic mechanism instead of vasopressin release is a more necessary aspect of AV3V and VMH-ME lesions. The loss of function following regional lesions in the central nervous system could

result from destruction of specific nuclei or from interruption of neural tracts originating from the brain.

The role of the peripheral adrenergic nervous system in the development of 2-kidney, 1 clip Goldblatt hypertension is still unsettled. Douglas et al. (67) and Fernandes et al. (78) demonstrated that elimination of peripheral sympathetic nerve activity with 6-hydroxydopamine or guanethidine did not prevent the initiation of hypertension due to renal artery constriction. In contrast, Antonaccio et al. (6) reported that 6-hydroxydopamine pretreatment for 2 weeks prior to clipping the renal artery reduced blood pressure but did not decrease plasma renin activity in rats. Chemosympathectomy plus adrenal medullectomy produced more pronounced reduction in blood pressure in these rats (6). However, adrenal medullectomy or adrenalectomy alone did not influence the development or maintenance of 2-kidney, 1 clip Goldblatt hypertension (56,84).

In established 2-kidney, 1 clip Goldblatt hypertension in the rat and cat, some studies demonstrated that administration of propranolol or 6-hydroxydopamine reduced blood pressure (19,109, 239) but other studies with either guanethidine or propranolol injection failed to confirm the hypotensive response (67,221). Zimmerman et al. (330) demonstrated that a combination of guanethidine and saralasin produced a greater hypotensive effect than saralasin alone, indicating a sympathetic component involved in maintaining hypertension. Bellini et al. (19) observed that in

hypertensive rats at day 5 postclipping, ganglionic blockade resulted in a fall of blood pressure equal to that obtained in normal rats. But at day 12 and day 40, at an equivalent blood pressure, ganglionic blockade induced a greater fall in blood pressure than at day 5. This increased sensitivity to ganglionic blockade may suggest a progressive neurogenic influence on blood pressure in later phases of hypertension. However, plasma norepinephrine concentration and norepinephrine turnover in aorta, mesentery artery, hypothalamus, midbrain, pons-medulla and left ventricle of 2-kidney, 1 clip Goldblatt hypertensive rats are not different from normal (53,252,294).

The resetting of baroreceptor activity at a higher blood pressure level in Goldblatt hypertensive animals has been demonstrated (5,185). The resetting phenomenon appears to be a result instead of a cause of the elevated blood pressure since it does not appear until after the blood pressure has become elevated. The mechanism of the resetting is not clear. Coleman et al. (48) demonstrated that alterations in endogenous angiotensin levels achieved by sodium deprivation, converting enzyme inhibition and infusion of saralasin did not change baroreceptor responsiveness. Cowley et al. (51) and Liard et al. (161) reported that vasopressin might attenuate the efficiency of baroreceptor feedback. Nevertheless, there is no demonstration that a primary baroreceptor resetting is a major factor in initiating hypertension.

The renal nerves have been shown to exert a direct stimulating effect on proximal tubular reabsorption of sodium (49,63). This

neural control of sodium and water excretion may be of significance in sodium homeostasis. In addition, it has been reported that there is a topographical relationship between the renal nerves and the neural area in the hypothalamus involved in the regulation of arterial pressure and fluid balance (23,47). Bilateral renal denervation or unilateral renal denervation coupled with contralateral nephrectomy did not prevent the initiation of hypertension due to renal artery constriction in the dog, although these maneuvers have been shown to be effective in reducing blood pressure in established 1-kidney and DOCA-salt hypertensive rats (138,139).

In summary, both central and peripheral nervous systems may be involved in the maintenance but not in the initiation of hypertension in the 2-kidney, 1 clip model. The nervous system may participate in sustained hypertension via a direct increase in the function and the number of adrenergic terminals in the peripheral vascular beds (22) or through an indirect action of the RAS (233, 329,330).

C. Sodium balance

The significance of sodium retention in 2-kidney, 1 clip Goldblatt hypertension is not as well defined as in the 1-kidney model. In the latter, the pathogenesis is characterized by an initial rise in PRA and sodium retention (so called renin-dependent phase which lasts about 5 to 7 days in rats) and a subsequent body fluid expansion which is responsible for maintaining the elevated blood pressure (so called volume-dependent phase). In the 2-kidney

model, the role of sodium retention is still controversial. Maxwell et al. (182) reported that, during the first day postclipping in dogs, there was a transient positive sodium and fluid balance, increased cardiac output and a simultaneous increase in peripheral resistance. Thereafter, sodium balance reached equilibrium whereas blood pressure, plasma renin, cardiac output and total peripheral resistance remained elevated and stable. Watkins et al. (317) observed sodium retention during the first 3 days after unilateral constriction of renal artery in dog. However, a similar degree of sodium retention was also obtained in the sham-operated dogs. Bianchi et al. (24) found an increase in blood pressure and sodium retention on day 7 postclipping when clipping was performed on anesthetized dogs but not when the operation was carried out in conscious dogs. Recently, Watson et al. (318) demonstrated that 2 days after renal artery constriction there was a significant decrease in packed cell volume without changes in plasma sodium concentration, indicating a state of sodium and water retention. When the accumulated sodium and fluid were removed by hemodialysis and the animals were maintained on a low sodium diet, there were no immediate changes in blood pressure. The blood pressure was reduced slightly during the ensuing 7 days and again increased after a normal sodium intake was resumed. The PRA remained elevated during the period of low sodium intake. This indicates that early sodium retention occurs following constriction of the renal artery but it is not primarily responsible for the rise in blood pressure.

In the 2-kidney model of hypertensive rats, Swales et al. (292) observed a progressively negative sodium balance during the development of hypertension and no early phase of sodium retention. In contrast, Mohring et al. (201-203) showed sodium retention and increased blood volume and water turnover for 2 to 5 weeks postconstriction in the benign type of 2-kidney, 1 clip hypertension with moderate increase in blood pressure (less than 180 mmHg). Leenen et al. (158) also found that the sodium retention per gram body weight in hypertensive rats was greater than sham-operated controls during the first 10 days. In rabbits, Lohmeier et al. (164) did not see any changes in sodium balance. In sheep, Blair-West et al. (27) and Lohmeier et al. (165) demonstrated negative sodium balance. Taken together, the sodium balance state in the 2-kidney, 1 clip form of Goldblatt hypertension seems to vary with species. Dogs and rats show early sodium retention and rabbits and sheep fail to exhibit this.

Exchangeable sodium has been measured during the established phase of hypertension in the 2-kidney, 1 clip Goldblatt model. Tobian et al. (310) reported that the exchangeable sodium in 2-kidney model of Goldblatt hypertensive rats clipped for 3 months did not differ from that of sham-operated rats. Doyle et al. (68) found that rats with severe hypertension and elevated PRA had increased exchangeable sodium, whereas those with a small rise in blood pressure did not have this change in sodium during the first 4 weeks of the hypertension. Similarly, Albertini et al. (2)

observed that only those hypertensive rats that responded to angiotensin blockade with a fall in blood pressure greater than 20 mmHg had elevated exchangeable sodium. In this regard, Antonaccio et al. (6) questioned the significance of measuring the absolute change in exchangeable sodium in plasma without considering the distribution of sodium in tissues. They suggested that the distribution of sodium in vascular tissues could be more important than that in plasma. In fact, the sodium content of the aorta of hypertensive rats has been shown to be increased (242,251).

Body fluid distribution in 2-kidney, 1 clip Goldblatt hypertensive rats has been measured in several studies but consistent results have not been obtained. Bianchi et al. (24) and Taquini et al. (295) failed to find any change in plasma and extracellular fluid volume on the first day or the 11th postoperative day. De la Riva et al. (61) demonstrated a tendency to develop negative water balance in rats with benign hypertension and positive water balance in rats with malignant hypertension (blood pressure greater than 180 mmHg). Sodium balance was not different from normal in both types of hypertensive rats.

In contrast, Mohring et al. (201) observed a significant increase in plasma and blood volume in this model. The increment was about 5% at 10 days after constriction of renal artery and 10% at 29 days after clamping. Kunes and Jelinek (154) also reported increases in extracellular fluid volume, intracellular fluid volume, blood volume and hematocrit, an unchanged plasma volume and a decrease in the ratio of plasma volume to intracellular fluid

volume in 2-kidney, 1 clip Goldblatt hypertensive rats 2 months after constriction of renal artery. Mohring et al. (203) further proposed that a shift of sodium and water from the intra- to the extravascular compartment may occur during the development of hypertension. They suggested that this shift of sodium and water could be due to a glucocorticoid mediated action since the plasma level of glucocorticoids increased in their hypertensive rats. However, Singer et al. (276) indicated that corticosterone secretion did not increase in 2-kidney, 1 clip Goldblatt hypertensive rats. An alternative explanation for the shift of fluid from intravascular to interstitial compartments is the increase in venous resistance and subsequent elevated capillary filtration pressure secondary to increased sympathetic nervous system activity.

In order to assess the contribution of sodium to the development or maintenance of 2-kidney, 1 clip Goldblatt hypertension, experiments have been carried out in which the sodium intake of animals under study has been altered before or after renal artery constriction. In dogs, Watkins et al. (317) found that chronic hypertensive dogs (30 days' duration) with sodium intake restriction for 4 days did not exhibit a significantly lower arterial pressure. Watson et al. (318) demonstrated that removal of the initial accumulation of sodium and water by hemodialysis 2 days after constriction of renal artery in hypertensive dogs did not significantly reduce blood pressure. Most studies have indicated that sodium depletion neither prevents the rise in blood pressure

(68,211,282,295,305) nor reduces the level of blood pressure during the chronic stage of hypertension in the rat (291,295). However, Miksche et al. (194) suggested that a sodium deficient diet could prevent the development of hypertension in the 2-kidney, 1 clip Goldblatt rat and that restriction of sodium intake was followed by a fall in blood pressure to normal levels in this model. The apparent inconsistencies among these studies could be due partly to differences in sodium content of the various so called low-sodium diets. The sodium content of the diet used by Miksche et al. (194) was lower than that used by others.

When 2-kidney, 1 clip Goldblatt hypertensive rats were treated with high sodium diets or 0.9% NaCl solution as drinking water, neither the induction of hypertension nor the level of established hypertension was influenced (93,255). Schomig et al. (265) studied drinking behavior and total fluid and sodium intake after operation in 2-kidney, 1 clip Goldblatt hypertensive rats. They observed that when water alone was offered as drinking fluid, the increase in blood pressure was more marked than when the hypertensive rats had a choice of drinking water or 2% NaCl solution. Withdrawal of saline from those hypertensive rats with high sodium intakes reduced food intake and body weight within 2 days, but water intake continued to increase and blood pressure remained high. They concluded that the drinking of saline may be a compensatory mechanism which serves the maintenance of sodium balance.

Viewed together, it can be concluded that an initial sodium retention may occur in dogs and rats after constriction of one

renal artery when the contralateral kidney is left in place. The sodium and water retention may play a role in the pathogenesis of hypertension in this model but is not absolutely required for the initiation of the hypertension.

D. Renal prostaglandins

It has been shown that the kidney has an antihypertensive system (107,205,309). The renomedullary tissues contain vasodepressor lipids which include prostaglandins (PGs), neutral lipids, renin inhibitors and alkyl ether analogues of phosphatidylcholine (206, 208). Thus the kidney plays a dual role on blood pressure regulation, either by a dominant prohypertensive system (RAS) or by a weakening of the antihypertensive system; both of which may induce the development of hypertension.

Renal prostaglandins were first isolated from the renal medulla of rabbits by Lee et al. in 1963 (156). Within the kidney, PGs are synthesized in the medullary interstitial cells, tubular epithelium of the cortical and medullary collecting ducts, glomerular and arteriolar endothelium and Bowman's capsule. They act locally and are autocoids. Most of the circulating prostaglandins are rapidly removed during passage through the lung except prostacyclin (PGI_2). Thus PGI_2 has been considered to be the major circulating prostaglandin (101). PGE_2 is a vasodilator in most species including man but has been found to produce vasoconstriction in rat kidney. PGI_2 is a marked renal and systemic vasodilator (10,100). PGE_2 and PGI_2 can also modulate sympathetic nerve activity. In

dogs and rabbits, renal nerve stimulation and norepinephrine administration were found to increase PGE_2 production (54,70). PGE_2, but not PGI_2, acts at presynaptic sites to inhibit norepinephrine release evoked by nerve stimulation (168,169). Intrarenal infusion of PGE_2 and PGI_2 reduce the renal vasoconstriction response to exogenous norepinephrine and adrenergic stimuli (168,169). In rats, however, adrenergically induced vasoconstrictor responses are enhanced by PGE_2 and PGI_2, suggesting major species differences in the modulating action of prostaglandin at the neuroeffector junction (169). Intrarenal PGE_2 has also been found to antagonize vasopressin (150) and to stimulate the renal kallikrein-kinin system (188) and RAS (65,155). The effect of PGs on sodium excretion has been controversial over natriuretic/antinatriuretic properties due to different states of sodium and water balance, intrarenal hemodynamics and PRA level. Most of the clearance studies show that PGs are natriuretic. In vivo micropuncture and in vitro microperfusion studies suggest that PGs have no effect on reabsorption in the proximal tubule and loop of Henle but may inhibit sodium transport across the distal tubule (147).

The role of renal prostaglandins in the pathogenesis of hypertensin has been studied by measuring the kidney and renal venous prostaglandin levels, infusing prostaglandins into the established hypertensive animals and injecting inhibitors of prostaglandin synthetase before and after constriction of renal artery. Acute constriction of the renal artery causes prostaglandin release (184,186,261), suggesting that prostaglandins may have a role in

protecting the kidney against ischemia. In established hypertension, renal PGE_2 has been reported to be either increased (128,281) or decreased (249,277) in the clipped kidney and unchanged (128, 281) in the nonclipped kidney of hypertensive dogs and rats. Similarly, conflicting results regarding renal venous PGE_2 have been obtained: it has been reported to be increased (66) or decreased (281) in the clipped kidney and unchanged (281) or increased (66) in the nonclipped kidney. In interpreting these experiments, it must be noted that prostaglandins are not stored. Thus, tissue concentrations might not be a valuable indicator of prostaglandin synthesis. Haux et al. (120) measured PGE_2 synthetase activity in 2-kidney, 1 clip Goldblatt hypertensive rats clipped for 27 days. They found a rise in the clipped kidney and a fall in the nonclipped kidney of these animals.

Intravenous infusion of PGI_2 into chronic 2-kidney, 1 clip Goldblatt hypertensive rats and dogs has been shown to lower blood pressure (46,264). Intraperitoneal injection of PGE_2 into 2-kidney, 2 clip hypertensive rats (both kidneys are intact but clipped) also reduced blood pressure (189). However, caution must be exercised when considering the renal or blood pressure response to systemic administration of prostaglandins, since renal prostaglandins are predominantly synthesized in the inner medulla. The effect of exogenous prostaglandin may not truly reflect the endogenous prostaglandin activity.

Interpretation of observations made on blood pressure and renal responses to inhibition of prostaglandin synthesis in animals

with established hypertension is complicated by differences in species and duration of hypertension. Yun et al. (326) showed that indomethacin did not influence renin release, sodium excretion or blood pressure of hypertensive dogs clipped for 6 to 18 months. Romero and Strong (257) reported that 10 days of indomethacin treatment decreased PRA and renal venous PGE_2 but failed to reduce the elevated blood pressure in rabbits. McQueen and Bell (189) observed that meclofenamate produced hypotensive effects in early but not in the chronic phase of 2-kidney, 2 clip hypertensive rats. Conversely, Jackson et al. (126) reported that indomethacin administration to the 2-kidney, 1 clip Goldblatt hypertensive rats on the 7th day after aortic coarctation significantly reduced blood pressure from 179 to 156 mmHg associated with a reduction in PRA. However, percentage changes in blood pressure were much smaller than in PRA. Further the post-treatment blood pressure did not return to normal. When inhibition of prostaglandin synthesis was performed immediately before or after clipping the renal artery, the blood pressure was found to be higher in the treated, clipped rat than in the nontreated, clipped rat (42,249). In a comprehensive study performed on conscious, renal denervated and propranolol pretreated 2-kidney, 1 clip Goldblatt hypertensive dogs, Dietz et al. (65) gave indomethacin to the animals 9 days after clamping. They found a striking reduction in PRA to normal levels while blood pressure fell only slightly. Similar inhibition of prostaglandin synthesis did not alter PRA or blood pressure of chronic 1-kidney, 1 clip Goldblatt hypertensive dogs (65). Renal prostaglandin may

also affect renal hemodynamics in 2-kidney, 1 clip hypertensive dogs, as demonstrated by a study of Zimmerman et al. (332) in which decreases in PRA and renal blood flow and increases in renal vascular resistance were observed after inhibition of prostaglandin synthesis.

In summary, published studies have shown that infusion of prostaglandin consistently reduces blood pressure in 2-kidney model of Goldblatt hypertension. Inhibition of prostaglandin synthesis is accompanied by a marked reduction in PRA, but the blood pressure may or may not be reduced during the early phase of hypertension. Pretreatment of indomethacin exacerbates the severity of hypertension due to renal artery stenosis. These observations suggest that prostaglandin may participate in modulation of PRA and regulation of blood pressure after constriction of the renal artery in this model. However, the quantitative role of prostaglandin in the pathogenesis of hypertension in this model remains to be defined. Observations regarding changes in renal prostaglandin levels in hypertensive animals are conflicting. Nevertheless, the quantitative changes and the differences in renal prostaglandin levels between the clamped and the nonclamped kidneys appear to be smaller than those of renal renin activity in the respective kidneys.

E. Renal kallikrein-kinin system

Kallikrein is an endogenous proteolytic enzyme that acts on plasma substrate (kininogen) to release kinins. Urinary kallikrein originates in the kidney and is identical to kidney kallikrein. In

the kidney, kallikrein and kininase I, a kinin degradating enzyme, have distinctive distributions. Kallikreins localize on the cortical distal tubules whereas kininases I reside in the proximal tubule (230,269,316). Thus urinary kallikrein excretion has been generally used as a measure of intrarenal kallikrein activity since most of the plasma kinins are metabolized in the proximal tubule and appear in the urine only to a slight extent.

The role of the renal kallikrein-kinin system in renal excretory function and in blood pressure regulation is not fully understood. The zonal distribution and the experimental evidence that urinary and renal kallikrein can be stimulated by aldosterone, mineralocorticoids, low sodium, high potassium and furosemide and supressed by spironolactone (160,174,177), suggest that the renal kallikrein-kinin system can modulate sodium and volume hemeostasis. Systemic or intrarenal administration of bradykinin causes renal arteriolar vasodilation and increases in sodium and water excretion (16,219,320). However, it is not yet clear whether kinins affect the function of the nephron directly or indirectly.

A relationship between the kallikrein-kinin system and hypertensive disease was first reported by Elliot and Nuzum (71) in a hypertensive patient who had a decreased urinary excretion of kallikrein. This finding was confirmed by Margolius et al. (176) 37 years later and has led to extensive studies and numerous speculations. Yet, there is still no conclusive evidence showing whether the change in renal kallikrein-kinin system is a cause or an effect of hypertension in man and animals. Generally, urinary

kallikrein excretion is found to be decreased in patients with essential and renovascular hypertensive but not in labile hypertensives; decreased in Okamoto spontaneous hypertensive rats (SHR), in Dahl salt sensitive rats and 1-kidney Goldblatt hypertensive animals but increased in DOCA-salt hypertensive rats. In 2-kidney, 1 clip Goldblatt hypertensive animals, observations regarding urinary kallikrein excretion, renal kallikrein activity and plasma kininogen concentration are conflicting. Decreased urinary kallikrein has been found in most studies (3,175,244), but Johnston et al. reported that the urinary kallikrein falls immediately after constriction of the renal artery and then rises progressively (136). Carretero et al. (44) showed that renal kallikrein activity was decreased in both clipped and nonclipped kidneys after 34 days of renal artery constriction. Barton and Schachter (18) found no difference in total kidney kallikrein activity between clipped and nonclipped kidneys and between the normal kidney and the kidney of the 2-kidney, 1 clip Goldblatt hypertensive rats (18). Albertini et al. (3) found that urinary kallikrein activity remained unchanged at the 5th week postclamping but decreased by the 8th week. Kidney kallikrein was unaltered and there was no difference between the clamped and the nonclamped kidneys. Plasma kininogen increased significantly.

Several studies have indicated that kinins interact with prostaglandin and with the RAS (155,188,212,299). Angiotensin I and angiotensin II can compete with bradykinin and cause the vasodepressor dose response curve of bradykinin to shift to the left

(299). There is evidence that the renal effect produced by kinins may be associated with prostaglandin release (188,209,212,215). In addition, urinary kallikrein and kinin excretion may be altered independently in response to decreased renal blood flow and to CEI administration (195,225). Therefore, changes in the kidney or plasma kallikrein-kinin system may not necessarily imply participation of this system in the development of hypertension. A better understanding of the role of the kallikrein-kinin system in the regulation of renal function and in the pathogenesis of hypertension requires a more comprehensive study of the interaction between RAS, prostaglandins, kallikrein-kinin system and other pressor and depressor factors. Unfortunately, there is no specific inhibitor for kinins available for such studies.

F. Renin inhibitors

The naturally occurring renin inhibitor is a lysophospholipid that has been extracted from rat kidney. It has been synthesized but not extensively studied. This renin inhibitor has no effect on blood pressure and PRA in normal rats (271). However, in 1-kidney or 2-kidney Goldblatt hypertensive rats clipped for 4 weeks or longer, daily intramuscular injections of renin inhibitor or renin preinhibitor have been found to bring the blood pressure nearly to normal levels (270,271,273). This course of treatment caused significant reductions in PRA in 2-kidney, 1 clip Goldblatt hypertensive rats (271). Oral administration of the renin inhibitor or

preinhibitor produces the same effect but a larger does is required. Since phospholipase A_2 is necessary for conversion of the inactive renin preinhibitor into active renin inhibitor, this enzyme has been thought to be a factor that regulates the availability of the renin inhibitor. Zachariah et al. (327) developed an assay method for phospholipase A_2 in rat serum to evaluate the role of this enzyme in Goldblatt hypertension. They found that 2-kidney, 1 clip hypertensive rats with elevated PRA had decreased phospholipase A_2 levels. This finding seems to point to the importance of the renin preinhibitor-inhibitor system in this model of experimental hypertension. However, these substances are active only in rats. The precise role of this system in cardiovascular and renal regulation remains to be further elucidated.

G. Neutral lipids and other renomedullary vasodepressor substances

Vasoactive neutral lipids and other lipid derivatives are synthesized primarily in the renomedullary interstitial cells. Auto- or isotransplantation of renomedullary interstitial cells has been shown to reverse the hypertension in volume-expanded hypertensive rats (205,207,208). In the 2-kidney, 1 clip form of Goldblatt hypertension, Ishii and Tobian (125) found that the papillary granules which contain vasodepressor lipids were decreased significantly in both the clipped and the untouched kidneys. Reduction in

papillary granules has also been observed in other forms of hypertension, suggesting that the reduction in number of granules may be secondary to the hypertension.

Using the technique of iso- or autotransplantation, Manthorpe (172) demonstrated that subcutaneous transplantation of normal renal medulla to hypertensive rats reduced blood pressure from 198 mmHg to 170 mmHg during days 1 to 8 after injection. The blood pressure had not been normalized and remained at this low level by day 17. The subsequent second transplantation of normal renal medulla did not induce a further fall of blood pressure. Removal of the transplant caused blood pressure to rise to the pretransplantation level within the following 6 days. Transplantation of medulla from the clipped kidney of hypertensive donor produced a similar depression of blood pressure, whereas medulla from the untouched kidney had little effect.

In a later study, he further found that a single intravenous injection of CEI (SQ20881) decreased blood pressure in both transplanted and nontransplanted hypertensive rats. However, the drop in blood pressure was significantly greater in the transplanted rats. A combined treatment with renomedullary transplants and intravenous infusion of saralasin nearly normalized the blood pressure of hypertensive rats. Administration of indomethacin to these hypertensive rats with or without renomedullary transplants caused a slight fall in blood pressure, indicating that the antihypertensive activity of renomedullary transplants is not due to prostaglandin (173). Transplantation of renomedullary tissue of

nonclipped kidney fails to induce hypotensive response, suggesting that the nonclipped kidney might have lost its secretory antihypertensive function during the development of hypertension. The antihypertensive action of transplanted renomedullary tissue was further demonstrated by a study of Muirhead et al. (207) using cultured renomedullary interstitial cells. Subcutaneous injection of these cultured cells into rats with established hypertension induced a significant reduction of blood pressure from 173 to 148 mmHg over 10 days. Blood pressure remained maximally depressed for 25 to 30 days. Thereafter it gradually recovered to initial hypertensive levels by day 70.

It is noteworthy that, although the transplanted renomedullary interstitial cells exerted a vasodepressive effect on 2-kidney, 1 clip Goldblatt hypertensive rats, they did not normalize the blood pressure. Repeated injections of these cells did not enhance the hypotensive effect. However, the combination of RAS blockade and the tissue transplant restored blood pressure to normal, suggesting that the RAS is important in maintaining hypertension in this model. These observations point to the possibility that the clipped kidney may be primarily responsible for secreting vasodepressor lipids to antagonize the action of vasopressor agents released from the ipsilateral kidney. Failure of the nonclipped kidney to produce an antihypertensive effect may be associated with the development of hypertension.

In summary, the renomedullary interstitial cells can secrete vasoactive neutral lipids. Transplantation of medullary tissue of

normal or clipped kidney to 2-kidney, 1 clip Goldblatt hypertensive rats significantly reduces, but not normalizes the blood pressure in this hypertensive model. This suggests that the clipped kidney play a non-excretory antihypertensive role in 2-kidney, 1 clip Goldblatt hypertension. However, it is unable to prevent the development of the hypertension in this model.

H. Vasopressin

The association of vasopressin with the pathogenesis of hypertension has been demonstrated in certain models of experimental hypertension such as DOCA-salt hypertension, spontaneous hypertension and renoprival hypertension. It is uncertain whether vasopressin plays a role in the 2-kidney, 1 clip model of Goldblatt hypertension. Johnston et al. (136) found that plasma vasopressin and renin activity increased whereas urinary kallikrein excretion fell in 2-kidney, 1 clip Goldblatt hypertensive rats clipped for 4 weeks. However, it is difficult to establish an etiologic role for any single hormone in the pathogenesis of the hypertension based on data provided by this study. Mohring et al (202) demonstrated that plasma vasopressin increased by 60% in 2-kidney, 1 clip Goldblatt hypertensive rats with benign hypertension, and by 5-fold in rats with malignant hypertension. Intravenous administration of vasopressin antiserum into conscious rats with malignant hypertension caused half (4/8) of these rats to normalize their blood pressure within 6 to 8 minutes and then the elevated blood pressure recovered within 28 to 56 minutes. In the remaining hypertensive

rats, the blood pressure either slightly decreased or remained unaltered. Based on these and previous observations, they proposed that the elevated angiotensin coupled with sodium and water loss stimulated vasopressin release and caused systemic vasoconstriction in malignant hypertension.

However, in another study performed in rats with hereditary diabetes insipidus (Brattleboro strain having genetic defect in vasopressin synthesis), they found that constriction of the renal artery induced rises in plasma renin activity and arterial pressure and that the final blood pressure levels reached were not different from those of normal clipped rats (199,200). The occurrence of hypertension in rats with hereditary diabetes insipidus apparently contradicts the suggestion that the vasoconstrictor action of vasopressin is important in the development of the 2-kidney, 1 clip model of Goldblatt hypertension. It is possible, however, that vasopressin contributes to blood pressure regulation via its effects on water retention and renin release (149,199).

It is also possible that vasopressin may influence blood pressure by modulation of neural mechanisms or by enhancement of vascular reactivity to pressor agents. Cowley et al. (51) demonstrated that the pressor responsiveness to vasopressin increases in baroreceptor denervated dogs. Liard et al. (161) showed that intravertebral artery injection of vasopressin attenuates baroreceptor reflex responses in normal rats. These studies suggest that vasopressin can modulate central mechanisms in order to decrease the baroreceptor feedback gain. It has also been demonstrated that

systemic vascular reactivity to vasopressin or to norepinephrine increases in rabbits in which the renal artery has been constricted for 3 days (123,133). Hyperresponsiveness to these pressor agents can be abolished by angiotensin II antagonists (133), indicating that the increased systemic vascular reactivity may be angiotensin mediated. In addition, intraventricular injection of angiotensin II increases systemic blood pressure. The increment in blood pressure has been shown to correlate with the concomitant increase in plasma vasopressin (111) which, in turn, is partly dependent on central prostaglandin release (275).

In summary, the vasoconstrictor activity of vasopressin is not essential for the development of 2-kidney, 1 clip Goldblatt hypertension in rats. However, the antidiuretic action and perhaps the modulating effect of vasopressin on central control of cardiovascular function may contribute to the severity of hypertension in this model.

Characteristics of bilateral renal function in Goldblatt hypertension

A. Kidney renin

After renal artery clipping, renin content and juxtaglomerular cell granularity are increased in the clipped kidney and decreased in the contralateral, nonclipped kidney (26,35,108,193,214,247, 266). The ratio of renin content between the clipped and nonclipped kidneys is greater than that in normal rats (7.5 - 35 vs. 1.0 - 1.5). Detectable increases in renal renin content in the clipped kidney appear within 3 to 14 days postclipping; depletion

of the renin content of the nonclipped kidney occurs later (26,108, 266). There is evidence that the angiotensin II content of the nonclipped kidney may not fall to the same extent as renin content (193). There is a correlation between renal renin content and plasma renin activity but not between blood pressure and systemic plasma renin activity in 2-kidney, 1 clip Goldblatt hypertensive rats (108,236). Systemic blood pressure during the development of hypertension is correlated with the renal venous renin activity of the clipped kidney, however (157). Direct measurements of venous renin secretion rates from individual kidneys of hypertensive rats have been made in vivo (190) and in vitro (142,214). These showed the same directional changes as the renin content of the corresponding kidney. Renal angiotensinogen content has been found to be either unchanged (29) or decreased in both the clipped and the nonclipped kidneys (26).

B. Renal hemodynamics and excretory function

Kidney function in 2-kidney, 1 clip Goldblatt hypertensive animals was first investigated by Kramer and Ochwadt in rats (152). They devised a technique to split the urinary bladder into two separate chambers and studied the function of individual kidneys for a period of 18 days following unilateral constriction of the renal artery. They found that the inulin and PAH clearances of the nonclipped kidney were higher than those of the clamped kidney only during the first postoperative day and that these did not differ from those of normotensive rats. However, urine flow and sodium

and potassium excretion from the unclipped kidney were much higher than those from the clipped kidney. Sodium excretion was greater in the nonclipped kidney than in the normal control kidney. Despite the elevated osmolar clearance and fractional excretion of water, the nonclipped kidney had a higher negative free water clearance than the clipped kidney, suggesting that there was a tendency to reabsorb more water in the collecting ducts of the nonclipped kidney (152). When kidney function was evaluated 3 to 4 weeks after renal artery constriction, the excretory function of the nonclipped kidney was still greater than that of the clipped kidney (153). However, total sodium excretion did not differ from that of normal controls (153).

The excretory function of the nonclipped kidney has been shown to be reset at a new level which requires a higher perfusion pressure to excrete a given amount of sodium (300). The right shift of the arterial pressure sodium excretion curve may be of significance in the maintenance of high blood pressure without sodium loss. The clamped kidney also exhibits a similar resetting (300).

In conscious 2-kidney, 1 clip Goldblatt hypertensive dogs, DeForrest et al. (59) found that renal plasma flow and GFR of the stenotic kidney decreased for 2 weeks and subsequently returned to preoperative levels, but the sodium, potassium and water excretions remained depressed. The renal plasma flow and GFR of the untouched kidney increased slightly, but not significantly from control levels. A similar observation was obtained by Zweig et al. (333), but the latter investigators found that the reduced excretion of

sodium and water was associated with persistent decreases in renal plasma flow and GFR.

Girndt and Ochwadt (102) found alterations in renal blood flow distribution in the non-clipped kidney, but not in the clipped kidney, of the hypertensive rat 4 weeks postclipping. Using the ^{86}rubidium uptake technique, they observed that the cortical blood flow of the nonclipped kidney was unaltered but that flow to the outer medulla increased by 40%, to the inner medulla by 50% and to the papilla by 70% as compared to normal rats. There was no change in cardiac output. In contrast, Ganguli (95) reported decreased papillary plasma flow as measured by radioactive albumin uptake in both clamped and nonclamped kidneys.

Increased total renal vascular resistance of the nonclipped kidney has been demonstrated in vivo and in vitro studies (88, 179,245,267,328,331). Administration of CEI or saralasin has been shown to reduce the total renal vascular resistance, suggesting that the elevated renal vascular tone is angiotensin II mediated. At the nephron level, Schwietzer and Gertz (268) showed that the preglomerular vascular resistance of the clipped kidney increased by 21% with no change in the postglomerular vascular resistance, while the preglomerular vascular resistance of the nonclipped kidney increased by 51% and postglomerular vascular resistance decreased by 25%. These observations suggest that there is active dilatation of the postglomerular arterioles of the nonclipped kidney. However, Folkow et al. (88) demonstrated that the GFR-renal arterial pressure relationship of the isolated, nonclipped

kidney was identical to that of the normal kidney, suggesting that there was no change in the pre- to postglomerular resistance ratio. The glomerular hydrostatic pressure decreased in the clamped kidney and increased in the nonclamped kidney (210,268).

Using isolated and perfused kidney preparations from 2-kidney, 1 clip Goldblatt hypertensive rats, Collis and Vanhoutte have (50) demonstrated that both the clipped kidney (17 and 31 days) and the nonclipped kidney (17-104 days) showed increased sensitivity to angiotensin II. This suggests that bilateral supersensitivity to angiotensin II is associated with hypertension, but is not solely a result of high blood pressure. Responses to renal nerve stimulation in both kidneys from hypertensive rats were not significantly different from those of normal kidneys. However, responses to renal nerve stimulation were reduced in clipped kidneys (1 day postoperative) and these kidneys were supersensitive to exogenous norepinephrine (1-31 days) when compared with nonclipped kidneys of the same rat. This unilateral norepinephrine supersensitivity was also noted between clipped and contralateral kidneys from sham-operated control rats (clipped with a nonconstricting clip of 1 to 2 mm aperture). These observations suggest that renal nerve function of isolated kidney is unchanged in this hypertensive model, but clipping may partially denervate the kidney causing depressed nerve function and unilaterally norepinephrine supersensitivity, unrelated to hypertension.

C. Renal autoregulation

The autoregulation of renal blood flow and GFR and the feedback efficiency of the distal tubule-glomerular feedback mechanism in hypertensive rats have been evaluated by several groups of investigators (210,245,247,263). Variation of renal perfusion pressure over the range of 160 to 114 mmHg did not change total kidney GFR and single nephron GFR measured on the basis of distal tubule fluid collections in the clipped kidney of hypertensive rats after acute removal of the clip (247,263). Increases in late proximal perfusion rates elicited reductions in single nephron GFR and early proximal tubular flow in the clamped kidney with or without a clip in place (210,247,263). These observations indicate that the clamped kidney has an efficient autoregulation mechanism. In the nonclipped kidney; however, the effectiveness of the autoregulation of renal blood flow and GFR in response to reduced arterial pressure had been found to be markedly attenuated (245, 247,263). Stumpe et al. (286) claimed that the superficial nephrons, but not the juxtamedullary nephrons, were able to autoregulate nephron GFR. However, it must be pointed out that in the study of Stumpe et al. (286), conclusion was based solely on individual measurement of single nephron GFR (SNGFR) at native blood pressure in hypertensive rats and there was no comprehensive evaluation of hemodynamic responses to direct variations in renal artery pressure.

D. Nephron function

The superficial nephron GFR of the nonclipped kidney has been shown to be either increased (247,263,268) or unchanged (286,287) as compared to that in normal kidneys. In the clipped kidney, the single nephron GFR was found to be lower than the normal or contralateral kidney SNGFR when the clip was in place (166,268). When the clip was acutely removed, the nephron GFR was not different from that of the nonclipped kidney (263). The hydrostatic pressures in the proximal tubules of both the clamped and the nonclamped kidneys remained unchanged (166,245,268). Distal tubular pressure of the nonclipped kidney increased slightly (245). The peritubular capillary pressure was either unchanged (245) or increased (268) as compared to that in normal kidneys. No observations regarding the distal tubular and the peritubular capillary pressures of the clipped kidney are available.

There are relatively few studies directly assessing tubular reabsorptive function in hypertensive animals. Using micropuncture techniques, Stumpe et al. (287) evaluated tubular reabsorption in rats with normal blood pressure, spontaneous hypertension and Goldblatt hypertension. Based on the pooled data, they found that reabsorption by the proximal tubule of the nonclamped kidney did not vary with increased blood pressure. Lowitz et al. (166) also showed that reabsorption in the proximal tubule of both the clipped and the nonclipped kidneys did not differ from that of normal kidney. On the other hand, the reabsorptive function of the loop of Henle in the nonclipped kidney, but not in the clipped kidney,

was found to be depressed (166,287). Observations made on distal tubular reabsorption are conflicting. Stumpe et al. (287) reported pressure-associated decreases in fractional reabsorption of sodium and fluid in the early distal tubule of the nonclipped kidney, whereas Lowitz et al. showed an increased distal tubular reabsorption in the nonclipped kidney and a decreased reabsorption by distal tubule in the clipped kidney (166).

In summary, there are differences in renal hemodynamics and tubular function between the clipped kidney, which is not exposed to the elevated artery pressure, and the contralateral kidney, which is exposed to the elevated arterial pressure. Generally, the nonclipped kidney exhibits increased renal blood flow, GFR and water and sodium excretion as compared to those of clipped kidney. On the other hand, the clipped kidney has demonstrated an increased renal renin content. Impariment of renal autoregulation has been noted in the nonclipped kidney. However, it is not fully understood whether these alterations in renal function in 2-kidney, 1 clip Goldblatt hypertension are a consequence of changes in renal perfusion pressure, local RAS, circulating angiotensin II or a combination of these factors.

Effects of renin-angiotensin system on kidney function

A. Salt repleted normotensive animals

Angiotensin II administration has been shown to exert a more marked vasoconstriction in the renal than in the other vascular beds (11,170). This observation has led to the consideration that

angiotensin may play an important role in the regulation of renal function. Many earlier studies with intravenous or intrarenal infusion of angiotensin II produced variable changes in renal function, particularly sodium and fluid excretion. The inconsistent observations are mainly due to the dose, the route of administration, the state of sodium balance and the renal hemodynamics prior to the experiment (219). Generally, intravenous or intrarenal administration of subpressor or mildly pressor doses of angiotensin II consistently induces reductions in GFR and renal blood flow, primarily in the outer cortex. The decrease in renal blood flow is proportionately greatly than in GFR. The resulting increased filtration fraction has been utilized as an index of increased postglomerular or efferent arteriolar resistance.

However, this is not always true, since some additional effect induced by angiotensin II may be relevant to the relationship between GFR and renal blood or plasma flow. For example, angiotensin exerts a greater influence on the outer than the inner cortical blood flow, since the outer cortex have a higher blood flow but a lower filtration rate (129), a preferential outer cortical vasoconstriction can result in an increase in the filtration fraction. Also, the vasopressor and the intraglomerular actions of angiotensin might alter intraglomerular perfusion which could modify the surface area available for filtration. Thus changes in filtration fraction may or may not be due to a preferential action of angiotensin on efferent arterioles (113,114,218).

It has also been shown that angiotensin II can reduce the glomerular ultrafiltration coefficient (K_f) and glomerular plasma flow without inducing changes in SNGFR due to the counteraction of increased postglomerular resistance and glomerular hydraulic pressure (28). Intrarenal administration of either (Des-Asp^1)-angiotensin I and angiotensin III or angiotensin II and angiotensin III have equal vasoconstrictor effects on the renal vasculature of dogs (33,90). However, Satoh et al. (260) demonstrated that angiotensin II was more potent than angiotensin III in increasing systemic blood pressure and in reducing renal blood flow when given either intravenously or intrarenally to phenoxybenzamine-treated, anesthetized dogs. They believed that the discrepancy would be related to the influence of angiotensin II on the peripheral adrenergic nerve (330,332). Blockade of RAS usually results in increases in renal blood flow (21,218,331) and sodium excretion (218), while GFR and K_f may not change (218).

The intrarenal mechanism responsible for autoregulation of renal blood flow and GFR still remains unclear. One of the hypotheses first suggested by Thurau et al. is that the renin-angiotensin system mediates the intrarenal feedback mechanism (301). This hypothesis suggests that an increase in sodium concentration in the distal tubule is sensed by the macula densa and may increase renin release by juxtaglomerular cells; the resulting angiotensin II then leads to constriction of afferent arterioles and thereby produces autoregulation of renal blood flow and GFR.

However, there are several lines of evidence against this hypothesis. For example, renin depletion, infusion of angiotensin II and angiotensin blockade all fail to alter the autoregulatory ability of the kidney (94,137). Also, renin is always released concomitant with vasodilatory autoregulation in response to reduced renal arterial pressure, increased ureteral pressure and renal vein pressure (87,144,314).

It is well documented that RAS plays an important role in the regulation of body fluid and electrolyte balance via its indirect effect on aldosterone secretion. In addition, angiotensin has been proposed to have a direct intrarenal effect on sodium reabsorption. Earlier studies with angiotensin infusions yielded dose-dependent changes in sodium and fluid excretion, ranging from antinatriuretic/antidiuretic to natriuretic/diuretic or biphasic responses. Most studies demonstrating a decrease in sodium and fluid excretion have been associated with reduced renal blood flow and GFR. When physiological doses of angiotensin II (0.5-5 ng/Kg·min) were administrated intrarenally or intravenously, there were consistent reductions in sodium excretion and urinary sodium concentration that did not correlate with changes in GFR, renal plasma flow or intracortical distribution of blood flow (15,74,134,143). The antinatriuretic effect on angiotensin II has also been demonstrated in the acutely denervated kidneys (319). These observations suggest that angiotensin II directly stimulates sodium reabsorption.

More direct evidence suggesting that angiotensin II stimulated tubular reabsorption has been demonstrated in microperfusion studies by Harris and Young (118) and Harris (116). They showed that microperfusion of Val^5- of Ile^5- angiotensin II into the peritubular capillary surrounding the proximal tubule in a dose ranging from 10^{-10} to 10^{-13}M directly stimulated proximal tubule reabsorption of sodium in rat kidney. An inhibitory effect on sodium reabsorption was observed when a higher dose of angiotensin was perfused. Steven and Thorpe (283) reported that microperfusion of 4×10^{-4} ng/min of Ile^5- angiotensin II into the peritubular capillary inhibited proximal tubule reabsorption. This effect could be prevented by adding saralasin to the angiotensin-containing perfusate. However, they also observed concomitant increases in peritubular capillary and intratubular hydrostatic pressures which might inhibit tubular reabsorption and influence the equilibrium state during microperfusion (117). Perfusion of angiotensin III at 10^{-10} to 10^{-12}M reduced proximal tubule reabsorption which was opposite to angiotensin II (117).

The intrarenal sodium retaining effect of angiotensin may be of importance in the development of hypertension. It has been hypothesized that an altered relationship between the renal excretory function and arterial pressure might be responsible for long-term hypertension (110). If this hypothesis is valid, then factors altering this relationship should be able to produce hypertension. This concept has received support from studies with prolonged intrarenal infusion of angiotensin II (57,162,325). Lohmeier and

Cowley (162) demonstrated that intrarenal infusion of 1 ng/Kg·min of angiotensin II into normal dogs for 10 days produced sodium retention and a blood pressure elevation of 15 mmHg at the end of experiment. Young et al. (325) performed a similar study utilizing intravenous infusions of angiotensin II for 8 days and observed similar sodium retention and sustained elevation in blood pressure without changes in blood volume and cardiac output. DeClue et al. (57) showed that increases in sodium intake over a 100-fold range during angiotensin II infusion induced an increase in blood pressure by 39 mmHg while a mere 3 mmHg rise in blood pressure was noted in the control receiving the identical sodium load without angiotensin infusion. These observations suggest that angiotensin II infusion alters the renal excretion, leading to an increase in arterial pressure in order to reestablish normal sodium homeostasis.

B. Normotensive animals with altered sodium and fluid balance

The RAS is of significance in maintaining normal and renal hemodynamics and excretory function in animals with elevated RAS due to sodium depletion, water deprivation and thoracic vena cava constriction. Administration of angiotensin antagonists or CEI into these animals consistently produced remarkable increases in renal blood flow and fluid and electrolyte excretion (9,43,91,113, 114,159,163,197,312). These blocker-induced renal vasodilation and diuretic and natriuretic responses were independent of changes in aldosterone (114) and occurred in adrenalectomized dogs (163). In

a micropuncture study by Steiner et al. (284), blockade of angiotensin by saralasin decreased both the absolute and the fractional reabsorption of fluid by the proximal tubule in spite of increased nephron GFR in sodium depleted rats. This indicates that elevated RAS due to sodium depletion enhances proximal tubular reabsorption of fluid.

C. Goldblatt hypertensive animals

In 2-kidney, 1 clip Goldblatt hypertensive dogs and rats, an angiotensin II-dependent increase in renal vascular resistance of the nonclipped kidney has been demonstrated (179,267,328,330,331). Bengis and Coleman (20) studied the long term effects of captopril on blood pressure and renal excretory function. They observed that captopril decreased blood pressure in both benign and malignant hypertensive rats. In the benign group, 24-hour urinary sodium excretion increased slightly. In the malignant hypertensive group, a decreased urine flow and varied changes in sodium excretion were observed during captopril infusion. Zimmerman et al. (331) demonstrated that intrarenal injection of 0.1 mg/Kg of captopril into the nonclipped kidney of unanesthetized, hypertensive dogs reduced blood pressure by 12 mmHg and increased renal blood flow by 36%. An increase in the captopril dose induced greater hypotensive and renal vasodilatory responses. Similarly, Masaki et al. (179) observed that teprotide administration induced significant increases in renal blood flow, GFR and excretion of sodium and water in the nonclipped kidney. Schwietzer (267) evaluated the influence

of circulating angiotensin on renal hemodynamics of the untouched kidney of hypertensive rats by intravenous infusion of saralasin. He found that 30 minutes of saralasin infusion reduced blood pressure by 13 mmHg and renal vascular resistance by 35% and increased renal blood flow by 23%. These studies suggest that the elevated RAS induces an increase in renal vascular tone in the nonclamped kidney. Administration of a RAS blocking agent reverses the elevated vascular resistance and results in renal vasodilation.

II. Proposal

Based on published reports, it is clear that the elevated RAS is the primary factor for the initiation of and perhaps also responsible for the maintenance of hypertension in 2-kidney, 1 clip Goldblatt hypertension. As previously discussed, this form of hypertension is characterized by a renin-rich, clipped kidney being perfused with normal blood pressure and a renin-depleted, nonclipped kidney subjected to high blood pressure. The presence of the nonclipped kidney in a progressively elevated PRA and blood pressure environment and the failure of this kidney to prevent the development of hypertension may indicate that the increased circulating angiotensin II levels exert a substantial influence on this kidney. Thus the purpose of the present study was to assess the contribution of RAS on the possible changes in both kidneys of this hypertensive model.

The first series of experiments was designed to evaluate the renal hemodynamics and excretory function of both the clipped and nonclipped kidneys. In order to avoid the controversy regarding the specificity of blockers, an angiotensin I converting enzyme inhibitor and an angiotensin II receptor antagonist were employed in this study. Since these blockers have been shown to inhibit both the circulating and the intrarenal RAS, changes in renal hemodynamics and excretory function after blockers infusion were assumed to reflect the influence of the RAS on the affected kidney. In addition, a separate group of hypertensive rats was used for determination of PRA and kidney renin activity.

Blockade of RAS was expected to produce a significant fall of blood pressure in hypertensive rats. The hypotensive effect might mask the renal responses, particularly in the clipped kidney that had a normal blood pressure distal to the clip. In order to eliminate this possible influence of hypotension, an adjustable clamp was placed on the suprarenal aorta of another group of hypertensive rats during acute experiments. By constricting the aortic clamp, the blood pressure was reduced to levels comparable to those seen during blocker infusion and the renal functional responses were then followed.

The next phase of this study was to explore the possible alterations in segmental nephron reabsorptive function of the nonclipped kidney. Using the micropuncture recollection technique, both late proximal tubule and early distal tubule fluid samples were taken before and during CEI infusion. The segmental nephron

reabsorptive patterns were evaluated in order to define the tubular loci responsible for observed changes in tubular function. The hydrostatic pressures in the proximal and the distal tubules and in peritubular capillaries were also measured. Again, a separate group of hypertensive rats with mechanically reduced blood pressure was used in order to exclude the influence of hypotension due to blocker infusion on the tubular reabsorptive function. The tubular reabsorption data provided a basis for interpretation of the clearance results obtained from the whole kidney experiments.

METHODS

I. Animals

Two-kidney, 1 clip Goldblatt hypertensive rats were prepared 3 - 4 weeks prior to acute experiments by placing an U-shaped silver clip with an internal gap of 0.25 mm on the right renal artery while the contralateral kidney remained untouched. The clip was placed, under pentobarbital anesthesia (5.0 mg/100 g,i,p.), in 90 to 130 g Sprague-Dawley rats obtained from Charles River Breeding Laboratories (Wilmington, MA). In pilot study, 4 sham-operated rats clipped with 0.5 mm clip showed no difference in blood pressure and renal response from normal rats. Therefore, normal rats served as controls and data from sham-operated rats were incorporated as controls. All animals were maintained on complete rat chow containing 0.15 mEq of sodium per gram of chow (Wayne Lab Blox, Chicago, IL) and tap water ad libitum.

II. Chemicals

Polyfructosan (Inutest) was obtained from Laevosan-Gesellschaft, Inc. (Linz, Austria). Inutest clearance was used as a measure of GFR. Sodium aminohippurate (PAH) was obtained from Merck Sharp and Dohme, Inc. (West Point, PA). PAH clearance was used to estimate

renal plasma flow. SQ20881 is an angiotensin I converting enzyme inhibitor (CEI). It was kindly supplied by Dr. Z. Horowitz and the Squibb Pharmaceutical Co. (Princeton, NJ). Saralasin (angiotensin II competitive analogue) was obtained from Eaton Laboratories (Norwich, NY). Angiotensin I and angiotensin II were obtained from Peninsula Lab. Inc. (San Carlos, CA).

III. Experimental Protocols

Studies were performed on 4 series of acute experiments.

Series 1: Bilateral renal function responses to blockade of renin-angiotensin system.

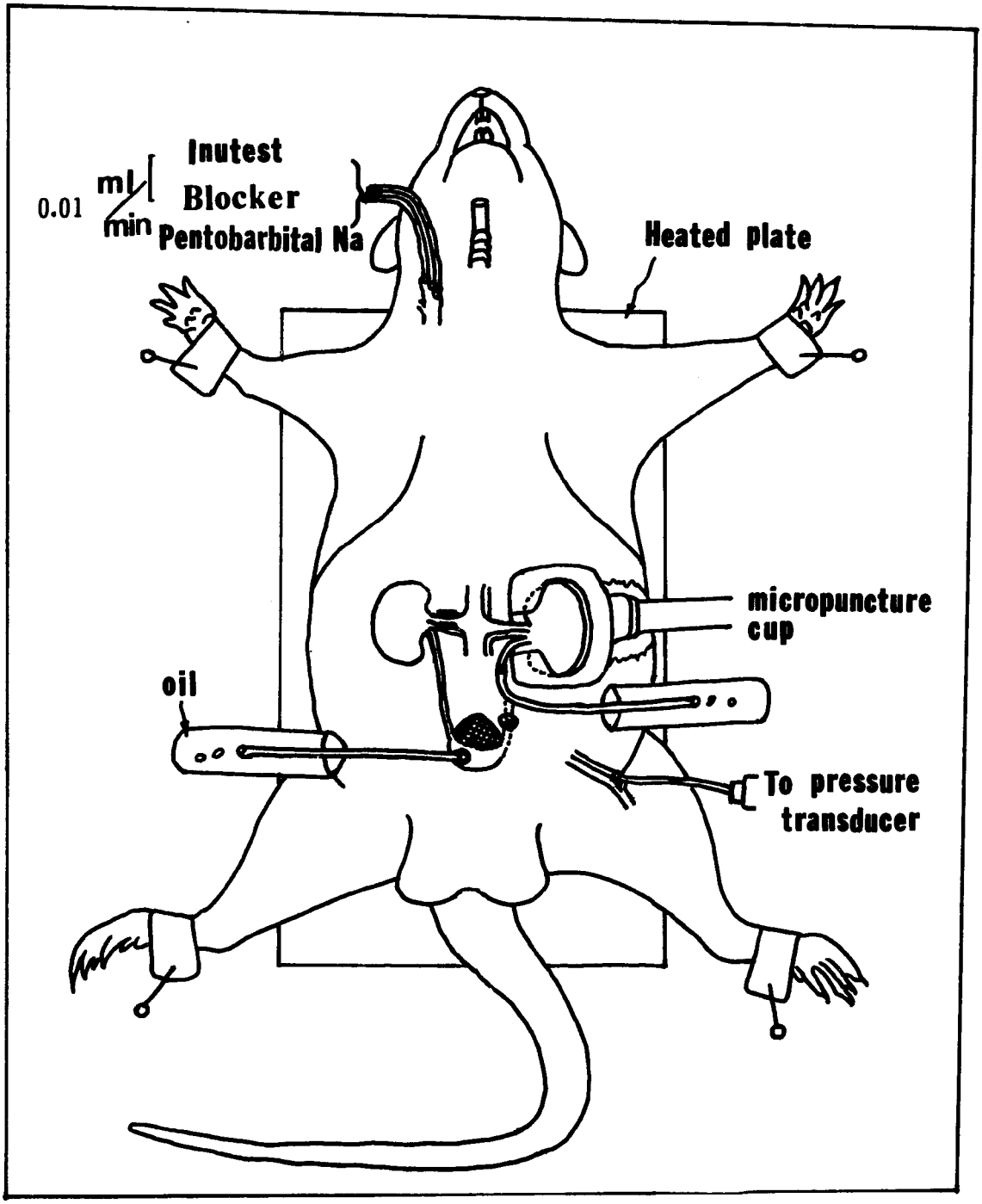
Four groups of rats were used: group 1 was 2-kidney, 1 clip Goldblatt hypertensive rats (N=17) receiving CEI; group 2 was normotensive rats (N=12) receiving CEI; group 3 was 2-kidney, 1 clip Goldblatt hypertensive rats (N=10) receiving Saralasin; group 4 was normotensive rats (N=5) receiving Saralasin.

Both hypertensive and normotensive (control) rats were anesthetized with sodium pentobarbitol (5.0 mg/100 g body weight, i.p.). Rats were prepared for clearance experiments on a servo-controlled heated table, and body temperature was maintained at 37°C by a thermostatic system that monitored the rectal temperature. Surgical preparation included insertion of a tracheal cannula, cannulation of the right external jugular vein with 3 PE-10 tubes for infusion of drugs, inutest, PAH and supplemental anesthetic, and catheterization of the femoral artery to collect blood

samples and measure blood pressure. Arterial blood pressure was continuously monitored using a Statham P23 DC transducer (Gould-Statham Instruments Inc., Hato Rey, Puerto Rico) and recorded on a P7 Grass polygraph (Grass Instrument Co., Quincy, MA). Clipped rats having a mean arterial pressure less than 145 mmHg at the beginning of acute experiments were discarded. The left kidney was isolated through a flank incision and placed in a Lucite cup to expose the ureter which was cannulated with a short polyethylene catheter of 0.45 to 0.5 mm internal diameter. The urinary bladder was also cannulated with a polyethylene tube (PE 160) through an abdominal incision to collect urine from the right kidney. This approach allowed collection of sequential urine samples from both kidneys simultaneously (Fig. 1).

At the beginning of surgery, an intravenous infusion of isotonic saline was initiated at 0.02 ml/min. After completion of surgery, a priming dose of 0.2 ml of a 0.9% saline solution containing 15% polyfructosan was administered. In 15 rats whose renal plasma flow was measured, a solution containing polyfructosan (10 g/dl) and para-aminohippurate (2 g/dl) was used. The priming dose was followed by a sustaining infusion of the same solution at a rate of 0.01 ml/min. In order to obtain an appropriate reading, the administered dose was calculated on the basis of producing a plasma Inutest concentration of 0.3-0.4 mg/ml and plasma PAH concentration of 0.02 mg/ml. The total volume of the infusion was kept constant by reducing the rate of saline infusion to 0.01 ml/min. Thirty minutes were allowed for the animal to reach a steady

Figure 1 Sketch of animal preparation.


0.01 ml/min
Inutest
Blocker
Pentobarbital Na
Heated plate
micropuncture cup
oil
To pressure transducer

state and then two control period urine collections of 30-minute duration each were initiated. Urine samples were collected under oil in preweighed containers. Blood samples were taken at the midpoint of each clearance period. Plasma was separated by centrifugation and saved for analysis, blood cells were returned to the animals.

Following two consecutive control clearance periods, 2 mg/ml of CEI was administered intravenously into groups 1 and 2 at an initial dose of 1 mg and then followed by a constant infusion of 0.3 mg/100 g·hr without changing the total volume of infusion. The effectiveness of this dose of CEI was tested by determining the vasopressor response to intravenous doses of 50 and 100 ng of angiotensin I before and during CEI administration.

In groups 3 and 4, saralasin in normal saline was infused intravenously at a rate of 0.12 ng/100 g·hr. The saralasin solution replaced the saline infusion at a rate of 0.01 ml/min without changing the total infusion volume. The effectiveness of angiotensin antagonism by saralasin was confirmed by demonstrating complete blockade of vascular response to intravenous injections of 20 and 50 ng of angiotensin II. Following administration of CEI or saralasin, 30 minutes were allowed to elapse to achieve a new steady state and to allow washout of urinary dead spaces.

Subsequent urine samples were collected for 5 additional clearance periods of 30 minutes each. The CEI or saralasin infusion was then terminated and an additional 30 minutes were allowed to elapse before new control urine collection periods. At the end

of experiment, both kidneys were removed, blotted, dried and weighed.

Series 2: Bilateral renal responses to aortic clamping.

CEI or saralasin infusion caused a marked decrease in arterial pressure of hypertensive rats. In order to assess the direct renal effects of reduced arterial pressure in the absence of blockers, an adjustable constrictor clamp was placed around the aorta above the origin of the renal arteries in five hypertensive rats. By constricting the clamp, arterial pressure to the kidney was reduced to levels comparable to those observed during blocker infusion and clearance determinations were made.

Series 3: Measurements of plasma renin activity and renal renin activity.

Plasma renin activity and renal renin activity were determined in 7 hypertensive rats and 6 control rats. After administering pentobartital, an abdominal incision was quickly made, the renal pedicle ligated, and the kidney removed immediately. A blood sample was then taken through a carotid artery catheter. All of the kidney and blood samples were taken at the same time of day with identical techniques to minimize possible changes due to circadian rhythm (59) and sampling techniques. Kidneys were frozen immediately in acetone and dry ice, weighed, and stored at -20°C until extraction. Blood samples were collected in chilled tubes containing EDTA (1 mg/ml). The blood was chilled, centrifuged at 4°C, and the plasma was separated, frozen, and stored at -20°C until the time of analysis.

Series 4: Segmental nephron reabsorptive function in response to CEI.

Preparation of hypertensive rats and femoral arterial pressure recording were the same as those of acute experiments described previously for clearance studies except that no urinary bladder catheterization was performed. The left (nonclipped) kidney was placed on a Lucite cup. The kidney surface was bathed constantly with warm (38°C) isotonic saline through the tip of a quartz rod light conductor. The kidney was immobilized by filling the unoccupied space in the cup with melted agar.

Rats were infused intraventously with isotonic saline at a rate of 0.02 ml/min at the beginning of surgery. Upon completing the surgery, a priming dose of 0.2 ml of a solution containing 15% polyfructosan was administered. The priming dose was followed by a sustaining infusion at a rate of 0.01 ml/min without changing the total volume infusion as described in clearance experiments. One hour was allowed for the animal to reach a steady state before initiating the experimental procedures.

Late proximal tubules and early distal tubules from different superficial nephrons were located using 2-3 rapid injections of lissamine green dye into randomly selected early proximal tubules via an identification micropipette with a tip diameter of 2-3 μm. The position of each of these segments was mapped for later identification.

Micropipettes with tips of 8-10 μm for proximal tubule punctures and 5-7 μm for distal tubule punctures were filled with Sudan

black tinted castor oil and were used for timed tubular fluid collections. For proximal tubule collections, the collection pipette was inserted at the latest accessible proximal tubule segment and a partial collection was taken. Complete early distal tubule fluid samples were collected by inserting an oil block of 3-5 tubular diameters in length and tubular fluid was allowed to flow spontaneously into the collection pipette. Three timed collections from proximal tubules and three to four timed collections from distal tubules of different nephrons were taken during the control period. A timed urine sample was also collected throughout each period. Blood samples were taken at the beginning and at the end of the control period, and the separated plasma was pooled for analysis.

Upon completing the control collections, converting enzyme inhibitor (CEI, SQ20881) was administered in an initial bolus injection of 0.5 mg and followed by a constant infusion at a rate of 0.3 mg/100 g·hr. The effectiveness of this dose had been tested previously. Thirty minutes were allowed to elapse to achieve a new steady state and to allow washout of urinary dead space. Recollections of the proximal and the distal tubule fluids from the same sites were taken during CEI infusion. The urine and blood samples were taken using the same time protocol as that used during the control period.

Micropuncture experiments were performed on 3 groups of hypertensive rats.

Group 1: time and recollection controls (n=7). In this group, both the first (control) collections and recollections were taken under spontaneous blood pressure without administration of CEI.

Group 2: uncontrolled blood pressure (n=18). In this group, micropuncture procedures were first conducted at the spontaneous blood pressure and repeated during CEI infusion. Two subgroups of hypertensive rats were studied. In subgroup 2a, 13 rats were used for tubular fluid collections. In subgroup 2b, an additional 5 rats were used for measurement of tubular pressure without collecting tubular fluid. The hydrostatic pressure in the proximal tubule, the distal tubule and the peritubular capillary were measured with a micropressure servo-null device (Instrumentation for Physiology and Medicine, San Diego, CA) and recorded on a Grass polygraph.

Group 3: reduced blood pressure (n=15). Since CEI induced both direct effects on the kidney as well as indirect effects due to decreases in arterial blood pressure, this group of rats was studied at the same arterial pressure. Renal perfusion pressure was reduced to levels comparable to that achieved during CEI infusion by constricting the aorta between the renal arteries. After the control tubular fluid collections (subgroup 3a, n=9) or hydrostatic pressure measurements (subgroup 3b, n=6), the aortic clamp was released and then SQ20881 was administered. During the CEI infusion period, the data were collected as in group 2 except that in a few rats (3/9), the blood pressure was adjusted by a modest

aortic constriction so that the arterial pressure to the kidney would be similar to that obtained during the reduced blood pressure period.

IV. Analytical Procedures

Urine volumes were determined gravimetrically (Mettler H78AR, Mettler Instrument, Hightstown, NJ).

Polyfructosan concentrations in plasma and urine were measured with a semimicroanthrone colorimetric technique (246). Plasma protein was first precipitated with trichloracetic acid, then the supernatant of plasma and urine samples were treated with anthrone reagent which reacted with keto group of fructose and produced chromophore. The intensity of color development was measured using a Gilford spectrophotometer (Gilford Instruments Lab Inc., Oberlin, OH) at a wave length of 620 nm.

Plasma and urinary PAH concentrations were determined with a colorimetric method. The method depends on diazotizing the p-amino group of PAH with HNO_2, destruction of HNO_2 with sulfamate and coupling with N-(1-nathyl)ethylenediamine. The color intensity was measured with spectrophotometer at a wave length of 540 nm.

Plasma sodium and potassium concentrations were determined with a flame photometer (Model 443, Instrumentation Laboratory, Lexington, MA).

Plasma and urinary chloride concentrations were determined using a Buchler Digital Chloridometer (Buchler Instruments, Fort Lee, NJ).

Plasma and urine osmolalities were measured with a vapor pressure osmometer (Wescon, Logan, UT). Hematocrit was determined by autocrit centrifuge (Autocrit II, Clay Adams, Inc., Parsippany, NY).

Tubular fluid volumes were measured in a pre-calibrated constant bore micropipette with a slide comparater (Gaertner Scientific Co., Chicago, IL). An aliquot (10 nl) of the tubular fluid was placed in a cuvette containing a Dimedone reagent (5,5-dimethyl-3-cyclohexanedione in 85% phosphoric acid). The tubular fluid polyfructosan reacted with reagent to yield fluorescence which was then measured using a Fluorocolorimeter (American Instrument Co., Aminco, Silver Springs, MD). The remaining tubular fluid was then separated into two aliquots for the measurement of chloride concentration and osmolality. Tubular fluid chloride concentrations were analyzed by means of electrometric titration (Model FT-2230 microtitration, W-P Instruments, New Haven, CO). Briefly, the procedure involves pipetting about 1 nl of sample onto a silver wire immersed in paraffin oil. Then two $NaCO_3$ (agar)/$AgNO_3$/Ag electrodes were dipped into the droplet of sample for injecting current and measuring the droplet potential in order to monitor the titration endpoint. The amount of current needed to titrate standard solutions containing 50, 100 and 150 mEq/L of chloride was

measured. A current-concentration standard curve was then obtained. The unknown chloride concentration in the distal tubule fluid was measured and obtained using this standard curve. Tubular fluid osmolalities were determined by freezing point depression method using a nanoliter osmometer (Clifton Technical Physics, Hartford, NY). Duplicate samples of approximately 1 nl of tubule fluid were placed in paraffin oil and were frozen until ice crystals formed in the droplets. The samples were then gradually warmed. When there were no remaining ice crystals, osmolality was read directly from the osmometer.

Tissue renin content was determined by radioimmunoassay after extraction of homogenized rat kidney as described by Serban et al. (274). Briefly, the procedures involved extraction of kidney renin by thawing and freezing the kidney 3 times using vortex, and immersing in acetone and dry ice mixture. The kidney was then homogenized using cold saline in an ice bath with cold saline. The homogenate was centrifuged at 4°C and 2000 rpm, and diluted with cold saline to give a concentration of approximately 10 mg tissue/ml of suspension. Two volumes of supernatant were then mixed with 1 volume of 3×10^{-3} M $CuSO_4$. After centrifugation, 100 µl of 10% EDTA were added to 3 ml of supernatant. The kidney renin extractions were serially diluted and incubated with fixed amount of renin substrate for 1 hour at 37°C. The angiotensin I generated was assayed and tissue renin concentration reported as nanograms of angiotensin I per milligram wet kidney weight per hour incubation. The renin substrate pool was plasma from rats nephrectomized for

24-48 hours. The pooled plasma was subjected to transitory acidification to reduce the activity of angiotensinases. Recovery of added angiotensin I after incubation at 37°C for 24 hours was 92.5% and linear angiotensin I generation was documented. Plasma renin activities were determined by radioimmunoassay as described by Menard and Catt (191).

V. Calibration of Instruments

The Statham pressure transducer and servo-null micropressure system were periodically calibrated with a mercury manometer as a standard. Calibration curves were reproducible and the instruments were found to be highly accurate and reliable. The osmometer, chloridometer and flame photometer all had a high degree of accuracy and reproducibility.

For the chemical determinations, duplicate series of measurements were made if sample volumes were sufficient. The working standards for Inutust and PAH were freshly prepared. The standard colorimetric curve was nearly linear and quite reproducible. Standards for sodium, potassium, chloride and osmolality were obtained from the supplied companies and internal calibration of the instrument was precisely made each time prior to measurement.

VI. Calculations and Statistical Analysis

Kidney GFR was calculated from urine and plasma Inutest concentrations $(U/P)_{In}$ and urine flow rate ($\dot{V}$).

$$GFR = (U/P)_{In} \times \dot{V}$$

Renal plasma flow was computed from urine and plasma PAH concentrations and urine flow rate. Because of the difficulties of repetitive blood sampling from renal veins for measuring PAH extraction, PAH clearance was used as an uncorrected index of renal plasma flow.

$$RPF = (U/P)_{PAH} \times \dot{V}$$

Estimated renal blood flow was calculated from RPF and hematocrit.

$$RBF = \frac{RPF}{1-Hct}$$

where Hct is hematocrit.

Total renal vascular resistance was calculated as the quotient of renal blood pressure and renal blood flow and expressed in peripheral resistance units (mmHg·min/ml). No vascular resistance calculation for the clipped kidney was made because of the lack of measurement of renal perfusion pressure of this kidney.

Filtration fraction was calculated as the ratio of GFR and estimated renal plasma flow.

Sodium, potassium or chloride concentration in urine (U_{Na}; U_K; U_{Cl}) and urine flow ($\dot{V}$) gave the absolute sodium, potassium or chloride excretion rate ($U_{Na} \times \dot{V}$; $U_K \times \dot{V}$; $U_{Cl} \times \dot{V}$).

$$\text{Fractional excretion of sodium } (FE_{Na},\%) = \frac{(U/P)_{Na}}{(U/P)_{In}}$$

$$\text{Fractional excretion of potassium } (FE_K,\%) = \frac{(U/P)_K}{(U/P)_{In}}$$

$$\text{Fractional excretion of chloride } (FE_{Cl},\%) = \frac{(U/P)_{Cl}}{(U/P)_{In}}$$

Single nephron GFR was determined by distal tubule fluid collections.

$$SNGFR = (TF/P)_{In} \times \dot{V}_{dtf}$$

where $\dot{V}_{dtf}$ is distal tubule flow, and $(TF/P)_{In}$ is tubular fluid to plasma Inutest ratio.

Fractional reabsorption of fluid up to the collection site $(^{FR}H_2O, \%) = 1 - (P/TF)_{In}$

Fractional reabsorption of chloride up to the collection site $(FR_{Cl}, \%) = 1 - \frac{(TF/P)_{Cl}}{(TF/P)_{In}}$

Fractional reabsorption of total solute up to the collection site $(FR_{osm}, \%) = 1 - \frac{(TF/P)_{osm}}{(TF/P)_{In}}$

Absolute fluid reabsorbed up to the proximal tubule collection site = SNGFR x $^{FR}H_2O$-p where $^{FR}H_2O$-p is fractional reabsorption of fluid up to the proximal tubule collection site.

Absolute fluid reabsorbed up to the distal tubule collection site = SNGFR - $\dot{V}_{dtf}$

Absolute amount of chloride reabsorbed up to the collection site = SNGFR x P_{Cl} x FR_{Cl}

where P_{Cl} is plasma chloride concentration.

Absolute amount of total solute reabsorbed up to the collection site = SNGFR x P_{osm} x FR_{osm}

where P_{osm} is plasma osmolality.

Absolute reabsorption of fluid, chloride or total solute between two collection sites was calculated as the difference between the amount remaining at the proximal and the distal tubule collection sites.

Fractional reabsorption of fluid, chloride or total solute between two collection sites was the ratio of absolute reabsorption to total amount remaining at the proximal tubule collection site.

Statistical analysis was carried out using t-test for paired and unpaired comparisons. The linear regression analysis was used where appropriate. All results are expressed as Mean ± SEM.

RESULTS

I. The Effectiveness of CEI and Saralasin

The effectiveness of the does of CEI used in this study was tested by determining the vasopressor response to intravenous administrations of 50 and 100 ng of angiotensin I before and during CEI infusion. Before CEI infusion, 50 ng and 100 ng of angiotensin I caused an increase in arterial pressure of 19 ± 3.0 mmHg and 25 ± 2.3 mmHg (n=5) in hypertensive rats, respectively. During CEI infusion, the responses to 50 ng of angiotensin I were not perceptible and the responses to 100 ng of angiotensin I were markedly reduced to 3.6 ± 0.5 mmHg. These results are similar to those observed on normal rats (246). The effectiveness of angiotensin blockade by saralasin was evident by 94% and 89% inhibition of vasopressor responses to, respectively, 20 ng and 50 ng of exogenous angiotensin II in hypertensive rats. Before saralasin administration, the mean arterial blood pressure increased by 18 ± 1.2 and 28 ± 1.5 mmHg after 20 and 50 ng of angiotensin II, respectively. During infusion of saralasin with the same doses of angiotensin II resulted in increases of arterial blood pressure of 1.0 ± 0.6 and 3.0 ± 0.7 mmHg.

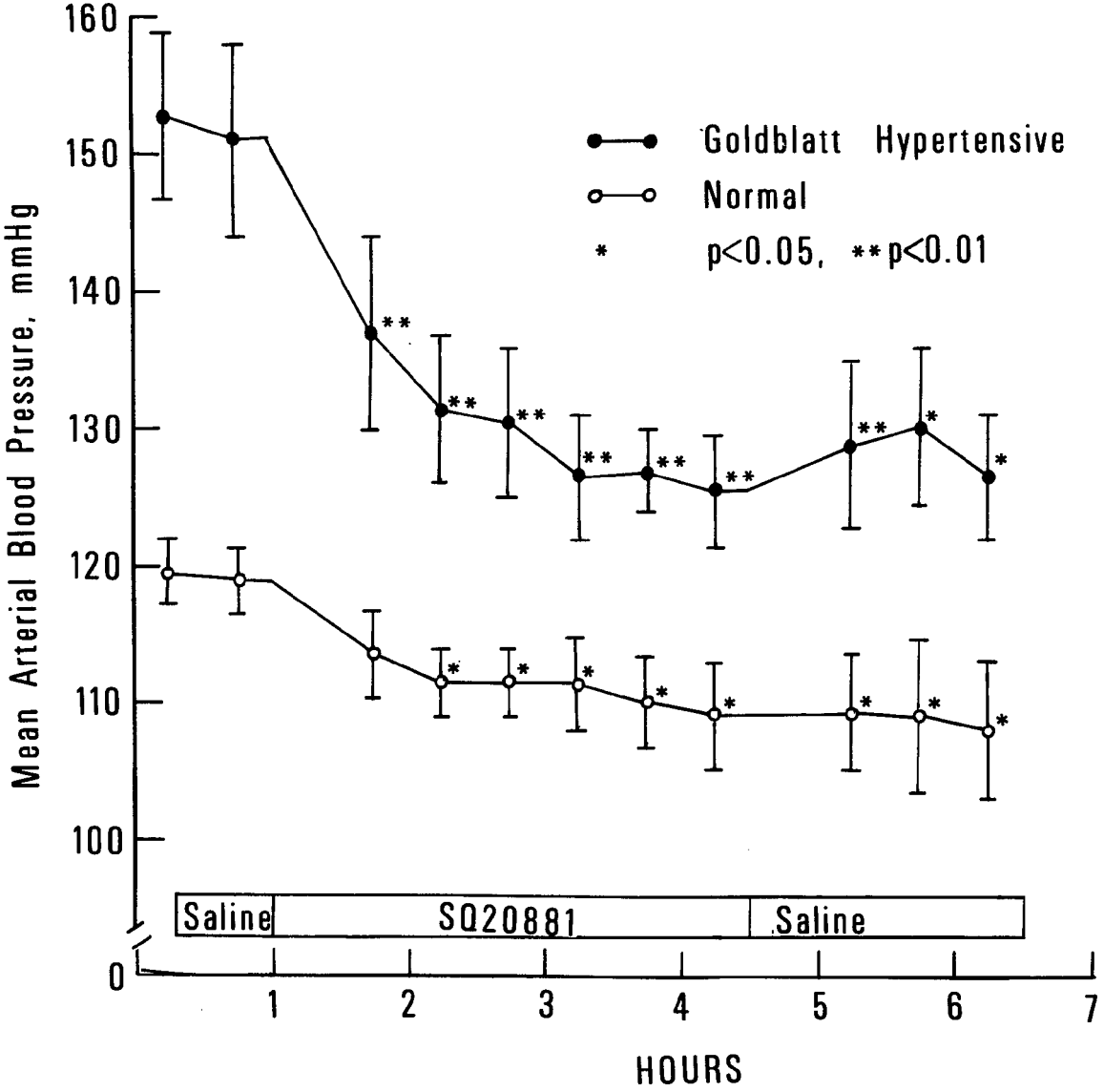
II. Blood Pressure Response to CEI

The effect of CEI infusion on the arterial blood pressure of hypertensive and control rats is shown in Fig. 2. CEI infusion during a 3.5 hours period caused greater reductions in arterial blood pressure in hypertensive rats than in control rats. The mean arterial blood pressure in hypertensive rats fell from the preinfusion level of 153 ± 6.9 to 137 ± 7.3 mmHg after 30 minutes of CEI infusion; arterial pressure continued to decrease during CEI infusion, and a maximal decrease of 27 ± 4 mmHg was achieved by the end of the infusion period. After cessation of CEI infusion, there was a tendency for blood pressure to return to previous level, although it did not reach control preinfusion levels during the ensuing 1-hour period. Control rats exhibited a preinfusion blood pressure of 119 ± 3 mmHg and CEI infusion produced a slight hypotensive effect by the first 30 minutes. Continuous infusion of CEI resulted in a progressive decrease in arterial pressure. The maximal decrease averaged 8.4 ± 3.4 mmHg, a value significantly less than that achieved in hypertensive rats.

III. Bilateral Renal Responses to CEI

The body weights of hypertensive and control rats were 289 ± 11 g and 283 ± 16 g, respectively. In hypertensive rats, the weight of the nonclipped kidney was significantly greater than that of the clipped kidney (1.29 ± 0.03 vs 1.08 ± 0.05 g). In control

Figure 2 Effects of CEI infusion on the arterial blood pressure of Goldblatt hypertensive and normotensive rats. Values shown are Mean ± SEM. Data points are plotted at the midpoint of each clearance period which extended 15 minutes on each side of the point. Asterisks denote significant internal changes from controls: * $P < 0.05$; ** $P < 0.01$. Goldblatt hypertensive rats = 17; normotensive rats = 12.

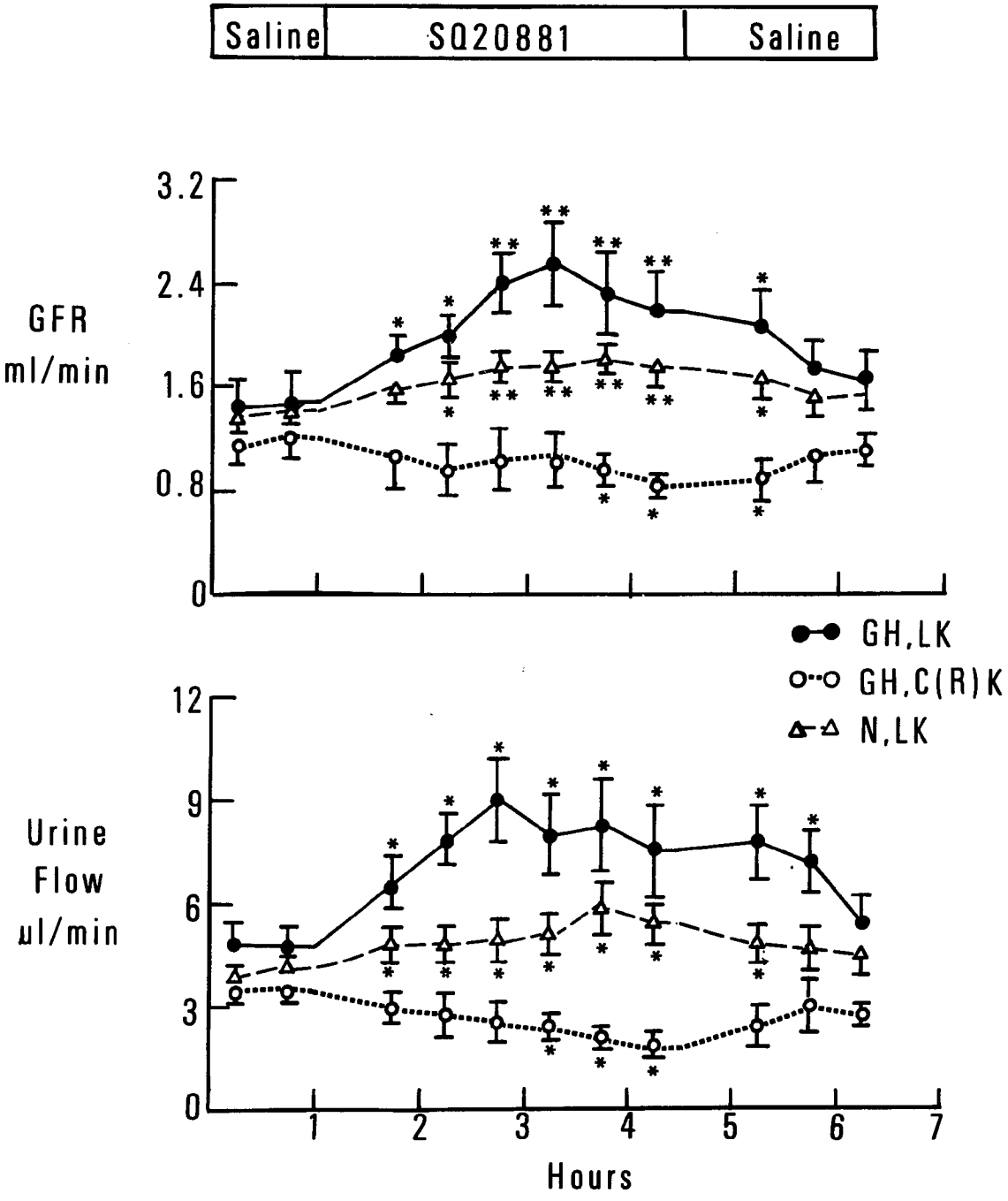

160
150
140
130
120
110
100
0
Mean Arterial Blood Pressure, mmHg
Goldblatt Hypertensive
Normal
* p<0.05, ** p<0.01
Saline
SQ20881
Saline
1
2
3
4
5
6
7
HOURS

rats, the weight of both kidneys were similar (1.19 ± 0.06 g for left kidney and 1.23 ± 0.06 g for right kidney), and also similar to the weight of nonclipped kidneys in hypertensive rats.

The control GFR before CEI infusion was 1.45 ± 0.06 ml/min for the left, nonclipped kidneys of hypertensive rats and 1.46 ± 0.11 ml/min for the left corresponding kidneys of control rats. The GFR of the clipped kidneys of hypertensive rats averaged 1.18 ± 0.15 ml/min which was significantly less than that for the nonclipped kidneys ($p < 0.05$). When factored by kidney weight, GFR was comparable in nonclipped kidneys of hypertensive rats and corresponding kidneys of control rats (1.16 ± 0.04 vs 1.23 ± 0.07 ml/min per g). Also, GFR in the clipped kidneys of hypertensive rats (1.04 ± 0.11 ml/min per g) was not significantly different from that of the nonclipped kidneys when the differences in kidney weight were considered.

As shown in Fig. 3, GFR increased significantly in the nonclipped kidneys of hypertensive rats following 30 minutes of CEI infusion and continued to increase during the period of CEI infusion. The GFR was still elevated one hour after cessation of CEI infusion and then decreased toward preinfusion levels during the next hour. Increases in GFR were also seen in the corresponding left kidneys of control rats; however, these increases in GFR were significantly less than those observed in hypertensive rats. In contrast, slight but consistent decreases in GFR were observed in the clipped kidneys of hypertensive rats during CEI infusion and GFR was significantly lower than control level by the last hour of

Figure 3 Effects of CEI infusion on GFR and urine flow of the clipped kidney, the nonclipped kidney and the corresponding left kidney of control rat. The mean maximal increase of GFR was 73% and of urine flow was 104% for the nonclipped kidney. The corresponding values for kidney of control rat were 22% and 44%, respectively. Statistical notation is identical to that shown on Figure 2. GH = Goldblatt hypertensive rat (n=17); LK = left kidney in normotensive or nonclipped kidney in hypertensive rat; C(R)K = clipped (right) kidney; N = normotensive rat (n=12).

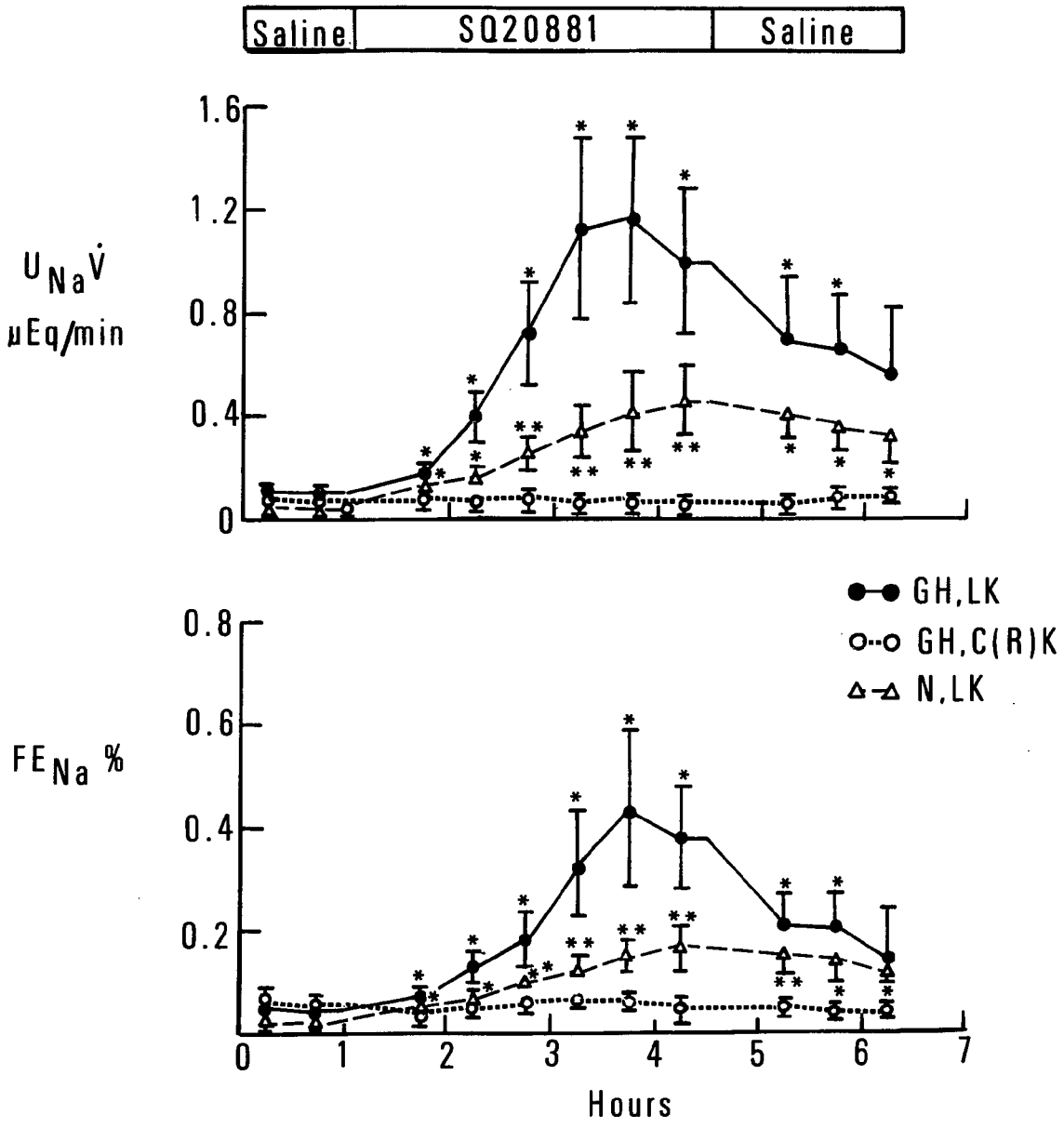

Saline
SQ20881
Saline
GFR
ml/min
3.2
2.4
1.6
0.8
0
GH,LK
GH,C(R)K
N,LK
Urine
Flow
µl/min
12
9
6
3
0
1
2
3
4
5
6
7
Hours

CEI. The right kidneys of control rats corresponding to the clipped kidneys had increases in GFR, urine flow, and sodium excretion similar to those shown for the left kidney.

The urine flow responses during CEI occurring in the clipped and nonclipped kidneys of hypertensive rats are shown on the bottom of Fig. 3. The responses of left kidneys of control rats are also shown for comparison. A significant diuresis was observed from the nonclipped kidneys of hypertensive rats during CEI infusion in spite of the concomitant reduction in arterial pressure. During the first 30 minutes of CEI infusion, urine flow was increased by 42%. Urine flow increased to even greater levels in spite of the progressive fall of arterial pressure. A diuretic response was also noted in the corresponding left kidneys of control rats during CEI infusion; however, the magnitude of increase in urine flow was significantly less than that observed in nonclipped kidneys of hypertensive rats. The average maximal increase in urine flow of hypertensive rats was 104% as compared to 44% in control rats. In contrast, an initially slight but subsequently significant decrease in urine flow was noted from the clipped kidneys. With termination of CEI infusion, urine flow returned toward the preinfusion values in both kidneys of hypertensive rats.

The absolute and fractional excretions of sodium in response to CEI infusion are illustrated in Fig. 4. CEI infusion resulted in marked natriuretic responses from the nonclipped kidneys of hypertensive rats with a maximum 10-fold increase of sodium excretion. The natriuresis was the result of increased urinary sodium

Figure 4 Effects of CEI infusion on absolute and fractional sodium excretions. The mean maximal increase of absolute excretion ($U_{Na}V$) was 1045% and of fractional excretion (FE_{Na}) was 655% for the nonclipped. The corresponding values for the kidney of control rat were 730% and 50%, respectively. Statistical notation, abbreviation and animal number are identical to those shown on Figure 3.


Saline
SQ20881
Saline
$U_{Na}\dot{V}$
µEq/min
1.6
1.2
0.8
0.4
0
FE_{Na} %
0.8
0.6
0.4
0.2
0
1
2
3
4
5
6
7
Hours
GH,LK
GH,C(R)K
N,LK

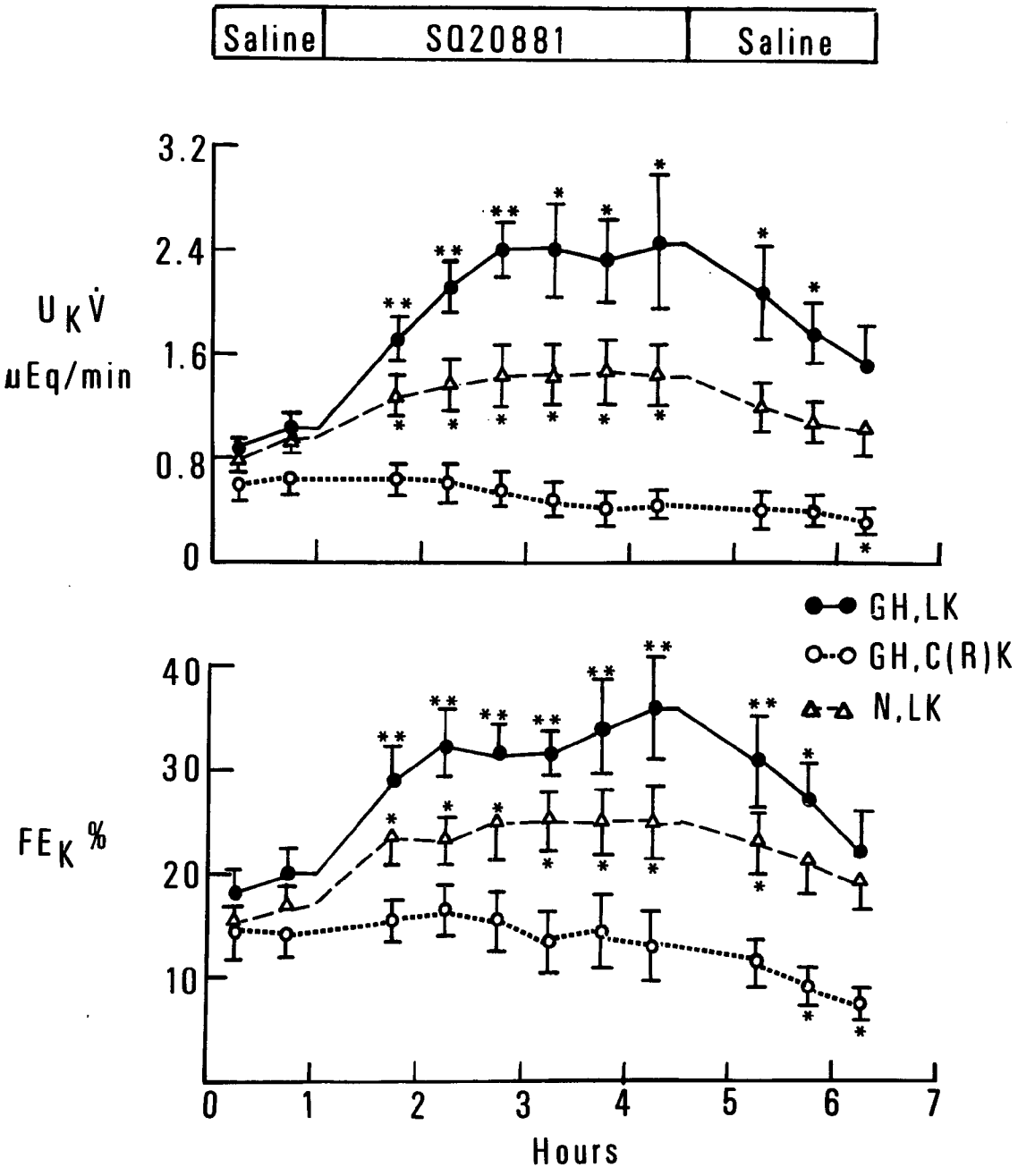
concentration as well as volume flow. Sodium excretion rate decreased after discontinuing the CEI infusion. A natriuresis of lesser magnitude was observed in control rats. In clipped kidneys, the urinary sodium excretion rate decreased slightly during CEI infusion. The quantitatively greater increases in fractional sodium excretion following CEI in the nonclipped kidneys indicate that these kidneys excreted a much greater percentage of filtered sodium when compared to those of either clipped kidneys of hypertensive rats or kidneys of control rats.

Alterations in the potassium excretion during CEI infusion are shown in Fig. 5. A kaliuresis was also seen during CEI infusion from the nonclipped kidneys of hypertensive rats and the kidneys from control rats. After cessation of CEI infusion, potassium excretion decreased toward control values. A parallel increase in the fractional potassium excretion was also observed. As with sodium excretion, the relative responses of the nonclipped kidney were greater. In contrast, a slight decrease in potassium excretion from the clipped kidneys of hypertensive rats was noted.

IV. Blood Pressure and Bilateral Renal Responses to Saralasin

Ten hypertensive rats and five normal rats were used for this series of experiments. The average body weight of the hypertensive rats at the time of study was 270 ± 13 g. The weight of the nonclipped kidneys was significantly greater than those of the clipped

Figure 5 Effects of CEI infusion on absolute and fractional potassium excretions. The mean maximal increase of absolute excretion (U_KV) was 179% and of fractional excretion (FE_K) was 140% for the nonclipped kidney. The corresponding values for the kidney of control rat were 75% and 80%, respectively. Statistical notation, abbreviation and animal number are identical to those shown on Figure 3.

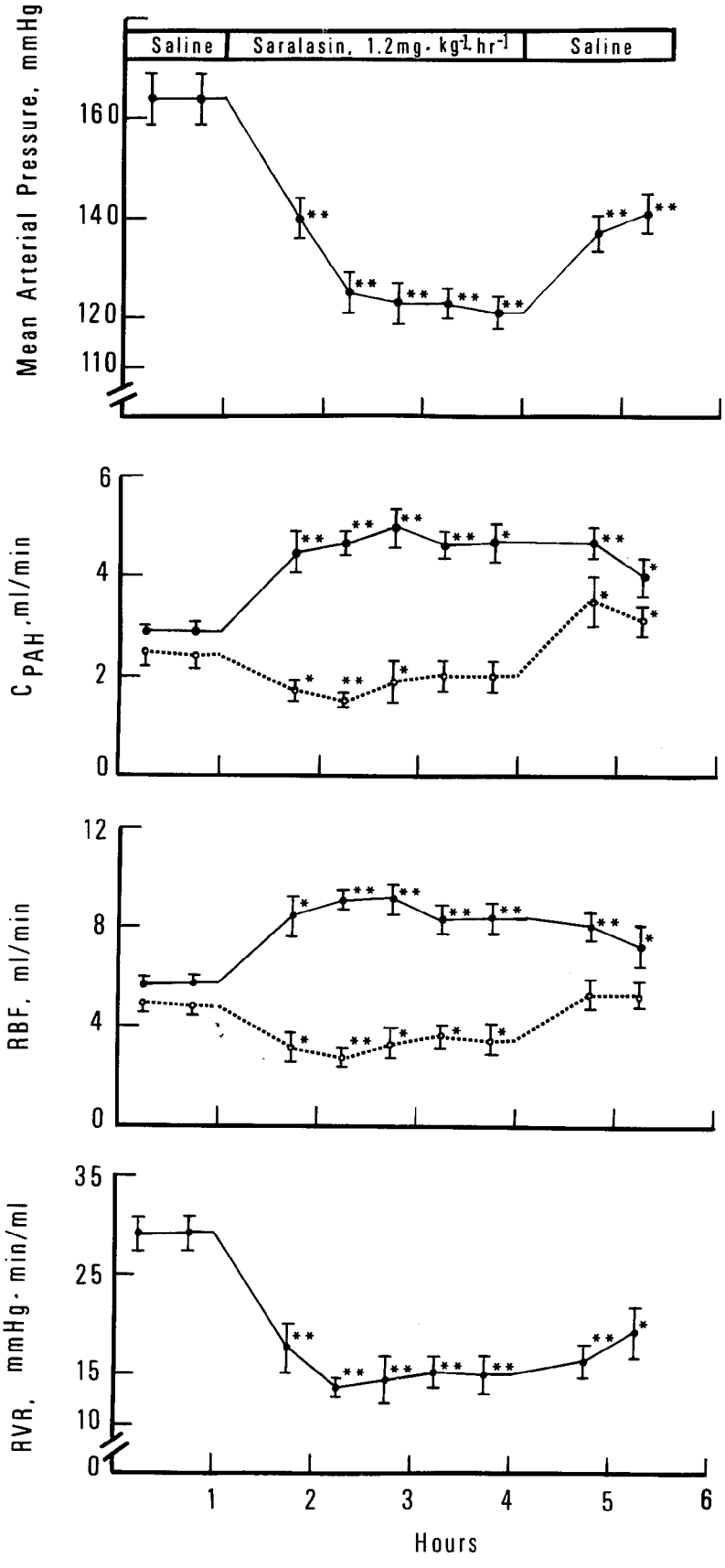

Saline
SQ20881
Saline
3.2
2.4
1.6
0.8
0
$U_K\dot{V}$
μEq/min
GH,LK
GH,C(R)K
N,LK
40
30
20
10
FE_K %
0
1
2
3
4
5
6
7
Hours

kidneys (1.35 ± 0.07 vs 1.06 ± 0.03 g, $p < 0.001$). In the nonclipped kidney, the control GFR and estimated renal blood flow were 1.46 ± 0.10 ml/min and 5.82 ± 0.22 ml/min, respectively. In the clipped kidney, the corresponding values were 1.17 ± 0.10 ml/min and 4.93 ± 0.26 ml/min. Although the GFR and the renal blood flow for the nonclipped kidney were greater than those for the clipped kidney, these differences were insignificant when factored by kidney weight (1.10 ± 0.10 vs 1.07 ± 0.10 ml/min per g for GFR and 4.32 ± 0.37 vs 4.58 ± 0.32 ml/min per g for renal blood flow).

Effects of saralasin infusion on the blood pressure and bilateral renal hemodynamics of hypertensive rats are shown in Fig. 6. Saralasin administration resulted in a significant reduction in arterial pressure from control level of 164 ± 4 mmHg to 140 ± 4 mmHg during the first hour of infusion of the antagonist. The blood pressure then declined slowly over the next two hours and reached 121 ± 4 mmHg by the end of the saralasin infusion. Following termination of the saralasin infusion, blood pressure rose gradually to 142 ± 4 mmHg by one and a half hours.

The nonclipped kidney responded to angiotensin blockade with marked vasodilation despite the dramatic fall of blood pressure. Following 30 minutes of saralasin infusion, the renal plasma flow increased significantly from the control values of 2.87 ± 0.13 to 4.46 ± 0.45 ml/min. The renal blood flow increased from 5.82 ± 0.22 to 8.51 ± 0.82 ml/min, while the total renal vascular resistance decreased from 29.2 ± 1.8 to 17.7 ± 2.7 mmHg·min/ml. The renal vasodilation was maintained throughout the infusion period in

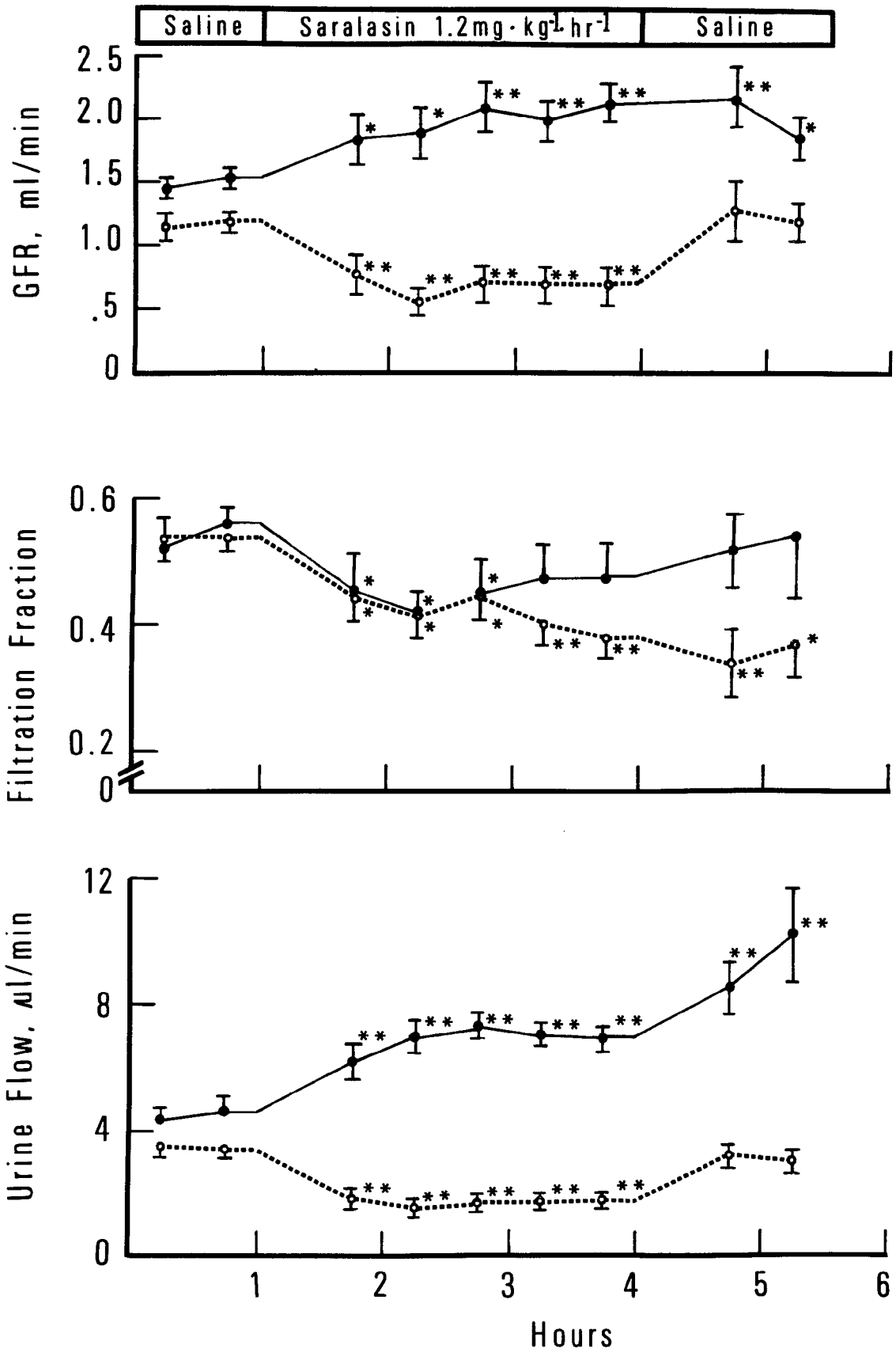
Figure 6 Effects of saralasin infusion on arterial blood pressure and renal hemodynamics in hypertensive rats. Solid and dotted lines represent the nonclipped kidney and the clipped kidney, respectively. C_{PAH} = PAH clearance; RBF = renal blood flow; RVR = renal vascular resistance. Statistical notation is identical to that for Figure 2. Rat number = 10.


Saline
Saralasin, 1.2mg·kg⁻¹·hr⁻¹
Saline
Mean Arterial Pressure, mmHg
160
140
120
110
C PAH, ml/min
6
4
2
0
RBF, ml/min
12
8
4
0
RVR, mmHg·min/ml
35
25
15
10
0
1
2
3
4
5
6
Hours

spite of progressive decreases in arterial pressure. The maximal increase of the renal blood flow was 57 ± 12% and the maximal decrease in total renal vascular resistance was 50 ± 6%. After cessation of saralasin infusion, renal vasodilation persisted for approximately one hour and then dissipated in association with progressive increases of systemic arterial pressure. In contrast, the clipped kidney exhibited directionally opposite renal hemodynamic changes; the renal plasma flow and the renal blood flow declined significantly during saralasin infusion. These hemodynamic alterations were partially reversed after the saralasin infusion was discontinued. Changes of renal vascular resistance for the clipped kidney could not be computed since measurements of the renal arterial pressure beyond the clip were not performed.

The GFR, filtration fraction and urine flow responses to saralasin of both the clipped and the nonclipped kidneys are shown in Fig. 7. In the nonclipped kidneys, GFR increased significantly from 1.46 ± 0.10 to 1.82 ± 0.23 ml/min after the first hour of angiotensin antagonism and increased further to 2.18 ± 0.14 ml/min by the end of saralasin administration. The maximal increase in GFR was 49 ± 9%. This augmented GFR presisted for one hour after discontinuing saralasin infusion and then declined toward values observed for the initial control period. Filtration fraction was significantly decreased during the initial phase of angiotensin blockade but these changes were less pronounced during the later periods of saralasin infusion. The filtration fraction returned to preinfusion values following termination of saralasin infusion.

Figure 7 Effects of saralasin infusion on GFR, filtration fraction and urine flow for the clipped and nonclipped kidneys. Solid and dotted lines represent the nonclipped and the clipped kidneys, respectively. Statistical notation is identical to that for Figure 2. Rat number = 10.


Saline
Saralasin 1.2mg·kg⁻¹·hr⁻¹
Saline
GFR, ml/min
2.5
2.0
1.5
1.0
.5
0
Filtration Fraction
0.6
0.4
0.2
0
Urine Flow, µl/min
12
8
4
0
1
2
3
4
5
6
Hours

Significant diuretic responses from the nonclipped kidneys were also observed during antiotensin blockade. This diuresis was accentuated following discontinuation of saralasin when blood pressure had partially returned to control levels and GFR remained at a level greater than that observed during control conditions. For the clipped kidney, GFR, filtration fraction and urine flow all decreased significantly during saralasin administration but tended to recover following termination of infusion of the antagonist.

Table 1 summarizes the renal excretory observations for sodium and potassium in response to infusion of saralasin. Absolute and fractional sodium excretions from the nonclipped kidneys were initially unchanged and then subsequently increased. Kaliuresis was observed during the entire period of infusion of the antagonist. Increases in electrolyte excretion were even greater after cessation of saralasin infusion as the arterial pressure increased gradually. Both sodium and potassium excretions from the clipped kidney were decreased during infusion of saralasin.

The blood pressure and renal function responses for the left kidneys of normal rats which correspond to the nonclipped kidneys of hypertensive rats are shown in Table 2. Arterial blood pressure decreased significantly during angiotensin blockade. Slight but insignificant increases in renal blood flow and minor decreases in renal vascular resistance were seen during saralasin infusion. Although the increases of GFR were significant, the magnitudes of these changes were much smaller than those observed for hypertensive rats. Sodium excretion did not change significantly though

Table 1. Effects of Saralasin Infusion on the Absolute and Fractional Excretions of Sodium and Potassium from the Non-clipped and the Clipped Kidneys of Goldblatt Hypertensive Rats. (n = 10; Values are Mean ± SEM)

		Control	Saralasin Infusion (hrs) 0.5-1.5	Saralasin Infusion (hrs) 1.5-3.0	Cessation of Saralasin
$U_{Na} \cdot \dot{V}$	Nonclipped	0.14 ± 0.04	0.17 ± 0.05	0.30 ± 0.12	0.74 ± 0.25*+
μEq/min	Clipped	0.10 ± 0.03	0.03 ± 0.01*	0.04 ± 0.01*	0.07 ± 0.03
FE_{Na}	Nonclipped	0.07 ± 0.02	0.07 ± 0.02	0.11 ± 0.05	0.29 ± 0.11*+
%	Clipped	0.06 ± 0.01	0.04 ± 0.01*	0.05 ± 0.01	0.04 ± 0.02
$U_K \cdot \dot{V}$	Nonclipped	0.90 ± 0.07	1.76 ± 0.18*	2.18 ± 0.17*	2.18 ± 0.18*
μEq/min	Clipped	0.66 ± 0.10	0.34 ± 0.05*	0.27 ± 0.04*	0.33 ± 0.05
FE_K	Nonclipped	18.6 ± 1.4	30.7 ± 3.8*	33.3 ± 2.5*	32.5 ± 3.5*
%	Clipped	16.2 ± 1.8	14.5 ± 1.2	11.5 ± 0.9*	9.0 ± 1.1*

Abbreviations: $U_{Na} \cdot \dot{V}$ = Absolute rate of sodium excretion; $U_K \cdot \dot{V}$ = Absolute rate of potassium excretion; FE_{Na} = Fractional excretion of sodium; FE_K = Fractional excretion of potassium. * $p < 0.05$ when compared to control; + $p < 0.05$ when compared to last period of Saralasin infusion.

Table 2. Effects of Saralasin Infusion on Mean Arterial Pressure and Renal Function of the Left Kidneys of Normal Rats. (n = 5; Values are Mean ± SEM)

	Control	Saralasin Infusion (hrs) 0.5-1.5	Saralasin Infusion (hrs) 1.5-3.0	Cessation of Saralasin
BP, mmHg	116 ± 2	102 ± 2*	100 ± 2*	105 ± 6
RBF, ml/min	6.34 ± 0.44	6.86 ± 0.74	7.16 ± 0.94	4.65 ± 0.62*+
RVR, $\frac{mmHg \cdot min}{ml}$	18.5 ± 1.4	15.9 ± 2.0	14.9 ± 1.5	24.9 ± 4.0
GFR, ml/min	1.37 ± 0.11	1.57 ± 0.10*	1.58 ± 0.12*	1.34 ± 0.05
FF, %	0.42 ± 0.04	0.44 ± 0.03	0.43 ± 0.06	0.54 ± 0.09+
$\dot{V}$, µl/min	5.2 ± 1.1	4.2 ± 0.7	4.7 ± 0.8	4.4 ± 0.8
$U_{Na} \cdot \dot{V}$, µEq/min	0.03 ± 0.01	0.03 ± 0.01	0.14 ± 0.10	0.15 ± 0.08
$U_K \cdot \dot{V}$, µEq/min	0.75 ± 0.15	0.59 ± 0.09	0.68 ± 0.10	0.59 ± 0.06

Abbreviations: BP = Mean arterial pressure; RBF = Estimated renal blood flow; RVR = Total renal vascular resistance; GFR = Glomerular filtration rate; FR = Filtration fraction; $\dot{V}$ = Urine flow; $U_{Na} \cdot \dot{V}$ = Absolute rate of sodium excretion; $U_K \cdot \dot{V}$ = Absolute rate of potassium excretion. * and + see Table 1 for statistical notation.

Body weight = 254 ± 13 g; left kidney weight = 1.11 ± 0.07 g.

there was a tendency to increase by the later periods of saralasin infusion and following termination of infusion of the angiotensin antagonist.

V. Bilateral Renal Responses to Aortic Clamping

As described previously, blockade of RAS resulted in opposite responses from the clipped and the nonclipped kidneys of hypertensive rats. Increased GFR and excretory function were observed in the nonclipped kidneys and decreases in these indices of renal function were noted in the clipped kidneys. In order to determine the extent to which the responses of the clipped kidney occurred as the direct result of the associated reduction of arterial pressure during CEI infusion, another group of 5 hypertensive rats was used to evaluate the renal function following reduction in arterial pressure by aortic clamping to values seen during CEI infusion. The effect of this reduction in arterial pressure is shown in Fig. 8 and Fig. 9. In clipped kidneys, parallel decreases in GFR, urine flow, absolute sodium excretion and fractional sodium excretion were noted when arterial pressure was reduced by CEI infusion or by aortic clamping. The effect of aortic clamping was reversible. The arterial pressure, GFR, urine flow and sodium excretion recovered to control level after releasing the aortic clamp. In nonclipped kidneys, aortic clamping produced decreases in GFR, urine flow and sodium excretion while CEI infusion resulted in

Figure 8 Effects of reduction of arterial pressure on GFR and urine flow of the clipped and nonclipped kidneys. ●———● CEI infusion; o———o reduction of blood pressure by aortic clamping; o------o release of aortic clamping; $\dot{V}$ = urine flow. Rat number = 5.

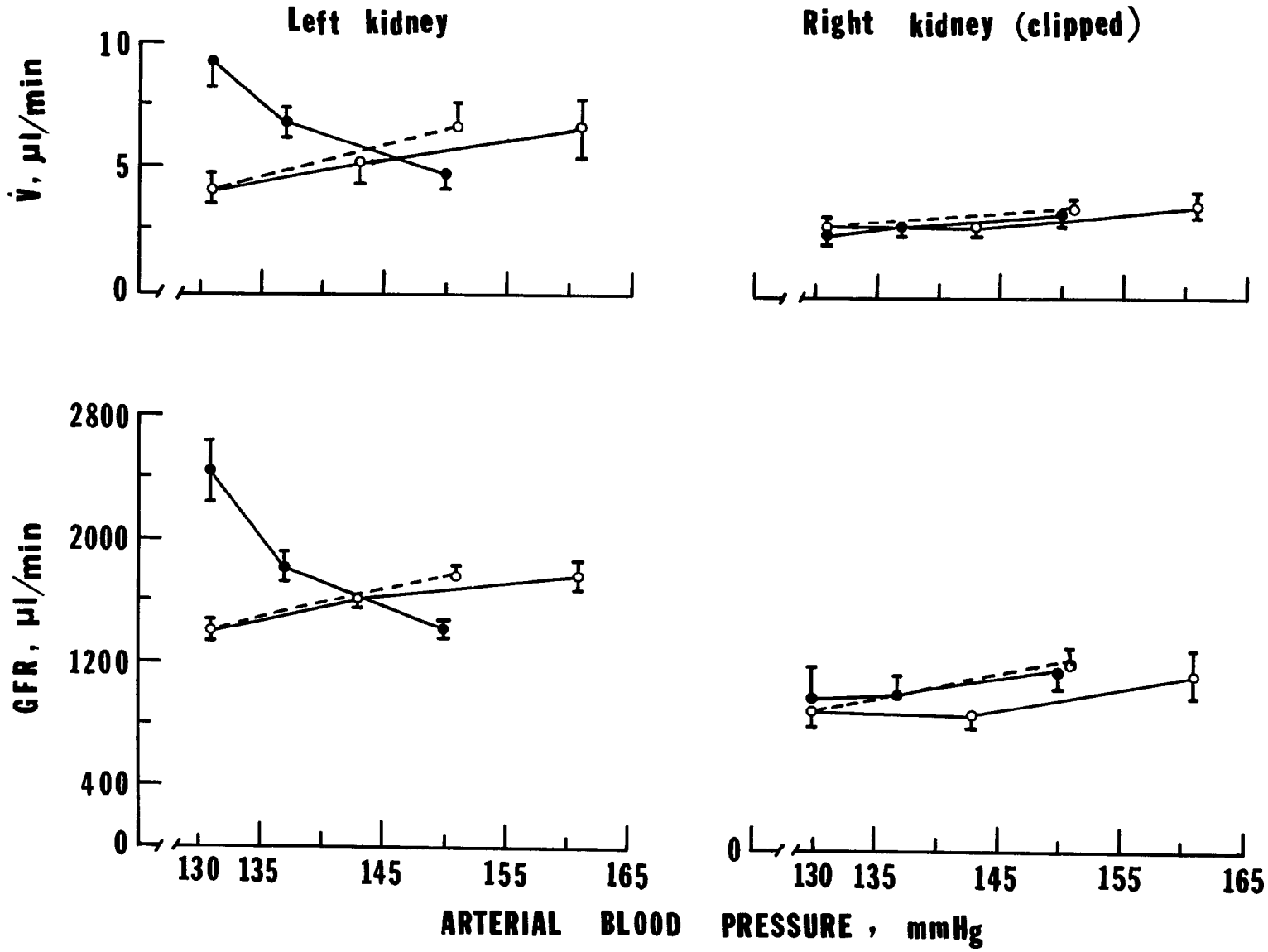
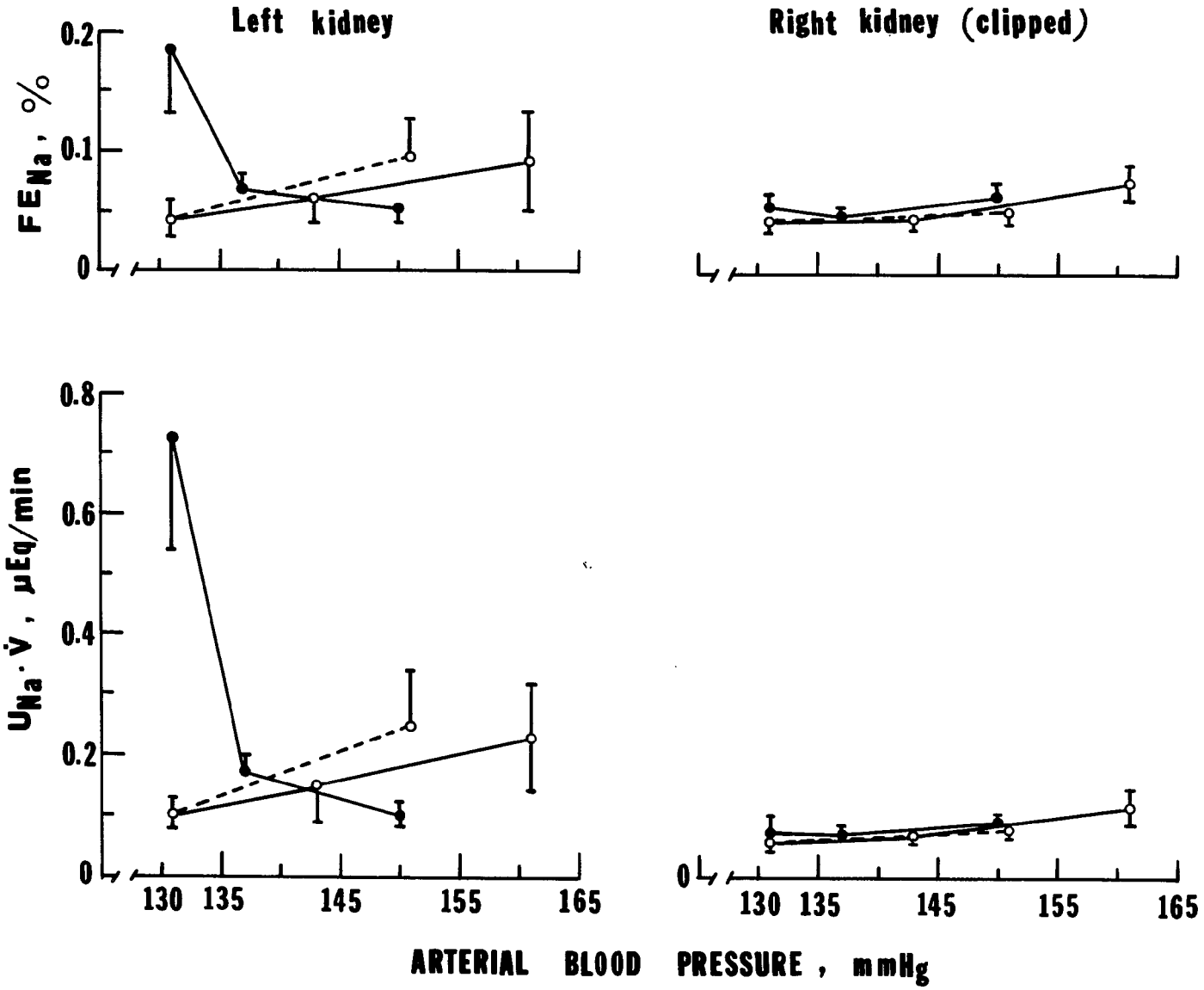

Left kidney
Right kidney (clipped)
V̇, µl/min
10
5
0
GFR, µl/min
2800
2000
1200
400
0
130
135
145
155
165
ARTERIAL BLOOD PRESSURE, mmHg

Figure 9 Effects of reduction of arterial pressure on absolute and fractional sodium excretion from the clipped and nonclipped kidneys. ●———● CEI infusion; o———o aortic clamping; o------o release of aortic clamping; $U_{Na} \cdot \dot{V}$ = absolute sodium excretion; FE_{Na} = fractional sodium excretion. Rat number = 5.


Left kidney
Right kidney (clipped)
FE_{Na}, %
0.2
0.1
0
$U_{Na} \cdot \dot{V}$, µEq/min
0.8
0.6
0.4
0.2
0
130
135
145
155
165
ARTERIAL BLOOD PRESSURE, mmHg

increased GFR, diuresis and natriuresis despite the concomitant reduction of arterial pressure.

VI. Plasma Renin Activity and Kidney Renin Activity

Seven hypertensive rats and six normal rats were used for this series of experiments. Results of the PRA and kidney renin measurements are shown in Table 3. There were no significant differences in body weight between these two groups of rats. However, the nonclipped kidneys were significantly larger and the clipped kidneys were significantly smaller than control kidneys from normal rats. The plasma renin activity of hypertensive rats was significantly higher than that of normal rats. Renal renin activity was found to be markedly decreased in the nonclipped kidneys of hypertensive rats. Renal renin activity of the clipped kidneys was slightly but not significantly higher than that measured in normal rat kidneys.

VII. Segmental Nephron Reabsorptive Function in Response to CEI.

These experiments were performed on 3 groups of hypertensive rats: group 1 was a time control group in which 7 rats were used for tubular fluid collections; group 2 was an uncontrolled blood pressure group in which 13 rats were used for tubular fluid collections (subgroup 2a) and 5 rats were used for tubule hydrostatic pressure measurements (subgroup 2b); group 3 was a reduced blood

Table 3. Comparison of Blood Pressure, Kidney Weight, Plasma Renin Activity and Kidney Renin Activity of Normal and Goldblatt Hypertensive Rats (Mean ± SEM)

	ANIMAL	BP (mmHg)	BW (g)	KIDNEY WT. (b) Left (L)	KIDNEY WT. (b) Right (R)	PRA ng/ml/hr	KIDNEY RENIN ng/mg/hr Left	KIDNEY RENIN ng/mg/hr Right
	Normal (N)	119	293	1.47	1.43	12.8	239	217
	(6)	±3	±14	±0.06	±0.06	±3.4	±54	±45
	GH	164	308	1.69	1.28	24.0	14	293
	(7)	±6	±11	±0.05	±0.02	±2.7	±5	40
				(nonclipped)	(clipped)		(nonclipped)	(clipped)
P	N vs. GH	<0.001	NS	<0.05	<0.05	<0.05	<0.001	NS
	L vs. R of GH			<0.001			<0.001	

GH = Goldblatt hypertensive.

PRA = Plasma renin activity.

pressure group in which 9 rats were used for tubular fluid collection (subgroup 3a) and 6 rats were used for tubular pressure measurements (subgroup 3b).

The mean arterial blood pressure and renal function response to CEI in the 3 groups of rats used for tubular fluid collection are summarized in Table 4. In the time control group, there were no significant changes in blood pressure, GFR, and excretory function between the control collections and recollections. In subgroup 2a, CEI reduced arterial pressure by an average of 24 ± 3 mmHg. As described earlier, GFR and urine flow increased significantly and a dramatic increase in sodium excretion was observed. Potassium and chloride excretion rates also increased but to a lesser extent than that of sodium. These hypotensive and renal function responses were consistent with those of the previous clearance study. In the third group of rats, the initially spontaneous arterial pressure was 158 ± 6 mmHg. When the renal perfusion pressure for the control period was reduced to a level comparable to that seen during CEI infusion, there were significant increases in GFR and fluid and electrolyte excretion.

The data obtained from the tubular fluid collections are shown in Table 5. SNGFR, measured on the basis of distal tubular fluid collections, increased slightly but significantly (12%) during CEI infusion in spite of the substantial fall of arterial pressure in subgroup 2a. When the arterial pressure was maintained at a comparable level (123 mmHg during control vs 124 mmHg during recollection period), a more pronounced increase (42%) in SNGFR was obtained

Table 4. Responses of Arterial Blood Pressure and Renal Function of the Nonclipped Kidney to CEI in the Goldblatt Hypertensive Rat

Group	Collection Period	MABP mmHg	GFR ml/min	$\dot{V}$ µl/min	$U_{Na}\dot{V}$ µEq/min	FE_{Na} %	$Uk\dot{V}$ µEq/min	FEk %	$U_{Cl}\dot{V}$ µEq/min	FE_{Cl} %
1 (n=7)	Spontaneous BP (1st collection)	152 ±5	1.44 ±0.13	5.81 ±1.02	0.177 ±0.096	0.09 ±0.05	1.002 ±0.196	16.56 ±2.91	1.106 ±0.313	0.532 ±0.112
	Spontaneous BP (re-collection)	150 ±3	1.42 ±0.12	6.25 ±0.94	0.203 ±0.133	0.10 ±0.06	1.092 ±0.165	19.30 ±2.60	1.026 ±0.209	0.566 ±0.089
2a (n=13)	Spontaneous BP (1st collection)	160 ±5	1.41 ±0.12	5.31 ±1.07	0.080 ±0.017	0.05 ±0.01	0.900 ±0.127	16.08 ±2.15	0.649 ±0.118	0.414 ±0.069
	CEI (re-collection)	137*** ±6	1.91*** ±0.13	8.15*** ±1.66	0.370* ±0.137	0.16* ±0.05	1.679** ±0.243	26.12* ±5.45	1.388** ±0.285	0.645* ±0.128
3a (n=9)	Reduced BP^{+} (1st collection)	123 ±3	1.13 ±0.08	3.58 ±.053	0.088 ±0.051	0.06 ±0.03	0.523 ±0.121	12.99 ±2.66	0.422 ±0.184	0.159 ±0.058
	CEI (re-collection)	124 ±4	1.75** ±0.19	9.29** ±1.49	0.612* ±0.317	0.26* ±0.14	2.050*** ±0.378	35.86* ±4.83	1.382* ±0.477	0.698* ±0.232

1. Body weight: group 1 = 210 ± 20 g; group 2 = 245 ± 13 g; group 3 = 215 ± 8g.
2. Kidney weight: group ± = 1.01 ± 0.08 g; group 2 = 1.15 ± 0.07 g; group 3 = 1.10 ± 0.09 g.
3. + : the initially spontaneous blood pressure = 158 ± 6 mmHg.
4. Abbreviations: CEI = Converting enzyme inhibition; MABP = Mean arterial blood pressure; GFR = glomerular filtration rate; $\dot{V}$ = urine flow; $U_{Na}\dot{V}$ = absolute sodium excretion; FE_{Na} = fractional sodium excretion; $U_K\dot{V}$ = Absolute potassium excretion; FE_K = Fractional potassium excretion; $U_{Cl}\dot{V}$ = Absolute chloride excretion; FE_{Cl} = Fractional chloride excretion.
5. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ as compared to the corresponding first collection.

Table 5. Superficial Nephron SNGFR, Tubular Flow and Tubular Fluid Composition Responses to CEI in Goldblatt Hypertensive Rats

Group	Period	SNGFR nl/min	Late Proximal Tubule $(TF/P)_{in}$	Flow nl/min	[Cl] mEq/L	Osmolality mOsm/kg H_2O	Early Distal Tubule $(TF/P)_{in}$	Flow nl/min	[Cl] mEq/L	Osmolality mOsm/kg H_2O
1	Spontaneous BP (1st collection)	25.6 ±2.5	1.69 ±0.11	15.89 ±1.22	134.4 ±5.3	305.9 ±3.6	6.63 ±0.83	4.44 ±0.65	44.1 ±5.8	168.2 ±12.5
	Spontaneous BP (re-Collection)	25.0 ±1.8	1.61 ±0.09	16.54 ±0.88	131.2 ±4.4	303.5 ±4.9	5.76 ±0.90	5.25 ±1.04	44.5 ±4.4	160.0 ±12.7
2a	Spontaneous BP (1st Collection)	24.6 ±1.7	1.94 ±0.15	14.21 ±1.30	129.5 ±3.1	304.8 ±3.8	7.36 ±0.74	4.42 ±0.38	34.9 ±2.3	157.3 ±6.3
	CEI (re-Collection)	27.5* ±1.6	1.45*** ±0.08	19.30*** ±1.52	124.2* ±3.6	301.6 ±3.8	4.83** ±0.42	6.87*** ±0.55	43.3* ±4.1	165.3 ±10.9
3a	Reduced BP (1st Collection)	18.6 ±1.8	1.88 ±0.12	10.94 ±1.51	135.9 ±3.1	304.2 ±3.4	9.93 ±1.85	2.42 ±0.46	39.2 ±4.0	185.1 ±8.4
	CEI (re-Collection)	26.4** ±1.5	1.36** ±0.10	20.13*** ±1.72	134.1 ±2.9	298.4 ±4.6	4.16** ±0.45	5.79*** ±0.65	40.1 ±5.1	180.0 ±9.4

Values shown are Mean ± S.E.M.; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ when compared to the control collection.

during CEI infusion. SNGFR was not altered significantly in the time control rats. The tubular fluid to plasma Inutest ratio for late proximal tubule fluid decreased significantly from the preinfusion level, while the proximal tubular flow rate increased by an average of 5.7 ± 0.9 nl/min in the uncontrolled blood pressure group (subgroup 2a) and 9.2 ± 1.9 nl/min in the reduced blood pressure group (subgroup 3a). The distal tubular fluid to plasma Inutest ratio decreased significantly in these two subgroups of hypertensive rats. Accordingly, early distal tubular flow increased significantly during CEI infusion in both subgroups 2a and 3a. The urine to plasma Inutest ratio also decreased significantly (384 ± 37 vs 290 ± 24 for subgroup 2a; 374 ± 55 vs 220 ± 31 for subgroup 3a).

The calculated values for fractional reabsorption of fluid, chloride and total solute up to the late proximal tubule are illustrated in Fig. 10. In the uncontrolled blood pressure group, CEI infusion induced significant decreases in fractional reabsorption of fluid ($^{FR}H_2O$, 44.8 ± 3.6 to 28.1 ± 3.7%), chloride (FR_{Cl}, 38.1 ± 6.3 to 22.7 ± 3.3%) and total solute (FR_{osm}, 43.7 ± 3.8 to 26.6 ± 2.7%). As shown in Fig. 11, there were associated decreases in the net absolute proximal reabsorption. In the absence of the influence of the CEI induced reductions in arterial pressure (subgroup 3a), the decreases in fractional reabsorption were also observed ($^{FR}H_2O$ 45.8 ± 4 to 24.4 ± 5%; FR_{Cl} 35.6 ± 2.9 to 16.7 ± 3.3%; FR_{osm} 45.7 ± 4.8 to 24.9 ± 5.2%). There were concomitant reductions in absolute reabsorption of these parameters despite

Figure 10 Effects of CEI on fractional reabsorption of fluid, chloride and total solute up to the proximal tubule collection site.

FR_{H_2O} = fractional reabsorption of fluid;
FR_{Cl} = fractional reabsorption of chloride;
FR_{osm} = fractional reabsorption of total solute;
C = the first (control) collection;
R = recollection. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ as compared to control collection.

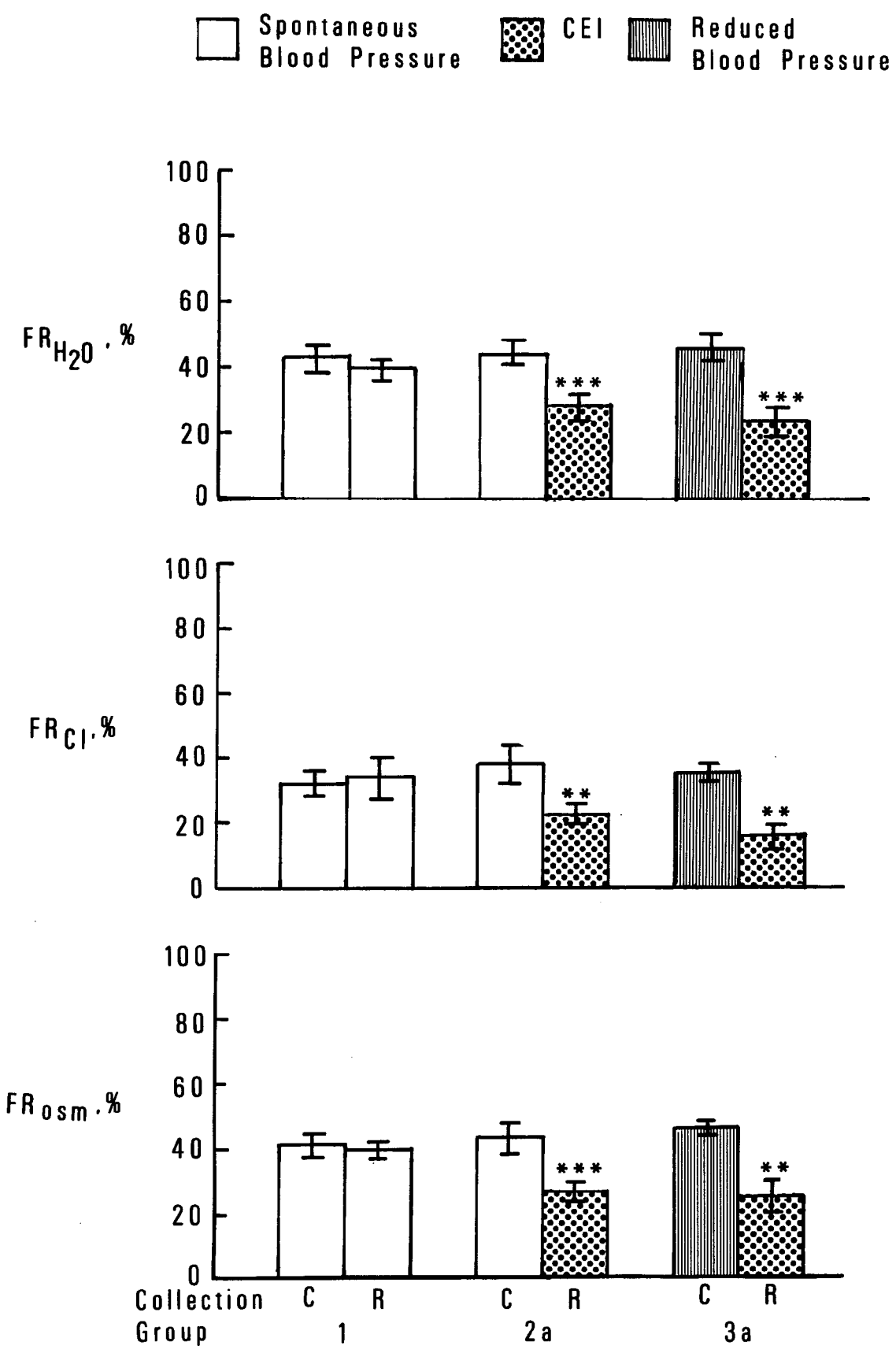
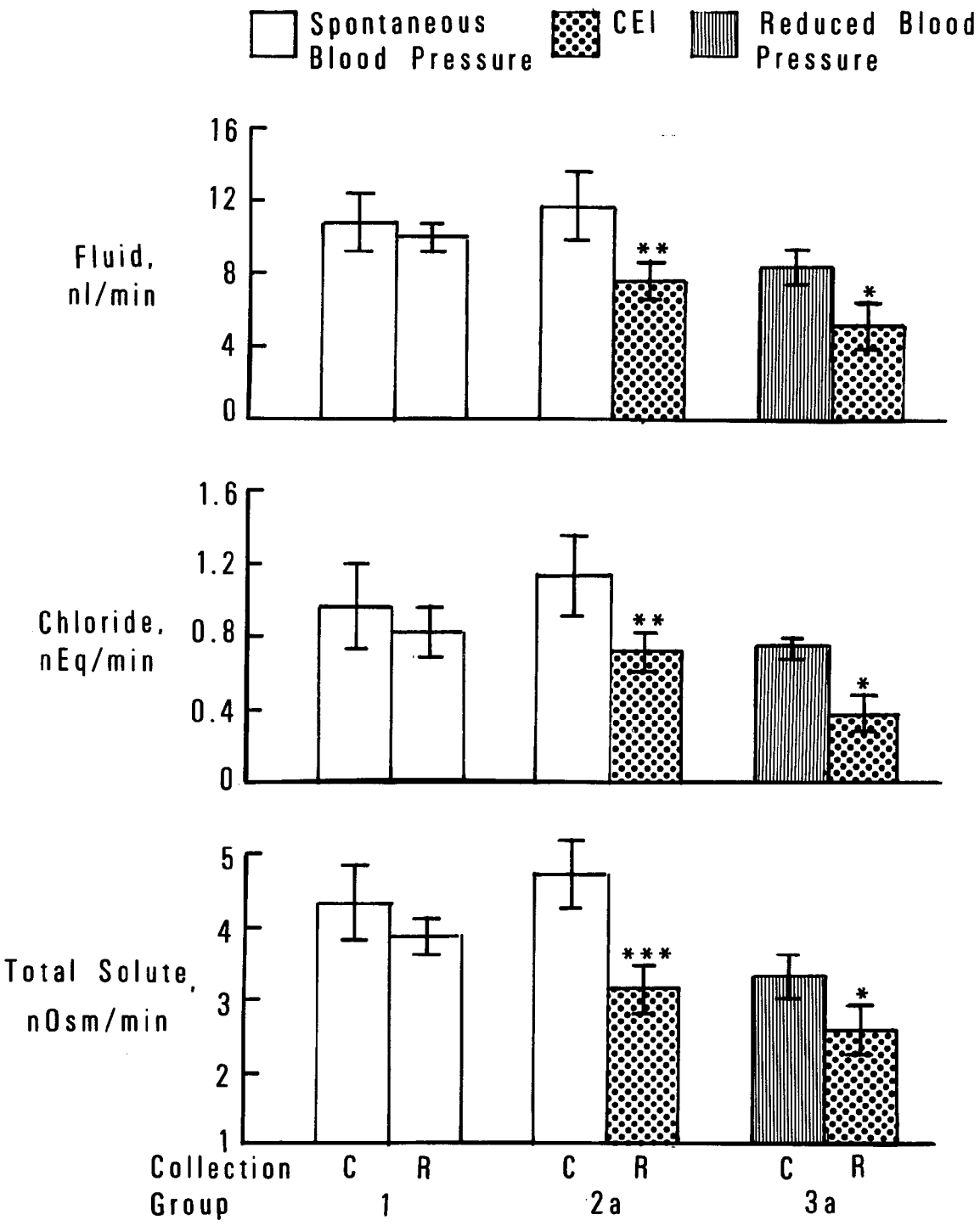

Spontaneous Blood Pressure
CEI
Reduced Blood Pressure
FR_{H_2O} . %
FR_{Cl} . %
FR_{osm} . %
100
80
60
40
20
0
***
**
Collection
C
R
Group
1
2a
3a

Figure 11 Effects of CEI on absolute reabsorption of fluid, chloride and total solute up to the proximal tubule collection site. Statistical notations are identical to those shown in Figure 10.


Spontaneous Blood Pressure
CEI
Reduced Blood Pressure
Fluid, nl/min
16
12
8
4
0
**
*
Chloride, nEq/min
1.6
1.2
0.8
0.4
0
**
*
Total Solute, nOsm/min
5
4
3
2
1
***
*
Collection
C
R
C
R
C
R
Group
1
2a
3a

increases in filtered load. In the time control group, neither fractional reabsorption nor absolute reabsorption of fluid, chloride and total solute were observed.

Changes in fractional reabsorption up to the early distal tubule (Fig. 12) were less pronounced than those of the proximal tubule. In the uncontrolled blood pressure group, $^{FR}H_2O$ decreased from 83.7 ± 1.2 to 75.2 ± 2.1%; FR_{Cl} decreased from 94.1 ± 0.6 to 89.5 ± 1.7% and FR_{osm} changed from 90.1 ± 1.9 to 85.3 ± 1.8%. In the reduced blood pressure group, these changes were more remarkable ($^{FR}H_2O$ 84.8 ± 2.4 to 70.6 ± 2.8%; FR_{Cl} 94.4 ± 1.2 to 88.9 1 1.9%; FR_{osm} 91.1 ± 1.3 to 81.2 ± 1.9%). However, the absolute reabsorption of fluid, chloride and total solute were not significantly altered during CEI infusion in the uncontrolled blood pressure group and actually increased in the reduced blood pressure group (Fig. 13).

Assessment of reabsorption patterns by the nephron segment between the proximal tubule and the distal tubule collection sites revealed that there was an increase in reabsorption by this segment. As shown in Fig. 14, the absolute reabsorption of fluid increased significantly in both the uncontrolled blood pressure group and the reduced blood pressure group. Increased reabsorption of chloride and of total solute were also observed. These increases in absolute reabsorption of fluid, chloride and total solute by this intermediate nephron segment are results of elevated load emerging from the late proximal tubule during CEI infusion as

Figure 12 Effects of CEI on fractional reabsorption of fluid, chloride and total solute up to the distal tubule collection site. Abbreviations and statistical notations are identical to those shown in Figure 10.

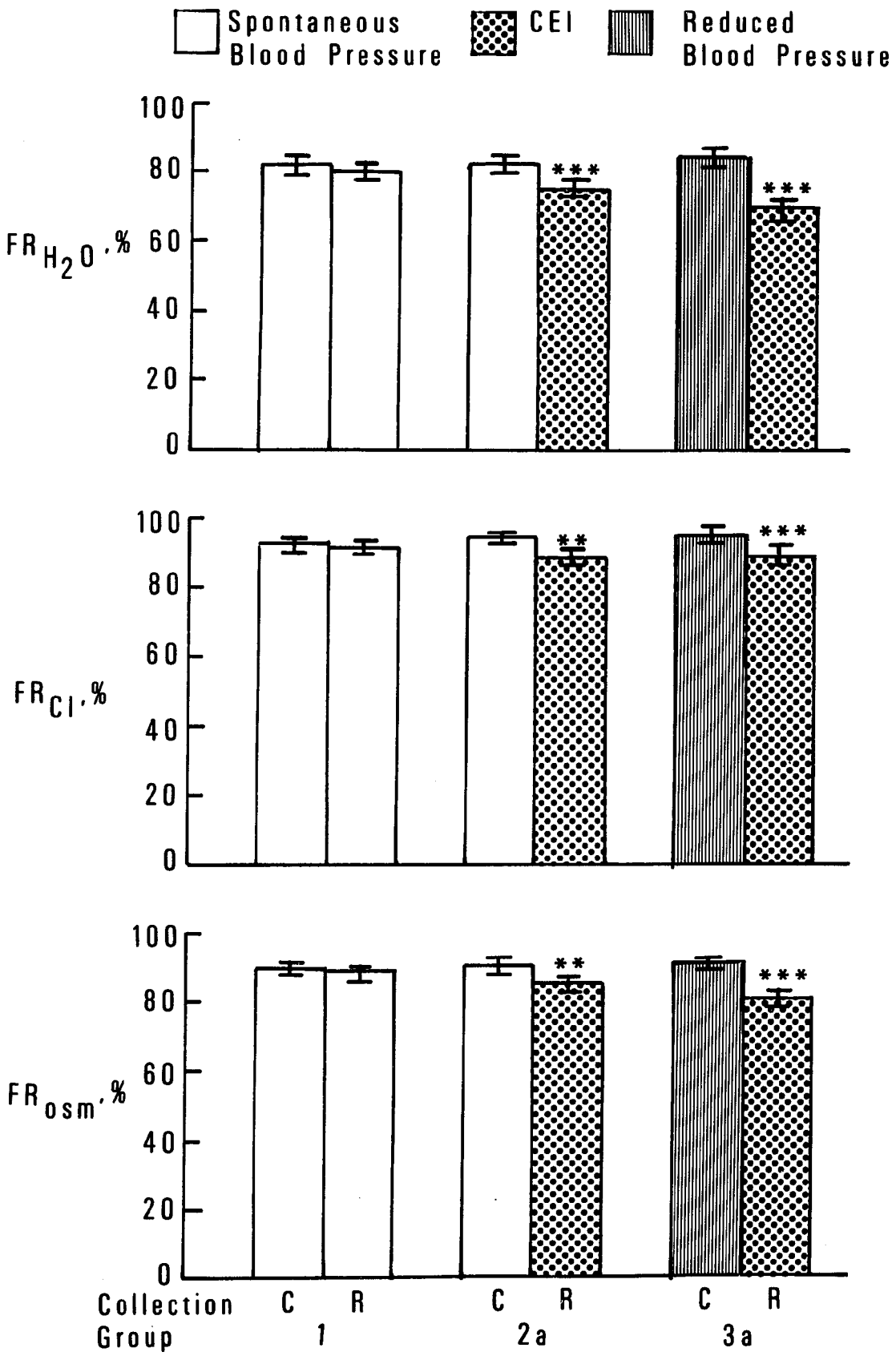

Spontaneous Blood Pressure
CEI
Reduced Blood Pressure
FR_{H_2O},%
FR_{Cl},%
FR_{osm},%
100
80
60
40
20
0
***
**
Collection
Group
C
R
1
2a
3a

Figure 13 Effects of CEI on absolute reabsorption of fluid, chloride and total solute up to the distal tubule collection site. Statistical notations see Figure 10.

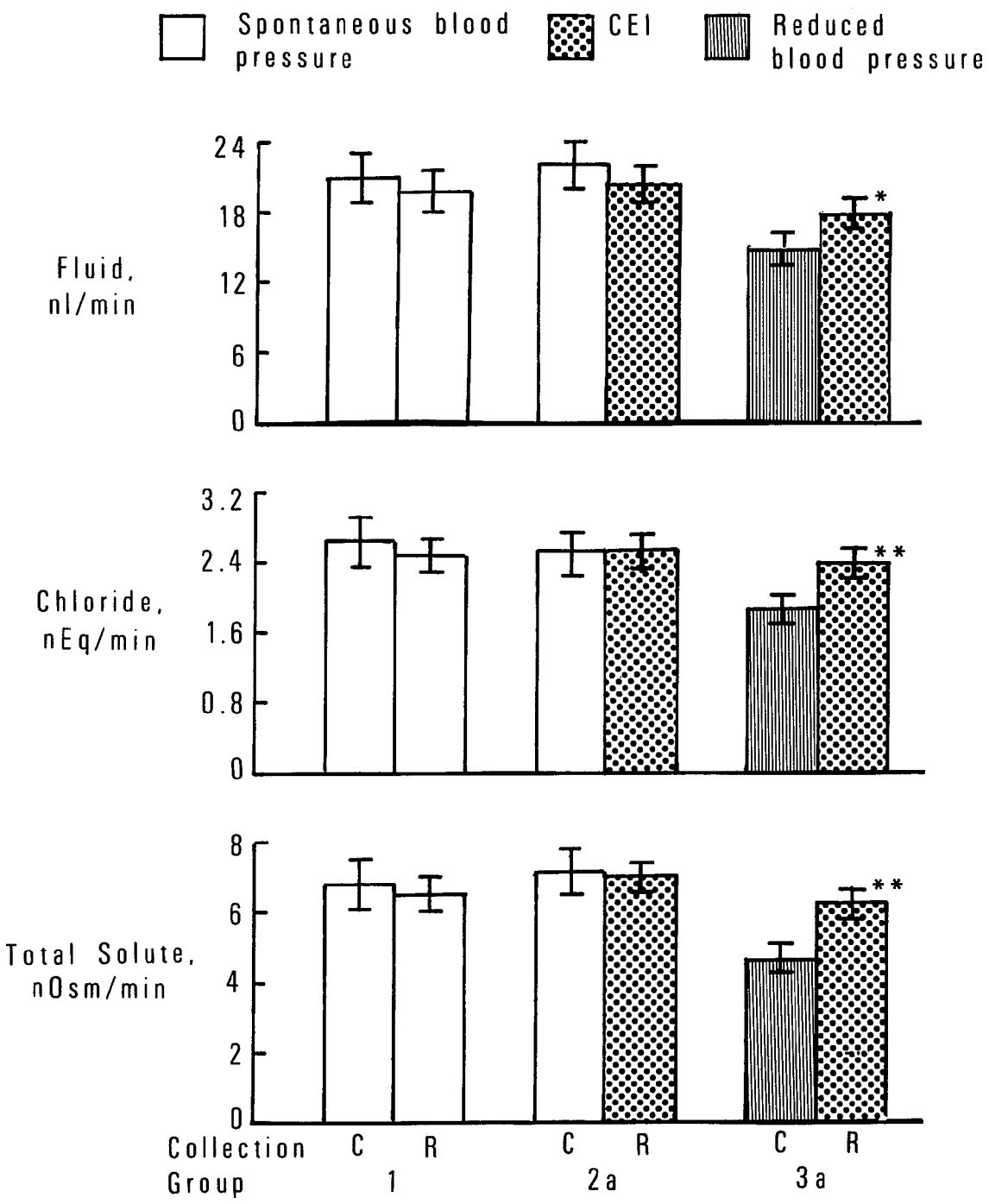
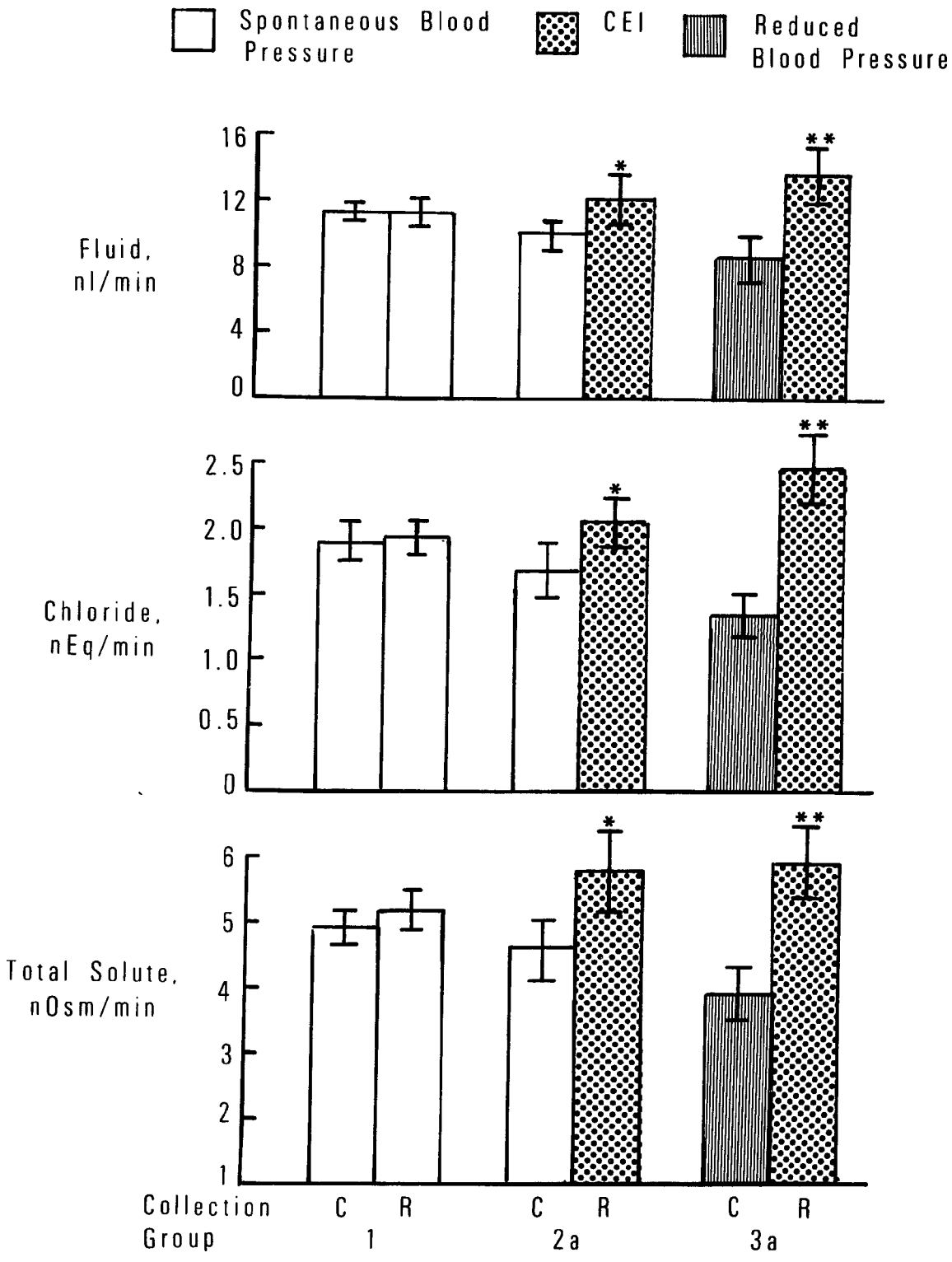

Spontaneous blood pressure
CEI
Reduced blood pressure
Fluid, nl/min
24
18
12
6
0
*
Chloride, nEq/min
3.2
2.4
1.6
0.8
0
**
Total Solute, nOsm/min
8
6
4
2
0
**
Collection
C
R
C
R
C
R
Group
1
2a
3a

Figure 14 Effects of CEI on absolute reabsorption of fluid, chloride and total solute at the nephron segment between the proximal tubule and the distal tubule collection sites. Statistical notations see Figure 10.


Spontaneous Blood Pressure
CEI
Reduced Blood Pressure
Fluid, nl/min
16
12
8
4
0
*
**
Chloride, nEq/min
2.5
2.0
1.5
1.0
0.5
0
*
**
Total Solute, nOsm/min
6
5
4
3
2
1
*
**
Collection
C
R
C
R
C
R
Group
1
2a
3a

shown in Fig. 16 and 17. Yet, this enhancement in absolute reabsorption was not sufficient to prevent decreases in fractional reabsorption at this nephron segment. As illustrated in Fig. 15, FR_{H_2O}, FR_{Cl} and FR_{osm} decreased during CEI infusion in both groups.

Tubular and peritubular capillary pressure measurements were obtained in separate groups of hypertensive rats. The arterial blood pressure and renal function responses to CEI were basically similar to those of rats used for tubular fluid collections as shown in Table 6. In the uncontrolled blood pressure group (subgroup 2b), CEI elicited an augmented GFR and increased fluid and electrolyte excretion despite the fall of blood pressure. In the reduced blood pressure group (subgroup 3b), the kidney GFR decreased during aortic clamping and subsequently increased during CEI infusion. Fluid and electrolyte excretion decreased during mechanically reduced blood pressure and then reversed to diuresis and natriuresis in response to CEI infusion.

Fig. 18 presents the pressure data obtained in the uncontrolled blood pressure group and in the group first subjected to aortic constriction. In the uncontrolled blood pressure group, the free flow proximal tubule pressure increased significantly from 13.6 ± 1.1 to 15.4 ± 0.8 mmHg and the distal tubular pressure increased from 6.8 ± 0.5 to 7.7 ± 0.3 mmHg. A slight decrease in peritubular capillary pressure from 12.1 ± 1.2 to 10.7 ± 0.7 mmHg was not statistically significant. In the group first subjected to aortic clamping, the free flow tubular pressure changed from 12.5 ± 0.6 to 11.4 ± 0.4 mmHg for the proximal tubule and 7.8 ± 0.6 to

Figure 15 Effects of CEI on fractional reabsorption of fluid, chloride and total solute at the nephron segement between the proximal tubule and the distal tubule collection sites. Abbreviations and statistical notations are identical to those shown in Figure 10.

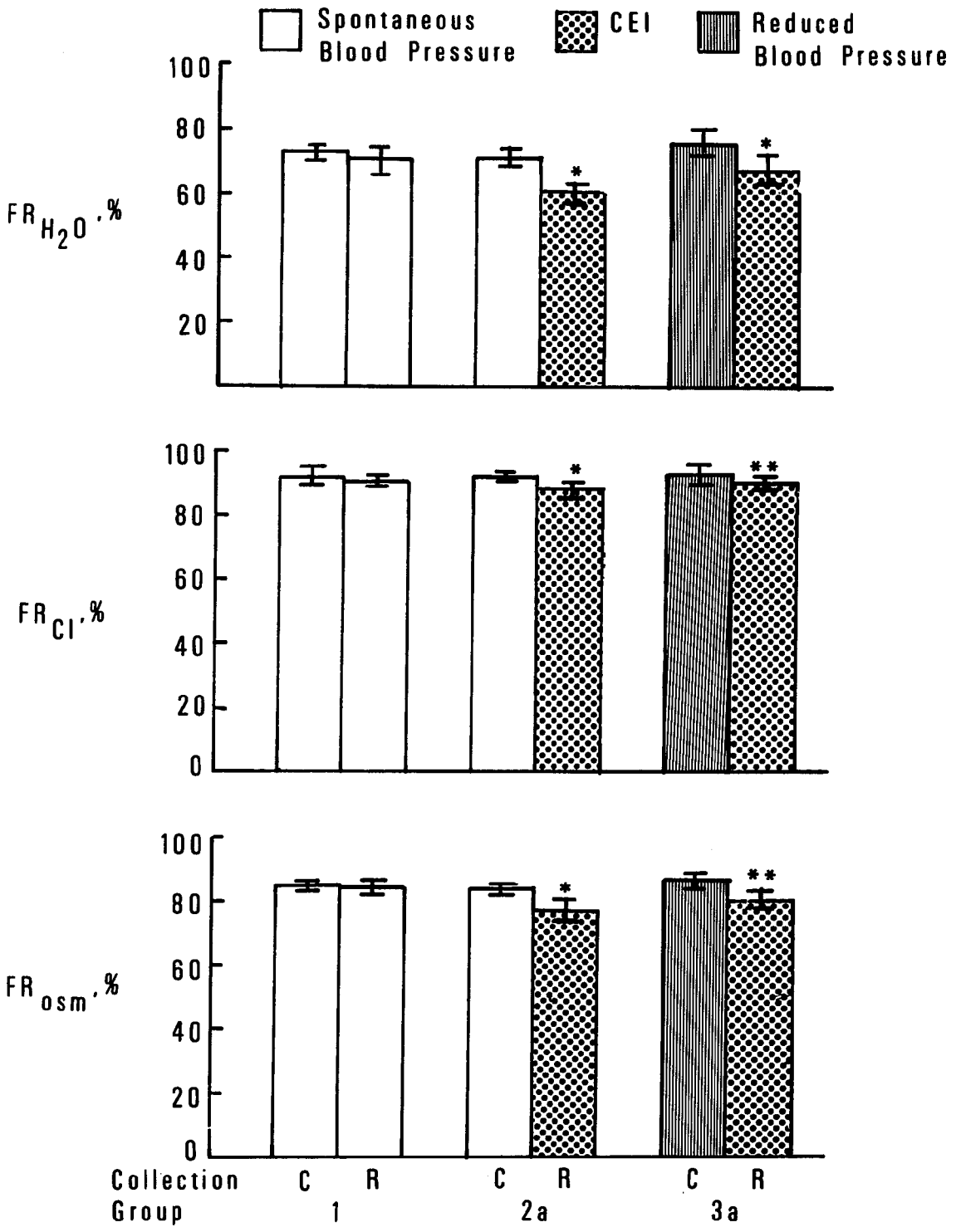

Spontaneous Blood Pressure
CEI
Reduced Blood Pressure
FR_{H_2O},%
FR_{Cl},%
FR_{osm},%
100
80
60
40
20
0
*
**
Collection Group
C R C R C R
1 2a 3a

Figure 16 The relationship between the late proximal tubular flow and the absolute reabsorption of fluid by the intermediate nephron segment between the proximal and distal tubular collection sites. γ = correlation coefficient.

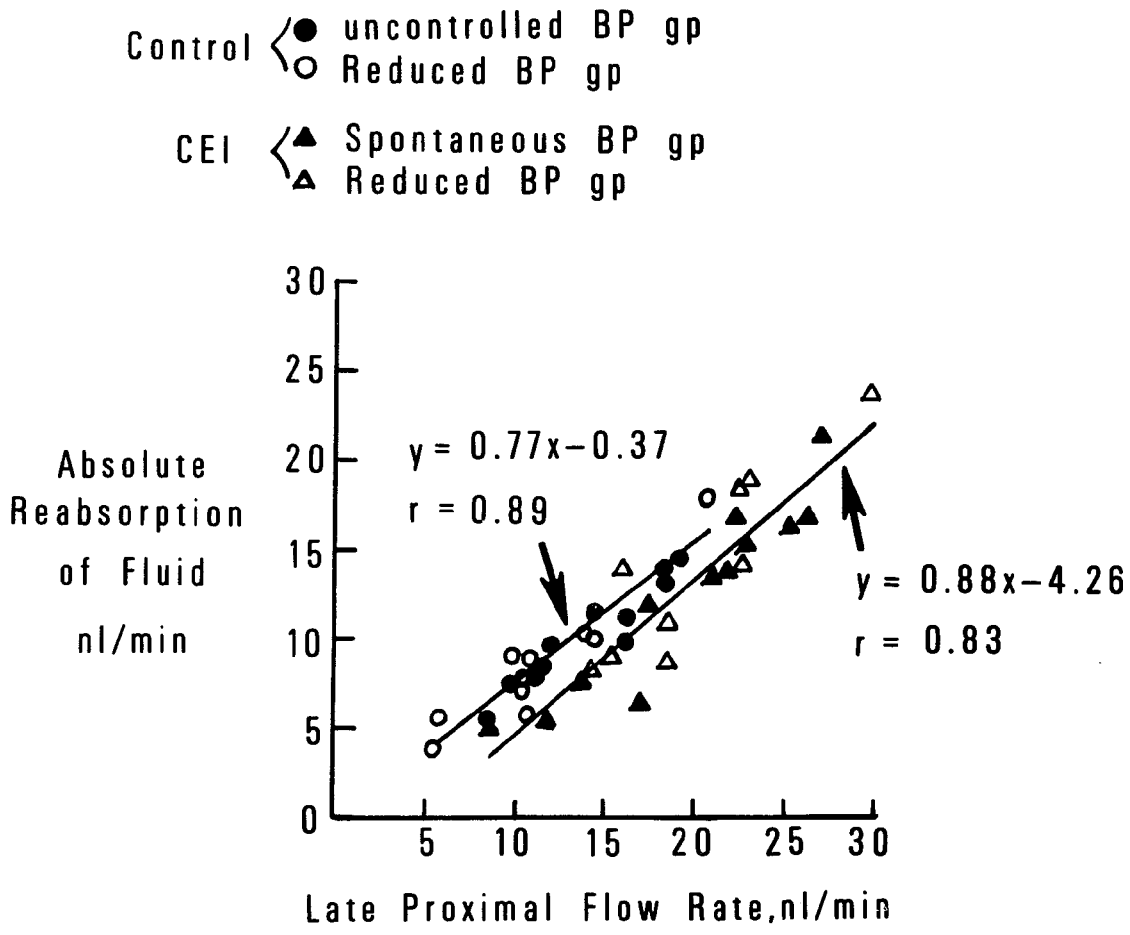

Control
uncontrolled BP gp
Reduced BP gp
CEI
Spontaneous BP gp
Reduced BP gp
Absolute Reabsorption of Fluid nl/min
30
25
20
15
10
5
0
y = 0.77x−0.37
r = 0.89
y = 0.88x−4.26
r = 0.83
5
10
15
20
25
30
Late Proximal Flow Rate,nl/min

Figure 17 The relationship between the total Cl^- remaining at the late proximal tubule and the absolute reabsorption of Cl^- by the intermediate nephron segment between the proximal and distal tubular collection sites. γ = correlation coefficient.

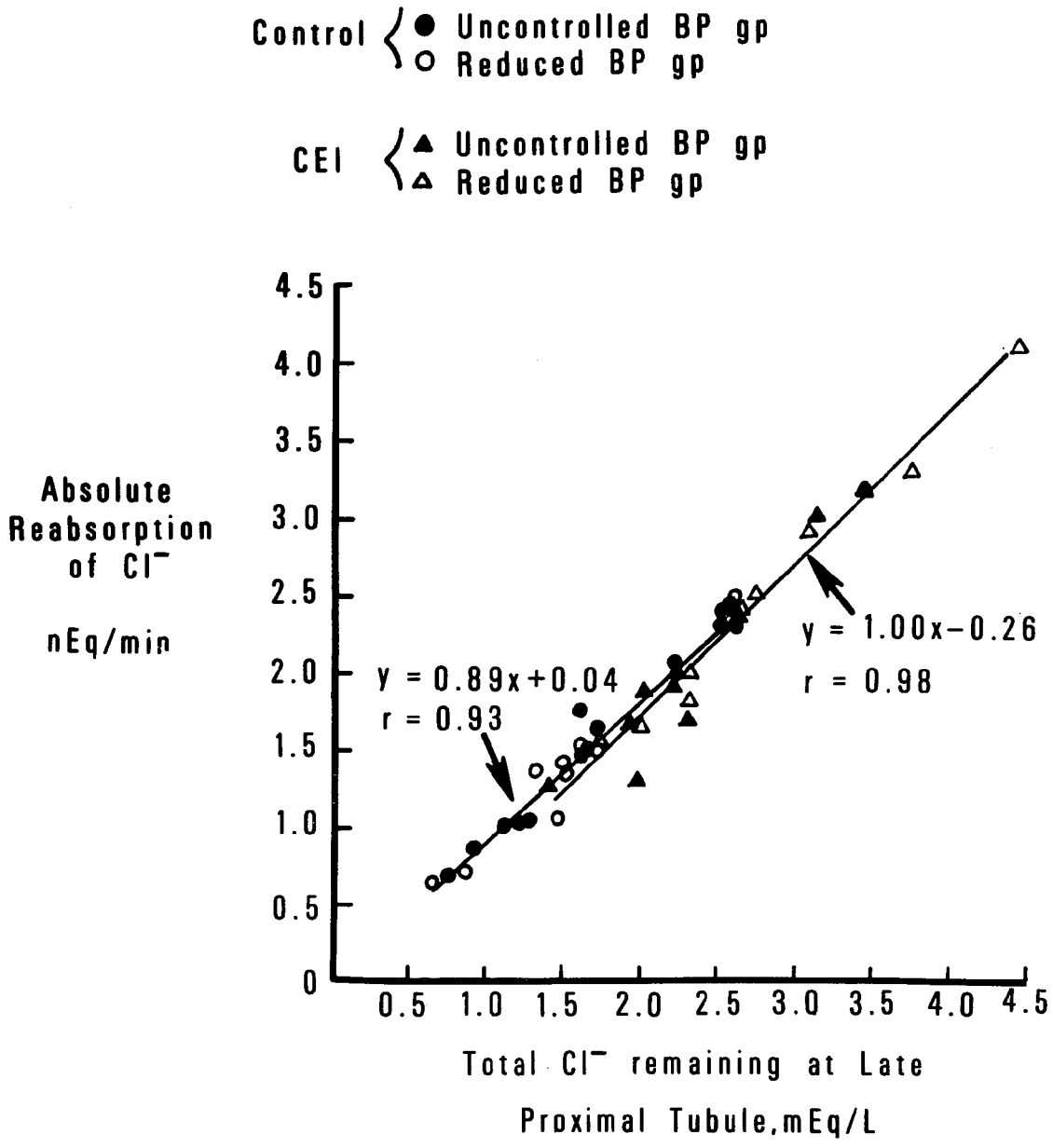
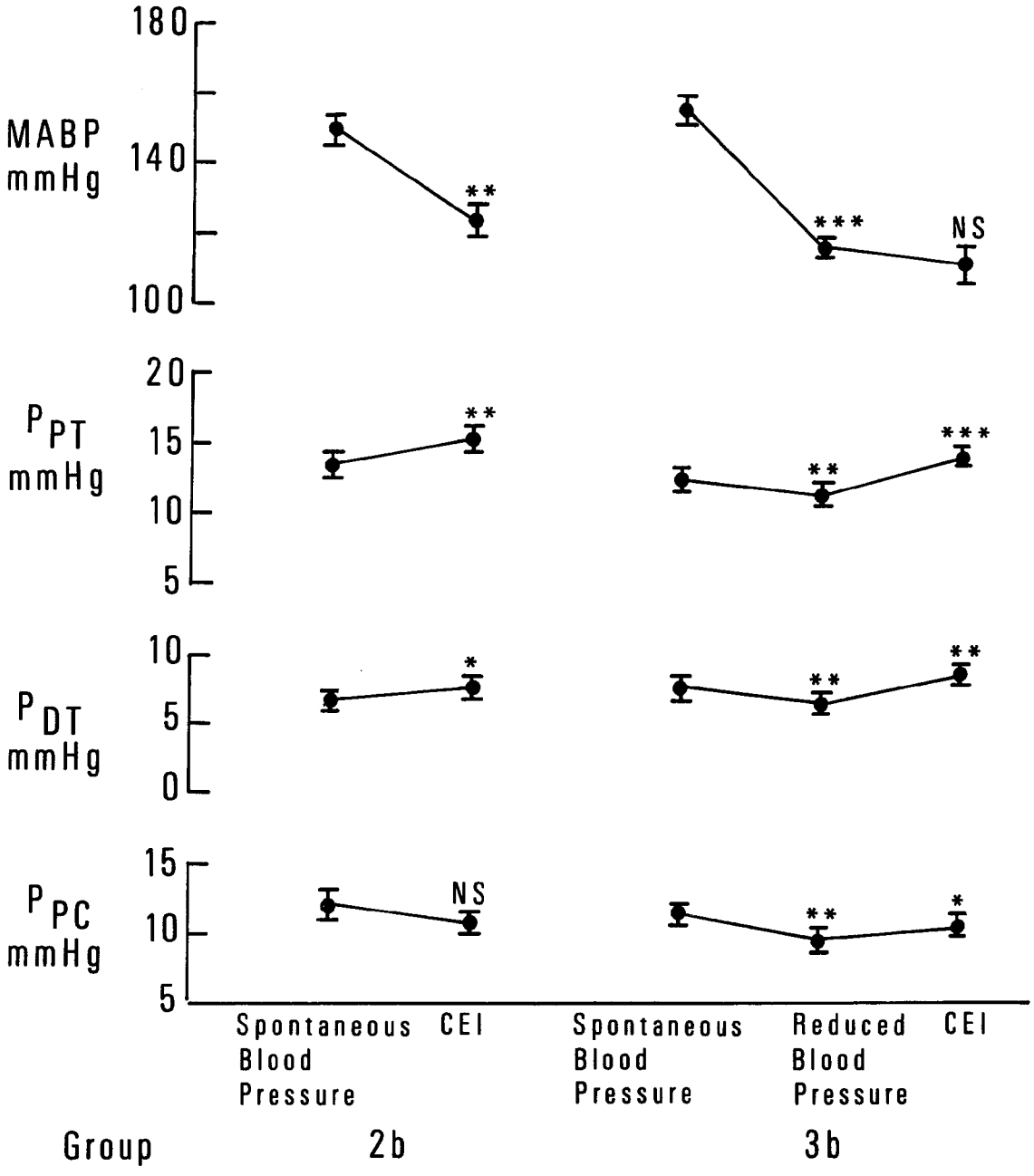

Control
Uncontrolled BP gp
Reduced BP gp
CEI
Uncontrolled BP gp
Reduced BP gp
Absolute Reabsorption of Cl⁻
nEq/min
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5
y = 0.89x+0.04
r = 0.93
y = 1.00x−0.26
r = 0.98
Total Cl⁻ remaining at Late Proximal Tubule, mEq/L

Table 6. The Arterial Blood Pressure and Renal Function Responses to CEI in Goldblatt Hypertensive Rats Used for Intratubular Hydrostatic Pressure Measurements

Group	Period	Mean Femoral AP mmHg	GFR ml/min	Urine Flow µl/min	Absolute Sodium Excretion mEq/min	Fractional Sodium Excretion %	Absolute Potassium Excretion µEq/min	Fractional Potassium Excretion %
2b (n=5)	Spontaneous Blood Pressure	150 ± 4	1.12 ±0.14	3.9 ±0.5	0.053 ±0.042	0.06 ±0.05	1.13 ±0.21	32.0 ±8.8
	CEI	124** ± 5	1.45** ±0.18	5.4* ±0.6	0.138* ±0.075	0.11* ±0.08	2.14** ±0.30	44.8* ±9.6
3b (n=6)	Spontaneous BP	157 ± 5	0.98 ±0.11	4.6 ±0.5	0.234 ±0.088	0.16 ±0.06	0.935 ±0.204	23.4 ±3.1
	Reduced BP	117*** ± 1	0.73* ±0.07	2.3** ±0.4	0.024* ±0.007	0.02* ±0.00	0.353* ±0.098	11.3** ±2.2
	CEI	112 ± 7	1.24** ±0.13	4.4* ±0.6	0.355* ±0.199	0.17* ±0.08	1.057* ±0.280	23.4* ±5.4

1. Body weight: Group 2b = 202 ± 11 g; group 3b = 200 ± 15 g.
2. Kidney weight: Group 2b = 0.977 ± 0.026 g; group 3b = 0.953 ± 0.011 g.
3. Values shown are Mean ± S.E.M. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ when compared to the preceding period.

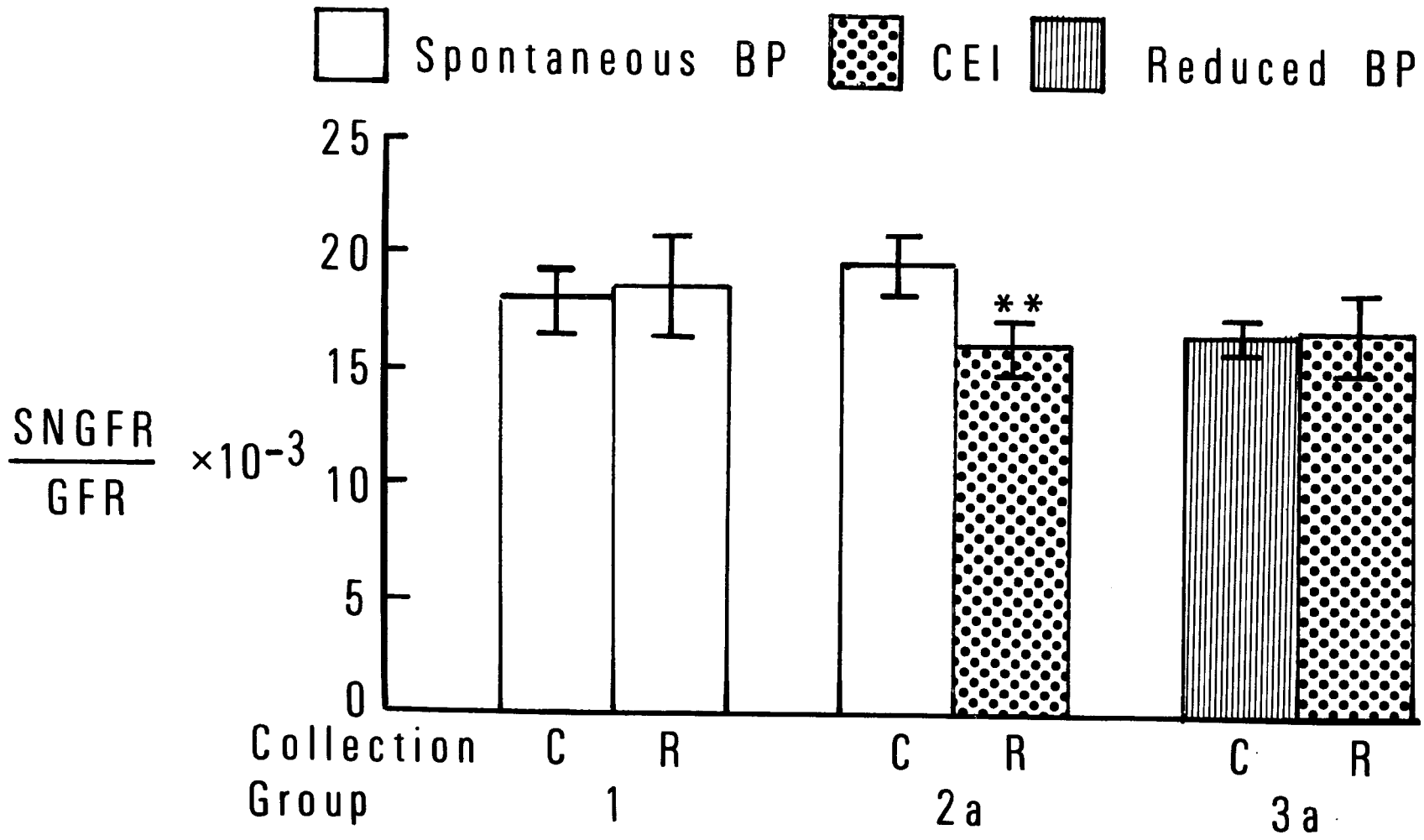
Figure 18 Responses of arterial blood pressure, proximal tubule and distal tubule hydrostatic pressures, and peritubular capillary pressure to converting enzyme inhibition and to aortic clamping. MABP = mean arterial blood pressure; P_{pt} = proximal tubule pressure; P_{dt} = distal tubule pressure; P_{pc} = peritubular capillary pressure; NS = no significance. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ as compared to the preceding phase. Rat number: group 2 b = 5; group 3 b =6.


180
140
100
MABP
mmHg
**
***
NS
20
15
10
5
P PT
mmHg
**
**
***
10
5
0
P DT
mmHg
*
**
**
15
10
5
P PC
mmHg
NS
**
*
Spontaneous Blood Pressure
CEI
Spontaneous Blood Pressure
Reduced Blood Pressure
CEI
Group
2b
3b

6.5 mmHg for the distal tubule during reduction in blood pressure from 157 ± 5 to 117 ± 1 mmHg. During the CEI period, the arterial pressure decreased slightly to 112 ± 7 mmHg but was not significantly different from the preceding level. The proximal tubule pressure rose to 14.2 ± 0.2 mmHg and the distal tubule pressure increased to 8.4 ± 0.4 mmHg. Peritubular capillary pressure decreased significantly from control level of 11.3 ± 0.5 to 9.6 ± 0.6 mmHg during aortic clamping and then rose to 10.5 ± 0.6 mmHg during CEI infusion.

CEI infusion resulted in a greater increase in kidney GFR than that in SNGFR. This disproportionate change in GFR may be associated with uneven distribution of filtration rate in response to CEI. In order to evaluate this possibility, the ratio of SNGFR to kidney GFR was calculated and illustrated in Fig. 19. There were no differences in this ratio in time control and in the reduced blood pressure groups. However, a significant decrease in the ratio occurred in uncontrolled blood pressure group, indicating a redistribution of GFR within the nonclipped kidney in response to the decrease in arterial pressure occurring during CEI infusion.

FIGURE 19 The ratio of superficial SNGFR to kidney GFR. BP = blood pressure; SNGFR = single nephron GFR. Statistical notation is identical to that shown in Figure 10.


Spontaneous BP
CEI
Reduced BP
SNGFR / GFR ×10-3
25
20
15
10
5
0
**
Collection
C
R
C
R
C
R
Group
1
2a
3a

DISCUSSION

Change in kidney function has been hypothesized to be involved in the pathogenesis of hypertension (89,110). However, their quantitative contribution is still unclear. In the 2-kidney model of Goldblatt hypertension, the renin-depleted, nonclipped kidney is perfused at a high blood pressure. The inability of the nonclipped kidney to respond to elevated blood pressure with a pressure diuresis and natriuresis and hence the failure to correct hypertension suggest that a functional derangement occurs in this kidney. In addition, angiotension II has been demonstrated to stimulate renal tubular reabsorption of sodium and water (15,43,74,116,118,134, 159). If the elevated circulating renin-angiotensin system has exerted its influence on kidney function, then blockade of this system would expected to disclose the underlying influence. With this approach and this intriguing hypertensive model, the contribution of the RAS to the development of hypertension and to the alteration in kidney function was assessed. Results of the present study show that there are angiotension II mediated alterations in renal hemodynamics and tubular reabsorption existing in the renin-depleted, nonclipped kidney. These changes in kidney function may lead to sodium and water retention which, in turn, may contribute to the pathogenesis of hypertension.

Arterial Pressure Response to CEI and Saralasin

The marked decreases in arterial blood pressure in response to CEI and saralasin infusion confirm the previous suggestions that activation of the renin-angiotensin system is partially responsible for the increase in blood pressure in this 2-kidney, one clip model of Goldblatt hypertension. It is recognized that studies involving interruption of the renin-angiotensin system with either CEI or angiotensin II analogues have inherent disadvantages due to the nonspecificity of CEI (52,82,226) or possible agonist effects of angiotensin analogues on vascular receptors (198,235). Since both of these agents exerted similar vasodepressor effects as shown in Figures 2 and 5, it would seem that the major portion of the blood pressure reductions occurred through a common mechanism involving blockade of the renin-angiotensin system. The high plasma renin activity and significant reduction in blood pressure observed in the present study suggest that these hypertensive rats remain highly angiotensin-dependent for periods of up to three to four weeks following renal artery constriction. There was a difference, however, in terms of the patterns of blood pressure recovery following cessation of CEI or saralasin infusion. Arterial blood pressure recovered to within 30% of control one hour after cessation of saralasin infusion. In contrast, the hypotensive effect of CEI persisted for up to two hours. This difference in blood pressure recovery following termination of blockade infusion is consistent with previous observations (40,72), indicating a relatively longer duration of action of SQ 20881 (72,241).

Bilateral Renal Hemodynamics and Excretory Responses

The present study demonstrates that renal hemodynamics and excretory function in the nonclipped kidneys increased markedly and to a greater extent than in the corresponding kidneys of normotensive rats in response to administration of either CEI or saralasin. The increases in estimated renal plasma flow, renal blood flow and GFR and the decreases in total renal vascular resistance of the nonclipped kidney were in accordance with those obtained in other studies (179,267,328,331). These renal vasodilatory responses during CEI and saralasin infusions provide further support to the suggestion that an angiotensin mediated increase in renal vascular resistance exists in the nonclipped kidney (179,267,328). It should be noted that vasodilation and enhanced GFR and urinary excretion occurred in spite of the profound decreases in arterial pressure. Thus the decreases in renal vascular resistance provide a more accurate reflection of the absolute magnitude of these effects. These responses to acute blockade of RAS support the hypothesis that renal hemodynamics and sodium excretion in the nonclipped kidney of hypertensive rats are substantially under the influence of the RAS and that at least some of the derangements in resistance, GFR and urinary fluid and electrolyte excretion which occur in the nonclipped kidney of hypertensive rats may be reversed by instituting RAS blockade (20,89).

An additional interesting finding in this study was related to the difference in the temporal recovery patterns of arterial blood pressure and renal hemodynamics after discontinuing the infusion of

saralasin. Arterial blood pressure returned from 121 ± 4 mmHg to 137 ± 4 mmHg within one hour; however, estimated renal plasma flow and renal blood flow as well as GFR of the nonclipped kidney remained elevated for one hour before beginning to return to control values. These different patterns of recovery could reflect difference characteristics of the inhibition of angiotensin receptors by saralasin between the renal and the peripheral vascular receptors. It has been reported that the renal vascular bed is more sensitive than the peripheral vasculature to exogenous angiotension II (11, 170). Furthermore, the saralasin inhibition of angiotensin II induced vasocontriction has been indicated to be greater in the kidney than in the hindlimb (41,296). The asynchronized dissipation of saralasin mediated responses observed in the present study is consistent with the suggestion that angiotensin receptors in the renal vasculature are different from those of other vascular beds (41). Moreover, the relatively delayed reversal of renal hemodynamic effects and the maintenance of elevated GFR after cessation of saralasin infusion allowed the influence of arterial pressure on fluid and electrolyte excretion to be increasingly manifested. As arterial pressure returned toward hypertensive levels, very substantial natriuretic effect became apparent.

As shown in Table 3, this 2-kidney Goldblatt hypertensive model is characterized by an elevated plasma renin activity, a high tissue renin in the clipped kidney and a low intrarenal renin activity in the nonclipped kideny. This result is consistent with previous studies (35,108,214,247). Although it has been reported

that actual intrarenal angiotensin II levels in the nonclipped kidney may not be depressed to the same extent as renin activity (193), administration of CEI has been shown to suppress both the circulating and the intrarenal angiotensin III levels (192, 204). One the other hand, CEI has been shown to retard bradykinin degradation (52,82,226) and to stimulate prostaglandin synthesis (70, 186,188). Thus, there was a concern that the CEI induced responses might mediated partly by bradykinin or by prostaglandin rather than exclusively by decreases in angiotensin II formation (178,290,302). Although this consideration still remains controversial as discussed in the literature review (112,130,178,183,196,290,322). At present, there are no specific blocking agents for RAS or kinins without secondary effect. Hence, no clear cut data exist to allow precise evaluation of these possibilities. The present study does not completely rule out the possibility of non-angiotensin mediated effects; however, blockade of RAS with saralasin produced similar vasodepressor and renal hemodynamic responses. In previous studies similar effects on blood pressure and renal function were observed when either CEI or angiotensin II receptor antagonists were used in normal, sodium restricted and hypertensive animals (9,179,196,267, 328,331). Inhibition of prostaglandin synthesis with indomethacin did not block the increase in renal blood flow resulting from captopril (322). Furthermore, there is no evidence that prostaglandins affect proximal tubule reabsorption (147). Therefore, it seems reasonable to suggest that the changes in renal hemodynamics and tubular reabsorptive function observed in this study were mediated mainly through by blockade of RAS.

It should be noted that even though one renal artery was clipped, the control GFR values prior to CEI infusion were similar in both kidneys (1.04 ml/min per g for the clipped kidney and 1.15 ml/min per g for the nonclipped kidney). These values are comparable to those reported by Girndt et al. (102) and Lowitz et al. (166) in which the clipped kidney was clamped with a smaller (0.2 mm) clip. In preliminary experiments, it was found that while it was possible to conduct control clearance measurements from kidneys clipped with a 0.2 mm clip, anuria often developed following initiation of CEI infusion. In order to obtain renal clearance measurements not only during control conditions but during the CEI period, a 0.25 mm clip was chosen for the present experiments. With this size clip, hypertension developed in rats with a level of renal function in the clipped kidney adequate to allow evaluation even after the marked decrease in arterial pressure during CEI infusion. In addition, previous reports indicated that the clipped kidney had higher (35,108), lower (29) or the same (266) levels of renal renin as compared to normal kidney. In the present study, the kidney renin level of the clipped kidneys of hypertensive rats did not differ significantly from that of the control rats. The failure to demonstrate any significant increase in renin content of the clipped kidney may be due to the size of the clip used for the present study. Perhaps the arterial pressure perfusing the clipped kidney was near normotensive level when the steady state hypertensive stages were reached (166).

Comparison of Saralasin Effects With CEI on Renal Excretion

The increases in urine flow and potassium excretion by the nonclipped kidney in response to saralasin were similar to those caused by CEI. However, the natriuretic response was delayed and persisted even after discontinuation of saralasin infusion. Inconsistent responses in sodium excretion to saralasin have been reported previously. In sodium restricted animals, saralasin administration produced either unaltered (91,197) or increased (114,143) urinary sodium excretion. In the 2-kidney model of hypertensive rats, Riegger et al. noted a tendency for decreased sodium excretion in hypertensive rats receiving saralasin compared to hypertensive rats receiving dextrose infusion, but no quantitative data were reported (253). De Franca Borges et al. (60) reported that saralasin had intrinsic agonistic activity which could stimulate renal tubular reabsorption of sodium in hypertensive patients.

In the present study, the sodium excretion from the nonclipped kidneys of hypertensive rats varied substantially. Four of ten rats responded to saralasin with significant natriuresis; three rats exhibited a reduced sodium excretion during the first two clearance periods and then increased excretion of sodium; and the remaining rats responded with antinatriuresis throughout the period of saralasin infusion but subsequently had an increased sodium output following termination of saralasin infusion. The dissociation between sodium excretion and renal vasodilation during saralasin administration may be attributed to several mechanisms. First, it is commonly accepted that sodium excretion is a function

of renal perfusion pressure (245,300). Saralasin induced rapid and precipitous decreases in blood pressure that might have attenuated or masked the appearance of natriuresis resulting from the angiotensin blockade directly. Second, a partial agonistic action of saralasin on renal tubular reabsorption of sodium might have been responsible for the delayed or variable sodium excretion responses. Finally, other humoral factors such as aldosterone as a result of failure of saralasin to block these receptors, or even possible agonistic effects on the adrenal gland, could also contribute to the observed response.

In contrast to the enhanced renal function seen in the non-clipped kidney, the clipped kidney exhibited slight reductions in renal excretory function during the blockade of RAS. These decreases in renal clearance and excretory function in the clipped kidney were associated with reductions in systemic blood pressure. As shown in Figures 8 and 9, when arterial blood pressure was reduced by mechanical aortic clamping to levels comparable to those induced by CEI infusion, decreases in GFR, urine flow and sodium excretion were parallel to those observed during CEI infusion in clipped kidneys. These parallel renal responses suggest that a profound fall of pressure perfusing the clipped kidney contributed to the depressed renal function of the clipped kidney with the clip in situ. Lowitz et al. (166) indicated that the blood pressure distal to the clip that actually delivered to the clipped kidney was 123 mmHg when the systemic blood pressure was 180 mmHg. This substantial difference in renal perfusion pressure is presumed to

exist between the clipped and the nonclipped kidneys. In response to CEI, the pressure perfusing the clipped kidney would decrease as much or perhaps even more than the systemic arterial pressure depending on the influence of the decreased resistance that took place in the clipped kidney. Thus it appears that reduced arterial blood pressure can adequately explain the alterations in the function of the clipped kidney during blockade of RAS, although this depressor effect could mask or override possible direct effect of CEI on the function of the clipped kidneys.

Tubular Reabsorptive Responses to CEI

As demonstrated in the micropuncture study, the tubular fraction reabsorption of the nonclipped kidney decreased in response to CEI infusion. The major reduction of tubular reabsorption was seen in the proximal tubule. Both absolute and fractional reabsorption of fluid, chloride and total solute decreased significantly despite a significant increase in filtered load and a decrease in arterial blood pressure. When the CEI-induced hypotensive influence was eliminated by mechanical clamping the aorta and tubular reabsorption was measured at a comparable arterial pressure, CEI administration also elicited significant decreases in both absolute and fractional reabsorption by the proximal tubule though a greater increased SNGFR was observed. The remaining segments of the nephron exhibited variable changes in tubular reabsorption. The flow rate and tubular load leaving the late proximal tubule increased as a result of decreased reabsorption from the earlier

nephron segment. Thus, an enhanced reabsorption by the nephron segments between the proximal and the distal tubule collection sites was observed. This load-dependent increase in tubular reabsorption of fluid, chloride and total solute did not influence by CEI as shown in Figures 16 and 17. Most of the increased tubular load was reabsorbed by this intermediate portion of the nephron segment, the decreased fractional reabsorption could have been due to the increased load and it is not clear if an impaired reabsorptive capability was present. The fractional reabsorption up to the early distal tubule was also reduced significantly. The significant fall of urine to plasma Inutest ratio suggests that the reabsorptive function by the rest of the nephron after distal tubular collection site was also altered.

As a means of assessing changes due to the direct effect of CEI on the kidney versus those resulting from the associated decrease in arterial pressure, comparisons were made between the values obtained at the uncontrolled hypertensive levels and those obtained following mechanical reduction of arterial pressure to normotensive levels. As shown in Tables 4 and 5 and in Figure 18, the kidney GFR, SNGFR and intratubular hydrostatic pressures of the nonclipped kidney were significantly lower at the reduced arterial pressure than at the spontaneous blood pressure even though these arterial pressure levels remained within the normal autoregulatory range. These results provide further support to the previous finding that autoregulatory efficiency of the superficial nephrons

and the whole kidney are substantially impaired in the nonclipped kidney of Goldblatt hypertensive rats (245,247,263).

The characteristic alterations in proximal tubule reabsorption seen in the present study do not support the observation made by previous investigators (166,287). Stumpe et al. (287) showed that proximal tubular reabsorption did not change as blood pressure increased in hypertensive rats. However, it must be noted that their conclusion was based on observations obtained from a heterogeneous group of rats including spontaneous hypertensive, Goldblatt hypertensive and normal rats. Lowitz et al. (166) also failed to see changes in proximal tubular reabsorption which was measured at spontaneous blood pressure in hypertensive rats. The reason for the inconsistency between the present study and their observations is unclear. It could be due to different experimental approaches. As demonstrated earlier (185,245,263,300), the nonclipped kidney has been adjusted to a higher blood pressure. Therefore, it appears that the elevated status of the RAS and high blood pressure may be important for the nonclipped kidney to function without appreciable differences from the normal kidney. In the present study, tubular reabsorption was evaluated at the same loci before and during supression of circulating and intrarenal angiotensin II. This approach makes it possible to unmask a dysfunction of tubular reabsorption. Also, it allows the assessment of the cause-effect relationship between the elevated RAS and tubular reabsorption.

It is recognized that in addition to the influence of changes in filtered load and of humoral agents, changes in the peritubular

capillary Starling forces could possibly alter tubular reabsorption (17,75,250,262). Decreases in tubular reabsorption could be due to decreases in filtered load, tubular flow and pressure, peritubular capillary oncotic pressure and increases in peritubular capillary hydrostatic pressure. In the present study, CEI infusion caused increased SNGFR, tubular flow and intratubular hydrostatic pressure and decreased peritubular capillary hydrostatic pressure. The increased SNGFR would be expected to increase absolute reabsorption due to the process of glomerulo-tubular balance. Furthermore, the reduction in arterial pressure and the associated decreases in peritubular capillary pressure might also be expected to lead to an increased reabsorption. Thus, these changes would not be expected to be indirectly responsible for the reduced absolute as well as fractional proximal reabsorption.

However, there is the possibility that reductions in peritubular capillary oncotic pressure contributed to the decreased reabsorption. The peritubular oncotic pressure was not determined during the micropuncture experiment, but the filtration fraction has been shown to be either unchanged (179,196) or slightly decreased (Fig. 4) in response to RAS blockade. The available evidence does not allow this investigator to determine to what extent the reduced tubular reabsorption resulted from changes in peritubular oncotic pressure. The alternative possibility is that angiotensin II was exerting a direct effect on the proximal tubule to stimulate reabsorption. As was discussed in the literature review, some clearance and microperfusion studies have demonstrated that

angiotensin II directly affects tubular reabsorption of sodium (43,116,118,134, 159). Also, chronic intrarenal infusion of angiotensin II may produce sodium retention and a sustained elevation in arterial pressure (162,325).

In normal rats, CEI administration did not alter tubular reabsorption by the proximal tubule or the loop of Henle though it decreased the reabsorption up to the early distal tubule (246). The increased SNGFR of normal rats in response to CEI (7%) was less than that of hypertensive rats observed in the present study (12% in uncontrolled blood pressure group and 42% in the reduced blood pressure group). This observation is consistent with the earlier clearance experiments in which the responses in renal blood flow, GFR and excretion to CEI were smaller in normal rats than those seen in hypertensive rats. Thus, it would appear that the changes in proximal tubular reabsorption occurring in normal rats were too small to detect.

In sodium depleted rats with elevated RAS, Steiner et al. (284) showed that saralasin reduced the absolute and fractional reabsorption of fluid by the proximal tubule despite an increased SNGFR. In spontaneous hypertensive rats, Arendshorst et al. (8) showed that fluid reabsorption by the whole superficial nephron did not differ from the control Wistar rats but a reduction of sodium and water excretion did occur after volume expansion with saline, when renal perfusion pressure was reduced to normal. In addition, acute elevation of arterial pressure by carotid occlusion in normal rats produced a decrease in proximal tubule reabsorption (69,145).

Thus it seems apparent that the elevated RAS, rather than high blood pressure per se, is responsible for the enhanced tubular reabsorptive function and the augmented reabsorption can be reversed by blockade of RAS.

The increases in superficial SNGFR following CEI were not proportional to increments of whole kidney GFR changes in the uncontrolled blood pressure group. This disproportionate change could be related to uneven distribution of regional blood flow within the kidney in response to CEI infusion. The significant decrease in SNGFR to kidney GFR ratio obtained in uncontrolled blood pressure group (Fig. 19) indicates an unequal distribution of filtration rate in response to CEI administration. In sodium restricted rats, Mimran et al. (196) demonstrated that blockade of RAS with SQ 20881 or saralasin preferentially increased glomerular blood flow to deep nephrons. The proportionately smaller increase in superficial SNGFR in hypertensive rats may be a consequence of the anatomical characteristics of the superficial and deep nephrons and their linked interlobular arteries. It has been suggested that there is a significant pressure drop along the interlobular artery which acts as a resistance vessel and accounts for half of the preglomerular resistance in normal rats (13,30). If the afferent arteriole of the superficial nephron dilates without a simultaneous proportional vasodilation occurring in the associated interlobular artery, the pressure drop along the interlobular artery would increase and result in reduced perfusion pressure which could compromise the increase in superficial SNGFR (13). Boknam et al.

(30) also suggested that the preglomerular arteries of superficial nephrons are more vasodilated as compared to deep nephrons. If there is also a similar type of gradient in the nonclipped kidney of hypertensive rats, the CEI-induced vasodilation might be expected to be relatively greater in the deep nephrons than in the superficial nephrons.

Collectively, blockade of the RAS in 2-kidney, 1 clip Goldblatt hypertensive rats significantly decreased arterial blood pressure. Meanwhile, a blood pressure-associated reduction in renal function was observed in the renin-rich, clipped kidney. In contrast, the renin-depleted, nonclipped kidney responded to the RAS blockade with a renal vasodilation and increases in fluid and electrolyte excretions. This enhanced excretory function is attributed to decrease in tubular reabsorption, mainly in the proximal tubule, and increase in GFR during blockade of the RAS. These data suggest that the circulating angiotensin II substantially influences the renal function of the nonclipped kidney, leading to an increased renal vascular resistance and enhanced tubular reabsorption. The altered renal function may be associated with the failure of this kidney to exert an antihypertensive effect through a pressure-mediated natriuresis during the development of hypertension in this model.

SUMMARY

The present study delineated the contribution of the renin-angiotensin system to the alteration of renal function occurring in the 2-kidney, 1 clip Goldblatt hypertensive rats. Blockade of this system was achieved by using angiotensin I converting enzyme inhibitor (CEI) or angiotensin II receptor antagonist (saralasin). Renal hemodynamics and excretory function were evaluated in whole kidney clearance experiments during blockade infusion. Tubular reabsorptive function was directly assessed by in vivo recollection micropuncture technique. Results of these experiments are summarized as follows:

1. Constriction of one renal artery of rats with a 0.25 mm silver clip without contralateral nephrectomy produced Goldblatt hypertension with a mean arterial blood pressure of 159 ± 4 mmHg 3 to 4 weeks postclipping. Administration of converting enzyme inhibitor (SQ20881) or saralasin significantly reduced arterial blood pressure of these hypertensive rats.
2. The plasma renin activity of the hypertensive rats was significantly higher than that of normotensive rats. The renal renin activity of the nonclipped was considerably depleted as compared to that of the clipped kidney or the corresponding kidneys of normotensive rats.

3. In the renin-depleted, nonclipped kidney, CEI infusion produced a significant reduction in total vascular resistance, increases in renal blood flow, GFR, urine flow and absolute and fractional excretions of sodium and potassium. The filtration fraction decreased slightly. The renal vasodilation and enhanced excretory function occurred in spite of a marked decrease in arterial blood pressure. Administration of saralasin caused similar renal hemodynamic and excretory function responses though a delayed natriuresis was observed.
4. Quantitation of the segmental nephron reabsorptive function by micropuncture experiments during CEI infusion showed that there were significant decreases in absolute and fractional reabsorption of fluid, chloride and total solute by the proximal tubule, while the tubular flow and SNGFR were significantly increased. The absolute reabsorption along the nephron segment between the proximal tubule and the distal tubule sampling sites was enhanced. However, the fractional reabsorption was still depressed. The fractional reabsorption, but not the absolute reabsorption, up to the distal tubular collection site also was reduced.
5. When the CEI-induced hypotensive influence was eliminated by aortic clamping so that tubular reabsorption was assessed at a comparable arterial pressure, the reduction

in proximal tubule reabsorption in response to CEI infusion was even greater.

6. The intratubular hydrostatic pressures in the proximal tubule and in the distal tubule increased significantly in response to CEI infusion. The peritubular capillary hydrostatic pressure decreased slightly.
7. In the clipped kidney, blockade of RAS induced slight decreases in renal plasma flow, renal blood flow, GFR, urine flow and excretion of sodium and potassium.
8. When arterial blood pressure was reduced by aortic clamping in the absence of CEI, a parallel reduction in GFR and excretory function were obtained in both kidneys of hypertensive rats.

From these results, it can be concluded that there are angiotensin-mediated alterations in the renin-depleted, nonclipped kidney of 2-kidney model of Goldblatt hypertensive rats. These derangements include increased renal vascular resistance and enhanced tubular reabsorption of sodium and water occurring mainly in the proximal tubule. These changes in renal hemodynamics and reabsorptive function may lead to retention of sodium and fluid which, in turn, may contribute to the pathogenesis of hypertension. Blockade of RAS reverses the altered renal function and corrects blood pressure.

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