KIDNEY IN ESSENTIAL HYPERTENTION

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PREFACE

The kidney, similar to the heart, plays a three-fold role in essential hypertension. First, it participates in the pathogenesis of arterial hypertension. Second, it suffers as a target organ of long-standing hypertension, and third, it experiences the effects of antihypertensive therapy. Perhaps most contested at the present time is the involvement of the kidney in the pathogenesis of essential hypertension. More than a century ago, William Osler put forward three basic hypotheses about the "genuine contracted kidney."[1]

1. "The hypertrophy can be regarded as an effect to overcome a sort of stop-cock action of the vessels when under the influence of an irritating ingredient in the blood greatly contracted and increased the peripheral resistance."

Clearly this hypothesis of an "irritating ingredient" is perhaps the most convincing nowadays, and numerous attempts have been made to identify a specific vasoconstrictive agent in the blood in essential hypertension.

2. "The obliteration of a large number of capillary territories in the kidney materially raised the arterial pressure. An additional factor of diminished excretion of water also heightened the pressure within the blood vessel."

Today we know that fluid volume overload in the presence of reduced renal mass seems to be the most likely mechanism accounting for renal parenchymal hypertension and, as shown by Guyton's group, for certain forms of experimental hypertension.

3. "When part of both kidneys have undergone atrophy the blood flow to the parts that remain must <u>caeteris paribus</u> be as great as it would have been to the whole of the organs if they had been intact. But in order that such a quantity of blood should pass through the restricted capillary area now open, an excessive pressure must obviously be necessary."

Despite the impressive amount of data that have been collected over the past decades, the mechanisms by which the kidneys participate in the pathogenesis of essential hypertension still remain speculative as evidenced by the contributions in the the first section of this book. In contrast, our knowledge of the kidney's response to elevated arterial pressure has become very sophisticated as evidenced in Part II. Finally, Part III elucidates the effects of antihypertensive drugs on renal blood flow, glomerular filtration rate, water, and electrolyte excretion as well as on endocrine function of the kidney. Becoming increasingly more important is our awareness that although antihypertensive therapy lowers the blood pressure and therefore often lowers the patient's cardiovascular risk, the concomitant adverse effects upon the kidneys may potentially annihilate these beneficial effects.

This monograph, written by an outstanding faculty, is a comprehensive overview of the present knowledge of the kidney's role in essential hypertension. The contents should be of primary interest to fellow nephrologists and cardiologists as well as those of us involved with the study of hypertensive disorders.

I am indebted to several people for their invaluable contributions to this project. The present monograph would not have been possible were it not for the expertise of Jeffrey K. Smith, senior editor at Martinus Nijhoff. Also my thanks to the Medical Editorial Department, specifically Carole Morrison and Marion R. Stafford for their invaluable help in preparing the manuscripts. I would like to express my gratitude to Paul Rossano, M.D. of the Robert A. Becker Agency for his invaluable administrative assistance. We gratefully acknowledge the financial support from Merck, Sharp, and Dohme for this project.

Franz H. Messerli

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1. THE RELATION OF A CIRCULATING SODIUM TRANSPORT INHIBITOR TO ESSENTIAL HYPERTENSION

H. E. de Wardener and G. A. MacGregor

ABSTRACT

It is postulated that the increase in peripheral resistance in essential hypertension is largely due to the observed rise in the circulating level of a sodium transport inhibitor. Evidence is presented to suggest a link between a genetic abnormality in the kidney's capacity to excrete sodium, the excessive secretion of a sodium-transport inhibitor, salt intake, the rise in peripheral resistance, and ultimately the development of essential hypertension.

When the volume of body fluids is expanded, the plasma acquires natriuretic properties (1), and its capacity to inhibit sodium transport increases (2). It is not known whether these two phenomena are due to a change in the concentration of the same substance. Some workers (3, 4) claim that one substance is responsible, that it is of small molecular weight (approximately 1000 daltons), that it is present in plasma and urine, that it inhibits Na^+-K^+-ATPase, cross-reacts against digoxin antibodies, and displaces tritiated ouabain from the surface of red cells. Others, including ourselves, would agree with the first group that there is a substance of small molecular weight present in plasma and urine which inhibits Na^+-K^+-ATPase (5), but we do not find that it cross-reacts with digoxin antibodies or displaces tritiated ouabain from the surface of red cells (unpublished observation). A third group has obtained a larger substance (probably greater than 5000 daltons) from the left auricle which is natriuretic but does not inhibit Na^+-K^+-ATPase (6, 7, 8). It is not yet known whether this substance is present in the plasma

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or the urine. This paper presents the relation to essential hypertension of the substance present in the plasma and urine which inhibits Na^+-K^+-ATPase but does not otherwise resemble digoxin.

EVIDENCE FOR THE PRESENCE OF A CIRCULATING Na^+-K^+-ATPase INHIBITOR IN NORMAL MAN

The techniques we are using to measure the presence of the Na^+-K^+-ATPase inhibitor are cytochemical, that is, they quantitatively measure enzyme activity within intact cells. Cytochemical assays have great sensitivity. For instance, we use plasma dilutions of 1 in 500 to 1 in 10,000, but perhaps even more importantly, they have a measure of specificity which is totally lacking in the usual biochemical methods which measure Na^+-K^+-ATPase activity. The first technique we used was one which quantitatively measures Na^+-K^+-ATPase activity in guinea pig kidney (9). With this method we showed that plasma of normal man on a high sodium intake inhibits Na^+-K^+-ATPase at 6 min about 25 times more than plasma from the same subjects on a low sodium intake (10) (Figure 1).

The cytochemical technique employed to measure Na^+-K^+-ATPase activity directly is new, capricious, and still needs developing, whereas the cytochemical technique used to measure G6PD activity has been in use for several years, is easier to use, and is a technique with which we are familiar. It is fortunate, therefore, that inhibition of Na^+-K^+-ATPase in an intact cell is associated with a rise in glucose-6-phosphate dehydrogenase activity (11). Fenton et al (5) have confirmed on alternate sections of a segment of guinea pig kidney that ouabain simultaneously inhibits Na^+-K^+-ATPase activity and stimulates G6PD activity in vitro. And they then demonstrated that plasma and purified urinary extract also do this. Both inhibit Na^+-K^+-ATPase maximally at 6 min, and stimulate G6PD maximally at 2 min. It was also found that the rise in G6PD activity induced by a wide range of concentrations of both plasma and the urinary extract were parallel. The identity of the time course of the changes in activity and of the dose response curves of the plasma and

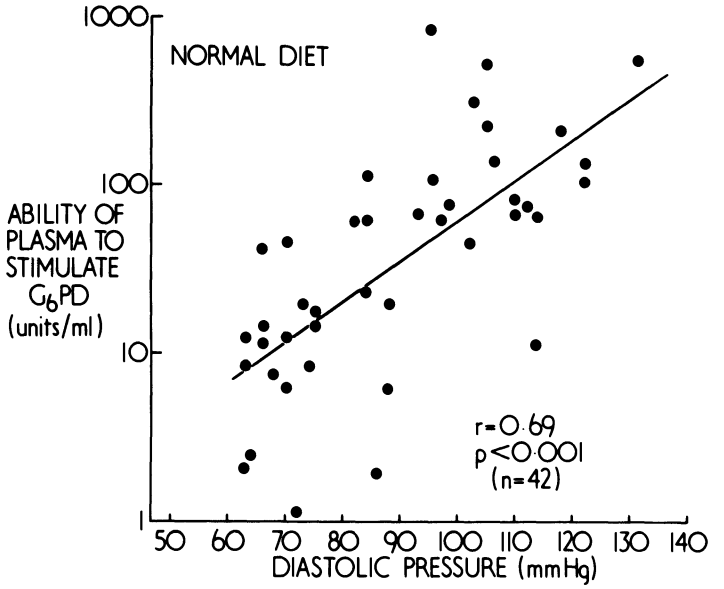

Figure 1. Ability of plasma to stimulate guinea pig renal glucose-6-phosphate dehydrogenase (G6PD) activity in vitro plotted against diastolic pressure in 42 individuals taking their normal diet. (Reproduced from the British Medical Journal (20) with kind permission.)

the urinary extract suggest that the substance which inhibits Na^+-K^+-ATPase activity and increases G6PD activity in the plasma and the urine are similar. Fenton et al (5) therefore attempted and were then successful, in developing an assay to measure the capacity of biological fluids to stimulate G6PD activity at 2 min in intact cells in vitro as a marker of their ability to inhibit Na^+-K^+-ATPase activity. The relative specificity of the assay was demonstrated by finding that of the substances in Table I tested at physiological and pharmacological concentrations, only ouabain showed any cross-reactivity. And no cross-reactivity was obtained with dilutions of acetone extracts of rat cerebral cortex, pituitary, adrenal, heart, lung, liver, kidney, muscle, bone, stomach, small intestine, large intestine, pancreas and spleen. An acetone extract of rat hypothalamus, however, showed intense activity (12). Using this technique

Table 1. Substances known to act on the nephron tested at physiological and pharmacological concentrations for their effect on G6PD activity (5).

Adrenaline	60 & 600 ng/l
Aldosterone	3 & 30 µg/l
Angiotensin II	10, 100 & 1000 ng/l
Arginine-vasopressin	1, 10 & 100 ng/l
Calcitonin	10, 100 & 1000 ng/l
1,25-dihydroxycholecalciferol	10, 100, 1000 & 10,000 ng/l
Dopamine	5, 50 & 500 ng/l
Luteinizing hormone releasing hormone	1 & 100 ng/l
3-methyoxy-4-hydroxyphenyl ethylamine	60 & 600 ng/l
Noradrenaline	0.3 & 3 µg/l
Oleic acid	0.315 & 3.15 mmol/l
Parathyroid hormone	1, 10, 100 ng/l
Prolactin	100 & 1000 mu./l
Sodium orthovanadate	20 µmol/l
Thyrotrophin releasing hormone	1 & 100 ng/l
3,3'5-tri-iodo-L-thyronine	2 & 20 nmol/l
Ouabain octahydrate	20 & 200 µmol/l

it was found that plasma from sodium loaded subjects stimulated G6PD activity at 2 min about 20 times more than plasma from the same subjects on a low sodium diet (5).

Nature and possible site of production

We have used the G6PD assay procedure in the purification of the material we obtain from urine and have found that, when highly purified, the fraction which stimulates G6PD activity at 2 min (and inhibits Na^+-K^+-ATPase activity at 6 min) does not cross-react with digoxin antibody or displace tritiated ouabain from the surface of red cells (unpublished observation). The active material is very polar, and in impure extracts it is relatively resistant to acid hydrolysis and proteolytic enzymes (13). It is possible that the substance we are assaying comes from the hypothalamus, for we have found that the hypothalamus

is the only site in the rat which appears to contain any substantial quantity of G6PD stimulating substance (12). The G6PD stimulating activity from the hypothalamus is about 10,000 to 100,000 times greater than from 1 ml of plasma. The G6PD stimulating activity of hypothalamic extracts from rats which have been on a high sodium intake for 4 weeks is approximately 150 times more active than those obtained from rats which have been on low sodium diets. The G6PD stimulating activity of the corresponding plasma is six times more active (12).

Possible Afferent System

One of the afferent limbs which monitors blood volume and thus may control the secretion of natriuretic hormone is the intrathoracic blood volume, particularly the left atrial pressure. The overriding importance of the intrathoracic blood volume, rather than the total blood volume, in causing a rise in urinary sodium excretion has been demonstrated in man by whole-body immersion experiments. This procedure increases the intrathoracic blood volume and causes a sustained rise in urinary sodium excretion that continues despite a gradual fall in total blood volume. Extracts of urine excreted during the natriuresis caused by water immersion are significantly more natriuretic than extracts of control urine.

Blaustein's Hypothesis

Our work on hypertension was stimulated by Blaustein's hypothesis (14) which argued that a circulating Na^+-K^+-ATPase inhibitor could, theoretically, cause hypertension. He suggested that as there was no evidence of any alteration in vascular smooth muscle contractility in hypertension, it was likely that the increased tone was due to a rise in the concentration of intracellular free calcium, and that such a rise might be the final common path of most if not all forms of hypertension. He pointed out that the intracellular free calcium concentration is linked to the entry of sodium into the cell down its electrochemical gradient and that the energy thereby released is harnessed to move calcium out of the cell against its electro-

chemical gradient. Therefore, a rise in intracellular free sodium which diminishes the electrochemical gradient for sodium and reduces the entry of sodium into the cell also reduces the outward movement of calcium out of the cell. Thus any phenomenon which increases the intracellular sodium concentration of smooth muscle will increase its tone. According to existing knowledge, it appears that a change of intracellular sodium of only 5% would increase the intracellular free calcium concentration in smooth muscle by about 15% and cause a 50% increase in tone! Ouabain which inhibits Na^+-K^+-ATPase and raises intracellular sodium concentration increases the tone of vascular smooth muscle. Blaustein proposed if the sodium pumps of smooth muscle were inhibited by a mammalian endogenous sodium transport inhibitor, or if this same substance enhanced passive sodium entry into the cell, it might influence arterial pressure and venous tone. And if such a substance were present in excess, it might cause hypertension. He also noted that such a hypothesis would explain the hypotensive effect of a natriuretic drug in hypertension. As the body stores of sodium are depleted, the concentration of the sodium transport inhibitor would fall. This in turn would reduce the effect of the substance on smooth muscle so that the intracellular sodium and calcium concentration would fall, as would smooth muscle tone and arterial pressure. This hypothesis is supported by the findings of Haddy, Pamnani and Clough (15) that in experimental hypertension in rats the rubidium uptake, which is probably a function of Na^+-K^+-ATPase activity, in the tail artery is decreased.

Evidence for a circulating Na^+-K^+-ATPase inhibitor in essential hypertension

We have worked on essential hypertension. Our first experiments were to study the mechanisms responsible for the documented decrease in the ouabain sensitive sodium efflux rate constant of whole fractions of leucocytes from hypertensive patients (16). In order to find out if the fall might be due to a circulating substance, leucocytes from normotensive subjects were incubated in the serum of hypertensive patients (17). It was found that

the leucocytes developed an impairment of sodium transport similar to that found in the hypertensive patients' own white cells, in that the ouabain-sensitive component of the sodium-efflux rate constant was reduced. The efflux rate constant of normotensive white cells incubated in the serum of another normal subject did not change. The results suggest that the serum of patients with essential hypertension contains a raised concentration of a substance which inhibits Na^+-K^+-ATPase. The intracellular sodium concentration of lymphocytes obtained from normotensive subjects also rises after incubation in the plasma of hypertensive patients (18). Edmondson and MacGregor (19) demonstrated that the sodium efflux rate constant of leucocytes from hypertensive patients whose plasma renin activity was low is significantly lower than the rate constant of leucocytes from hypertensive patients whose plasma renin activity was normal.

We then measured the plasma's capacity to stimulate G6PD as a marker of its ability to inhibit Na^+-K^+-ATPase activity in 19 hypertensive patients and 23 normotensive control subjects (20). The ability of the plasma from the hypertensive patients to stimulate G6PD was much higher than the plasma of the control subject ($p < 0.001$). When the two groups were combined, there was a significant correlation between the systolic blood pressure, mean blood pressure, and diastolic blood pressure and the ability of plasma to stimulate G6PD (Figure 1). In addition, the plasma's ability to stimulate G6PD in the 7 patients whose plasma renin activity was low was significantly higher than in the hypertensive patients with normal plasma renin activity ($p < 0.001$). And in the hypertensive patients, there was a significant inverse correlation between the ability of the plasma to stimulate G6PD and plasma renin activity. There was no such correlation in the normotensive subjects. Following the report of an endogenous digoxin-like material in the plasma of volume expanded dogs (4) and hypertensive monkeys (21), we have tested the plasma of hypertensive patients and control subjects for digoxin-like immunoreactivity. We found minimal digoxin-like immunoreactivity in the plasma of both groups but could not detect any difference between the two groups (unpublished observations).

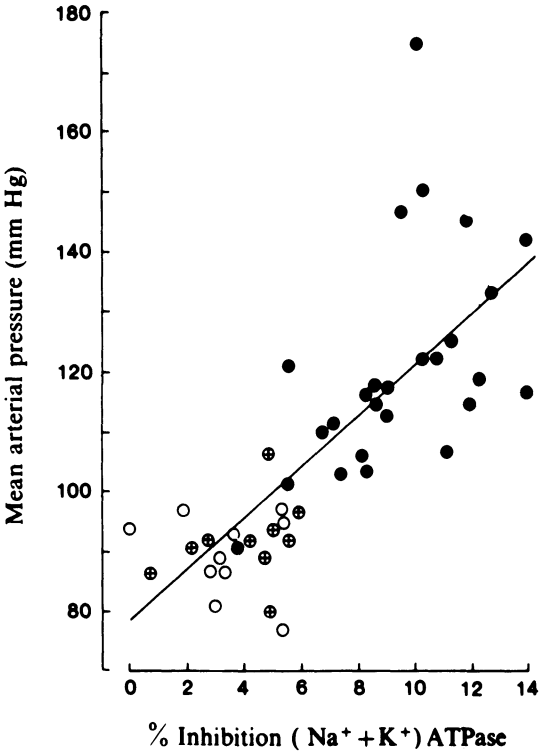

Figure 2. The ability of plasma to inhibit (Na^+ + K^+) ATPase activity in 46 individuals plotted against mean arterial pressure. (Reproduced from Nature (22) with kind permission.)

More recently Hamlyn et al (22) have measured the plasma's capacity to inhibit Na^+-K^+-ATPase using a preparation of dog Na^+-K^+-ATPase. The technique used involves the regeneration of enzymatically hydrolysed ATP coupled to the oxydation of NADH. The action of the inhibitor on Na^+-K^+-ATPase activity can thus be monitored continuously by recording the absorbance of NADH. Plasma is boiled, spun and the supernate diluted 1 in 2 in an "assay cocktail" to neutralize the effect of substances known to effect Na^+-K^+-ATPase activity (K^+, Ca^{++}, etc.). The plasma from 20 normotensive individuals and 26 patients with essential hypertension was assayed for its effect on Na^+-K^+-ATPase activity. A significant correlation between mean arterial pressure and the plasma's capacity to inhibit Na^+-K^+-ATPase was found ($p < 0.0005$) (Figure 2). Hamlyn, et al., (22) were unable

to demonstrate a significant elevation of digoxin-like immunoreactivity in plasma samples that inhibited Na^+-K^+-ATPase, and there was no correlation between the two assays.

Evidence for a circulating vasoactive substance

Michelakis et al (23) injected 15-20 µl of plasma from hypertensive patients and from normotensive subjects into bilaterally nephrectomised rats under the influence of pentolinium. Plasma from hypertensive patients, particularly those with low plasma renin activity, increased the vascular reactivity of the rats to noradrenaline and angiotensin, whereas plasma from normotensive subjects did not have these effects. In the isolated rabbit femoral artery perfused with plasma by means of a constant flow pump, the perfusion pressure rose more when noradrenaline was added to plasma from hypertensive patients than when it was added to plasma from normotensive subjects (24).

In rats there are two forms of inherited hypertension, the Dahl salt-sensitive and salt-resistant form in which the rise in arterial pressure is dependent on a large sodium intake, and the spontaneous form, in which the rise in arterial pressure occurs on a normal sodium diet. These inherited forms of hypertension in the rat have many points in common with essential hypertension in man. It is interesting, therefore, that the blood of salt-sensitive hypertensive rats causes a significant rise in the vascular resistance of cross-perfused hindquarters of normotensive salt-resistant rats (25). Greenberg et al (26) have made the remarkable observation that the portal vein of a normotensive strain rat paraboised to a spontaneously hypertensive rat acquires the properties of the portal vein of the spontaneously hypertensive rat, in that it becomes less distensible, develops medial hypertrophy and the vein's contractility when challenged with noradrenaline is greater. It is not known whether the vasoactive substance causing these vascular changes is the same substance as the circulating sodium-transport inhibitor.

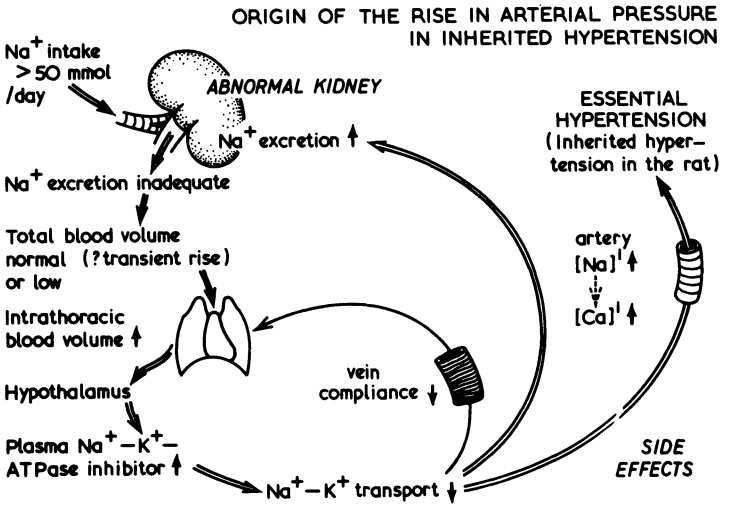

Figure 3. Sequence of events to explain a postulated inherited defect in the kidney's ability to secrete sodium, the observed rise in the concentration of a circulating sodium transport inhibitor and the rise in peripheral resistance in essential hypertension. (Reproduced from de Wardener, H. E., and MacGregor, G. A. The role of a circulating inhibitor of Na^+-K^+-ATPase in essential hypertension, American Journal of Nephrology, 1983 (in press) with kind permission.)

Hypotheses

I have already referred to Blaustein's hypothesis which gives an account of how a rise in the plasma concentration of a sodium transport inhibitor might increase the blood pressure. The following outline hypothesis suggests how such a rise in the concentration of the sodium transport inhibitor might occur (Figure 3).

We would propose that the primary abnormality is a genetic lesion of the kidney. Borst and Borst de Geus (27) were the first to propose that essential hypertension is due to an impairment in the kidney's control of sodium excretion. Convincing evidence to support this suggestion has come from cross-transplantation experiments in Dahl salt-sensitive hypertensive rats (28), in rats of the Milan hypertensive strain (29), and in

Okamoto spontaneously hypertensive rats (30). In all three "the hypertension follows the kidney," i.e., if a kidney from a young normotensive strain rat is placed into a young hypertensive strain rat, hypertension does not develop in the latter. The reverse also applies. It is difficult to exaggerate the importance of this finding, for it implies that all the abnormalities that have been described in these three forms of inherited hypertension in rats must be either secondary to a renal abnormality or that they are unrelated to the mechanism which causes the pressure to rise.

We would suggest from the available evidence that the genetic fault in the kidney is a difficulty in excreting sodium (31-34) and that the fault becomes more apparent the higher the sodium intake (35). The difficulty in excreting sodium may initially cause a transient increase in total blood volume with a rise in intrathoracic blood volume. This change stimulates the hypothalamus to secrete more of a circulating sodium-transport inhibitor, which in the kidney adjusts sodium excretion so that sodium balance is normal. Normal balance, therefore, is sustained only by a continued high level of the circulating sodium-transport inhibitor, which raises the tone and vascular reactivity of the smooth muscle of the arteries and veins, so that arterial pressure rises and venous compliance is diminished (36). The increased venous tone causes a shift of blood from the periphery to the center (37), which raises the intrathoracic pressure and perpetuates the stimulus for greater secretion of the sodium-transport inhibitor, even if the adjustment to sodium excretion has caused the total blood volume to fall to or below normal (38-40) as is usual.

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2. ATRIAL NATRIURETIC FACTOR

NICK C. TRIPPODO

ABSTRACT

Mammalian atrial myocytes contain specific granules that store a powerful rapidly acting natriuretic/diuretic factor, which is referred to as the atrial natriuretic factor (ANF). So far, ANF has been found in atrial extracts from rat, rabbit, dog, baboon and man. Injection of partially purified rat ANF into rats results in up to a 50-fold increase in urinary sodium chloride excretion within 10 minutes. The effect of ANF appears to be caused by inhibition of sodium chloride reabsorption in the ascending limb of Henley's loop or in the medullary collecting duct; although, alterations in intrarenal hemodynamics may also participate. The exact mechanism by which ANF alters renal tubular transport is unknown, but the substance does not appear to inhibit sodium-potassium ATPase. ANF does not act through release of a substance from the brain, does not require the intact nervous system for its action and is active in the isolated kidney. Biochemical studies suggest that ANF consists of one or more peptides with molecular weights of 4,000-6,000 daltons. It is also probable that one or more larger molecular species of ANF exist. Currently, the most reliable method for measuring ANF activity is to inject unknown test substances into anesthetized rats and determine the effect on renal sodium excretion. It is not known whether the atrial natriuretic factor is released into the blood stream, and thus its physiological relevance has not been determined. Elucidating the chemical structure of this powerful endogenous natriuretic substance and understanding its mechanism of action in the kidney may lead to the development of new specific diuretic drugs for treating millions of patients with hypertension and heart failure.

Messerli, F.H. (ed.), Kidney in Essential Hypertension.

INTRODUCTION

Recently, de Bold and his colleagues reported that a highly potent, rapidly acting natriuretic/diuretic factor was present in extracts of rat heart (atrial) tissue (1). These investigators found that when rat atrial muscle extracts were injected intravenously into anesthetized rats, urine sodium excretion increased 30-fold within 10 minutes. Similar injections of ventricular muscle extract had no such effect. These observations were confirmed by Trippodo, MacPhee, Cole, and Blakesley (2) and extended to include extracts from rabbit, dog, baboon, and man (3). Should this powerful natriuretic substance which is referred to as the atrial natriuretic factor (ANF), prove to be of physiological importance in the control of renal sodium excretion, it might help elucidate the mechanisms involved in the well known but poorly understood relationship between body sodium and hypertension. Even if ANF has little intrinsic physiological significance, knowledge of its chemical structure and the mechanism by which this endogenous diuretic substance produces natriuresis of such rapid onset and great magnitude might lead to the development of powerful and specific diuretic agents for treating essential hypertension.

Background

What was the rationale for examining the cardiac atria for the presence of a natriuretic/diuretic substance? For years anatomists knew of the existence of secretory-like storage granules in the atrial cardiocytes of mammals, including man (4-7) but did not know their function. These granules are now called the atrial specific granules since they are only rarely observed in ventricular myocytes. In addition, it was noted that mammalian atrial myocytes contained well developed rough endoplasmic reticulum and Golgi complexes enabling them to produce and package a secretory product (4-7). Since the atrial specific granules seemed to vary in number according to the water and electrolyte balance of the animal, it was suggested that the function of these granules was

related to an as yet undefined role of the atria in the control of body water and salt (8,9). This led de Bold et al to examine crude atrial extracts for the presence of a substance that would alter renal sodium excretion (1).

Physiological Characterization

An important point concerning the purported actions of ANF is that since this substance has not yet been isolated, all studies on its effects so far have been done with atrial extracts in various degrees of purification. Some of the actions attributed to ANF in these early studies, then, may very well be due to contaminants. Obviously, the following discussion must be considered with the caveat that a more certain assessment of the actions of ANF can only take place after it is available in pure form.

The most striking characteristic of ANF is the rapidity and magnitude of its action on renal function. For instance, within 1½ minutes after intravenous injection of partially purified ANF into anesthetized bioassay rats, there is a marked increase in urinary sodium chloride excretion. The effect reaches a peak by 3-5 min, declines precipitously during the next 5-7 min and is complete by 20 min (1-3). At maximum doses of partially purified ANF, urinary sodium excretion rate increases 30- to 40-fold and in some rats up to 50-fold, while urine output and urinary potassium excretion increase 10- to 15-fold and 100%, respectively. The time course and magnitude of change in the urinary chloride excretion resulting from ANF injection parallels the changes in sodium excretion (1). De Bold et al suggested that the effect was due largely to inhibition of sodium chloride reabsorption and that the increase in urine volume was attributed to the osmotic action of these ions. The relatively smaller increase in urinary potassium excretion was accounted for by the high tubular flow rate (1).

The time course of action and the relative effects of ANF on sodium, potassium and chloride excretion are quite similar to those of furosemide (3). Sonnenberg et al found that the effect of ANF to increase renal sodium excretion was inhibited by pro-

benecid, which also inhibits the action of furosemide by retarding proximal tubular organic acid secretion (10). These results suggest that ANF may act through a mechanism similar to that of furosemide. In this same study, it was found that pretreatment of rats with probenecid attenuated their natriuretic response to acute volume expansion (10). These data provide circumstantial evidence that ANF plays a role in the control of renal sodium excretion during acute volume expansion.

Glomerular filtration rate (GFR) did not change after ANF injection (1) and supported the notion of a tubular action. Since the effect appeared to be specifically on sodium chloride transport, the ascending limb of Henley's loop and the medullary collecting duct were suggested as possible sites of action (1). Further preliminary studies from Sonnenberg's laboratory suggested a primary action in the outer medullary collecting duct (11). That the natriuresis resulting from ANF injection is caused largely by alteration of NaCl transport along the collecting tubules and collecting ducts was also suggested by the micropuncture studies of Briggs et al (12). In addition, these investigators found an increase in GFR after high but not low doses of ANF (12). Kleinert et al (13) reported preliminary work showing a 75% increase in GFR and a 480% increase in fractional excretion of sodium in isolated rat kidneys exposed to rat atrial extract. These findings suggest that at high doses the action of ANF may be related to both glomerular and tubular effects.

The rapid onset of action of ANF suggests that it has a direct effect on the kidneys and does not require the generation of a secondary substance from the blood or from another organ. Indeed, injection of ANF into headless rats produced the same natriuretic response as that in intact rats, indicating that ANF does not act through release of a substance from the brain and that it does not require an intact nervous system for its action (2). Moreover, the fact that ANF is active in the isolated kidney confirms that its natriuretic action is mediated through direct renal effects (13).

Atrial extract was incubated with fresh rat plasma before injection into assay rats to determine if the characteristic rapid abatement of the natriuretic activity was due to circulating enzymatic degredation (2). However, the plasma-incubated extract had the same natriuretic activity as that of the control suggesting that the rapid decay in activity of ANF involves a metabolic process other than circulating factors. This observation also suggested that plasma does not contain elements that potentiate the activity of ANF. In the isolated kidney preparation, ANF was active for at least 30-min suggesting that the kidney itself does not inactivate ANF (13), although in the intact animal part of the action of ANF may be eliminated by urinary excretion. Other possible sites of ANF degradation are the liver and the lungs.

As mentioned above, ANF seems to have a powerful effect on NaCl transport in the collecting tubular system. The exact mechanism by which ANF alters transport here is unknown, but the substance does not appear to inhibit sodium-potassium ATPase (14,15). Whether the effect is mediated through a change in the permeability of the tight junctions and thus enhancement of diffusion of NaCl back into the collecting tubular system has not been explored.

The hemodynamic effects of ANF are controversial. De Bold et al (1) reported a slight depressor effect in intact assay rats, whereas the preliminary results of Pamnani et al (16) showed a small increase in mean arterial pressure in bilaterally nephrectomized rats pretreated with hexamethonium. The lack of an effect of ANF on GFR in intact rats observed by de Bold et al (1) suggests little action on renal hemodynamics, whereas an increase in GFR in isolated kidneys observed by Kleinert et al (13) suggests that ANF causes efferent arteriolar constriction and/or redistribution of flow in the isolated kidneys. Perhaps, some of this disparity can be explained by differences in the amount of contaminants in the different extracts. For instance, the immediate decrease in mean arterial pressure observed after injection of crude atrial extract in intact assay rats is the same as when crude ventricular extract is injected, even though ventricular extract has no natriuretic activity, suggesting at least that this immediate depressor

response is due to impurities (2). Injection of partially purified atrial extract (i.e., after gel filtration) produced much less of a decrease in mean arterial pressure (2) which further supports this notion.

Biochemical Characterization

At least three laboratories have reported similar findings on the chemical properties of ANF (2,15,17). ANF can be extracted in acetic acid or phosphate buffered saline. Its activity is not abolished by boiling or by treatment with concanavalin A and prolidase, but is destroyed by incubation with several proteases, including trypsin, chymotrypsin, aminopeptidase A, and carboxypeptidases B and C. ANF's sensitivity to proteases suggests that it is proteinacious in nature, while its resistance to boiling suggests that its activity does not require a complex tertiary structure. Unpublished data from our laboratory indicate that ANF activity is not abolished by RNase, DNase, collagenase or neuraminidase. Thus, ANF appears to be a peptide. According to its chromatographic properties, ANF has a molecular weight of 4,000-6,000 daltons (15,17), although it is possible that one or more larger molecular species of ANF are also present (2,17). More recently de Bold and Flynn reported purification of an atrial natriuretic factor of 5273 molecular weight, which was one of four active peaks after reverse phase high performance liquid chromatography. Amino acid analysis of this substance, which they named cardionartin I, showed the peptide had 47 residues, including one cystine (18).

By applying a technique previously used by others (19) to isolate ventricular myocytes, Trippodo et al (20) made extracts from rat atrial myocytes isolated by collagenase dispersion. Injection of the atrial myocyte extract into assay rats produced a natriuretic response similar to that observed after injection of whole atrial extract. These results suggested that ANF is localized within the atrial myocytes rather than in neural endings or in interstitial cells. The intracellular localization of ANF was

examined by de Bold (21) and by Garcia et al (22). The atrial specific granules were isolated from other subcellular fractions using differential and density gradient centrifugations. Extracts were made from the different fractions and injected into assay rats. The highest natriuretic activity was found in the fraction containing the highest concentration of specific granules indicating that these granules are probably the site of storage for ANF (21,22).

Bioassay of ANF

Currently, the most reliable method for measuring ANF activity is the injection of the unknown test substances into anesthetized rats and determining the effect on renal sodium excretion. Trippodo et al found that the response of the rat assay to rat and human ANF was linearly related to log dose (3). Furthermore, since the log dose-response curve using furosemide was parallel with that using ANF, it was suggested that furosemide be used as a standard against which the potencies of unknowns can be compared (3). By giving each rat an injection of unknown and an injection of furosemide, the amount of ANF in the unknown can be quantitated relative to the rat's response to furosemide. Thus, one unit of ANF was defined as that amount which will increase the 10-min urinary sodium excretion in an anesthetized 200-g rat by the same amount as injection of 0.1 mg/kg of furosemide (23). This definition of unitage provides a universal standard that can be used in the quantitative analysis of ANF activity.

SUMMARY

Mammalian atrial myocytes contain specific granules that store a powerful rapidly acting natriuretic/diuretic factor. This substance may be one or more peptides with molecular weights of 4,000 to 40,000 daltons. It is not known whether the atrial natriuretic factor is released into the blood stream under physiological circumstances, and thus its physiological significance has not been determined. Elucidating the chemical structure of this

powerful endogenous natriuretic substance and learning how it acts in the kidney to induce natriuresis of such rapid onset and large magnitude could lead to the development of new specific diuretic drugs for treating millions of patients with hypertension and heart failure.

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3. THE PHYSIOLOGY AND CELL BIOLOGY OF THE RENIN-ANGIOTENSIN SYSTEM IN HYPERTENSION

RICHARD RE, MD

ABSTRACT

This brief review of the renin-angiotensin-aldosterone system in hypertension suggests that renin plays a supportive or causative role in much of human hypertension. The classical kidney-based renin-angiotensin system figures prominently in the maintenance of normal blood pressure and sodium balance. It almost certainly plays the primary role in the development of renovascular hypertension in man. Additionally, extrarenal compartmentalized renin-angiotensin systems, such as that in the vasculature, could potentially play an important part in the genesis of essential hypertension and in the hypertensive patient's response to therapy. Finally, a tissue or intracellular renin-angiotensin system may well be an important determinant of cellular homeostasis and protein synthesis in some tissues.

INTRODUCTION

The demonstration by Tigerstedt and Bergmann in 1898 that a saline extract of minced rabbit kidneys could, when injected in a second animal, induce a pressor response marked the beginning of our knowledge of the renin-angiotensin system (1). However, renin was not clearly established as an important physiologic principle until the pioneering work of Harry Goldblatt in 1934 demonstrated that renal artery constriction could induce hypertension (2). In the ensuing years, the isolation of angiotensin, the development of assay methods for renin, angiotensin, and aldosterone of ever-increasing sophistication, and the development of inhibitors of the renin system have greatly expanded the known physiological role of the renin-angiotensin-aldosterone system in the maintenance of blood pressure control (3). More recently, work on the

biosynthesis of renin has brought to light the possible existence of other nonrenal renin systems with potentially profound implications for the understanding of hypertension.

The renin-angiotensin system is a hormonal cascade (3) which may be described as a negative feedback loop. In general, if renal perfusion pressure falls or delivery of sodium to the macula densa declines, modified smooth muscle cells (the so-called juxtaglomerular cells) secrete the enzyme, renin. In the blood, this enzyme acts upon an $alpha_2$ globulin synthesized by the liver to generate the decapeptide, angiotensin I. This compound has little or no intrinsic pressor or aldosterone-stimulating activity, but is converted by the enzyme, kininase II (converting-enzyme), located on vascular endothelium as well as in plasma, to the octapeptide, angiotensin II. Angiotensin II is a potent vasopressor and secretogogue for aldosterone. This peptide hormone may undergofurther cleavages in target tissues to such forms as desaspartate-angiotensin II (angiotensin III) which appears to have less pressor activity than angiotensin II but equal or greater capacity to stimulate aldosterone synthesis (4). Both the sodium retention produced by aldosterone secretion (a relatively longterm effect) and the vasoconstriction with attendant blood pressure elevation produced by angiotensin (a rapid effect) tend to restore renal perfusion and to suppress subsequent renin secretion. Thus, a feedback loop is produced.

Although angiotensin II is an extremely potent pressor, it is important to note that its impact on blood pressure is in large part modified by sodium balance. The role of intravascular volume in determining blood pressure response to the renin-angiotensin system is illustrated by the study described in Figure 1. Here a normal subject was administered the intravenously-active converting enzyme inhibitor, teprotide, a drug which effectively blocks the generation of angiotensin II. As demonstrated, the infusion of this peptide has little effect on blood pressure in the sodium-deficient subject when supine. However, when this normal subject was both sodium-depleted and treated with the drug teprotide, he was unable to maintain blood pressure during upright

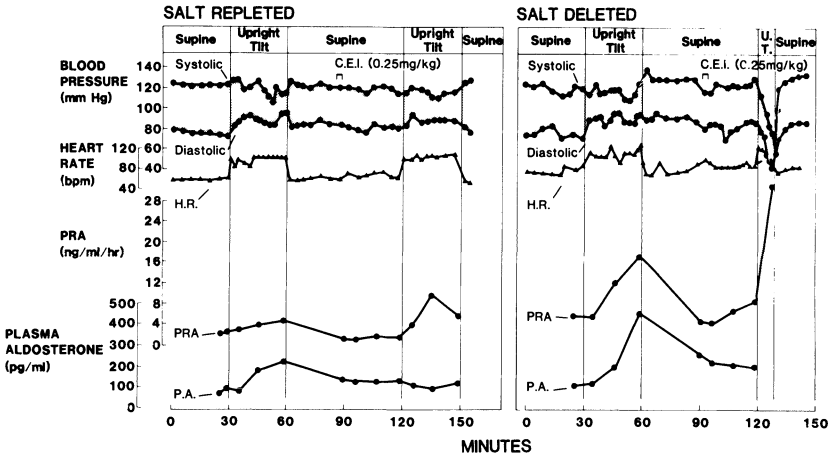

Figure 1. Hormonal and blood pressure responses of a normal subject to the administration of the converting-enzyme inhibitor teprotide (C.E.I.). Note that a significant fall in blood pressure with upright tilting following C.E.I. occurs in the sodium-depleted state. (From Sancho J, Re RN, Burton J, Barger AC, Haber E: Circulation 53:401-442, 1976, reprinted with permission)

tilt. In the sodium-replete state, teprotide was without significant effect and the blood pressure dropped little, if at all. The importance of sodium balance upon the level of functioning of the angiotensin II system cannot be overemphasized. This point is similarly confirmed by the fact that patients with hyperaldosteronism have suppressed renin and angiotensin II levels and yet are hypertensive based in large part on sodium retention.

Just as sodium balance and intravascular volume are critical determinants of blood pressure in normal man, so too, are they in hypertensive man. The response to inhibitors of the renin-angiotensin system varies dramatically in hypertensive subjects, depending on sodium balance. In the case of the angiotensin II competitive antagonist, saralasin, this relationship is all the more complex because in the sodium-replete state, the agonistic activities of the peptide become manifest leading to elevation of blood pressure. For these reasons, mild sodium restriction is advocated prior to the use of saralasin as a diagnostic test for

renovascular hypertension. This problem of agonistic activity is not noted with the converting enzyme inhibitors (captopril, teprotide, or enalapril), but nonetheless, blood pressure response to these agents in hypertensive man is dependent upon sodium balance and intravascular volume.

The role of the renin-angiotensin-aldosterone system in hypertension is controversial. There seems to be little doubt that in renovascular hypertension, renin secretion plays an important role in the development of hypertension (2,5-7). However, the role of the renin system in other forms of hypertension, and more particularly in essential hypertension, remains controversial. At the very least, however, all hypertension can be divided into low, normal, or high renin forms, and this division serves not only pedigogical purposes, but also holds important implications for the patient's response to therapy (8).

It has long been known that approximately 25% of the hypertensive population demonstrates suppression of plasma renin activity in the face of sodium deprivation or diuretic administration (9). Only a very small fraction of these patients appear to have classical hyperaldosteronism (Conn's syndrome) or idiopathic hyperaldosteronism. The vast majority are not hypokalemic and display normal suppression of aldosterone after sodium loading. These so-called low-renin hypertensives tend to be black and older than the normal and high-renin groups. Clinical studies have shown that mineralocorticoid antagonists, such as spironolactone (10) or mineralocorticoid inhibitors (11) are capable of reducing blood pressure in these patients. Additional studies showed that the aldosterone levels in the plasma of these patients are inappropriate for the level of plasma renin activity, thus suggesting the possibility that the disorder represents a forme fruste of hyperaldosteronism (12,13). Other explanations for the syndrome are suggested by the finding that the adrenal glands of patients with this disorder demonstrate increased sensitivity to the pressor hormone, angiotensin II, as manifested by enhanced secretion of aldosterone (14). Thus, in this view, high aldosterone and low angiotensin II and renin are compatible. Similarly, the

excessive secretion of mineralocorticoids other than aldosterone could potentially play a role in the genesis of hypertension in these patients (15,16). Our own data suggest that not only is plasma aldosterone inappropriate for the level of plasma renin activity in low renin patients, but the dynamics of aldosterone secretion are also impaired. Figure 2 demonstrates the normal diurnal variation of plasma aldosterone in a normotensive subject as compared to a subject with low-renin hypertension. These subtle abnormalities of aldosterone secretion suggest the possibility that the control of aldosterone secretion is deranged in these patients and make plausible the argument that abnormalities in dopaminergic tone to the adrenal glands or other similar mechanism affecting the secretion of adrenal (and possibly pituitary) hormones could play a role in the disorder (17).

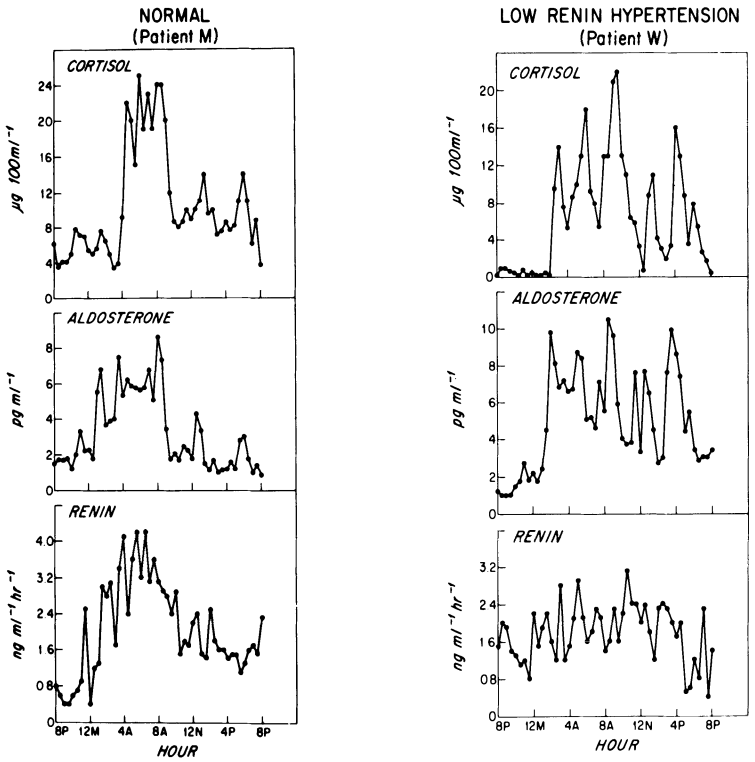

Figure 2. Hormonal variation in a normal (a) and low renin hypertension (b) subject under conditions of continuous supine posture. (Unpublished data of Sancho J, Re RN, Haber E.)

The role of renin in hypertension is nowhere more clear than in the case of renovascular hypertension. A large body of work has demonstrated that renin plays an important if not primary role in the development of renovascular hypertension and its maintenance. Extensive studies in dogs by Barger and coworkers have demonstrated that the converting enzyme inhibitor, captopril, as well as specific anti-renin antibodies are capable of normalizing blood pressure in the first two to three days following renal artery constriction (3,5,6). Thereafter, however, these agents are much less effective in lowering pressure unless the animals have been pretreated with a diuretic or are otherwise sodium deleted. These experiments once again indicate the interrelationship between intravascular volume and the role of the renin-angiotensin system in the determination of blood pressure. It would appear that the initiation of renovascular hypertension is, in large part, mediated by renin hypersecretion. With time, however, the attendant sodium retention is capable of so increasing intravascular volume in man as to blunt renin hypersecretion and acute responses to converting enzyme inhibition. Not only is aldosterone hypersecretion at work in expanding intravascular volume, but studies from several laboratories (18-22) demonstrate an apparent direct effect of angiotensin II on renal sodium retention. When we studied normal supine human subjects on balanced sodium diets (either 10 mEq sodium or 110 mEq sodium) who were infused with the converting enzyme inhibitor, teprotide, the clearance of sodium (expressed as a ratio to the clearance of creatinine) rose in both patient groups (high and low sodium diet) when the converting enzyme inhibitor was administered (19,20). This response was extremely rapid and was not accompanied by any significant change in blood pressure or plasma aldosterone levels (19,20). Although a direct effect of the drug, or even secondary effects on kinins, could be involved in this phenomenon, it seems likely that the effect is due rather to the elimination of angiotensin II from the renal circulation, thereby further implying a direct angiotensin II effect on sodium reabsorption. Thus, by direct angiotensin II effects on the kidney and more importantly

on the stimulation of aldosterone secretion, hypersecretion of renin tends to cause volume expansion and subsequent suppression of plasma renin activity. This relative volume expansion is important in diagnostic testing which employs inhibitors of the renin-angiotensin system. For this reason, as previously mentioned, diuretic administration is recommended prior to testing with saralasin.

Just as inhibition of the renin system can be helpful in making the diagnosis of renin-dependent hypertension, it can be similarly used as a secretogogue at the time of renal vein sampling for suspected renovascular hypertension. Saralasin has been so used, and we have found teprotide to be similarly helpful (23). Figure 3 demonstrates the renal vein renin ratios of patients suffering from renovascular hypertension and essential hypertension when given teprotide. The administration of the agent clearly augmented our ability to demonstrate a significant unilateral renovascular lesion (23). Similar responses can be seen following the administration of the orally active converting-enzyme, captopril. This enhanced diagnostic sensitivity results in part from hypotension-induced renin stimulation and in part from elimination of a direct angiotensin II suppressive effect on renin secretion.

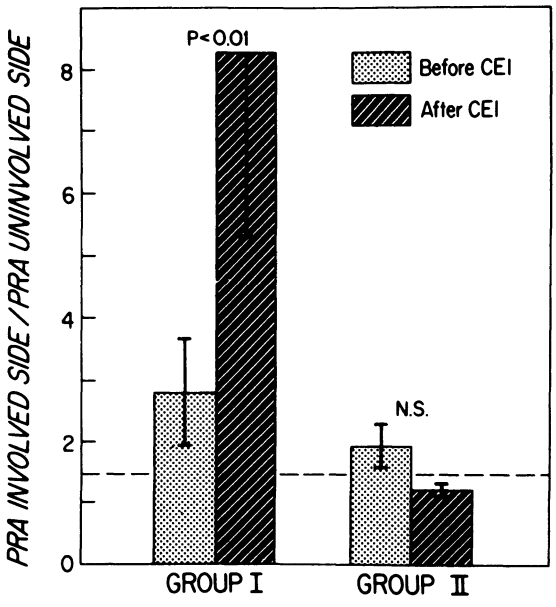

Figure 3. Renal vein renin ratios before and after the administration of converting-enzyme inhibitor in patients with proven renovascular hypertension (Group I) and patients with essential hypertension (Group II). (From Re RN, Novelline R, Escourrou MT, Athanasoulis C, Burton J, Haber E: N Engl J Med 298:582-586, 1978, reprinted with permission)

It is our policy in these cases to measure plasma renin activity prior to admitting patients for renal vein study for two reasons: first, to be certain that the response to captopril or teprotide is not excessive (vide infra), and secondly, to be certain that ambient plasma renin levels are not so suppressed by prior drug therpy as to be essentially unstimulatable to the sensitive range of the renin assay. Because many patients coming to renal vein catheterization do in fact have renal artery stenosis and high renins, converting enzyme inhibition should be used with caution in these patients since prodigious falls in blood pressure can be seen. In general, assessment of plasma renin activity prior to study is sufficient to forewarn of potential danger. Also, should blood pressure fall significantly, the administration of saline during the procedure has been found to be helpful.

The role of the renin-angiotensin system in the development and maintenance of essential hypertension remains controversial. However, a significant amount of clinical data utilizing converting enzyme inhibitors as well as the competitive angiotensin II antagonist, saralasin, indicate that blood pressure reduction in hypertensive man occurs following the interruption of the renin system in proportion to the ambient level of renin. For example, data from Case and coworkers (24) as well as our data (23) demonstrate that teprotide will produce in essential hypertensive man a fall in blood pressure related to initial plasma renin activity. This observation has therapeutic as well as physiologic significance. It implies that therapies designed to lower normal or elevated plasma renin activity or to interrupt the renin system can be anticipated to lower blood pressure, at least initially. Similarly, these data suggest that the renin system plays at least a supportive role in the maintenance of hypertension in normal and high-renin hypertensives. One difficulty with this analysis is the clinical observation that the longterm blood pressure lowering effects of captopril are only poorly predicted by plasma renin activity (25). However, in clinical practice, it is clear that the initial response to the drug is exaggerated in patients with high renin activities. In our clinic we must often reduce the initial

dosage of this drug to 6.25 mg for patients with extraordinarily high renins. This does not always lessen the severity of the fall in blood pressure but does potentially shorten its duration. Also, whenever possible, we determine pretreatment plasma renin activities in our patients prior to beginning therapy with converting enzyme inhibition. Nonetheless, the lack of a high degree of correlations between plasma renin and the longer-term response to captopril has led to the belief that either direct effects of the drug on the vasculature, or effects on kinins play a role in captopril therapeutic actions.

An alternative analysis, however, of the clinical response to captopril and, therefore, potentially to other converting enzyme inhibitors can be given. Many authors have reported the presence of angiotensinogenase activity in the arterial wall of experimental animals (26,27), although some of these reports undoubtedly involve the measurements of nonrenin acid proteases and are, therefore, of lesser interest. Some, if not all, of the renin found in aorta is derived from serum and results from trapping and sequestration of the material rather than synthesis. However, renin activity and angiotensin II have also been detected in the brain of experimental animals leading to the possibility that the renin system may affect blood pressure through cerebral generation of angiotensin II with subsequent effects on the adrenergic nervous system (27).

Studies from our laboratory employing cultured aortic smooth muscle cells of dogs have demonstrated the capacity of these vascular cells to synthesize renin (28,29). Cultured cells from the media of dogs were found to generate angiotensin I at neutral pH and this activity was inhibited by a specific anticanine renin antibody. Moreover, as demonstrated in Figure 4, cytoplasmic immunofluorescence could be detected when this antibody was employed in studies of these cultured cells. This immunofluorescence was reduced when the antibody was preabsorbed with pure canine renin. Finally, in labeling studies, cells were administered ^{35}S-methionine and after 24 hours of incubation, were homogenized and treated with antirenin antibody or preimmune serum.

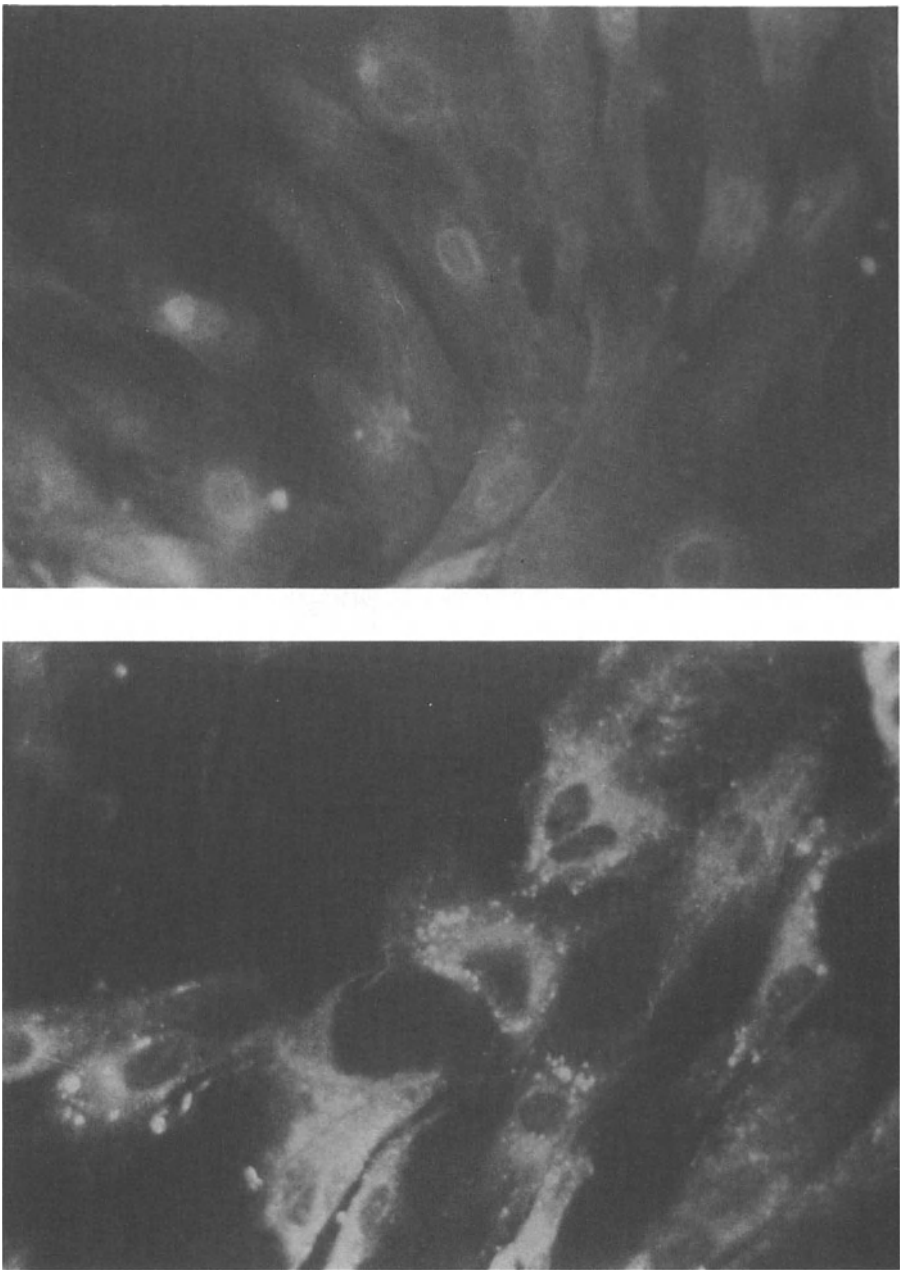

Fig. 4 Cultured canine aortic smooth muscle cells studied with (a) preimmune and (b) anti-renin antiserum. (From Re RN, Fallon JT, Dzau VJ, Quay S, Haber E: Life Sci 30:99-106, 1982, reprinted with permission)

Staphylococcal protein A was then used to precipitate immunocomplexes and these were autoradiographed following gel electrophoresis. As shown in Figure 5, these studies demonstrate the synthesis by the cell cultures of proteins with renin immunoreactivity having molecular weight approximately 50,000, 40,000, 38,000, and 24,000. These likely correspond to prorenin, normal renin, and a peptide cleavage product of renin, possibly the same species isolated by Corvol (30). These data strongly indicate

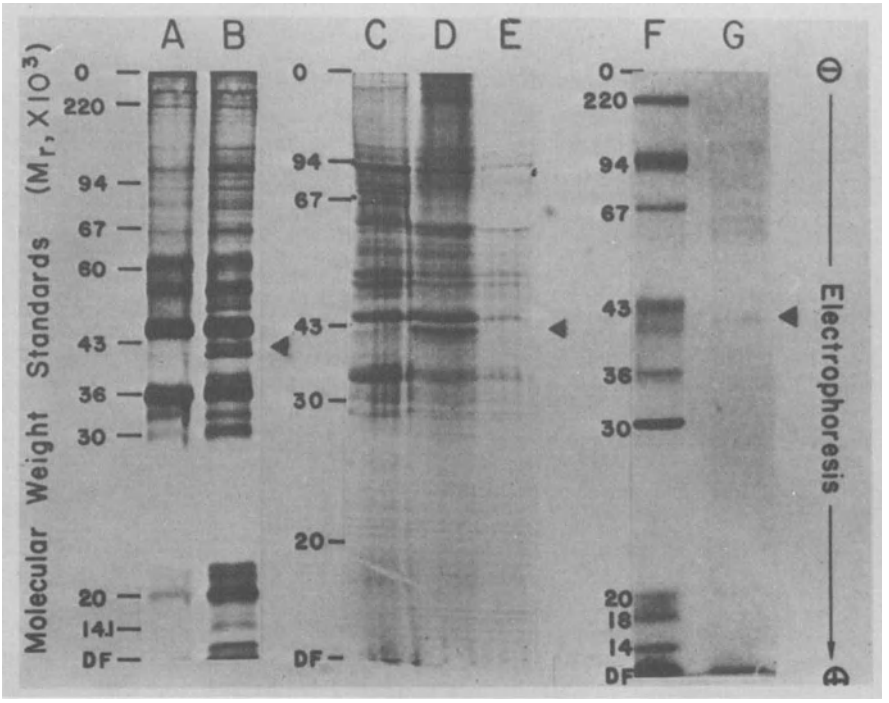

Figure 5. Tracks A-E show composite of SDS-polyacrylamide gel electrophoresis of immunoprecipitates prepared from cell homogenates of radiolabelled canine smooth muscle cells. A,B: autoradiograph of ^{35}S methionine labelled proteins immunoprecipitated with preimmune and postimmune rabbit serum, respectively; C,D: fluorogram ^{3}H amino acid labelled proteins immunoprecipitated with purified IgG prepared from preimmune and postimmune goat serum, respectively; E same as D except that pure canine renal renin was added during lst stage of immunoprecipitation; F: molecular weight standards (Pharmacia) stained by Coomosie blue; G: authentic canine renal renin stained by Coomosie blue. Arrows=renin; O=origin; DF=dye front. (From Re R, Fallon JT, Dzau V, Quay S, Haber E: Life Sci 30:99-106, 1982, reprinted with permission)

that vascular smooth muscle cells, at least under the appropriate conditions, are capable of synthesizing the enzyme renin. Some support for this observation comes from recent work by Ingami who has demonstrated an increase in the antibody inhibitable renin activity of the mesenteric and adrenal arteries of the spontaneously hypertensive rat (31). Thus, it is entirely possible that arterial renin in resistance vessels may contribute to the maintenance of blood pressure both in the experimental animal and potentially in human hypertension. The efficacy of captopril in reducing pressure unrelated to plasma renin activity may then relate to the ability of this compound to enter the arterial wall and interrupt an arterial renin-angiotensin system with subsequent diminution of intraluminal angiotensin II levels. Additionally, we have recently detected renin activity (inhibitable by specific antibody) in isolated rat cardiac myocytes raising the possibility that this enzyme plays a role in myocardial physiology (32). Indeed, a possible role for renin in the genesis of cardiac hypertrophy is suggested by the fact that captopril appears to cause regression of myocardial hypertrophy in hypertensive animals (33).

Both the presence of renin in arterial cells in culture and reports of renin in nervous tissue in culture led us to query whether there existed not only an arterial wall and neural angiotensin system, but whether perhaps there could be an intracellular renin angiotensin system. Essential to this hypothesis, however, is the demonstration of intracellular angiotensin II receptors and the demonstration of a potential effect mediated by intracellular angiotensin II. In an attempt to find an effect of this type, our laboratory studied isolated nuclei from rat liver. It will be recalled that liver is a target tissue for angiotensin II in that this peptide hormone increases hepatic protein synthesis. Nuclei were isolated by a method which does not disrupt the outer nuclear membrane (Fig. 6) and their ability to bind angiotensin II was studied. Displaceable binding was found to be present in these nuclei and the apparent K_d for this binding was approximately 1 nM (34). Precautions were taken to exclude significant membrane

contamination and the binding observed appeared to be nuclear in origin.

These findings would appear to confirm the earlier work of Robertson and Khairallah (35) employing the administration of tritiated angiotensin II to rats followed by autoradiography. These workers found grains in mitochondria and nuclei, and possibly our

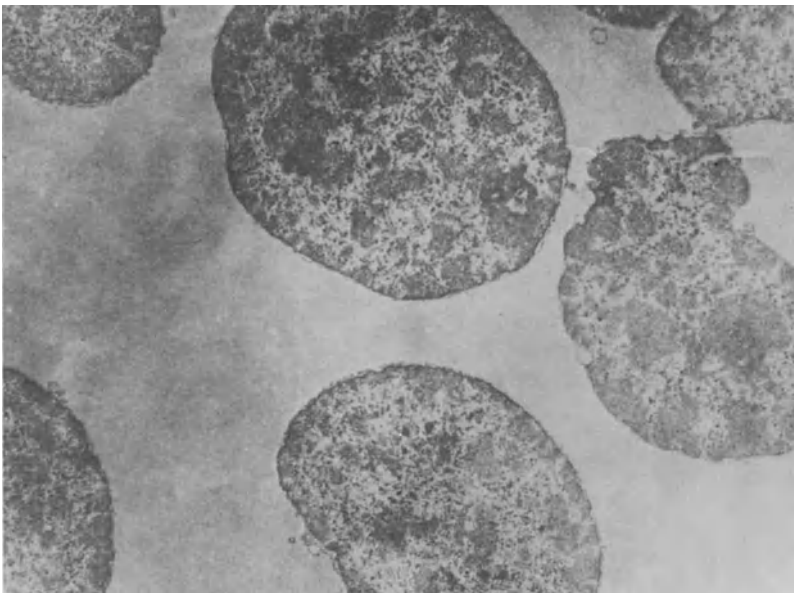

Figure 6. Electronmicrograph of purified rat hepatic nuclei employed in binding studies. (Electronmicrograph courtesy of Dr. John T. Fallon, Massachusetts General Hospital, Boston.)

in vitro preparation is measuring the same receptor. In order to further pursue these studies, we looked at the effect of low concentrations (10^{-9}M) angiotensin II on RNA synthesis by these nuclei. In our hands, nanomolar concentrations of angiotensin II produced a significant increase in RNA synthesis suggesting that interaction of the peptide with nuclear or other intracellular receptors in the broken cell preparation was sufficient for the generation of an effect on protein synthesis (36,37). Additionally, we studied the impact of the angiotensin II pretreatment

of nuclei on the solubilization of chromatin by endococcal nuclease. In these studies, nanomolar concentrations of angiotensin II increased the solubility of rat hepatic chromatin to endonuclease digestion indicating that the hormone produced chromatin conformational changes like those associated with the initiation of gene transcriptional activity (38). These results suggest the existence of an intracellular renin-angiotensin system with important effects on protein metabolism. Cells like the arterial smooth muscle cell and the cardiac myocyte contain renin and angiotensinogen. They may well therefore generate intracellular angiotensin capable of interacting with functional intracellular receptors. Additionally, it is entirely possible that angiotensin II internalized from the cell membrane can bind to intracellular receptors as originally suggested by Robertson and Khairallah (35). Both these hypotheses are consistent with the theory that the peptide hormone, angiotensin II, plays an important role in cellular metabolism and suggests that the hormone may also play a role in the development of vascular disease and cardiac hypertrophy. Further work in this area is ongoing.

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4. PROSTAGLANDINS AND HYPERTENSION

JOHN C. McGIFF

ABSTRACT

Increased activity of the renin-angiotensin and adrenergic nervous systems evoked by stressful stimuli enhances prostaglandin synthesis, which protects renal function from excessive effects of angiotensins and catecholamines. Prostaglandins not only antagonize the actions of pressor hormones and the adrenergic nervous system, they also contribute to the renal effects of kinins by augmenting their vasodilator and diuretic-natriuretic actions. Renal prostaglandin-dependent mechanisms are also important for the regulation of renin and kallikrein release and renal vascular resistance.

INTRODUCTION

More than a decade ago Weiner and Kaley (1) first advanced the hypothesis that prostaglandins are local regulators of the circulation. A prostaglandin of the E series was shown to dilate the rat mesenteric vasculature and to antagonize the constrictor actions of pressor hormones on these blood vessels. The findings of Weiner and Kaley (1) were crucial to future studies on prostaglandin mechanisms contributing to control of blood pressure. In particular, they showed that PGE_1 inhibited the vasoconstrictor effects of diverse stimuli, peptides as well as catecholamines, and that the inhibition lasted well beyond the waning of the direct vascular action. This capacity to antagonize pressor hormone-induced constriction of blood vessels was independent of the vasodilator effect of the prostaglandin; it is the basis for the proposed antihypertensive activity of PGE_2 whereby it acts as modulator of the adrenergic nervous system and vasoactive

peptides (2). For example, PGE_2 was shown to inhibit the vasoconstrictor response to adrenergic nerve stimulation in the isolated kidney of the rabbit at a concentration two hundredfold less than that which dilates this vascular bed (3). This concentration of PGE_2, 20 pg/ml, is likely to be realized intrarenally, as peak concentrations of PGE_2 in renal venous effluent and urine, which reflect tissue levels in the kidney, are well above this. Thus, as much as a hundredfold increase in prostaglandin levels in renal venous blood occurred during maximal depression of renal function produced by infusion of norepinephrine into the renal artery (4). When interpreting these findings, it is important to recall that prostaglandins probably act primarily as agents mediating mechanisms of defense; that is, they are released rapidly by a variety of stimuli which alter the basal or resting state of the animal. For example, in the isolated rat kidney, norepinephrine caused a dose-dependent efflux of PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$, the last an index of PGI_2 release (fig. 1). Peak levels occurred within 90 seconds followed by decline to control levels within

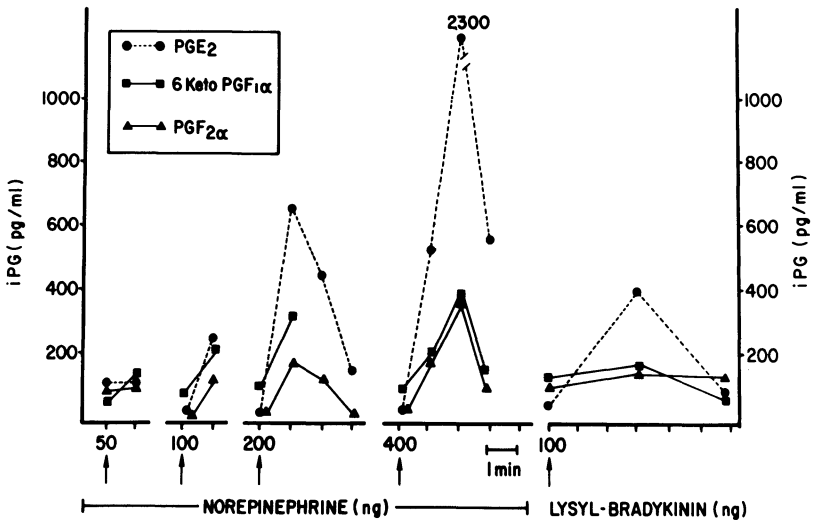

FIGURE 1 Norepinephrine-induced release of immunoreactive prostaglandins (*i*PG) from the rat isolated kidney. Norepinephrine, given by injection at the arrows, caused dose-related increases in perfusion pressure, from less than 10 mmHg to more than 100 mmHg (not shown).(Reproduced from Advances in Prostaglandin, Thromboxane and Leukotriene Research. Vol. 11, p. 482, eds. B. Samuelsson, R. Paoletti and P. Ramwell, Raven Press, NY, 1983).

several minutes (5). As noted, this mechanism serves a primary defensive role. It is evoked when renal function is threatened, as in response to excitation of renal nerves or activation of the renin-angiotensin system, and can be unmasked by inhibiting prostaglandin synthesis with indomethacin. For example, in the dog stressed by anesthesia and abdominal surgery, in contrast to the dog at rest, indomethacin caused a sharp decline in renal blood flow (6). Before administration of indomethacin, renal vascular resistance was identical in both stressed and resting dogs; however, prostaglandin concentrations in renal venous blood of surgically-stressed dogs were almost tenfold higher. In the surgically-stressed dog, indomethacin caused an increase in renal vascular resistance proportional to the decline in vasodilator prostaglandin release from the kidney, whereas in the resting dog, indomethacin did not affect renal vascular resistance. PGE_2 is the principal intrarenal mediator of prostaglandin-related mechanisms, attenuating the renal vasoconstrictor and antidiuretic effects of angiotensins, vasopressin and α-adrenergic nervous activity.

Activation of renal prostaglandin mechanisms is also associated with major alterations in zonal perfusion of the kidney (7) (i.e., blood flow redistributes from the outer to the inner cortex and medulla), a change that is not evident from measurement of total renal blood flow. Zonal redistribution of renal blood flow, also mediated by PGE_2, is a major determinant of salt and water excretion, as it affects the solute gradient within the medulla, thereby influencing the action of vasopressin. There is now general agreement that prostaglandin mechanisms localized within the kidney are essential for adaptation of renal function to stress and to disease.

Prostaglandins have been shown to be synthesized in all blood vessels thus far examined, irrespective of the organ of origin or the size of the blood vessel (8). Presumably, all endothelial cells lining the vasculature, including arterioles, capillaries and venules, as well as larger vascular

elements, contribute to the prostaglandin biosynthetic capacity of the circulation. Thus, Terragno et al. (9) have shown that all arterial elements within the kidney, including interlobular arteries and afferent arterioles, have a similar capacity to generate prostacyclin, and lesser amounts of PGE_2 and $PGF_{2\alpha}$, when related to the weight of the vascular tissue.

Since the discovery of prostacyclin in blood vessels by Moncada et al. in 1976 (10), it has been assumed to be the principal product of enzymic transformation of the cyclic endoperoxides, PGG_2 and PGH_2, in all vascular elements. Further, prostaglandin mechanisms within blood vessels are considered to be mediated by prostacyclin (11); other prostaglandins identified in vascular tissues have been suggested to have relatively unimportant roles or to be artifacts. However, several findings preclude the unqualified acceptance of prostacyclin as the only important vascular prostaglandin: 1) In some blood vessels there is evidence that prostacyclin is not the principal product of enzymic transformation of the cyclic endoperoxides (12); 2) PGE_2, which is also synthesized in the vascular wall (8), may be the principal modulator prostaglandin, affecting the vascular actions of vasoactive peptides and autonomic nervous activity (6); and 3) Prostacyclin may be transformed by some tissues to a more stable product, 6-keto-PGE_1, having similar biological potency (13,14). In addition, rapid termination of the action of prostacyclin can occur as it can be rapidly metabolized by 15-hydroxyprostaglandin dehydrogenase (15), an enzyme which is abundantly present in blood vessels. Thus, prostacyclin is susceptible to rapid degradation and transformation to other biologically-active products. Further, it is by no means certain that all endothelial cells of all regional vascular beds have a similar capacity to generate prostacyclin, or indeed, to synthesize prostacyclin as the principal product of arachidonic acid metabolism. In support of the latter, there is good reason to believe that if a major function of prostaglandins is to modulate the vasoconstrictor effects of pressor hormones on the circulation, then PGE_2, or a prostaglandin with equivalent vascular actions, would fulfill this important role. Thus, in contrast to PGE_2, PGI_2 does not

inhibit the effects of angiotensin on the microcirculation (16); this finding challenges a proposed modulator role for PGI_2.

Because of the considerable capacity of blood vessels to synthesize prostaglandins and the vascular effects of these hormones, they could serve as the long-sought mechanochemical transducer of the vascular wall, whereby changes in intramural tension are translated into altered rates of formation of the prostaglandin endoperoxides, PGG_2 and PGH_2, and variations in the subsequent enzymic conversion of the endoperoxides to products having different vascular effects, i.e., PGE_2, PGI_2 and $PGF_{2\alpha}$ and perhaps TxA_2.

A significant relationship between pressor and depressor factors, operating endogenously, was first established with the demonstration that one or more vasodepressor prostaglandins was released into renal venous blood during infusion of angiotensin II into the renal artery (17). Renal blood flow and urine flow were greatly decreased by angiotensin II, reflecting its vasoconstrictor and antidiuretic actions. However, within 2-5 minutes, both returned toward control levels despite continued infusion of angiotensin II. This recovery phase coincided with increased prostaglandin release. When this experiment was repeated, after inhibition of prostaglandin synthesis, the vasoconstrictor and antidiuretic actions of angiotensin II were increased and a recovery phase did not occur (18).

Prostaglandins are not only involved in determining the final effects of the renin-angiotensin system by modulating the actions of the peptide (17) but, in addition, prostaglandin-related mechanisms are also involved in controlling release of renin (19). The importance of a prostaglandin-dependent mechanism to the regulation of renin release has been recognized since the initial report in 1974 (20). However, it is uncertain that all of the known signals that can release renin must operate through a prostaglandin-related mechanism. There are studies which do not support this view and which suggest that such a mechanism serves only to amplify some of the signals. Which of the known prostaglandins acts as the mediator of prostaglandin-related renin release is also unsettled.

The proposal that prostacyclin is a mediator (21) of renin secretion has been supported by the in vitro experiments of Whorton et al. (22) who have shown that prostacyclin-induced stimulation of renin release from the rabbit kidney was time dependent; renin release from the cortical slices proceeded in a linear fashion after PGI_2 addition and continued unabated for 30 minutes. The prolonged response was unexpected, as PGI_2 is rapidly hydrolyzed to 6-keto-$PGF_{1\alpha}$ at physiological pH and temperature (23). The direct participation of PGI_2 in renin release has been challenged by Wong et al. (13,24) who have provided evidence that PGI_2 can be transformed to an active metabolite with biological activity similar to that of prostacyclin. The active metabolite, a stable substance at physiological pH, has been identified as 6-keto-PGE_1 or a related compound. The discovery of enzymatic activity in the liver capable of generating 6-keto-PGE_1 was soon followed by reports that this prostaglandin, like PGI_2, inhibited platelet aggregation (25) and produced hypotension and vasodilatation (26); in addition, it was a potent renin secretagogue (24). Moreover, interest in 6-keto-PGE_1 has been heightened by increasing evidence that PGI_2 may be transformed to biologically-active metabolites. However, it remains an open question whether some of the effects ascribed to PGI_2 may be dependent upon conversion of prostacyclin to 6-keto-PGE_1.

Interactions of the renal kallikrein-kinin system with prostaglandins are similar to those involving prostaglandins with the renin-angiotensin system; namely, prostaglandins modulate the peptide hormones (kinins/angiotensins) and contribute to regulating release of the proteolytic enzyme (kallikrein/renin). Studies on the participation of prostaglandin-dependent mechanisms in regulating kallikrein release are few and only touch upon this event tangentially. For example, furosemide causes immediate release of renal kallikrein, as well as renin, and as the drug-induced effect on renin is related to a prostaglandin-dependent mechanism it may be inferred that kallikrein release is also (27). More to the point is the study of Vio et al. that directly addressed the question of whether a

prostaglandin-dependent mechanism participates in the regulation of kallikrein release (28). They showed that arachidonic acid caused a dose-related increase of kallikrein release into the venous effluent of the rat isolated kidney, an effect dependent upon transformation of arachidonic acid to a prostaglandin as it was prevented by indomethacin.

An intimate relationship between the kallikrein-kinin and prostaglandin systems was suggested from a study conducted in conscious rats that was based on measurements of urinary excretion of prostaglandins and kallikrein, reflecting the intrarenal activity of the prostaglandin and kallikrein-kinin systems, respectively (29). Either augmentation or depression of urinary kallikrein excretion evoked a corresponding change in excretion of PGE_2. Mineralocorticoids were given to increase the activity of the renal kallikrein-kinin system; the kallikrein inhibitor, aprotinin, was used to reverse the stimulatory effects of mineralocorticoids on the kallikrein-kinin system. Either desoxycorticosterone (DOCA) or aldosterone, administered over a period of ten to fourteen days in the conscious rat, produced an initial transient antinatriuresis. A diuresis appeared on the second day of steroid treatment and persisted for the remainder of treatment, associated with a threefold increase in excretion of kallikrein and PGE_2. Injection of aprotinin, despite continued treatment with the mineralocorticoid, caused a rapid decline in urinary kallikrein activity and a secondary reduction in excretion of PGE_2, sodium and water. After three to four days, sodium and water excretion returned to the levels observed before administration of aprotinin, despite sustained reduction in excretion of PGE_2 and kallikrein. The importance of renal prostaglandins to the excretion of water was suggested by a surge of prostaglandins into the urine during diuresis induced by the mineralocorticoid. Moreover, the fall in PGE_2 excretion, produced by aprotinin in rats receiving a mineralocorticoid, was associated with decreased water excretion lasting several days.

Additional evidence for close-coupling of the renal kallikrein and prostaglandin systems was obtained in man by Abe et al. (30). They showed that the circadian rhythm of PGE excretion was synchronized with urinary kinin excretion but not with urinary kallikrein excretion. Further changes in sodium excretion and urine volume were closely correlated with PGE_2 and kinin excretion. Acute volume expansion produced by water loading indicated that augmentation of urinary excretion of kinin and PGE_2 correlated closely with excretion of water but not with sodium. Once again, the importance of prostaglandin-kinin interactions to regulation of water excretion is affirmed. Kramer et al. (31) have obtained evidence in the conscious rat that the acute response to volume expansion induced by salt loading requires a coupled reaction of the kallikrein-kinin-prostaglandin systems to the stimulus, whereas the stable phase of extracellular fluid volume expansion may be independent of a renal prostaglandin mechanism.

These several studies, when viewed in terms of the demonstrated capacity of kinins to generate prostaglandins in the collecting ducts and contiguous structures, point to the importance of kinin-prostaglandin interactions in the regulation of extracellular fluid volume. Conditions favor kinin-prostaglandin interaction in the distal nephron and collecting ducts. The cells lining the collecting ducts have a large capacity to generate prostaglandins and can be stimulated to prostaglandin generation by relatively low concentrations of kinins (32). Kallikrein enters the tubular fluid in the distal convoluted tubules (33) where it liberates kinins from kininogen. As indicated, the newly generated kinin may cause release of prostaglandins from the cells lining the collecting duct. PGE_2, if released, inhibits ADH (34), contributes to the regulation of medullary blood flow (7) and affects salt transport (35), as well as water excretion. A major determinant of the final consequences of kinin-prostaglandin interactions in the distal nephron and collecting ducts may be the activity of PGE-9-ketoreductase which transforms PGE_2 to $PGF_{2\alpha}$ (36). As PGE_2 can affect tubular and vascular function, whereas $PGF_{2\alpha}$ is without discernible effect on renal function, and as bradykinin has been

shown to affect the activity of this enzyme (37), the potential importance of this enzyme to the regulation of PGE_2-mediated effects of kinins on the regulation of extracellular fluid volume is evident. The activity of this enzyme has been found to be very high in the rabbit kidney, as infused PGE_2 is rapidly converted to $PGF_{2\alpha}$ (36). Thus, we regard the final event in the series of reactions beginning with release of renal kallikrein and ending with kinin-mediated prostaglandin generation in the collecting ducts to be decisively dependent on whether or not PGE_2 or $PGF_{2\alpha}$ is formed. This hypothesis, which was advanced by us in 1976 (38), is restated since subsequent studies have provided its justification: "Whether or not a PGE or PGF compound primarily results from kinin generation intrarenally will be a major determinant of the effects of any given level of activity of the renal kallikrein-kinin system on salt and water excretion." These interactions involving kinins and prostaglandins, both within the nephron and the vasculature, participate in the regulation of blood pressure. A deficiency of either PGE_2 or of kallikrein-kinin activity may lead to elevation of blood pressure.

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5. KALLIKREIN AND KININS IN EPITHELIAL ION TRANSPORT

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1. INTRODUCTION

Despite several decades of work there is still no evidence proving that tissue kallikrein and its kinin products have any causal, or compensatory role in any form of experimental or human hypertension. Nevertheless, such participation continues to be reasonable because of findings which established that: 1) changes in endogenous renal kallikrein-kinin activity are correlated with changes in renal excretory or hemodynamic behavior (1,2); 2) correlations are present between urinary kallikrein excretion rates and levels of blood pressure in some normal children (3); 3) altered urinary and renal kallikrein levels are present in various forms of renal and hypertensive diseases (4,5); and 4) changes in system component activity occur during treatment with antihypertensive and/or diuretic drugs (6).

To fully understand the significance of these findings, the principal functions of this enzyme and its peptide products must be discovered. Although the kallikrein-kinin system is widely considered as a possible endogenous vasodilator mechanism, the actions which could account for this, or other known effects of kinins are not clear. Because earlier work established relationships among urinary kallikrein, dietary sodium and sodium-retaining steroids (1,7), further connections among tissue kallikrein, kinins and epithelial electrolyte transport were looked for, at sites where tissue kallikrein or kallikrein-like enzymes were known to exist.

2. METHODS

2.1. Amiloride inhibition studies

The effects of this drug (a gift of Dr. Edward J. Cragoe, Jr., Merck Institute for Therapeutic Research) on the activities of purified rat and human urinary kallikreins (8,9) and membrane-bound kallikrein-like activities of rat

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renal cortical cells in suspension (10) or Bufo marinus urinary bladder pieces were evaluated as described previously (11). Substrates included ∝ N-tosyl-L-arginine [^{3}H] methyl ester (Tos-Arg-OMe), thiobenzyl benzyloxycarbonyl-L-lysinate (a gift of Drs. C. Kettner and E. Shaw, Brookhaven National Laboratory), and purified bovine low molecular weight kininogen (a gift of Dr. H. Kato, Protein Research Institute, University of Osaka). Radiochemical, spectrophotometric, and bioassays were carried out according to established and previously described methods (11).

2.2. Amphibian urinary bladder studies

The effects of reversible or irreversible serine protease inhibitors on the rate of net sodium transport was measured using the short-circuit current technique of Ussing and Zerahn (12), as described previously (13). Aprotinin was a gift from Professor G. Haberland, Bayer AG, and D-Phe-D-Phe-L-Arg chloromethyl ketone (DPPA) was a gift from Drs. Kettner and Shaw. Soybean trypsin inhibitor was obtained commercially. Urinary bladder Tos-Arg-O[^{3}H]Me esterase activity was measured in the absence or presence of DPPA using toad bladder pieces, harvested as described previously (11).

2.3. Rat descending colon studies

Specially constructed Ussing-type chambers (14) were used for measurement of short-circuit current or fluxes of ^{36}Cl, ^{22}Na and ^{86}Rb across the isolated descending colon from male Sprague-Dawley rats. The colon segment was stripped of serosa and as much muscle as possible before mounting. Stripped epithelium was lightly clamped between halves of the chambers and each surface bathed with Krebs-Henseleit solutions which were circulated independently using a 95% O_2:5% CO_2 mixture to operate air lifts. Solution composition could be changed at one surface independent of the other and likewise, the effects of drug or enzyme additions on each surface could be evaluated. The tissues were voltage clamped at zero potential (short-circuited) automatically and the current required to do this was continuously displayed on a pen recorder. The method developed to measure radioisotopic fluxes was designed to detect small changes in unidirectional flux caused by kinin, against a background of a large leak flux characteristic of this tissue (15).

3. RESULTS

Figure 1 shows that the activities of purified rat urinary kallikrein are inhibited by amiloride.

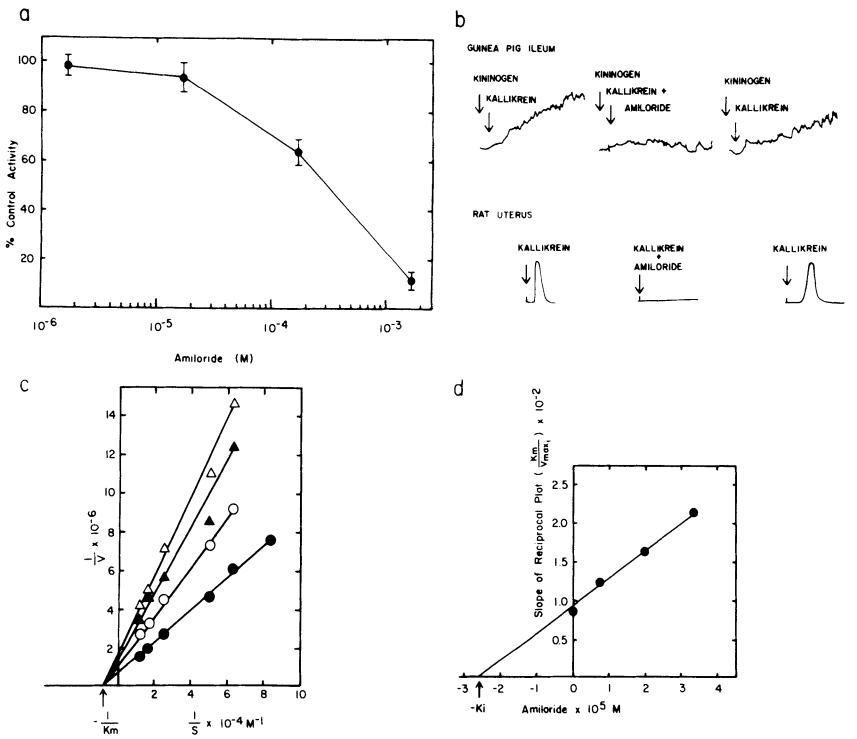

FIGURE 1. a) Inhibition of rat urinary kallikrein Tos-Arg-O[^{3}H]Me esterase activity by amiloride. Activity is expressed as the percent of control esterase activity in the absence of amiloride. Each value represents the mean ± 1 SEM in 12 experiments in duplicate. b) Bioassays of kallikrein in the absence and presence of amiloride. The contractile response of the guinea pig ileum (upper panel) produced by kinin liberation from 0.1 ml of heated dog plasma kininogen substrate incubated within the isolated tissue bath with 0.1 ml of purified rat urinary kallikrein (0.1 esterase unit/ml) is seen. The same quantity of enzyme was preincubated with 3 mM amiloride for 30 min at 37°C and a 0.1 ml aliquot was added to the bath. The response was inhibited by amiloride (bath concentration, 30 μM). After washing, the response returns. The contractile response of the rat uterus (lower panel) was induced by 0.01 esterase unit of the same kallikrein. The same quantity of enzyme was preincubated with 3 mM amiloride for 30 min at 37°C and a 0.1 ml aliquot was added to the bath. The response was inhibited by amiloride (bath concentration, 30 μM). After washing, the response returns. c) Lineweaver-Burk plot of initial reaction velocity, V, vs. substrate concentrations, S, in the absence (●) and in the presence of amiloride [6.7 μM, (○); 20 μM, (▲); 33 uM, (△)]. d) Secondary plot of the slopes from the primary Lineweaver-Burk plot vs. amiloride concentration. Data redrawn from ref. #11 and reprinted with permission.

The concentration of drug required to inhibit this or other kallikreins or kallikrein-like enzyme activity 50% ranges from 85 to 230 uM depending upon substrate, enzyme preparation or assay system. The kallikrein-like Tos-Arg-OMe esterase activity of isolated renal cortical cells in suspension was inhibited to a similar extent and with a similar (0.12 mM) IC_{50}. The typical Lineweaver-Burk plot from measurements of kallikrein activity on thiobenzyl benzyloxycarbonyl-L-lysinate shows no change in K_m (0.125 mM) but increasing $1/V_{max}$ with increasing amiloride concentrations, indicating non-competitive inhibition. Secondary plots of V_{max} vs. amiloride concentration indicate reversible inhibition. No other drugs tested including furosemide, hydrochlorthiazide, ethacrynic acid, spironolactone or ouabain in concentrations up to 1.7 mM inhibited kallikrein activity to any degree. Triamterene, 1.7 mM, produced slight inhibition (22.5 ± 4.2%, mean ± 1 SE, n=6).

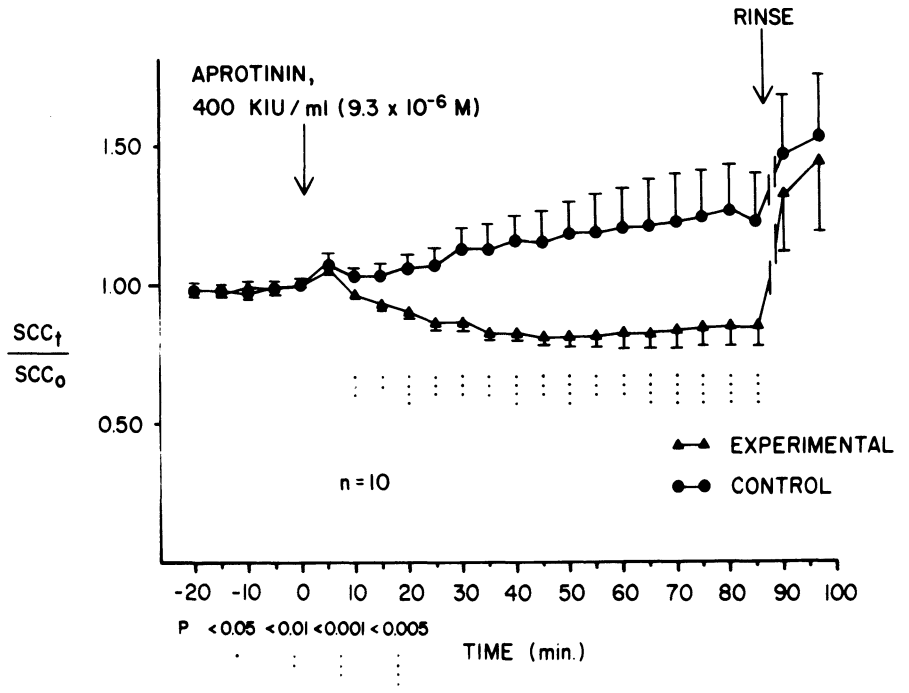

FIGURE 2. Effect of mucosal aprotinin on base-line short-circuit current (SCC). Aprotinin was added to the mucosal bath of 1 quarter-bladder (▲), the control quarter-bladder (●) receiving an equal volume of vehicle. Both were rinsed 3 times with inhibitor-free Ringer solution 90 min later and SCC again recorded. n=10. Reprinted from ref #13 with permission.

Because amiloride is a rapidly acting and potent inhibitor of short-circuit current in the amphibian bladder, and because a kallikrein-like enzyme is present at this site (11), we measured the effects of various serine protease inhibitors known to inhibit kallikreins on this current. Figures 2 and 3 show that aprotinin produces clearly significant inhibition of short-circuit current but that soya bean trypsin inhibitor produces no such inhibition. Aprotinin-induced inhibition is not complete, however (maximal inhibition = 29% at 7.0 x 10^{-6} M). Inhibition appears significantly earlier with mucosal than with serosal addition, and is reversible upon rinsing (Figure 2).

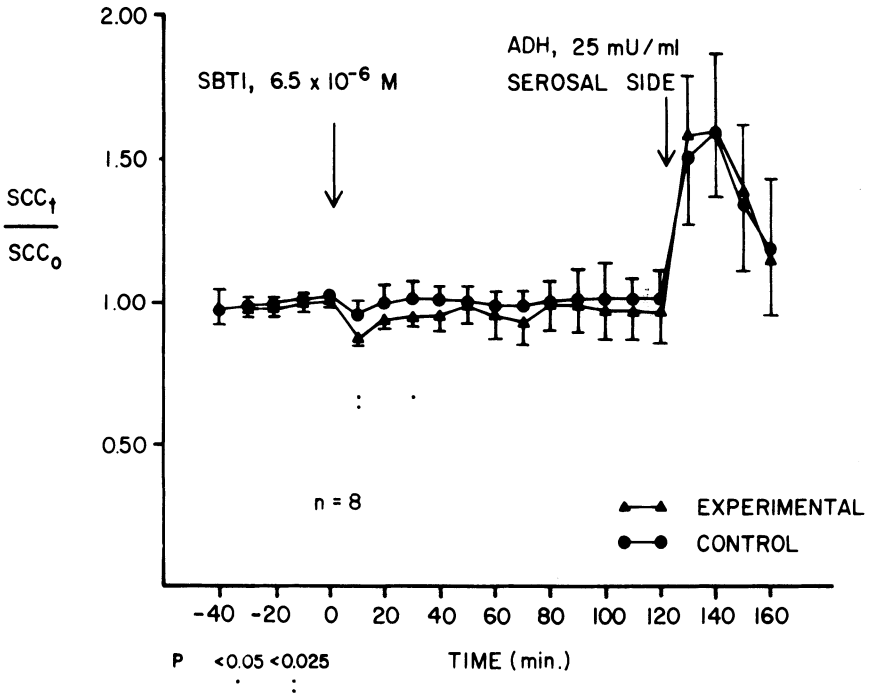

FIGURE 3. Lack of effect of mucosal soya bean trypsin inhibitor (SBTI) on base-line short-circuit current (SCC) and SCC response to vasopressin (ADH). SBTI 6.5 x 10^{-6} M was added to the mucosal bath of 1 quarter-bladder (▲), the control quarter-bladder (●) receiving an equal volume of vehicle. Vasopressin (ADH), 25 mU/ml, was added to the serosal solution of both quarter-bladders 120 min later. n=8. Reprinted from ref #13 with permission.

Figure 4 shows typical results obtained upon addition of purified rat urinary kallikrein, kallidin or mellitin to the solution bathing the stripped serosal surface of the isolated descending colon of the rat. Each substance caused an immediate increase in short-circuit current. In no case was any change in current seen with addition to the solution bathing the mucosal surface, even with kinin concentrations of 10^{-5} M or higher.

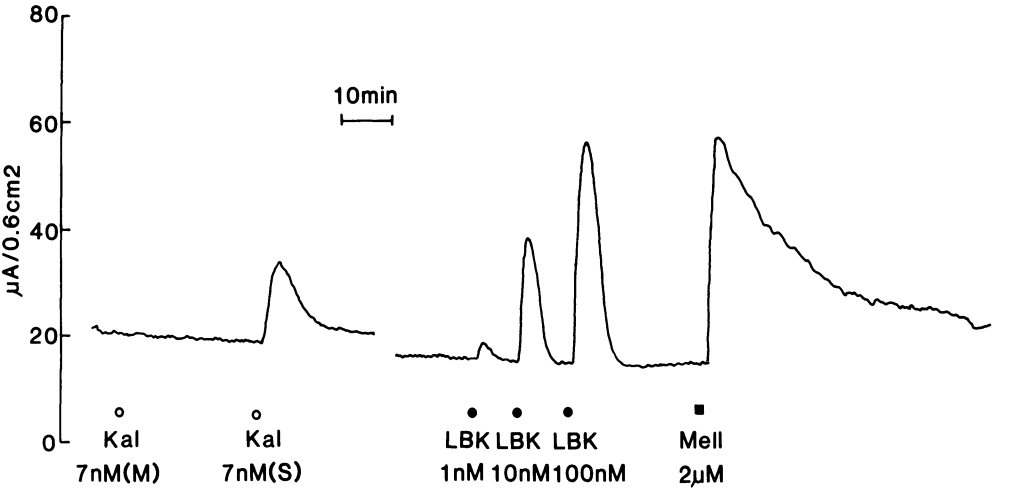

FIGURE 4. Effect of purified rat urinary kallikrein (Kal) or mellitin (Mell) on short-circuit current in the rat isolated descending colon. Responses relative to kallidin (LBK) in the same preparation are shown. "M" refers to mucosal bath and "S" to serosal bath. Addition of kallikrein, mellitin or kallidin to the mucosal bath never affected SCC, although kallikrein concentrations never reached the μM range. Reprinted with permission from ref. #14.

Table 1 shows that the changes in chloride ion movement across the colonic mucosa are more than adequate to account for the increases in short-circuit current observed. That is, the significant increase in $J_{SM}Cl$ and decrease in $J_{MS}Cl$ amount to 4.09 μEq $cm^{-2}hr^{-1}$, equivalent to ~137% of the current change caused by the kinin. Thus, the effects of kallidin are both to reduce chloride movement inwards from the lumen and to increase chloride efflux to similar extents. In other experiments, in which either ion fluxes or short-circuit currents were measured, the responses to kinins could be attenuated or abolished by furosemide (100 μM) or indomethacin (50 μM).

Table 1. Effects of kallidin on chloride fluxes in rat colon

J_{SM} (0-30)	J_{SM} (32-62)	ΔJ_{SM}	Δ SCC
16.95 ± 1.35	19.08 ± 1.57	2.13 ± 0.41	3.20 ± 0.40
	$p < 0.025$		
J_{MS} (0-30)	J_{MS} (32-62)	ΔJ_{MS}	Δ SCC
21.27 ± 1.36	19.31 ± 1.64	-1.96 ± 0.57	2.73 ± 0.56
	$p < 0.05$		

All values are given as μEq cm^{-2} h^{-1}. Each measurement is the mean value ± SEM for seven determinations. J_{SM} and J_{MS} refer, respectively to the serosal to mucosal and to the mucosal to serosal unidirectional chloride flux. Kallidin (1 μM) was present in the serosal bathing solution during the period 32-62 min, while 0-30 min was the control period. The values refer to changes in flux or in SCC caused by kallidin. Reproduced with permission, from reference 14.

4. DISCUSSION

The data summarized here do not allow construction of an obvious scheme which begins to explain the role of the tissue kallikrein-kinin system in epithelial ion transport. Nevertheless, they do support the possibility that the system could be importantly involved in such transport events. Some recent data tend to confirm the inhibitory relationship between amiloride and kallikrein described herein. Suzuki et al (16) showed that amiloride can block kallikrein-induced renin release from rat renal cortical slices. Carretero et al (17) showed that amiloride infusions intravenously reduced urinary kallikrein and kinins concomitantly with increased solute and water excretion. However, none of the data thus far collected establish that kallikrein inhibition by this drug is responsible for its principal pharmacologic effect, i.e., inhibition of sodium movement through lumenal plasma membrane sodium channels (18). The possibility that kallikrein could be involved in amiloride-induced natriuresis is supported, to some extent, by studies which suggested that the immunostainable enzyme exists at or near the lumenal plasma membranes where amiloride acts, e.g., renal distal tubule, salivary ducts, colon (19). However, any such claim must now deal with some convincing evidence that finds renal kallikrein activity is associated with renal cell baso-lateral membranes, rather than apical (lumenal) membranes (20,21).

The studies of kallikrein-like enzyme inhibition in the amphibian bladder provide only some support to the enzyme's involvement in epithelial sodium

transport. Here, we find that agents known to inhibit mammalian tissue kallikrein, inhibit short-circuit current and bladder Tos-Arg-OMe esterase activity comparably, but not completely. They act more rapidly with mucosal, than with serosal addition (13) and their effects to decrease short-circuit current are abolished in the presence of amiloride and amphotericin B (22), suggesting a site of action "upstream" of basolateral membranes.

Because the mammalian kinins, kallidin (lysyl-bradykinin) and bradykinin were without effect on short-circuit current in the toad bladder (Margolius and Cuthbert, unpublished observations), we chose to examine any ion transporting effects of these products in the rat isolated descending colon. This tissue is known to contain a tissue kallikrein, in predominantly inactive form (23), and to be aldosterone-sensitive. The availability of a highly purified homologous tissue (urinary) kallikrein (8) also allowed its effects on ion transport to be assessed. These studies established clearly that kinins are potent stimuli to short-circuit current and that the ionic movement responsible for this charge was an increase in net chloride secretion. Both kallikrein and mellitin, an activator of the membrane-bound enzyme (24) also increased short-circuit current. Each agent was effective only with serosal addition. A recent confirmation of this intestinal kinin-induced chloride secretion has also localized kinin receptors autoradiographically with highest density over the lamina propria, i.e., near the basolateral sides of mucosal epithelial cells (25). Thus, the presence of large amounts of tissue kallikrein in urine, saliva or feces; immunostaining of enzyme at or near lumenal surfaces; the inhibition of kallikreins by amiloride; and the effects of kallikrein inhibitors on sodium transport in the toad bladder, are seemingly confounded by: localization of a kallikrein activity to renal epithelial cell basolateral membranes; kinin receptors at or near such basolateral cellular sites in intestine (25); and effects of kinins, kallikrein and mellitin on ion transport only upon addition to the serosal surfaces of intestine.

We think that these contradictory findings and paradoxes compel further examination of the system's role in epithelial ion transport. Some of the questions which seem most important are stated in Table 2.

Table 2. Some questions concerning the role(s) of the kallikrein-kinin system

1. Are renal or intestinal kallikreins producing kinins locally to affect epithelial ion transport?

2. Do kinin effects on intestinal chloride secretion signify participation of intestinal kallikrein (and kinins) in intestinal diseases, specifically, the secretory diarrheas?

3. Are there associations between renal kallikrein and kinins and renal tubular chloride transport?

4. Do kallikrein and kinin effects on epithelial ion transport play any role in renal and/or hypertensive diseases?

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6. RENAL AFFERENT NERVES: EVIDENCE FOR A ROLE IN CARDIOVASCULAR REGULATION AND THE PATHOGENESIS OF EXPERIMENTAL HYPERTENSION

S. WINTERNITZ, J.M. WYSS AND S. OPARIL

ABSTRACT

Renal denervation has been shown to affect the development or maintenance of hypertension in a number of experimental models, including the spontaneously hypertensive rat of the Okamoto strain (SHR), the DOCA-salt hypertensive rat, and one- and two-kidney, one-clip Goldblatt hypertensive rats, indicating that the renal nerves play an important role in the pathogenesis of experimental hypertension. In both the SHR and DOCA-salt models the renal nerves influence the development of hypertension via an increase in renal efferent sympathetic activity, resulting in urinary sodium retention. In contrast, in the Goldblatt models studies indicate that the renal afferent nerves contribute to the maintenance of hypertension by modulating peripheral sympathetic activity, an effect that appears to be mediated via the central nervous system. In support of this hypothesis are a number of studies demonstrating that the renal afferent nerves play a role in cardiovascular regulation. Renal denervation has been shown to alter the catecholamine content of specific hypothalamic nuclei, suggesting that the renal afferents modulate central catecholaminergic activity. Electrophysiologic studies have shown that stimulation of the renal afferent nerves produces an increase in single unit activity of a number of regions in the hypothalamus and brain stem important in cardiovascular regulation and body fluid balance. In addition, the finding of both mechanoreceptors and chemoreceptors in the kidney provides a potential mechanism whereby manipulations such as clipping of the renal artery result in an increase in renal afferent nerve activity and an effect on systemic blood pressure. The recent demonstration that infusion of adenosine, a substance expected to be released during renal ischemia, into the renal artery of dogs produces sustained hypertension and increases renal afferent nerve activity provides indirect evidence for the functional role of renal chemoreceptors in the genesis of Goldblatt hypertension. Although these studies provide considerable physiologic evidence to support a connection between renal afferent nerves and central nervous system, few attempts have been made to define the anatomic projections of the renal sensory neurons. Preliminary studies indicate that dorsal root ganglion cells of the spinal cord receiving sensory input from the kidneys project to cardioregulatory centers in the brain stem.

Messerli, F.H. (ed.), Kidney in Essential Hypertension.

As early as 1945 the observation of Kottke et al that chronic renal nerve stimulation produced sustained hypertension in dogs suggested a role for the renal nerves in the regulation of arterial blood pressure (1). More recently, employing the technique of renal denervation, a number of investigators have found that the renal nerves are important in the pathogenesis of hypertension in several experimental models. In some models including the spontaneously hypertensive rat of the Okamoto strain (SHR) and the DOCA-salt hypertensive rat the renal nerves appear to influence the development of hypertension primarily via an effect on urinary sodium excretion (2,3). In others, including one-kidney and two-kidney one-clip hypertension in the rat and coarctation hypertension in the dog, evidence indicates that the renal afferent nerves influence arterial blood pressure by modulating sympathetic nervous system activity (4-7).

Several investigators have reported that renal denervation delays the development of hypertension in a genetic model, the spontaneously hypertensive rat of the Okamoto strain (SHR) (3,8-10). In one study, repeated denervations at 3 week intervals resulted in a chronic attenuation of hypertension (10). Experiments completed in our laboratory indicate that the depressor effect of renal denervation in SHR is due to interruption of efferent sympathetic input to the kidney (3). In those experiments male SHR had bilateral renal denervation or sham operation at 7 weeks of age. Systolic blood pressure and urinary sodium excretion were monitored for five weeks after operation. Renal denervation slowed the development of hypertension and resulted in a significant increase in urinary sodium excretion. As blood pressures of denervated and sham operated animals converged during the fifth week after operation, urinary sodium excretion was no longer different between groups. In an earlier study, Katholi et al reported similar findings in the DOCA-salt model of hypertension. The results of these studies provide evidence that in certain experimental models the renal nerves contribute to the development of hypertension by causing increased urinary sodium retention due to increased efferent sympathetic activity.

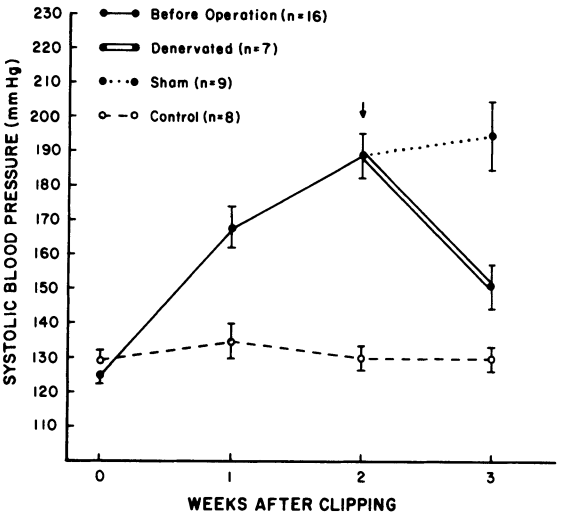

Figure 1. Effects of renal denervation on blood pressure of the one-kidney one-clip rat. Arrow indicates the time of renal denervation or sham operation. Values are means ± SEM.

More recently, studies of the effects of renal denervation in one-kidney one-clip Goldblatt hypertension indicate that the renal afferent as well as the renal efferent nerves are involved in the pathogenesis of experimental hypertension (4,5). In initial experiments with the one-kidney one-clip model (1-K) Katholi et al found that renal denervation performed two weeks after renal artery clipping resulted in a significant decrease in systolic blood pressure as shown in Figure 1 (11). There was no difference in urinary sodium excretion, plasma renin activity or creatinine clearance between denervated and sham operated animals. The lack of a change in renin, sodium excretion and renal function indicated that the depressor effect of renal denervation in 1-K was not due to interruption of the renal efferent nerves.

A subsequent series of experiments was undertaken to examine the hypothesis that the effects of renal denervation in 1-K are due to interruption of the renal afferent nerves (4,5). In these studies 1-K were again subjected to renal denervation or sham operation two weeks

after clipping. Uninephrectomized age and sex matched rats were used as controls. Renal denervation resulted in a significant decrease in blood pressure (200±7mmHg control versus 150±6mmHg 1wk post denervation). One week following denervation or sham operation plasma norepinephrine and mean blood pressure before and after ganglionic blockade were determined in conscious unrestrained animals as indices of peripheral sympathetic activity. Plasma norepinephrine was significantly higher in hypertensive sham operated rats than in control uninephrectomized animals (422±42 pg/ml, sham versus 282±25 pg/ml, control, $p<0.01$). Renal denervation resulted in a decrease in plasma norepinephrine to normal levels (273±22pg/ml). In addition, ganglionic blockade resulted in a significantly greater decrease in blood pressure in sham operated animals in comparison to renal denervated and control animals. These data indicate that the fall in blood pressure following renal denervation in 1-K is, in part, secondary to a decrease in peripheral sympathetic activity.

To determine if the effect of renal denervation on blood pressure and sympathetic activity is mediated via the central nervous system, central catecholamine stores were examined one week after renal denervation of 1-K (5). In those experiments renal denervation or sham operation was again performed two weeks after clipping. One week later animals were sacrificed by decapitation without anesthesia, spinal cords and brains removed and brains dissected into hypothalamus, midbrain and pons-medulla. Tissues were analyzed for catecholamine content using high performance liquid chromatography with electrochemical detection. In agreement with the findings of other investigators clipped sham operated animals showed a significant increase in the norepinephrine content of the hypothalamus. As shown in Figure 2, renal denervation resulted in a significant decrease in hypothalamic norepinephrine content to the level of controls. No changes were observed in other brain regions studied. Dopamine content was not different between groups in any region. These data, combined with the findings of a decrease in peripheral sympathetic activity following renal denervation, suggest that the renal afferent nerves may play a role in established 1-K by modulating central sympathetic outflow.

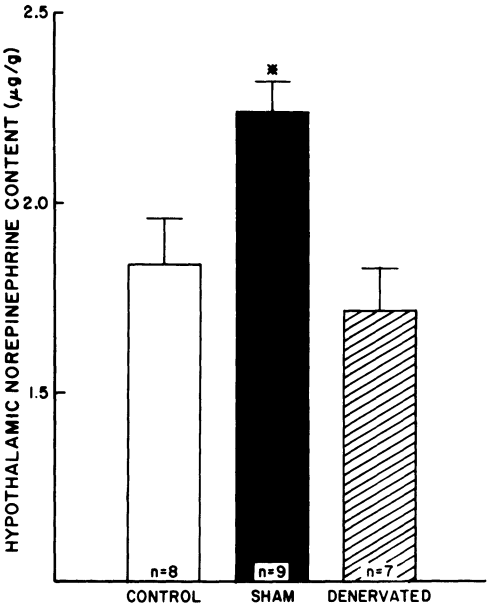

Figure 2. Hypothalamic norepinephrine content of renal-denervated, sham-operated, and control animals. Values are means ± SEM. *$p<0.01$, difference from control.

Additional evidence that the renal afferent nerves are involved in the pathogenesis of experimental hypertension comes from studies of the effects of renal denervation of two-kidney one-clip Goldblatt hypertension in the rat (2-K) and coarctation hypertension in dog (6,7). As observed in 1-K, denervation of the clipped kidney of 2-K with established hypertension resulted in a significant decrease in blood pressure. Plasma norepinephrine levels and the depressor response to ganglionic blockade in hypertensive 2-K were increased in comparison to those of normotensive unclipped controls. Renal denervation resulted in a return of plasma norepinephrine levels and the depressor response to ganglionic blockade to control levels, indicating that the attenuation of hypertension following renal denervation in 2-K results from a decrease in peripheral sympathetic activity. Whitlow and Katholi reported similar findings following

bilateral renal denervation in dogs with chronic coarctation hypertension (7).

Taken together, the aforementioned studies indicate that in a number of experimental models the renal afferent nerves contribute to the maintenance of hypertension and that the depressor effect of renal denervation in these models is, at least in part, secondary to a decrease in sympathetic nervous system activity.

In support of this hypothesis are a number of physiologic studies indicating that there are connections between the renal afferents and the central nervous system. Fernandez et al observed that renal denervation in the rat resulted in an increase in the norepinephrine content of whole hypothalamus without a significant change in blood pressure (12). In a more recent study, Caleresu and Ciriello examined the effects of renal denervation on the catecholamine content of specific hypothalamic nuclei (13). These investigators reported that following renal denervation, the norepinephrine content of the supraoptic nucleus is increased, the epinephrine content of the paraventricular and lateral hypothalamic area is increased and the dopamine content of the supraoptic nucleus, medial preoptic nucleus and lateral hypothalamic area is decreased. The findings of these studies suggest that the renal afferent nerves modulate central catecholaminergic activity and thereby may influence cardiovascular homeostasis.

More direct evidence is provided by studies examining the effects of direct stimulation of the renal nerves. Electrical stimulation of the renal afferent nerves has been shown by a number of investigators to produce a change in systemic arterial pressure, although there is disagreement as to whether this response is pressor or depressor (14-16). The apparent discrepancies in findings among laboratories have been attributed to differences in anesthesia (16). Stimulation of the renal afferents of one kidney has been shown to produce a reflex increase in efferent nerve activity and arteriolar vasoconstriction in the opposite kidney (17-19). The observation that this response is abolished by spinal cord sectioning suggests that this reno-renal reflex is mediated via supraspinal neurons (17-19). In addition, Brody and colleagues found that stimulation of the renal

afferent nerves in the rat resulted in changes in resistance in hind limb, mesenteric and renal vascular beds, and that this response was abolished by lesioning the periventricular tissue surrounding the anteroventral third ventricle, the AV3V region (20). These findings indicate that there is a feedback loop between the renal afferents and the anterior hypothalamus.

Studies of Caleresu and Ciriello provide additional evidence that the central connections of the renal afferent nerves are involved in cardiovascular regulation (21). These investigators measured the electrical activity of spontaneously firing single units in the medulla and hypothalamus during stimulation of the afferent renal nerves of anesthetized cats and found responsive units in a number of areas. Following nerve stimulation, changes in activity were observed in the lateral tegmental field, the area of the paramedian reticular nucleus and the dorsal vagal complex of the medulla, the lateral hypothalamic area, the lateral preoptic area and the paraventricular nucleus of the hypothalamus. Many of the regions where responsive units were detected are thought to be involved in body fluid regulation and cardiovascular homeostasis (21-25). In addition, most of the areas responsive to afferent renal nerve stimulation also responded to carotid sinus nerve stimulation.

The observation that there are both mechanoreceptors and chemoreceptors in the kidney provides a potential mechanism by which manipulations, such as clipping of the renal artery, result in increases in afferent nerve activity and an effect on systemic blood pressure. These receptors have been shown to respond to a variety of stimuli resulting in alterations in afferent renal nerve activity (14,26-30). Studying anesthetized dogs, Ueda et al showed that increases in intrarenal pressure produced by compression of the kidney, renal vein occlusion or elevation of perfusion pressure increased the action potentials of the afferent renal nerves (14). Niijima observed a similar increase in afferent renal nerve activity in the rabbit following an increase in arterial perfusion pressure (27). More recently, in extensive studies Recordati and Moss showed that stimulation of renal chemoreceptors resulted in increases in renal afferent nerve activity (28-30). These investigators demonstrated two

populations of chemoreceptors in the rat kidney, both of which are sensitive to renal ischemia and one of which senses changes in the ionic composition of the pelvic urine.

The potential importance of renal chemoreceptors in the regulation of arterial pressure is emphasized by the recently reported findings of Katholi et al (31). These investigators found that adenosine infusion into the renal artery of conscious and anesthetized dogs resulted in a significant increase in blood pressure. Afferent renal nerve traffic, recorded in anesthetized animals, was increased during unilateral renal artery adenosine infusion. In addition, there was an increase in vascular resistance in the opposite kidney suggesting activation of the peripheral sympathetic nervous system. The authors hypothesized that an increase in renal adenosine release in response to mechanically produced renal artery stenosis in one-kidney one-clip and two-kidney one-clip Goldblatt hypertension might be a mechanism for activation of the sympathetic nervous system via the renal afferent nerves.

Although the aforementioned physiologic studies provide support for an important physiologic role for the renal afferent nerves, little is known about the anatomic projections of the renal sensory neurons. Studies are underway in our laboratory which are designed to map the central projections of the renal afferent nerves (32,33). In initial experiments the fluorescent dye technique of Kuypers was used to demonstrate the location of renal sensory neurons in the dorsal root ganglia of the rat (32). In those studies, 200-250gm Sprague-Dawley rats were sacrificed 2-7 days following injection of either true blue or fast blue into both kidneys and the dorsal root ganglia examined using a fluorescence microscope (Leitz A filter system). The renal afferent nerves were seen to project to the sixth thoracic to second lumbar dorsal root ganglia. The greatest concentration of labeled cells was at the T_{13} ganglion on the left and the T_{11} ganglion on the right. In a more recent study, we employed double labeling techniques with nuclear yellow and true blue dyes to define the central projections of the dorsal root ganglia labeled by the renal afferent nerves (33). When injected at the terminal field of a projection, nuclear yellow labels the nucleus of the cell body of origin, and true blue labels the cytoplasm of the cell body of origin. The different

location as well as the different spectral emission frequencies of these fluorochromes allow easy differentiation of cells labeled by one or both. Nuclear yellow was injected into the posterior medulla oblongata, and true blue into the cortex of the kidney of Sprague-Dawley rats, and dorsal root ganglia were examined as described above. Although most were singly labeled (either yellow or blue), a number of doubly labeled neurons were observed. The finding of doubly labeled cells indicates that there are dorsal root ganglion cells receiving sensory information from the kidney that project to the posterior medulla and provides the first anatomic evidence for a direct neural connection between the renal afferents and the brain stem.

In summary, experiments examining the effects of renal denervation of the development of maintenance of increased arterial pressure in a number of experimental models have emphasized the importance of the renal nerves in the pathogenesis of experimental hypertension. While in some models, such as the SHR, the renal efferent sympathetic nerves appear to contribute to the development of hypertension by influencing urinary sodium excretion, in others, such as the one-kidney one-clip hypertensive rat, data suggest that the renal afferents modulate peripheral sympathetic activity by influencing central sympathetic outflow. In support of the latter interpretation are a number of physiologic studies indicating that there is a neural connection between the kidney and the central nervous system. Further, preliminary studies employing the flourescent dye technique have provided anatomical evidence for a monosynaptic connection from the renal afferent nerves to cardioregulatory centers of the brain stem.

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7. RENAL BLOOD FLOW AND FUNCTION IN ESSENTIAL HYPERTENSION

N.K. HOLLENBERG

ABSTRACT

An abnormality of the renal blood supply clearly is responsible for the hypertension in the patient with renal vascular disease: the possibility that an abnormality of the renal blood supply also participates in the pathogenesis of essential hypertension, as a factor initiating or sustaining the rise in blood pressure, has been the subject of recurring interest for many decades. There is clearly a functional abnormality, reflected in increased renal vascular tone easily reversed in about two-thirds of patients with uncomplicated, mild to moderate essential hypertension. The responsible mediators have not been identified, but local actions of angiotensin and norepinephrine have been implicated. In patients with advanced nephrosclerosis, a fixed, organic abnormality of the renal microvasculature is routinely present and probably contributes to the severity of the hypertension and renal failure. In another group of patients, perhaps reflecting 40-50% of patients with essential hypertension, there is an abnormality involving both the kidney and the adrenal, with disordered control via angiotensin. Substantial evidence points to a pivotal role of the kidney in sustaining hypertension, whatever the initial cause of the elevated blood pressure. A perfectly normal renal arterial tree, free of an organic or a functional abnormality, is distinctly unusual in essential hypertension, and is probably involved in the pathogenesis or maintenance of hypertension in many patients.

The observation that a reduction in renal blood flow induced by partial occlusion of the major renal artery can induce

Messerli, F.H. (ed.), Kidney in Essential Hypertension.

hypertension, an unequivocal phenomenon, continues to raise the interesting possibility that an abnormality in renal perfusion also contributes to the pathogenesis of a still-puzzling process, essential hypertension. The prominent role that the kidney must play in sustaining an increase in blood pressure, however the hypertension is initiated, has been brought into sharp focus by the system's analysis approach of Guyton and his co-workers (1). This essay will focus on the possibility that the kidney's participation involves the renal blood supply, and examine the available evidence on the nature of that participation. Whether the renal blood supply is involved in the initiation of the process is a question that remains unanswered.

Clearance techniques provided the first approach to assessing renal perfusion in man. Homer Smith concluded, over 40 years ago, that "the evidence in man argues against primacy of renal ischemia in the pathogenesis of essential hypertension", a conclusion supported by eight references from the then-recent literature on the first application of clearance techniques in attempts to answer this question (2). Not that clearance methods failed to reveal many patients in whom renal perfusion and function were reduced: indeed, Smith's own study revealed a diodrast clearance that was less than the average normal value in 57 of 60 patients with essential hypertension (3). The critical point was that renal perfusion in most patients was in the normal range. The renal biopsy and necropsy also often reveal normal vessels in patients with essential hypertension. The debate has continued about possible contributions of the renal blood supply, despite apparently negative evidence, because of intrinsic limitations of the earlier approaches, reviewed in detail elsewhere (4).

In the following review I will focus primarily on evidence for an abnormality reflecting increased renal vascular tone in about two-thirds of patients with essential hypertension. A second line of investigation indicates that a subgroup of patients with essential hypertension has a parallel abnormality in the renal blood supply and the adrenal. The abnormality

appears to reflect an alteration in their response to angiotensin with shifts in sodium intake.

Renal Vascular Tone in Essential Hypertension. Indicator dilution techniques, applied to assessing the renal blood supply in the patient with essential hypertension, have documented a frequent reduction in cortical perfusion, whether the index employed was the determination of Tm PAH (2), the character of xenon or krypton transit (4-13), the character of dye transit across the kidney (14, 15), or detailed analysis of radiohippuran transit (16). Despite the unanimity of the conclusions, the investigators have been unable to ascertain whether the reduction in cortical blood flow was due to parenchymal atrophy reflecting organic microvascular disease or vasoconstriction--although sometimes they favored the latter (15).

How does one assay vascular tone? We have used three approaches, all of which suggest that a functional abnormality, active vasoconstriction, plays an important - perhaps primary - role in the reduction in renal blood flow in most patients. Our working hypothesis in making that assessment was that an organic lesion, reflecting permanent vascular damage that is fixed, would be associated with a fixed reduction in renal blood flow. Conversely, a function abnormality might induce a more variable reduction in renal perfusion. A related hypothesis was that fixed organic lesions would be unresponsive to vasodilators, whereas a functional abnormality might be expected to show an enhanced response. All approaches have led to an identical conclusion: there is, indeed, increased vascular tone in the renal bed of two-thirds of patients with essential hypertension.

Some years ago a striking difference in renal perfusion between the two kidneys was noted when blood flow was measured by PAH clearance and bilateral ureteral catheterization was employed in patients with essential hypertension (17). The difference was attributed, not unreasonably, to asymmetric progression of organic microvascular disease. If an equivalent difference in renal perfusion was demonstrable in sequential measurements of blood flow in the same kidney, however, organic

changes could not be responsible. The lesion clearly is not fixed. We have demonstrated such a difference in sequential studies on the same kidney in patients with essential hypertension (11). Reanalysis of sequential studies performed with indicator dilution years earlier also showed an equivalent, three-fold increase in variability in comparison with normal subjects (4, 18): Renal blood flow ranged from normal to low in minutes.

Strong support has come from studies with a range of vasodilators. A dose and time-related increase in renal blood flow was documented in response to acetylcholine and dopamine in normal man, and the renal response was blunted strikingly in patients in whom organic microvascular disease might have been anticipated (19). Conversely, the response to both agents was potentiated in 69% of patients with mild essential hypertension. Does a potentiated response reflect vasoconstriction? An equivalent potentiation of the renal vascular response to acetylcholine was induced in normal subjects by increasing renal vascular tone pharmacologically, with angiotensin, suggesting that the potentiated vascular response to vasodilators indeed reflected an increase in tone.

Striking changes in the renal vascular response to vasodilators reflected in the renal arteriogram were in excellent accord with this notion: the potentiated response to acetylcholine and to dopamine in essential hypertension was associated with reversal of the small vessel abnormalities at the level of the distal interlobar and arcuate arteries, visualizable in the renal arteriogram (19). Conversely, the reduced renal blood flow response in advanced nephrosclerosis or renal parenchymal disease was associated with a reduced or absent response to the vasodilator evident in the renal arteriogram. Thus, this line of investigation, too, suggested an intrinsic increase in renal vascular tone in about two-thirds of patients with essential hypertension.

Candidates for the abnormality include an increase in the renal concentrations of endogenous vasoconstrictor agents, such as norepinephrine, angiotensin, or as yet unidentified

vasoconstrictor mediators; as an alternative there could be an increase in renal vascular responsiveness to normal concentrations of the vasoconstrictor agents. Substantial evidence indicates that vascular smooth muscle responsiveness in other beds is enhanced in essential hypertension (20, 21).

There are few reports on renal vascular reactivity in essential hypertension. A reduced, rather than potentiated, renal vascular response to angiotensin administrated intravenously was reported in essential hypertension, along with a reversal of the renal functional effects of angiotensin in these patients (22). Several groups have reported a striking increase in the renal vascular response to nonpharmacologic stimuli, emotion and exercise, in patients with essential hypertension (23-25).

The precise explanation for the enhanced renal response to vasodilators remains obscure. The fact that a potentiated response occurred to phentolamine, the alpha adrenergic blocking agent (19) and to converting enzyme inhibition (26-28) suggested that norepinephrine and angiotensin might both be involved. Enhanced responses occurred in patients with a normal plasma catecholamine and plasma-angiotensin II concentration. The fact that the concentrations of the hormones were normal and that both endogenous agonists appeared to be involved suggests that an enhanced vascular response to normal concentrations of the hormones is responsible. Unfortunately, neither the alpha adrenergic blocking agents nor converting enzyme inhibitors have sufficient specificity that responses to them lead to interpretations that are free of doubt.

The Renal Blood Supply and Aldosterone Release in Essential Hypertension. During the 1970's it became progressively more clear that the normal control of both the renal blood supply and the adrenal was dominated by angiotensin II, an advance that was heavily dependent on the development of effective means for achieving pharmacologic interruption of the renin-angiotensin system. At the same time evidence for striking variations in the responsiveness to angiotensin of these systems with changes in sodium intake was accumulating. These conceptual advances

had implications for two parallel, and apparently unrelated lines of investigation on the pathogenesis of essential hypertension.

Abnormal control of the renal circulation was identified in a substantial subgroup of young patients with essential hypertension, and the tentative suggestion was made that the abnormality reflected a subpopulation in whom the renal blood supply did not show the normal, anticipated response to changes in sodium intake (8). Continued experience confirmed that observation and extended it (11), making it possible to estimate the frequency of the abnormality - about one-third of the patients with essential hypertension studied, without reference to their status in a renin classification. The fact that one or both parents in this subgroup had hypertension in every assessible case provided an intriguing clue: perhaps these individuals inherited whatever the renal abnormality was?

At the same time an abnormality in adrenal responsiveness to volume challenge was identified in some patients with essential hypertension (29). Because plasma renin activity and plasma angiotensin II concentration in these patients was normal, it was reasonable to suggest that the underlying abnormality was an alteration in the angiotensin-aldosterone relationship, as was subsequently documented (30).

Because angiotensin is pivotal to the control of both the renal blood supply and to adrenal release of aldosterone as dietary sodium intake varies, it became reasonable to ask whether the abnormality was present in both systems in the same patient. The answer was unequivocal: parallel renal and adrenal abnormalities coexisted in the same patients with essential hypertension (31). Moreover, the abnormality was present in 40-50% of patients under the age of 30 years and with a documented, brief history of hypertension, sufficiently early in the course that it was unlikely to reflect the consequences of long-standing hypertension. Neither measurable differences in cardiac output nor in plasma volume could account for the phenomenon (31). The data were compatible with a parallel blunting of responsiveness to angiotensin in both systems.

Preliminary data suggest that the abnormality reflects disordered modulation, with shifts in sodium intake, of the renal vascular and adrenal response to angiotensin II (32), and that converting enzyme inhibition corrects the abnormality (33), an observation that could account for the stiking effectiveness of this class of agent when detailed analysis of the state of the renin-angiotensin system would otherwise not account for such effectiveness.

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8. THE KIDNEY AND EXPERIMENTAL HYPERTENSION

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ABSTRACT

This paper summarizes theoretical and experimental evidence which suggests that in various experimental forms of hypertension, increased renal perfusion pressure is an essential circulatory compensation that allows normal excretion of salt and water despite reduced glomerular filtration or increased tubular reabsorption which tend to decrease renal excretion. When renal perfusion pressure is prevented from increasing during chronic administration of antinatriuretic hormones such as angiotensin II or aldosterone, severe abnormalities of body fluid volumes occur often leading to pulmonary edema, ascites, or even death. Thus, chronic hypertension appears to be a homeostatic response to an inability of the kidneys to maintain sodium and water balance at normal arterial pressure.

1. INTRODUCTION

The importance of the kidney in the etiology of hypertension is widely recognized, but the quantitative importance of the different renal mechanisms in normal control of arterial pressure and how they are altered in hypertension are still very controversial.

Several connections between the kidney and blood pressure regulation have been suggested, including the various renal hormone systems such as the renin-angiotensin system, the kallikrein-kinin system, and the renal prostaglandins. The kidneys are also believed to be capable of stimulating reflex pathways, via renal afferent nerve fibers connected to the sympathetic nervous system (1). But perhaps the most basic renal mechanism for long-term control of arterial pressure is through the control of salt and water excretion, and therefore extracellular fluid volume. This mechanism for blood pressure control, often referred

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to as the renal-body fluid feedback system, is closely interrelated with the hormonal and neural control mechanisms of the kidney (2). For example, the renin-angiotensin system is a major controller of renal sodium and water excretion, and therefore can influence blood pressure regulation via the renal-body fluid feedback system (3,4).

The major goals of this paper are to briefly describe the main features of the renal-body fluid feedback system for blood pressure regulation, to discuss the major assumptions that this concept is based upon, and to show how abnormalities of this control system can lead to chronic hypertension.

2. RENAL-BODY FLUID FEEDBACK MECHANISM FOR ARTERIAL PRESSURE REGULATION.

A primary component of this feedback control system is the effect of renal perfusion pressure on excretion of salt and water; when renal arterial pressure increases, salt and water excretion also increases, and remains elevated above salt and water intake until arterial pressure returns to normal (Figure 1).

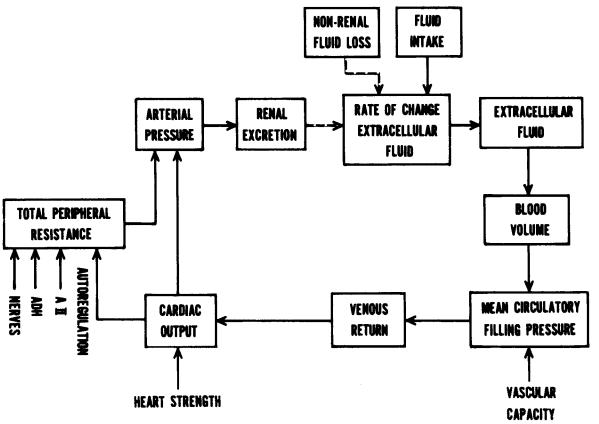

FIGURE 1. Basic components of renal body-fluid feedback system for regulation of arterial blood pressure. Solid lines indicate positive effects and dashed lines indicate negative effects.

As long as salt and water excretion exceeds intake of salt and water, extracellular fluid volume and blood volume will continue to decrease, lowering mean circulatory filling pressure, venous return, and cardiac output until arterial pressure returns to normal and salt

and water intake and output are in balance (2). Conversely, when renal arterial pressure decreases, the kidneys retain salt and water until arterial pressure is restored to normal.

A disturbance that decreases the kidneys' capability to excrete salt and water will tend to increase extracellular fluid volume and blood volume if salt and water intake remains constant thereby increasing mean circulatory filling pressure and venous return and leading to increased cardiac output and hypertension. Arterial pressure will continue to increase until renal excretion of salt and water is restored to normal, so that intake and output are in balance. Thus, the renal body-fluid feedback concept of blood pressure regulation implies that hypertension is a homeostatic response to an inability of the kidneys to maintain sodium and water balance at normal arterial pressure (5,6).

Contrary to the belief of many investigators, abnormalities of the renal-body fluid feedback mechanism for blood pressure control that lead to hypertension are not always associated with increased extracellular fluid volume, increased blood volume, or increased cardiac output. For example, an increase in total peripheral resistance associated with a decrease in the kidneys' ability to excrete sodium, as would occur with excessive secretion of certain vasoconstrictors, could lead to a decrease or no change in blood volume and cardiac output, but still cause hypertension through this mechanism. The long-term effect of a vasoconstrictor on body fluid volumes would depend upon the relative effects of the vasoconstrictor on the renal and peripheral vasculatures, since peripheral vasoconstriction would tend to raise arterial pressure above the renal set-point and cause natriuresis and diuresis, whereas renal vasoconstriction would tend to decrease salt and water excretion. Therefore measurements of body fluid volumes do not necessarily provide an adequate assessment of whether the kidneys' ability to excrete salt and water is reduced in various forms of hypertension.

2.1 Assumptions and Implications of the Renal-Body Fluid Feedback Theory of Blood Pressure Regulation. The renal-body fluid feedback system for blood pressure control is based on the assumption that renal perfusion pressure is an important factor in controlling salt and water excretion, an assumption that is supported by numerous short-term

studies that have clearly demonstrated the phenomena of pressure natriuresis and diuresis (7,8,9). However, the effects of chronic changes in renal perfusion pressure are much more difficult to quantitate and therefore only a few experimental studies have directly addressed this problem, as discussed below. But if one accepts the premise that arterial pressure has a long-term effect on renal excretion, then several conclusions regarding the role of the renal-body fluid feedback system in blood pressure regulation and hypertension become immediately apparent. First, it is clear that as long as the relationship between arterial pressure and renal excretion (i.e. the renal function curve) is unaltered, balance between fluid intake and output can occur at only one level of arterial pressure. When arterial pressure increases above this level, renal excretion will increase above the level of intake, decreasing extracellular fluid volume and blood volume, and eventually decreasing cardiac output and arterial pressure all the way back to the level at which fluid intake and output are balanced. Conversely, if arterial pressure falls below the set-point, renal excretion will be reduced below the level of intake, causing an increase in extracellular fluid volume, an increase in blood volume and cardiac output, and a return of arterial pressure all the way back to the initial set-point.

It is also clear that if salt and water intake remains constant, chronic hypertension can occur only if the renal function curve is altered and that factors which do not alter the steady-state relationship between arterial pressure and renal excretion can cause only a transient change in arterial pressure. For example, a primary increase in total peripheral resistance, with no change in the steady-state relationship between arterial pressure and renal excretion, is predicted to cause a transient increase in arterial pressure, which elevates renal excretion above the level of intake, decreases extracellular fluid volume and blood volume, and reduces cardiac output and arterial pressure toward normal; renal excretion would remain elevated, above the level of intake, and arterial pressure would continue to decrease until it returns all the way back to the set-point at which salt and water intake and output are in balance. A primary increase in cardiac output (i.e. caused by a decrease in vascular capacity or an increase in heart strength) would cause a similar

transient increase in arterial pressure, but unless there was a change in the steady-state relationship between arterial pressure and renal excretion there would be no long-term effect on arterial pressure because the renal-body fluid feedback system would continue to compensate until arterial pressure returned all the way back to the initial control level. Thus, a change in total peripheral resistance or cardiac output that is not associated with a change in the renal function curve would not cause a long-term change in arterial pressure, according to this concept.

Accordingly, the renal-body fluid feedback concept for blood pressure control implies that the sympathetic nervous system and the various hormonal systems of the kidney, including the kallikrein-kinin system, the renal prostaglandins, and the renin-angiotensin system, are important in long-term regulation of arterial pressure and in causing chronic hypertension only insofar as they affect the long-term relationship between arterial pressure and renal excretion. Their actions on the peripheral vasculature and on the heart may have important short-term effects on arterial pressure and on certain hemodynamic variables such as blood volume, cardiac output, and total peripheral resistance associated with long-term changes in pressure, but these effects do not influence the final level at which arterial pressure is regulated.

This concept of blood pressure control has been previously discussed in detail by Guyton (2,5) but has remained controversial despite the efforts of many researchers who have attempted to test these ideas experimentally. However, if the basic premise of the renal body-fluid feedback concept of blood pressure control is correct (i.e. if there is a long-term effect of arterial pressure on urinary salt and water excretion), then arterial pressure must adapt to whatever level is necessary to achieve sodium balance. And, one is forced to conclude that the primary long-term controller of arterial pressure is the kidneys' ability to excrete salt and water, and that hypertension is a consequence of the kidneys' inability to maintain salt and water balance at normal arterial pressure. However, if there is no long-term relationship between arterial pressure and urinary sodium excretion, then the kidneys must have the capability to <u>fully</u> adapt their excretion of salt and water to changes in blood pressure so that intake

and output are equal regardless of the level of arterial pressure. If so, changes in total peripheral resistance and cardiac output could play a major role in regulating arterial pressure chronically and the shift of the renal function curve along the arterial pressure axis that is observed in hypertension could be a consequence rather than a cause of hypertension.

3. SHIFT OF THE RENAL FUNCTION CURVE--A CAUSE OR A CONSEQUENCE OF HYPERTENSION?

It is clear that in chronic hypertension, urinary excretion of salt and water is approximately the same as in normotension indicating a shift of the renal function curve so that the same level of excretion is achieved at higher pressures. Thus, the key question is not whether there is actually a shift of the renal function curve in hypertension, but whether the shift of the renal function curve is a cause or a consequence of hypertension.

One explanation that has been proposed to explain the shift of the renal function curve in hypertension, is that renal excretory function decreases as a result of the hypertension and that a primary decrease in renal excretory capability (a shift of the renal function curve) is not necessarily involved in the etiology of hypertension (10,11). This concept predicts that a primary increase in total peripheral resistance (i.e. caused by constriction of the peripheral vasculature) or a primary increase in cardiac output (i.e. caused by a decrease in vascular capacity or increased heart strength) would raise the arterial pressure, temporarily increasing renal excretion of salt and water above the level of intake and decreasing extracellular fluid volume; the reduction in extracellular fluid volume is proposed to stimulate formation of antinatriuretic substances, such as angiotensin II (AII) and aldosterone, which would then decrease the slope of the arterial pressure-urinary output relationship so that normal water and electrolyte balance could be maintained at higher than normal arterial pressure. According to this view, a shift of the renal function curve would be a consequence of an increase in arterial pressure caused by increased total peripheral resistance or increased cardiac output and not the cause of the hypertension. This proposition necessarily leads to the conclusion that the kidney has the capability to completely

adapt or "autoregulate" its excretion irregardless of the level of arterial pressure, and that arterial pressure plays no role in determining the chronic level of urinary output. One obvious difficulty with this hypothesis is that almost all acute experiments that have been conducted suggest that increases in renal perfusion pressure would tend to suppress, rather than elevate, formation of the two primary known antinatriuretic hormones, AII and aldosterone (12).

At present, there is no direct support for the concept that the kidneys can completely reset their excretion as a consequence of hypertension caused by an extrarenal mechanism. However, two experimental studies often cited as evidence that hypertension can develop without a primary change in renal function deserve mention. Liard et al. (13,14) produced chronic hypertension by electrical stimulation of the left stellate ganglion or by chronic infusion of dobutamine (an inotropic agent) into the left coronary artery in conscious dogs. In these models of "cardiogenic" hypertension, there was an initial increase in cardiac output followed by a return of cardiac output toward normal and a gradual increase in total peripheral resistance associated with the chronic hypertension. One interpretation of these findings is that the kidneys could not fully correct for an increase in arterial pressure of extrarenal origin and that other mechanisms (humoral or intrinsic renal mechanisms) caused the renal function curve to shift after the initial increase in pressure so that a normal level of urinary sodium excretion was achieved despite increased arterial pressure. However, Liard (10) also noted that stellate ganglion stimulation or dobutamine infusion may have reflexly increased activity of the sympathetic nervous system, thereby shifting the renal function curve at the same time that cardiac output was elevated. Thus, while these experiments could be interpreted as being consistent with the concept that chronic hypertension can develop in the absence of a primary shift of the renal function curve, they also do not rule out the possibility that a change in renal function was associated with cardiac stimulation.

If changes in total peripheral resistance and cardiac output can cause sustained hypertension, in the absence of alterations in renal function, it becomes difficult to explain several pathophysiological conditions associated with large changes in cardiac output or total

peripheral resistance but with no abnormality of renal function and no chronic change in blood pressure. For example, opening a large arterio-venous fistula, which has no direct effect on renal function, decreases total peripheral resistance and transiently lowers arterial pressure. However, the reduction in arterial pressure also tends to cause salt and water retention, and cardiac output is usually elevated enough to offset the fall in total peripheral resistance so that arterial pressure is eventually restored to the normal level (2). Large increases in total peripheral resistance caused by sudden closure of an arterio-venous fistula, amputation of the limbs, or hypothyroidism also cause little change in the level at which blood pressure is regulated chronically (2). In all of these examples, changes in total peripheral resistance cause no long-term change in arterial pressure, but instead cause inverse changes in cardiac output. These observations are consistent with the concept that the renal-body fluid feedback mechanism is capable of preventing chronic changes in arterial pressure in the face of marked changes in total peripheral resistance or cardiac output if the kidneys' ability to excrete sodium and water is not altered.

3.1 Evidence that the Renal Function Curve Does not Fully Adapt to Changes in Arterial Pressure. In addition to examples cited above in which primary increases in total peripheral resistance or cardiac output failed to produce chronic hypertension in the absence of changes in renal function, there have also been some experimental studies which indicate that the kidneys do not completely adapt their excretory function to changes in arterial pressure.

Pan et al. (15) studied the chronic effects of changes in renal perfusion pressure on renal excretion by placing a clamp on the aorta between the two renal arteries so that constriction of the aorta decreased the perfusion pressure in one kidney while increasing pressure in the contralateral kidney. By utilizing a split-bladder technique, urine was collected from each kidney separately. Since both kidneys were exposed to the same efferent sympathetic nerve activity, the same circulating hormones and other blood-borne factors, the only major differences between the kidneys were the differences in perfusion pressure and the intrarenal changes caused by altered perfusion pressure. Pan et al. found that small changes in renal perfusion pressure, maintained for several days, were

associated with large changes in urinary sodium excretion. For example, with a pressure gradient of only 25 mmHg, the kidneys with the high perfusion pressure excreted almost 12 times as much sodium as the kidneys with reduced perfusion pressure. These observations suggest that renal perfusion pressure has a profound long-term effect on renal excretion.

Figure 2 illustrates another experiment in our laboratory in which the effects of a chronic reduction in renal perfusion pressure on renal excretion were examined.

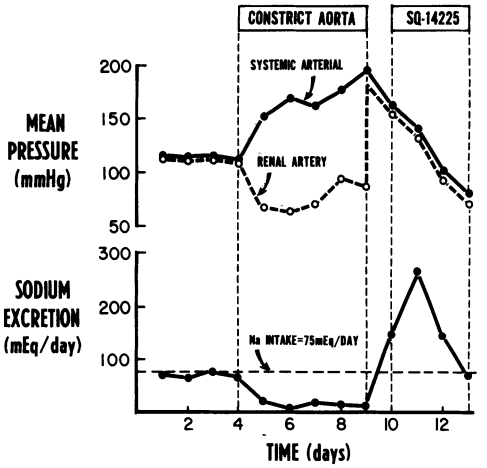

FIGURE 2. Effect of prolonged reduction in renal perfusion pressure on mean systemic arterial pressure and urinary sodium excretion.

In this experiment, perfusion pressure to both kidneys was reduced to approximately 70-80 mmHg with an externally adjustable aortic occluder and maintained at or near this level for 5 days by continuously adjusting the aortic occluder as the systemic arterial pressure increased. Note that sodium retention occurred during the entire 5 days of decreased renal artery pressure, again suggesting that the kidneys do not adapt their excretory function to chronic reductions in perfusion pressure and that sodium balance cannot be achieved as long as perfusion pressure is below normal. Also, note that during the last two days of this experiment, systemic arterial pressure above the aortic occluder increased progressively until an accelerated phase of hypertension developed with many of the features of malignant

hypertension. Thus, under these experimental conditions the kidneys do not appear to "reset" their excretory function to a chronic reduction in perfusion pressure, but instead continue to retain sodium leading to a progressive and unstable hypertension.

3.2 "Escape" from Salt and Water Retention During Angiotensin II and Aldosterone Hypertension. To further examine the validity of the renal-body fluid feedback concept for blood pressure control, we studied two models of hypertension, aldosterone and AII hypertension, to determine whether a primary shift in the renal function curve occurred in these forms of hypertension so that elevated arterial pressure was required to achieve sodium balance, as predicted by the renal-body fluid feedback theory of blood pressure control.

We have previously shown that during chronic infusion of low doses of AII there is a transient retention of sodium, lasting for 1-2 days, followed by a gradual return of sodium balance associated with moderate hypertension (16). According to the renal-body fluid feedback concept for blood pressure regulation, increased renal perfusion pressure is essential for the kidneys to achieve sodium balance, because of the effect of AII to increase tubular reabsorption and to shift the renal function curve along the arterial pressure axis (3,17). However, another interpretation of these results is that AII may have increased total peripheral resistance, directly or indirectly by increasing sympathetic nerve stimulation, and that this effect caused the hypertension while mechanisms other than the renal-body fluid feedback system (i.e. increased formation of various natriuretic hormones or intrinsic renal mechanisms) were responsible for "escape" from the sodium retaining effects of AII and the achievement of a balance between intake and output of sodium. To test these possibilities, we studied the effects of AII in experiments in which renal perfusion pressure was servo-controlled at the normal level that existed prior to AII infusion (18). This was done by using an electronically-controlled occluder placed on the abdominal aorta above both kidneys.

When renal perfusion pressure was prevented from increasing during continuous infusion of AII at a rate of 5 ng/kg per min, the kidneys did not escape the sodium-retaining actions of AII and cumulative sodium balance and systemic arterial pressure continued to increase

without stabilizing (Figure 3). In many cases, sodium and water retention became so severe that pulmonary edema developed within 4-6 days. When the servo-control system was stopped, and renal perfusion pressure was allowed to increase to the same level as systemic arterial pressure, urinary sodium excretion increased markedly and sodium balance and systemic arterial pressure gradually decreased back to the same level as observed in normal dogs during AII hypertension. These observations indicate that a rise in renal perfusion pressure is an essential mechanism for escape from the chronic sodium-retaining effects of hypertensive levels of AII, and therefore support the renal-body fluid feedback concept for blood pressure control.

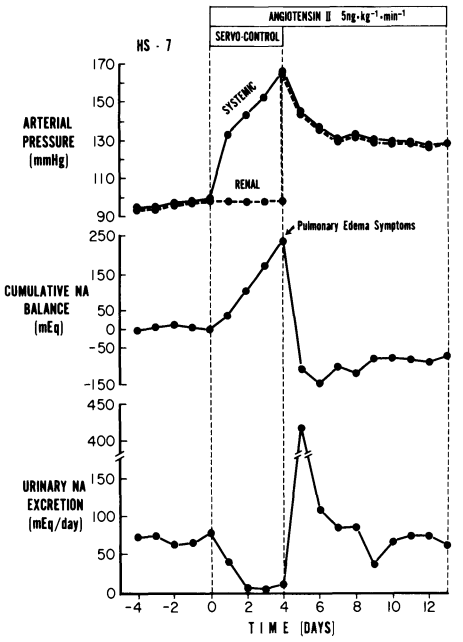

Figure 3. Effects of AII infusion 5 ng/kg per min in a dog in which renal artery pressure was servo-controlled at the normal level. After 4 days, the servo-controller was stopped and AII infusion was continued.

We conducted similar experiments to examine the role of increased renal perfusion pressure in allowing the kidneys to escape from the chronic sodium retaining actions of aldosterone. Typically, chronic aldosterone infusion causes sodium and water retention for 1-2 days followed by a gradual return of sodium and water balance associated with mild to moderate hypertension (19). According to the renal-body

fluid feedback concept, the increased renal perfusion pressure is a circulatory adaptation that allows the kidneys to escape from the chronic sodium-retaining actions of aldosterone. However, some investigators have suggested that mineralocorticoid hypertension is caused by a direct or indirect effect of mineralocorticoids to constrict the peripheral vasculature thereby raising total peripheral resistance (20,21). Furthermore, escape from the sodium retaining action of aldosterone has been postulated to be due to formation of increased levels of natriuretic hormone, increased levels of kinins, or increased secretion of prostaglandins rather than a rise in renal perfusion pressure (see ref. 22 for review).

To examine the possibility that the kidneys can escape from the sodium-retaining actions of hypertensive doses of aldosterone in the absence of increased renal perfusion pressure, we prevented the renal artery pressure from increasing during chronic aldosterone infusion by utilizing a servo-controlled occluder placed on the abdominal aorta above the kidneys (Figure 4).

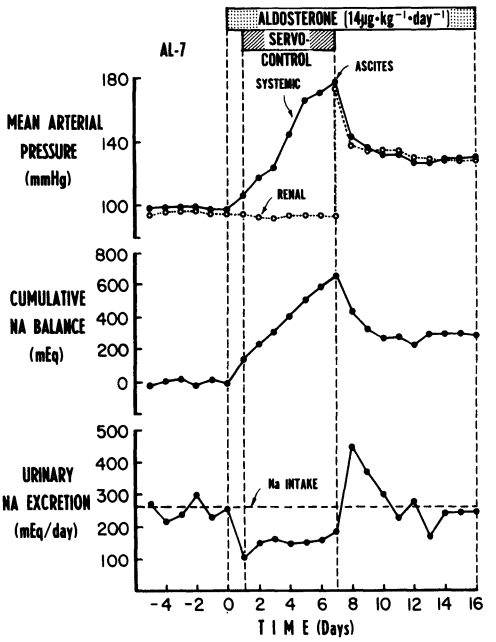

FIGURE 4. Effects of aldosterone infusion in a dog in which renal artery pressure was servo-controlled at the normal level. After 7 days, the servo-controller was stopped and aldosterone infusion was continued.

When renal perfusion pressure was servo-controlled at the normal level during aldosterone infusion, sodium and water retention continued to occur and mean systemic arterial pressure above the aorta occluder increased progressively. In many experiments, the animals developed ascites due to excessive fluid retention. When the servo-controller was stopped, and renal perfusion pressure was allowed to increase, cumulative sodium balance and mean systemic arterial pressure decreased back to the same levels as observed in dogs in which renal perfusion pressure was allowed to increase during aldosterone infusion. These data also support the renal body-fluid feedback concept for blood pressure regulation and indicate that aldosterone, as well as AII, caused a primary shift of the renal function curve; thus, hypertension was an adaptation that allowed the kidneys to escape the sodium retaining actions of these agents and therefore to achieve sodium balance. Apparently, all other natriuretic systems in the body were unable to completely offset the antinatriuretic actions of hypertensive doses of AII or aldosterone in the absence of increased renal perfusion pressure.

Thus, there is substantial experimental data to support the major premise of the renal-body fluid feedback theory that renal perfusion pressure exerts a profound long-term influence on renal excretion, and that the kidneys do not fully reset or adapt their excretory function in response to extrarenal disturbances (i.e. increased total peripheral resistance or increased cardiac output) that do not cause an initial change in renal function. Hypertension appears to be a necessary trade-off that enables the body to achieve sodium balance after a disturbance that decreases the kidney's ability to excrete salt and water. In circumstances where renal perfusion pressure is prevented from increasing in response to marked decreases in renal excretory capability, severe abnormalities of body fluid balance may occur, leading to ascites, pulmonary edema, or even death within a few days if sodium intake is unchanged.

4. ALTERATIONS IN RENAL FUNCTION IN ESSENTIAL HYPERTENSION.

Although many researchers have suggested that renal function is entirely normal in the early stages of essential hypertension, it is clear from an analysis of the relationship between arterial pressure

and urinary electrolyte excretion that renal function is not normal. In essential hypertension, the renal function curve is shifted along the arterial pressure axis so that normal urinary sodium excretion is achieved only at elevated arterial pressure (2). This observation alone indicates that renal function is not normal in essential hypertension and that the kidneys' ability to excrete sodium is reduced. However, the mechanisms responsible for the shift of the renal function curve in human essential hypertension are still unclear.

There have been several studies that suggest abnormalities of renal hemodynamics even in the early stages of essential hypertension. Kolsters et al. (23), reported that in early and late essential hypertension there are at least three major renal hemodynamic abnormalities: (1) a significant reduction in renal plasma flow, (2) more than a two-fold increase in renal vascular resistance, and (3) approximately a 40% increase in the filtration fraction. Also, their data show that the ratio of renal resistance to total peripheral resistance is increased markedly in essential hypertension, indicating that the renal vasculature is much more constricted than the peripheral vasculature. Hollenberg has also found an increase in renal vascular reactivity to constrictors such as angiotensin II in essential hypertension (24), and there is substantial evidence that long-standing hypertension can produce additional renal abnormalities, such as nephrosclerosis and glomerular membrane damage, which can increase the severity of the hypertension eventually leading to further deterioration of kidney function. However, these are only a few of the many renal abnormalities that could theoretically lead to decreased ability to excrete sodium and water and therefore to chronic hypertension. It is still not certain whether these changes in kidney function in essential hypertension are caused by neural, hormonal, or intrinsic disturbances that decrease the ratio of glomerular filtration/tubular reabsorption.

5. SUMMARY

In this paper we have discussed the importance of the renal-body fluid feedback system for long-term regulation of arterial pressure, and how abnormalities of this control mechanism can lead to hypertension. The key element of this feedback system that gives it extreme potency in long-term control of arterial pressure is the direct

relationship between arterial pressure and urinary excretion of salt and water.

Much of the controversy concerning the importance of the renal-body fluid feedback system in blood pressure regulation stems from the question of whether there is a long-term effect of blood pressure on excretion of salt and water. Although many acute studies indicate that renal arterial pressure has a marked effect on salt and water excretion, some investigators have suggested that the kidneys completely reset or adapt their excretory function in response to chronic increases in arterial pressure caused by elevated total peripheral resistance or cardiac output so that hypertension can be maintained in the absence of a primary change in renal function. This concept implies that there is no long-term effect of arterial pressure on renal excretion and that the renal-body fluid feedback mechanism is relatively unimportant in the etiology of hypertension or in normal blood pressure regulation. However, this notion is not supported by recent studies that have demonstrated a very powerful long-term effect of arterial pressure on renal excretion. Recent studies also indicate that in various experimental forms of hypertension, such as AII or aldosterone hypertension, increased renal perfusion pressure is an essential circulatory compensation for a primary decrease in the kidney's ability to excrete salt and water. In the absence of increased renal perfusion pressure, salt and water retention continue until extreme abnormalities of body fluid volumes occur, often leading to pulmonary edema or ascites. Thus, many experimental studies support the concept that abnormalities of the renal-body fluid feedback mechanism play a primary role in the etiology of various forms of experimental hypertension, and at present, there is no reason to believe that human essential hypertension is an exception to this general concept.

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9. DETERMINANTS OF EXAGGERATED NATRIURESIS IN ARTERIAL HYPERTENSION

F. C. LUFT AND M. H. WEINBERGER

1. ABSTRACT

To examine influences on sodium excretion after volume expansion in normal volunteers and patients with primary and secondary forms of hypertension, we studied the natriuretic responses of 404 normal volunteers, 159 patients with essential hypertension, 98 patients with renal vascular hypertension, 33 patients with primary aldosteronism, and 38 patients with labile hypertension after a 2L infusion of normal saline. In normals, the fractional excretion of sodium (FENa) during saline infusion correlated directly with age and the increase in systolic blood pressure during infusion. FENa correlated inversely with PRA and body surface area. In essential hypertensives FENa correlated directly with blood pressure and age, and inversely with PRA and body surface area. Race also influenced the relationship in that FENa tended to be greater in black hypertensives. Labile hypertensives had a greater FENa than normals, or age-, race-, and sex-matched essential hypertensives. In labile hypertensives FENa correlated directly with norepinephrine in plasma and urine. Patients with primary aldosteronism had the greatest FENa and also had a kaliuresis with saline infusion. In fixed hypertensives the "exaggerated natriuresis" is a feature of hypertension with renin suppression. In labile hypertensives, natriuretic responses following sodium administration may be related to sympathetic tone. The "exaggerated natriuresis" appears to be influenced

by various extra-renal factors in addition to elevated arterial blood pressure.

2. INTRODUCTION

Over forty years have passed since Farnsworth and Barker described a decreased reabsorption of chloride in patients with hypertension compared to normotensive control subjects (1,2). Since that time numerous investigators have examined the same phenomenon, primarily in the hope that by elucidating the mechanism behind the "exaggerated natriuresis" new information would be forthcoming regarding the pathogenesis of the hypertensive condition. Indeed, a large body of information has been obtained from studies of natriuresis in hypertension, which has contributed substantially to our understanding of the kidney's role in the maintenance of sodium homeostasis and in the regulation of blood pressure. The important relationship between pressure and natriuresis, and the entire global notion of the kidney's role as the mediator, or final common pathway, of blood pressure regulation have been recognized and developed largely because of research in this area (2,3). Nevertheless, the causes of exaggerated natriuresis have not been defined in detail, and the importance of the phenomenon with respect to the pathogenesis of hypertension has not been clearly established.

The renin-angiotensin-aldosterone system is implicated in various forms of secondary hypertension. Moreover, the activity of this system is heterogeneous in patients with essential hypertension. To clarify the influences of this system on sodium excretion after volume expansion, we examined the natriuretic response to saline infusion in normotensive subjects and in patients with various forms of essential and secondary hypertension. We found that the natriuretic responses were not only

products of blood pressure elevation, but were also related to the activity of the renin-angiotensin system and, in some instances, the sympathetic nervous system. These modulating influences may operate either by their influence on circulating fluid volume, or by a more direct effect upon the nephron.

3. METHODS:

The volume expansion protocol employed in these studies is described in detail elsewhere (5,6). The protocol formed an integral portion of our approach to the diagnosis of secondary hypertension. Briefly, after due approval, normotensive and hypertensive subjects were admitted to the Clinical Research Center, and underwent a complete history and physical examination. On the first day they received a diet containing 150 mEq sodium and 80 mEq potassium. Appropriate blood and urine specimens were obtained on that day. The following day the subjects were awakened at 0600 hr. While they remained recumbent, blood was obtained for renin (PRA), aldosterone (PA), and, in some instances, for norepinephrine (PNE) assays. The subjects then spent the next two hours in the upright position, and underwent the same measurements at 0800 hr. Thereafter, they again assumed the recumbent position, and received 2L normal saline intravenously over four hours. All urine was collected during this time. At the end of the infusion, blood specimens were again obtained for the determinations mentioned above. In addition, plasma creatinine concentration was measured. The urine specimens were analyzed for sodium, potassium, creatinine and, in some instances, for norepinephrine concentration.

Renin profiling was accomplished by means of the response of plasma renin activity to volume expansion and contraction maneuvers outlined

elsewhere (5). The diagnosis of renal vascular hypertension required the presence of renal artery stenosis documented by arteriogram and lateralization of renal vein PRA values with the subject tilted after sodium depletion (7). The diagnosis of primary aldosteronism required the presence of suppressed plasma renin activity in patients whose plasma aldosterone values could not be supppressed into the normal range after the infusion of normal saline (5). Labile hypertension was defined as the presence of both normal (<140/90 mmHg) and high (> 140/90 mmHg) blood pressure readings recorded on at least three separate outpatient visits in patients receiving no medication and who had not been instructed to reduce dietary sodium intake (8). Normotensive subjects were recruited by advertisement.

Sodium, potassium, and creatinine concentration were measured by automated techniques. The fractional excretions of sodium (FENa) and potassium (FEK) were calculated from values obtained from the four-hour urine collection during the saline infusion by means of the following formula: FEx% = (Cx/Ccr) 100, where the fractional excretion of X represents the percentage of filtered X appearing in the urine, Cx represents the clearance of X, and Ccr the clearance of creatinine. PRA and PA were measured by radioimmunoassay, while PNE and norepinephrine in urine (UNE) were determined by means of a radioenzymatic assay (9,10).

Statistical anaysis relied on analysis of variance, t-tests where indicated, and multivariate regression analysis where appropriate. The 95% limits of probability were accepted as significant. Fiducial limits are expressed as standard error of the mean (SEM).

4. RESULTS

Studies were performed on 404 normotensive volunteers, 159 patients

with essential hypertension, 98 patients with renal vascular hypertension, 33 patients with primary aldosteronism, and 38 patients with labile hypertension. Since the protocol was a clinical exercise designed to identify patients with secondary forms of hypertension, it underwent modifications and additions over the six years it was employed. Thus, not every measurement was obtained in each patient.

Table 1. Characteristics of the population (mean ± SEM).

Variable	NORMAL	LRH	NRH	HRH	RVH	ALDO	LABILE
Age (yrs)	30±1	42±2*	42±1*	36±2*	48±2*	47±2*	31±2*
Weight (kg)	69±1	78±3*	79±1*	75±2*	65±2*	74±4*	80±3*
Clearance Cr **	121±5	95±6	101±4	89±9	72±7*	100±13	100±8
24hr $^{U}Na^{V}$ ***	149±4	130±11	131±6	116±10	127±13	147±28	149±11
MABP (mmHg)	88±1	124±3*	121±1*	126±3*	133±8*	130±4*	105±2*
Upright PRA †	7.1±0.3	1.4±0.2*	7.7±0.4	22.1±2.3*	23.4±2.4*	0.8±0.2*	7.3±0.6
Upright PA ‡	34±1	25±2	40±2*	66±7*	76± 9*	59±10*	29±4

*Different from normals ($p < 0.05$). **(ml/min);***(mEq/24hr);†(μgAI/ml/3hr); ‡(ng/100ml)

Table 1 illustrates the general characteristics of the various groups studied, including an estimate of their sodium intake as reflected by 24 hr urine collections on the day prior to saline infusion and the results of PRA and PA obtained after upright posture prior to saline infusion. Sodium excretion among the subject groups was not significantly different. Their PRA and PA values reflect their subsequent categorization. Since body surface area was found to influence natriuresis, we included control groups of white and black men and women, both older and younger, who were matched for body weight and surface area. Blood pressure values in these subjects were obtained and catalogued both before and after saline infusion. Blood pressure data from all other subjects represent the mean of four determinations obtained on the day of saline infusion.

Figure 1 shows the FENa of all normal subjects and various categories

of hypertensive subjects during the four hour infusion of normal saline. Significant differences ($p < 0.05$) were found between normals and patients with NRH, the latter and those with LRH, and between those with LRH and ALDO. Figure 2 illustrates the kaliuretic responses of these same groups.

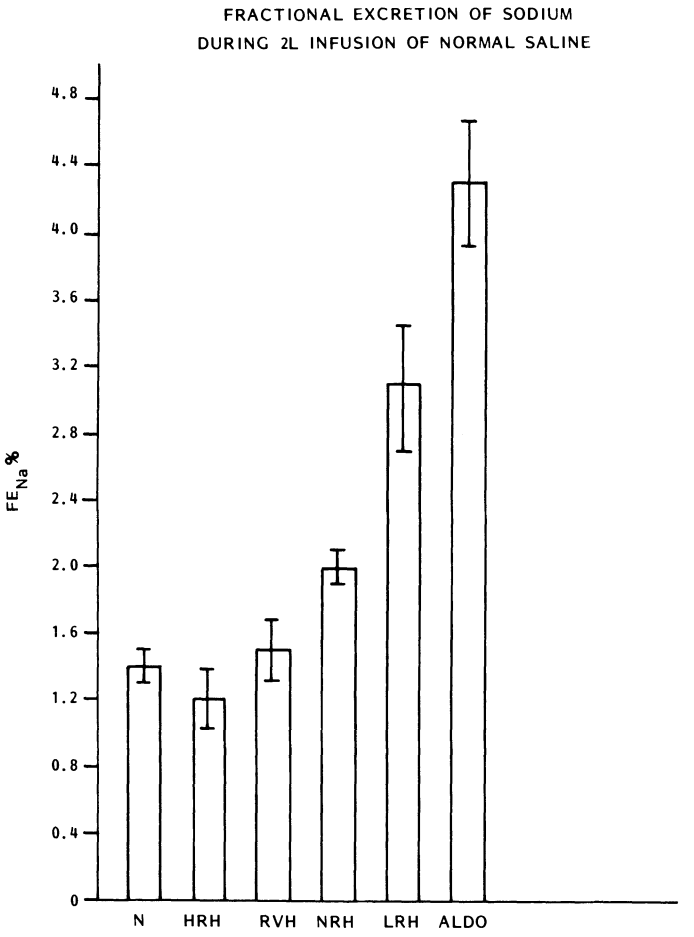

FIGURE 1. FENa in normals and in hypertensives. Significant differences were found between normals and NRH, NRH and LRH, and LRH and ALDO ($p < 0.05$).

Only patients with ALDO had elevated FEK values ($p < 0.05$). Figure 3 demonstrates the FENa during saline infusion of patients with labile hypertension as compared to age-,race- and sex-matched normal subjects and similarly matched hypertensives. The patients with labile hypertension had a greater FENa ($p < 0.05$) while their PRA and PA values were not different from other groups.

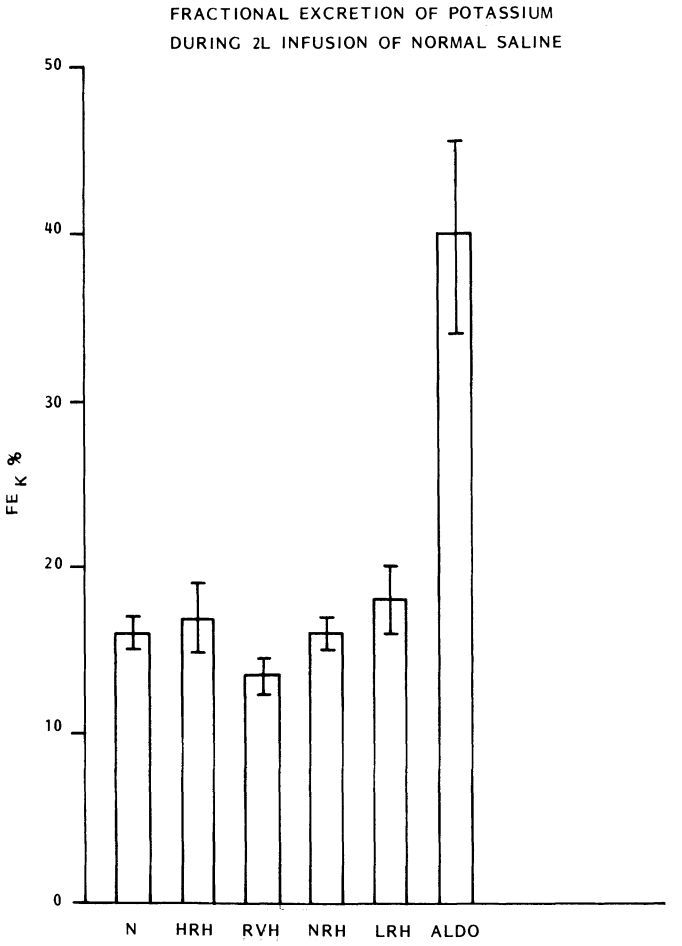

FIGURE 2. FEK in normals and hypertensives. Only patients with ALDO exhibited a significant kaliuresis ($p < 0.05$).

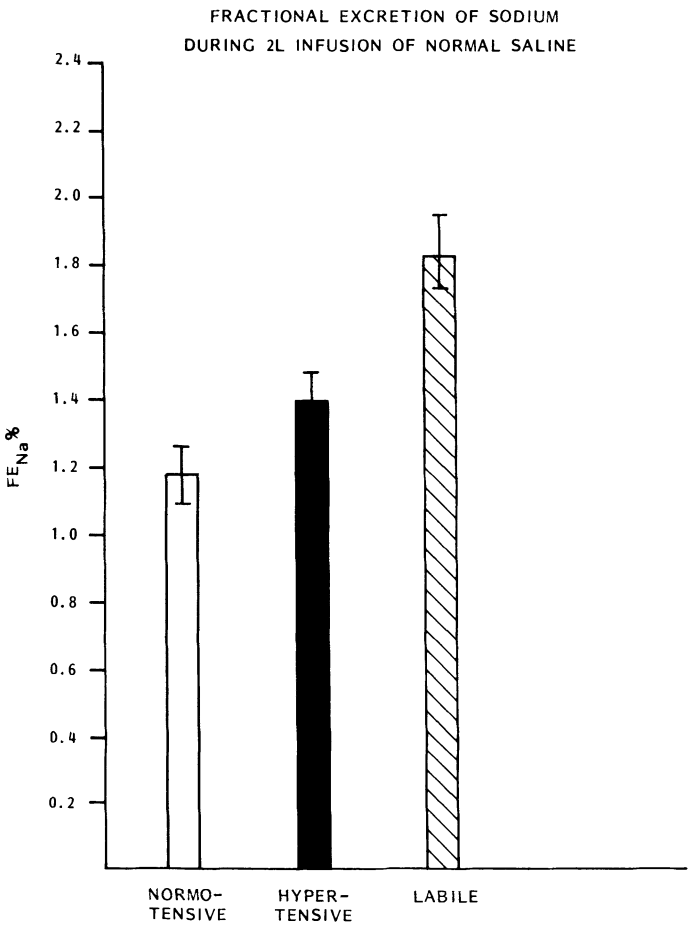

FIGURE 3. FENA in normals, fixed hypertensives and labile hypertensives matched for age, race and sex. The labile hypertensives are different from normals and fixed hypertensives ($p < 0.05$).

Table 2 shows the correlations between FENa and pertinent variables in normal subjects and patients with fixed, essential hypertension. Body surface area, age, mean blood pressure and PRA were correlated with FENa in these subjects ($p < 0.01$) while PA, PNE, and UNE excretion during the infusion showed no significant interaction with FENa. Interestingly, in patients with labile hypertension, whose PRA values were in a narrow

Table 2. Correlations with FENa.

Variable	Normal			Essential Hypertensive		
	(r)	(n)	(p)	(r)	(n)	(p)
Body Surface Area	- 0.20	366	<0.001	- 0.23	121	< 0.01
Age	+ 0.21	404	<0.001	+ 0.43	159	< 0.001
MABP	+ 0.07	402	NS	+ 0.50	153	< 0.001
PRA 0800hr	- 0.24	386	<0.001	- 0.36	153	< 0.001
PRA 1200hr	- 0.22	384	<0.001	- 0.22	152	< 0.01
PA 0800hr	+ 0.01	309	NS	+ 0.06	114	NS
PA 1200hr	- 0.03	306	NS	+ 0.08	114	NS
PNE 0800hr	- 0.02	125	NS	- 0.16	20	NS
PNE 1200hr	+ 0.15	125	NS	- 0.13	20	NS
UNE 4hr	- 0.09	280	NS	- 0.16	107	NS

normal range, PRA and FENa were not significantly correlated. Instead, in these subjects, both UNE and PNE were correlated with FENa ($r = 0.37$, $r = 0.70$, $p < 0.05$ respectively). These same labile hypertensives also exhibited a strong direct correlation between PA prior to saline and the subsequent FENa ($r = 0.82$, $p < 0.001$). In the sub-population of normal subjects whose blood pressure responses during saline could be analyzed, FENa was correlated with the increase in systolic blood pressure occurring during infusion ($r = 0.21$, $p < 0.05$). Not shown on the table is the relationship between PRA suppression during saline infusion and FENa in normals and essential hypertensives. This value was obtained by subtracting the 1200hr from the 0800hr PRA determinations. A consistent, inverse relationship ($r = 0.25$, $p < 0.001$) was found, but only in normals and essential hypertensives. PA and PNE suppression did not enter into this relationship.

Multiple regression analysis was performed to identify variables significantly associated with FENa in the sub-groups, and their mode of entry into relationships was identified. In normal subjects a relationship influencing FENa was identified which accepted PRA, body surface area, and age in that order. In patients with essential hypertension the

relationship accepted in order: mean blood pressure, age, race, PRA, PA, and body surface area.

5. DISCUSSION

Farnsworth and Barker were the first to observe that hypertensive individuals reabsorb chloride to a lesser extent than normal subjects when compared in terms of U/P inulin ratios (1,2). However, these investigators provided no information regarding their saline challenge if any, and did not employ the term "exaggerated natriuresis." Nevertheless, since those early observations, numerous investigators have studied the natriuretic and chloriuretic responses of hypertensives subjected to heterogeneous oral and intravenous sodium chloride loads, and have observed that most hypertensives excrete more sodium and chloride following the challenge than do normal control subjects (11-15). Green et al. (16) noted that the excretory responses of hypertensives were not uniform. They were able to divide their hypertensives into two groups, "high salt-excretors" and "normal salt-excretors." They found that these two groups of subjects differed markedly with respect to renal function, in that the "normal salt-excretors" had lower glomerular filtration rates. Cottier et al. (17) extended these observations when they studied the natriuretic responses of hypertensives following the intravenous infusion of hypertonic sodium chloride. They found that natriuresis was related to the degree of blood pressure elevation, until subjects were extremely hypertensive. Severely hypertensive subjects had impaired renal plasma flows and decreased glomerular filtration rates, which influenced their natriuretic response accordingly. Hollander and Judson (18-19) studied the specific role of blood pressure elevation in mediating the natriuresis, and observed that by lowering arterial blood pressure with drugs,

sodium excretory capacity was reduced towards normal. However, the correlation between blood pressure and sodium excretion was not great in their subjects, which suggested to the authors that additional factors operated to enhance sodium excretion in individuals with essential hypertension. They speculated that basal dietary sodium intake, extracellular fluid volume, total body sodium content, and adrenal cortical function were also important determinants of natriuresis following sodium chloride loads in hypertensives. Their views have subsequently been largely substantiated.

The influence of dietary sodium intake on natriuretic responses following sodium chloride loads was clearly shown by Papper et al. (20), who examined the "exaggerated natriuresis" at three different levels of sodium intake. Dietary sodium intake influenced the natriuretic responses directly. However, hypertensives had a greater natriuretic response at each level compared to normotensive subjects. The "exaggerated natriuresis" could not be attributed to increases in glomerular filtration rate, or to augmented blood pressure following saline in the hypertensive subjects. The influence of extracellular fluid volume on natriuretic responses following saline loads can be inferred from the work of Papper et al. (20). Moreover, studies from our laboratory (21) indicated that natriuresis following intravenous saline increased with increasing dietary sodium intake until intake reached very high levels (600 mEq/d). At that point FENa approached 6% in normal subjects, substantial weight gain occurred, and net total body sodium content was increased.

Adrenal cortical function clearly influences natriuretic responses following sodium chloride administration. Rovner et al. (22) demonstrated the brisk natriuresis which occurs in patients with primary aldoste-

ronism when saline is administered. This natriuresis was sharply attenuated when the subjects' adrenal adenomas were removed. Moreover, normal subjects exhibited accelerated natriuresis when treated with d-aldosterone, but only after "escape" had been established. Krakoff et al. suggested that "exaggerated natriuresis" was a phenomenon associated with renin suppression (23). We subsequently observed that patients with low renin hypertension had greater natriuretic responses after saline administration than patients with normal or high renin values (24). Patients with primary aldosteronism had the greatest natriuretic responses.

The present analysis confirms and extends our previous observations. The natriuretic response following saline was inversely related to PRA in hypertensive and in normal subjects. Mean blood pressure exerted an important influence, particularly in hypertensives, but other factors were also involved. Particularly interesting are the putative roles of aldosterone, and the sympathetic nervous system, as reflected by norepinephrine measurements in plasma and urine. In patients with primary aldosteronism, aldosterone clearly exerted an important influence as demonstrated not only by the natriuresis, but also by the kaliuresis which occurred only in that sub-group of subjects. In essential hypertensives and in normal control subjects aldosterone was not correlated with FENa following saline administration. However, in patients with labile hypertension, a condition ascribed to volume expansion as well as to altered sympathetic tone (8), we observed not only an association between FENa and aldosterone following saline, but also correlations between FENa and urinary and plasma norepinephrine values. These observations are consistent with a role for both volume expansion and

sympathetic tone in the mediation of the natriuresis. The subjects with labile hypertension demonstrate that arterial blood pressure may not be the overriding influence on natriuresis in some circumstances, since age-, race- and sex-matched hypertensive individuals with similar renin values failed to exhibit as great a natriuretic response.

Multiple regression analysis identified PRA, body surface area, and age as the primary correlates of natriuresis following a saline challenge in normal subjects. The blood pressure range of these subejcts was quite narrow which explains the failure of mean blood pressure to enter the relationship in normal subjects. Nevertheless, the incremental increase in systolic blood pressure occurring during the saline infusion was directly correlated with natriuresis. In patients with essential hypertension, blood pressure was the dominant variable; however, age, race, PRA, PA, and body surface area exerted important influences as well. The influence of factors other than blood pressure on natriuresis following sodium chloride loads raises the possibility that "exaggerated natriuresis" may precede the development of fixed arterial hypertension, and that elucidation of these factors may be of pathogenic significance. Studies in man and experimental animals support this view. Ben-Ishay et al. (25) reported an increased sodium and water excretion in hypertension-prone rats of the Dahl strain prior to the development of hypertension. Since these rats have low juxtaglomerular indices and reduced renal renin content, as well as increased secretion of 18-hydroxy-deoxycorticosterone, the authors suggested the possibility of a causal relationship between low plasma renin activity due to mineralocorticoid-induced volume expansion and the exaggerated response to saline loading (25).

In man "exaggerated natriuresis" has also been observed prior to the development of hypertension. Wiggins et al. (26) studied the sons of hypertensive parents and found that 8 of 20 such subjects exhibited an "exaggerated natriuresis" following a sodium chloride load. In studies of first-degree relatives of essential hypertensives we were unable to identify an "exaggerated natriuresis"; however, our protocol differed substantially from that employed by Wiggins et al. (27). Polgar et al. (28) found that normotensive subjects who exhibited hyper-responsive blood pressure elevations to infused norepinephrine also had exaggerated natriuretic responses following sodium chloride loading compared to normotensive individuals who were not hyper-responsive to norepinephrine infusion. The authors suggested that altered sympathetic tone in these subjects was responsible for the natriuretic response. The finding by Mroczek et al. (29) that beta blockade with propranolol obliterated the "exaggerated natriuresis" in hypertensives, as well as the association of urine and plasma norepinephrine values with natriuresis in our labile hypertensive subjects and normotensive control subjects lends support to their hypothesis. Additional evidence has been provided by Welner and Groen (30) who found that the "exaggerated natriuresis" could be substantially attenuated by a simple psychological deconditioning procedure which did not influence blood pressure.

In addition to the extrarenal influences discussed above, investigators have attempted to identify intrinsic renal abnormalities in patients with essential hypertension to account for the "exaggerated natriuresis." Buckalew and associates (31) observed that volume expanded hypertensive patients had reduced abilities both to generate free water during hydration and to reabsorb free water during hydropenia. The authors thus concluded that the ascending limb of Henle's loop was the

major site of impaired salt reabsorption. Their view is supported by experiments in animals. Stumpe and colleagues (32) conducted micropuncture studies in rats with two-kidney one-clip Goldblatt hypertension, and identified an impaired solute reabsorption in Henle's loop. DiBona and Rios (33) performed similar studies in spontaneously hypertensive rats of the Okamoto strain, and reached similar conclusions. The mechanism of the decreased reabsorption in the loop of Henle could not be explained by alterations in physical forces in the renal cortical microvasculature as measured by the authors. Indeed, peritubular capillary physical factors were examined in humans with essential hypertension by Willassen and Ofstad (34). These investigators could find no abnormalities in the physical factors, and concluded that these forces are not involved in the "exaggerated natriuresis." On the other hand, Schalekamp et al. (35) concluded that the transmission of systemic arterial pressure to the vasa recta was primarily responsible for an "exaggerated natriuresis" in essential hypertensives. They cited the work of Lowenstein et al. (36) who, contrary to the results of Willassen and Ofstad (34), identified an increased wedged renal venous pressure in essential hypertensives. Dal Canton et al. (37) performed saline loading studies in hypertensive and normotensive subjects, and also identified decreased sodium reabsorption in Henle's loop. However, they also identified an increase in hemodynamic pressure in the vasa recta of medullary nephrons. They implicated an intra-renal hemodynamic heterogeneity in the development of "exaggerated natriuresis."

Henle's loop is not the only intra-renal site implicated in the "exaggerated natriuresis." Chaimovitz et al. (38) observed an "exaggerated phosphaturia,"as well as an "exaggerated natriuresis" in patients with essential hypertension, and concluded that altered reabsorption of

solute in the proximal, rather than distal tubule best explained their results. Willis and Bauer (39) studied the "exaggerated natriuresis" in spontaneously hypertensive rats and observed that d-aldosterone obliterated the "exaggerated natriuresis" in the hypertensive rats while spironolactone produced a relative "exaggerated natriuresis" in the corresponding control rats. Further, they found that the spontaneously hypertensive rats had lower PA values than control rats. These observations led the authors to conclude that the "exaggerated natriuresis" was related to a decreased aldosterone-mediated distal tubular sodium reabsorption. This view receives some support from observations in man by Pedersen and Kornerup (40), who found that the "exaggerated natriuresis" was highly correlated with the suppressibility of PA in their subjects. We were unable to identify such a relationship in our subjects. Instead, we identified a consistent inverse relationship between PRA suppressibility and FENa in normals and in patients with essential hypertension.

Ulrych and co-workers (41) suggest that diuretic and natriuretic abberrancies in hypertensives following saline loading are circulatory rather than renal in origin. They found that hypertensives exhibited an excessive response in cardiac output following saline loading. They suggest that a deficient ability of capacity vessels to dilate in response to sudden increments in plasma volume is present in hypertensives compared to normal subjects.

In summary, most but not all patients with essential hypertension exhibit an "exaggerated natriuresis" following the administration of sodium chloride. The "exaggerated natriuresis" appears to antedate the development of fixed hypertension, which implies that its pathogenesis is not strictly related to blood pressure elevation. The phenomenon is related to arterial blood pressure elevation, but is also influenced by a

variety of other extra-renal factors including renin, aldosterone, and probably the sympathetic nervous system. "Exaggerated natriuresis" is a feature of hypertension with renin suppression and hypertension that is characterized by volume expansion. In patients with labile hypertension natriuretic responses may be directly related to sympathetic nervous system tone. Age, race, and body surface area also influence natriuretic responses. The loop of Henle appears to be the primary, but not necessarily the only site along the nephron, which is involved in the "exaggerated natriuresis." The role of peritubular physical factors in the production of the phenomenon remains controversial.

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10.

RENAL HEMODYNAMICS IN OBESE AND LEAN ESSENTIAL HYPERTENSIVE PATIENTS*

Efrain Reisin, Franz H Messerli, Hector O Ventura and Edward D Frohlich

ABSTRACT

We studied the renal and systemic hemodynamics of obese hypertensive patients and their lean controls matched for age, sex, race, and level of mean arterial pressure. The obese hypertensive patients had a greater cardiac output, renal blood flow and total blood volume. In contrast total peripheral and renal vascular resistances were less in the obese patients than in their lean counterparts. Therefore, we postulate that the high blood flow state with volume expansion in the obese hypertensive patient may predispose to cardiac complications, but, paradoxically, may also provide better renal vascular protection than in their nonobese controls.

1. INTRODUCTION

The association of essential hypertension and obesity is well established (1,2). Our group and others have reported the systemic hemodynamic characteristics of obese hypertensive patients in cross-sectional (3-7) and matched-pair studies (8). Their renal hemodynamic characteristics, however, remain to be described. This report details the renal and systemic hemodynamics of obese hypertensive patients and their lean controls, matched for age, sex, race, and level of mean arterial pressure.

2. MATERIALS AND METHODS

This study included 20 established hypertensive patients whose ambulatory systolic and diastolic pressure were consistently greater than 140 and 90 mmHg, respectively. All patients had normal renal function confirmed by normal BUN and serum creatinine levels. Ten obese hypertensive patients were pair-matched with lean hypertensive subjects of the same race, sex, age (±5 years), and mean arterial pressure (±10 mmHg). Each subject had been completely evaluated clinically to exclude secondary forms of hypertension, diabetes mellitus, and impaired cardiovascular and renal function. All antihypertensive drugs had

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been discontinued at least four weeks before hemodynamic study and signed consent forms approved by the institutional clinical investigation committee were obtained.

Hemodynamic assessment was done in the morning between 8 to 11 A.M. after overnight fasting and without premedication. Polyethylene tubing was introduced into an antecubital vein and brachial artery and advanced to the level of the superior vena cava and ascending aorta, respectively. Continuous intraarterial and venous pressures were obtained on a 12-channel Electronics-for-Medicine indirect writing recorder using a Statham P-23Db pressure transducer. Supine cardiac output was determined in triplicate using indocyanine green dye. Mean arterial pressure was recorded by electrical integration. The hemodynamic indices were calculated by standard formulae with a programmed Hewlett-Packard computer calculator (9). Renal blood flow was determined by a single injection of ^{131}I-iodinated sodium iodohippurate (9-12). Plasma volume was determined by injecting ^{125}I-iodinated human serum albumin into the venous line and measuring the decline of plasma radioactivity after 15 and 30 minutes of equilibration. Total blood volume was calculated from the measured plasma volume and the total body hematocrit (13). Statistical analyses were performed using the two-tailed Student's t-test for paired data comparison. All results are presented as the mean±1 SEM.

3. RESULTS

The average ages of the two groups, obese and lean essential hypertensive patients, were 43±1 and 43±2 years, respectively. Four patients in each group were men and six women; two were black and 8 white in each group. Obviously, the body weight and percent overweight of the obese group of patients were significantly greater than in the lean patients (93±4 vs 61±3 kg, $p<0.01$; and 58±5 vs +1±1%, $p<0.01$, respectively). The body heights and mean arterial pressures were similar in the obese and lean patient groups (168±2 vs 164±3 cm; and 110±4 vs 111±4 mmHg, respectively).

The obese hypertensive patients had a greater cardiac output, renal blood flow and total blood volume (Table 1). In contrast, total peripheral and renal vascular resistances were less in the obese patients than in their lean counterparts (Table 1).

Table 1. Comparative laboratory values between matched obese and lean essential hypertensive patients.

	Obese	Lean	P<
Cardiac output (L/min)	6.1 ± .3	5.1 ± .3	.05
Mean arterial pressure (mmHg)	110 ± 4	111 ± 4	NS
Total peripheral resistance (mmHg/L/min)	19 ± 1	22 ± 2	.01
Total blood volume (ml)	5171 ± 380	3913 ± 213	.01
Renal blood flow (ml/min)	1128 ± 85	876 ± 52	.01
Renal vascular resistance (mmHg/ml/min)	10 ± 1	13 ± 1	.01

4. DISCUSSION

The results of this study show that for any level of arterial pressure the obese hypertensive patients had a greater total blood volume, cardiac output and renal blood flow; however, their total peripheral and renal vascular resistances were less than the lean hypertensive patients. Thus, lean and obese hypertensive patients apparently have different hemodynamic characteristics, implying that target organ involvement and perhaps therapeutic approaches may also differ.

In the present study, and in earlier studies (3-5), the obese hypertensive patients had a significantly higher total blood volume and cardiac output than the lean hypertensive subjects. Earlier reports also demonstrated greater stroke volume, left ventricular stroke work, and left ventricular and diastolic pressures in the obese hypertensive than in normotensive patients (3-5, 8). Associated with those hemodynamic changes are different cardiac adaptations to obesity or lean body habitus (8). Thus the obese patients demonstrated left ventricular dilatation and hypertrophy, whereas the lean hypertensive patients showed concentric left ventricular hypertrophy. These disparate cardiac adaptative changes could explain the greater prevalence of cardiac failure in obesity (3).

Other organs generally affected by hypertensive vascular disease are the kidneys; however, renal parenchymal functional and hemodynamic changes produced by obesity have been mentioned only briefly in previous publications (14-16). These reports have shown a 25 percent greater glomerular filtration rate in obese patients than that of an age- and height-matched controls (14,15). Perera and Dannon (17) reported that obese hypertensive women seemed to have malignant hypertension and renal functional impairment less frequently than lean hypertensive women.

In the present study obese hypertensive patients had a significantly greater renal blood flow and lower renal vascular resistance than their lean matched

subjects, despite similar levels of mean arterial pressure. Therefore, we postulate that the high blood flow state with volume expansion in the obese hypertensive patient may predispose to cardiac complications, but, paradoxically, may also provide better renal vascular protection than in their nonobese controls.

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11. SODIUM AND WATER EXCRETION IN PATIENTS WITH CONGESTIVE HEART FAILURE AND CIRRHOSIS

Daniel Bichet and R. W. Schrier

ABSTRACT

Possible pathophysiologic mechanisms producing sodium and water excretion in patients with congestive heart failure and cirrhosis are reviewed. Sodium retention in cirrhosis seems to be mediated by a decreased central blood volume (afferent mechanism) and increased sympathetic activity, as well as stimulation of the renin aldosterone system (efferent mechanism). An increase in renal sympathetic activity appears to 1) diminish renal hemodynamics, 2) decrease distal fluid delivery, and 3) impair "escape" from aldosterone. Sodium retention in cardiac failure appears to be due to similar multifactorial mechanisms. Impairment in water excretion in association with congestive heart failure and cirrhosis seems to be mediated by a persistent non-osmotic release of AVP. In addition, the diminished fluid delivery to the distal diluting segment can contribute to the abnormal water excretion in cirrhosis and cardiac failure.

I. INTRODUCTION

The disturbances of body fluid metabolism in congestive heart failure (CHF) and in cirrhosis have captured the interest of many investigators over the past 30 years and have inspired many detailed reviews (1-7). In both of these clinical disorders, renal retention of salt and water occurs and is central to the maintenance of the edematous state (1-7). Common to these conditions is the development of increased total body sodium and water content, and the kidneys play an essential role in the retention of this sodium and water.

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In this article, we shall discuss the signals the kidneys receive for sodium and water retention in CHF and cirrhosis (afferent mechanisms). We shall also examine the means by which the kidney responds to these signals and retains sodium and water (efferent mechanisms). As will become apparent, these edematous states may share many of the same afferent and efferent mechanisms for sodium and water retention.

II. SODIUM AND WATER RETENTION IN CHF

The primary function of the heart is to pump oxygenated blood to the systemic circulation, where oxygen and nutrients are taken up by the tissues in exchange for carbon dioxide and the byproducts of intermediary metabolism. When the heart fails in its task as a pump, a complex set of compensatory reflexes is initiated to maintain circulatory integrity. The retention of sodium and water is the major renal compensation for a failing myocardium and accounts to a great extent for the familiar clinical syndrome of CHF.

A. Afferent mechanisms for sodium retention in CHF

Schrier and associates (8-10), using a model of low output CHF in the dog, demonstrated that constriction of the thoracic inferior vena cava (TVIC) was associated with a decrease in cardiac output, arterial pressure and urinary sodium excretion even when renal perfusion pressure and renal venous pressure were held constant. Renal denervation and adrenalectomy also did not abolish the antinatriuresis.

Furthermore, the sodium retention did not correlate with changes in glomerular filtration rate (GFR) or renal vascular resistance. Constriction of the thoracic superior vena cava to cause a similar decrease in cardiac output, as observed in the TIVC studies, resulted in a similar fall in urinary sodium excretion despite the absence of concomitant hepatic, renal and abdominal venous congestion. The authors, therefore, proposed that in this low output model of heart failure, the afferent stimulus for sodium retention was the low cardiac output or some consequence thereof. Of interest, these observations questioned

the primacy of the "backward theory of CHF introduced by Hope (11) and Starling (12) which states that increased venous pressure, due to right ventricular failure, causes edema formation by promoting transudation of fluid from the intravascular to the interstitial compartment. This in turn reduces intravascular volume and in some way signals the kidney to retain sodium and water. Alternatively, the results of Schrier et al (8-10) were most compatible with the "forward" theory of cardiac failure (13) suggesting that a primary decrease in cardiac output leads to renal hypoperfusion, which in turn leads to decreased sodium excretion. Low cardiac output cannot be the only cause of sodium retention in cardiac failure, however, because diminished renal sodium excretion is also seen in high output cardiac failure. The concept of "ineffective arterial filling" or decreased "effective arterial blood volume" (EABV) must then be introduced in order to explain the increased renal sodium retention in CHF. The EABV is a measure of how well arterial blood volume "fills" the capacity of the arterial circulation. In other words, "normal" EABV exists when the ratio of cardiac output to peripheral vascular resistance maintains venous return and cardiac output at normal levels. In this regard, the clinical and experimental states of high-output cardiac failure including anemia, beriberi and arteriovenous (AV) fistulae all are associated with a fall in peripheral vascular resistance such that the EABV is decreased (14-16). Studies in both dog and man demonstrate that closure of an AV fistula decreases urinary sodium excretion (15, 16). These changes in urinary sodium excretion have been found to correlate with the changes in arterial pressure and peripheral resistance rather than GFR and renal blood flow. This decrease in renal sodium excretion in low and high output cardiac failure is consistent with the theory that a decrease in EABV provides the stimulus for the kidneys to retain sodium.

From the foregoing we might speculate that EABV on peripheral vascular resistance may influence sodium handling by the kidney by activating an arterial or "high-pressure" receptor. Unfortunately, at the present time, the presence of an arterial

volume-receptor regulating sodium excretion has not been established except for the juxta-glomerular apparatus that governs renin release. Elucidation of possible afferent arterial receptors that are activated in congestive heart failure and are responsible for renal salt retention requires further investigation. Conversely, volume receptors localized on the venous side of the circulation or "low-pressure" sensors have received more attention than arterial "high-pressure" receptors (17). Since only approximately 15% of blood volume is contained in the high pressure circulation, whereas the venous or low pressure side contains the remaining portion of blood volume, the venous side of the circulation seems, therefore, to be a logical place for receptors sensitive to changes in blood volume to be found (17). The atria of the heart are highly distensible and are densely populated with nerve endings sensitive to small changes in passive distension (18). Maneuvers which result in increased filling of the thoracic vasculature would be expected to cause low pressure volume receptors to signal the kidney to increase urinary sodium excretion in order to return the blood volume to normal. Indeed, negative pressure breathing, head-out water immersion, recumbency, weightlessness and exposure to cold all result in natriuresis (2, 19-21). Conversely, measures which decrease intrathoracic blood volume such as positive pressure breathing, upright posture and application of tourniquets to the lower extremities, result in renal sodium retention (2, 22, 23). Thus effective "central" blood volume rather than EABV might be the preferable term to describe the afferent stimulus for regulation of renal sodium excretion. Although a role for right-sided low pressure volume receptors has been implicated (24), there is considerable evidence pointing to the left atrium receptors as influencing renal sodium retention in cardiac failure (17, 25, 26). In this regard, it is worthwhile to note that acute left atrial distension in dogs results in natriuresis and diuresis while chronic left atrial distension in CHF may not cause a natriuresis. In this setting, cardiac output is usually diminished so that high pressure volume receptors might also be activated and exert the predominant effect on sodium and water

retention. The relative importance and interrelations of these high and low pressure receptors deserves further studies.

B. Efferent mechanisms for sodium retention in CHF

As described above, a decrease in effective central blood volume sensed by high pressure baroreceptors and blunting of receptors in the low pressure system may affect renal function by a variety of mechanisms including alterations in renal sympathetic or vasomotor tone, changes in levels of circulating vasoactive substances, or activation of the renin-angiotensin-aldosterone axis. An increase in sympathetic efferent discharge with increased plasma norepinephrine concentrations could be of central importance in the abnormal sodium excretion in CHF. In this regard, plasma norepinephrine concentrations were recently found to be directly correlated with the degree of left ventricular dysfunction in patients with CHF (27-30). Renal vasoconstriction would then occur with a decrease in renal blood flow more than GFR and therefore the filtration fraction rises. This increase alters ultrafiltration of plasma and peritubular physical faces which may in turn increase proximal tubular readsorption. Additionally, changes in cardiac output and renal perfusion pressure also activate the renin-angiotensin-aldosterone system, and these hormones function to maintain blood pressure and extracellular fluid volume by virtue of the vasoconstrictor activity of angiotensin and the salt-retaining activity of aldosterone. In this regard there is both experimental (31) and clinical (32) evidence that increased renin activity and aldosterone secretion may be quite important in the generation of cardiac edema. In a dog model of heart failure, acute reduction of cardiac output by constriction of the thoracic inferior vena cava was accompanied by increased plasma renin and aldosterone and sodium retention (31). Over several days plasma volume and body weight increased and renin and aldosterone levels and sodium balance returned to control values. Chronic administration of converting enzyme inhibitor from the onset of caval constriction significantly attenuated sodium retention and volume expansion (31). As well, during severe decompensated

left ventricular failure before the development of extracellular fluid volume expansion, 14 patients had markedly elevated renin and aldosterone levels (32). In these patients, with stabilization of cardiac failure and extracellular fluid volume expansion, renin and aldosterone levels returned to normal (32). In summary, increase in sympathetic efferent activity and stimulation of the renin aldosterone system could be the two major efferent mechanisms for sodium readsorption in CHF.

C. Mechanisms for water retention in CHF

Water is often retained in excess of sodium in severe congestive heart failure, and hyponatremia is therefore frequently observed (33-36). Excess water retention can result from either increased release of vasopressin, decreased delivery of sodium and water to the distal diluting segment of the nephron, or both.

In experimental heart failure, decreased cardiac output and arterial pressure may be associated with diminished glossopharyngeal afferent tone from the carotid sinus and aortic arch baroreceptors, an effect which results in increased vasopression release from the pituitary (37). On the other hand, with left atrial distension, atrial receptors would be expected to increase vagal activity and suppress vasopressin release (38). However, the inhibitory influence of atrial receptors may be opposed by the stimulatory influence of decreased blood pressure and arterial filling on the carotid sinus and aortic baroreceptors. In chronic CHF and left atrial distension, blunting of the sensitivity of the left atrial receptors would also diminish the importance of the inhibitory influence of these receptors.

Recent experimental and clinical results from our laboratory indicate that both AVP and diminished fluid delivery to the diluting segment in the distal nephron are important in the impairment in the renal water excretion associated with low cardiac output (37). In dogs with constriction of the thoracic inferior vena cava, a model of low output cardiac failure, as cardiac output fell, urinary osmolality rose and free water clearance decreased (37). In animals hypophysectomized to

prevent vasopressin release, a decrease in cardiac output did not result in an increase in urinary osmolality, although free water clearance was moderately decreased secondary to decreased distal delivery of fluid (37). In a high output cardiac failure model in the rat, a defect in water excretion was again documented (39). As Brattleboro AVP deficient rats with the same degree of heart failure did not demonstrate any defect in water excretion, it was concluded that the primary mechanism mediating the abnormality in water excretion in high output heart failure was also persistent AVP release (39).

In a recent study from our laboratory, plasma AVP was found to be inappropriately elevated in 30 of 37 hyponatermic patients with congestive heart failure (35). The 30 patients with detectable AVP had higher levels of blood urea nitrogen and serum creatinine and higher ratios of blood urea nitrogen to serum creatinine than those 7 patients with undetectable levels of AVP. This latter finding could be dissociated from diuretic use, since it was still observed in 14 patients who had never received diuretics. The presence of prerenal azotemia provided evidence for an intrarenal component of the impaired water excretion, but also suggested that lower cardiac output mediated the nonosmotic stimulation of vasopressin release in a manner similar to that observed in experimental studies (37). Similar results were obtained by Riegger et al (36) and Rondeau et al (40) who examined plasma AVP levels in patients with severe heart failure. Of interest, a decrease in plasma AVP was observed after improvement in cardiac function by hemofiltration while no change in plasma AVP was observed after decreasing left atrial pressure with prazosin (36). These results, therefore, suggested that high pressure baroreceptors were the main pathway of nonosmotic stimulation of AVP in these subjects.

In summary, a decrease in effective central blood volume sensed by high pressure baroreceptors will decrease carotid sinus glossopharyngeal input to the hypothalamus via the midbrain (41); such a decrease in glossopharyngeal afferent tone would be expected to stimulate the nonosmotic release of AVP (41). Also, as described earlier, increased central sympathetic

efferent discharge would be expected as a consequence of the decreased effective blood volume (27-30). This increased sympathetic tone could then decrease GFR and increase proximal readsorption of solute, further impairing the ability of the kidney to excrete free water.

However, further studies examining systemic hemodynamics, vasopressin and norepinephrine levels, as well as the capacity of the kidney to excrete free water and sodium, must be undertaken to elucidate the mechanisms of sodium and water retention in CHF.

III. SODIUM AND WATER RETENTION IN CIRRHOSIS

A. Afferent mechanisms for sodium retention

Cirrhosis of the liver commonly leads to sodium retention, ascites and edema as the disease worsens and the hepatic fibrosis progresses. The development of ascites correlates best with the degree of hepatic venous obstruction and not to the extent of portal vein hypertension (6). Plasma transudate leaves the vascular space in obedience to Starling faces and forms hepatic lymph. The hepatic sinusoids, at least during the early cirrhotic process, are extremely permeable to albumin; therefore, the transsinusoidal oncotic gradient remains at zero (6). For this reason, hydrostatic pressure, a direct product of hepatic vein pressure, modulates the movement of fluid from vascular to extravascular spaces. Later on, during the cirrhotic process, structural changes occur in the hepatic sinusoid and the hepatic lymph protein concentration falls to about 50% or 55% of the plasma levels (6). Thus, at this later stage, not only venous outflow block but also diminished oncotic pressure both contribute to ascites formation. Hepatic lymph flow through the thoracic duct as high as 20 liters/day has been recorded in patients with ascites (42). Limitation of flow at the level of the thoracic duct ostium into the jugular vein may impair return of interstitial fluid to the circulation and thus enhance the development of ascites (42).

Two theories have been proposed to explain the stimulus for renal sodium retention and ascites development in cirrhosis.

The traditional view, often called the "underfilling" theory, suggests that because of primary changes in the liver with progressive hepatic venous obstruction, fluid is lost from the circulation into the abdominal cavity. This loss of intravascular volume results in decreased effective blood volume and renal sodium retention (3). Thus, the afferent mechanisms for sodium retention would be the same as those discussed earlier for heart failure. Against this theory is the frequent finding of increased rather than decreased plasma volume in cirrhosis (43). It has been argued, however, that because of splanchnic venous sequestration, EABV is reduced (3). In favor of this theory are the observations that increasing central blood volume by head-out water immersion or peritoneovenous transfer of ascites with a LeVeen shunt increases renal sodium excretion (44, 45).

In an effort to further test this "underfilled" view of renal salt and water retention in cirrhosis, we recently measured humoral markers of volume depletion in cirrhotic patients with ascites (46-48). Nineteen decompensated cirrhotic patients with ascites, who were unable to excrete an oral water load and who had virtually no sodium in their urine, were compared to 7 compensated cirrhotics who were able to excrete a waterload and were in sodium balance. The "non-excretor" patients had significantly higher plasma concentrations of renin, aldosterone, vasopressin and norepinephrine than did the "excretor" patients (46, 47). In subsequent studies we used head-out water immersion (HWI) to increase central blood volume in 8 non-excretor cirrhotic patients. HWI increased right atrium pressure, wedge pressure, and cardiac output and improved sodium and water excretion (48). The improvement in renal excretion of sodium and water was associated with significant decreases in plasma concentrations of renin, aldosterone, vasopressin and norepinephrine (48). Taken together, these findings support the traditional underfilling view at least in patients with decompensated liver disease.

A more recent theory proposed by Lieberman and colleagues suggests that, in some way, liver disease directly induces renal sodium retention (43, 49). The resultant increase in

extracellular fluid volume then spills into the peritoneal cavity under the influence of altered Starling forces, i.e., overflow hypothesis. Lieberman and Reynolds measured plasma volume and wedge hepatic pressure in a number of cirrhotic patients with and without ascites (43, 49). Total plasma volume was found to be expanded, not contracted, in patients with cirrhosis and ascites. Moreover, a correlation between plasma volume and hepatic wedge pressure suggested that the increase in plasma volume was, at least in part, secondary to increased splanching plasma volume. However, portal-caval anastomosis did not return plasma volume to normal. Lieberman and Reynolds concluded then that expanded plasma volume in cirrhosis was secondary to portal hypertension, but also to other factors which maintain increased plasma volume after shunting. In subsequent studies, total plasma volume failed to rise in 10 patients with the spontaneous loss of ascites (43). From these studies the authors concluded that the ascites formation should no longer be considered as a cause of renal sodium retention or mediated through contraction of effective plasma volume.

Two points deserve emphasis regarding these plasma volume measurements. First, the formation of ascitic fluid and edema is likely to be a dynamic process. Thus, measurements carried out after significant salt and water retention should demonstrate an increase in plasma volume (50). Secondly, Lieberman et al equate measured plasma volume with the "effective circulating plasma volume." It seems more appropriate to define effective plasma volume as the ratio of the non-portal plasma volume to the non-portal vascular holding capacity. This is of note since a feature of most patients with advanced liver disease is a decrease in systemic vascular resistance. A normal or even increased plasma volume, combined with a decrease in systemic peripheral resistance, could result in a decrease in EABV, the latter initiating urinary sodium retention.

In addition, the overflow hypothesis has also received support by a series of animal experiments carried out in the dog (51-53) and in the rat (54-55). Dogs fed the potent hepatotoxin, dimethylnitrosamine, develop liver cirrhosis over a 2-month

period. This hepatic cirrhosis is characterized by the presence of ascites, portal venous hypertension, portasystemic shunting, lymph formation, hepatic encephalopathy and gastrointestinal bleeding. In this dog model, sodium balance studies demonstrate that urinary sodium retention precedes the formation of ascites by about 10 days (51). Similar results have been reported in rats made cirrhotic with carbon tetrachloride inhalation and oral phenobarbital (55). Together, these observations suggest that renal sodium retention precedes the development of ascites in animal models of cirrhosis. In additional studies, systemic hemodynamic measurements were carried out in the cirrhotic dogs (53). Positive sodium balance and plasma volume expansion preceded any changes in cardiac output or peripheral vascular resistance (53). Regarding these latter studies, it is reasonable to question whether the current methodology of cardiac output and blood pressure measurements allows detection of subtle alterations in these parameters.

At this point in time, it is not possible to decide which of these two theories best explains the pathogenesis of renal sodium retention in cirrhosis; both may be involved (56).

B. Efferent mechanisms for sodium retention

There is indirect evidence for both enhanced proximal and distal tubular readsorption in human cirrhotic subjects. For example, maneuvers that expand plasma volume and increase distal nephron delivery of fluid (i.e., neck immersion and infusion of saline or mannitol) result in increased renal sodium excretion and free water formation independent of GFR and are in favor of enhanced proximal tubular readsorption in hepatic cirrhosis (44, 48, 57). However, micropuncture studies in the dimethylnitrosamine and bile duct ligated models of cirrhosis have clearly demonstrated enhanced distal nephron sodium readsorption (51, 54).

The mechanisms responsible for enhanced sodium readsorption at both proximal and distal sites have not been clearly defined and may be multifactorial. As noted above, decreased EAVB might cause enhanced renal sodium readsorption via changes in GFR, renal blood flow or filtration fraction. Recently, elevated

plasma levels of norepinephrine have been observed in cirrhotic patients with ascites (47). Plasma norepinephrine correlated positively with plasma vasopression and plasma renin activity (suggesting a lower EABV) and negatively with urinary sodium excretion (47). These findings suggest that increased renal sympathetic activity could also result in enhanced renal sodium readsorption.

The contribution of aldosterone to the enhanced sodium readsorption in cirrhosis is disputed (44). Of interest are the observations that cirrhosis without ascites fails to "escape" from the sodium retaining effect of aldosterone. These findings have been attributed to the absence of a natriuretic factor (58). Also, other humoral substances such as bradykinin and prostaglandin E_2 may play an effector role in modulating renal sodium excretion in cirrhosis (59, 60). In summary, the effector mechanisms involved in renal salt retention in cirrhosis are likely to be multifactorial.

C. Mechanisms for water retention

Hyponatremia with impaired ability to excrete a waterload occurs in a substantial number of patients with cirrhosis of the liver, thereby demonstrating an impairment in renal water excretion in these patients (46, 47, 61). Decompensated cirrhotic patients with ascites and/or edema have an abnormal response to water administration while cirrhotic patients without ascites or edema usually excrete water normally (46, 47, 61). There are two potential mechanisms for this inability to excrete free water: 1) a derangement in renal hemodynamics with decreased fluid delivery to the distal nephron; and 2) an extrarenal mechanism involving vasopressin release.

Four experimental models of altered liver function have recently been studied in our laboratory: 1) thoracic inferior vena cava constriction in the dog as a model of hepatic congestion (37); 2) acute portal vein constriction in the dog as a model of portal venous hypertension (62); 3) chronic bile duct ligation in the rat as a model of obstructive jaundice (63); and 4) carbon tetrachloride induced liver disease in the rat as a

model of chronic cirrhosis (64). In each of these experimental models, a predominant role for vasopressin in the impairment of water excretion was demonstrated. However, in each case, there was also evidence that diminished fluid delivery to the distal diluting segment contributed slightly to the abnormal water excretion.

Studies in patients with cirrhosis also point to the nonosmotic release of AVP as a major factor responsible for water retention in cirrhosis. Bichet et al (46, 47) studied cirrhotic patients who received a standard waterload (20 ml/kg). On the basis of their ability to excrete this waterload, patients could be separated into two groups: those able to excrete more than 80% of the waterload in 5 hours ("excretors") and those unable to excrete a waterload normally ("nonexcretors"). Nonexcretors had lower serum sodium concentrations and higher plasma vasopressin levels after the waterload. These nonexcretors were also found to have higher pulse, lower plasma albumin, higher plasma renin and aldosterone and higher plasma norepinephrine levels than normonatremic cirrhotic patients with normal water excretion (46, 47). A decrease in effective plasma volume is suggested by these studies and may provide the nonosmotic stimulus for AVP release in hyponatremic cirrhotic patients. In subsequent experiments, enhancement of central blood volume by water immersion to the neck suppressed vasopressin release and improved water excretion (48). In summary, experimental and clinical evidences suggest that the impairment in water excretion in association with cirrhosis is mediated predominantly by persistent release of AVP; diminished distal delivery of tubular fluid to the diluting segment of the nephron may also contribute.

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12. COMPARISON OF RENAL HEMODYNAMICS IN BLACK AND WHITE PATIENTS WITH ESSENTIAL HYPERTENSION

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ABSTRACT

Systemic, splanchnic, and renal hemodynamic data, determined in 60 male and female, black and white, untreated and uncomplicated essential hypertensive patients, confirmed our previous systemic hemodynamic findings. When black and white patients were matched for age, sex, and mean arterial pressure, cardiac index and total peripheral resistance were similar at all levels of pressure. This suggests that hypertensive vascular disease is no more severe in blacks. This conclusion could be confirmed further by our splanchnic hemodynamic findings. However, in contrast to these findings, renal blood flow was less and renal vascular resistance was higher at any mean arterial pressure (or total peripheral resistance) level in blacks--especially in men. These findings tend to support those reports suggesting that hypertensive disease--in particular, renal morbidity--is more severe in the black.

INTRODUCTION

Current clinical opinion holds that hypertension is more severe in the black than in the white patient. This is supported by certain epidemiological evidence. In the black patient: the disease is more prevalent (1-4); vascular disease may be more severe (5-7); cardiac involvement, stroke, and malignant hypertension may be more frequent; and renal involvement may follow a more rapid and severe course (2,5-11).

However, few physiological data are available to support these concepts. Information from our laboratory has indicated that at any level of arterial pressure, increased total peripheral resistance, the hemodynamic hallmark of hypertension, is similar

in black and white patients with essential hypertension (12). However, other data from our laboratory and others have demonstrated that certain other physiological differences do exist between the two racial groups: slower heart rate (12,13), greater prevalence of expanded intravascular volume (14,15), lower plasma renin activity (13,16,20), and lesser adrenergic participation occur in black patients (13,19,20).

Because of the apparent discrepancy between our earlier studies and the epidemiological data suggesting greater severity of renal vascular disease in the black, this study was designed to compare systemic and regional vascular changes in matched groups of black and white patients with uncomplicated essential hypertension.

METHODS

Sixty patients with essential hypertension were the subjects of this study. All had uncomplicated established essential hypertension as evidenced by sustained elevation of diastolic pressure ($\geq$ 90 mm Hg) when receiving no antihypertensive therapy. No patient demonstrated evidence of cardiac or renal functional impairment or failure; and in no patient was there evidence of a secondary cause of hypertension.

Hemodynamic studies were carried out in a quiet laboratory in the morning in all patients without prior premedication and in a fasting condition, having received no antihypertensive therapy for four weeks. Supine hemodynamics were performed after placing small polyethylene tubings into the superior vena cava and subclavian artery via an antecubital vein and brachial artery (21). Renal and splanchnic blood flows were determined from the disappearance of ^{131}I-tagged para-amminohippurate and indocyanine green dye, respectively. Plasma volume was measured using ^{125}iodinated human serum albumin. Calculations of hemodynamic data were derived from standard hemodynamic formulae. Statistical procedures were carried out using the student's t-test for group comparisons and two-way analysis of covariance method to test for sexual and racial differences while controlling for age and body habitus (22).

There were 15 men and 15 women in each of the two racial groups who were matched for age, body surface area, and mean arterial pressure. The slower heart rate found in our study (23) and other (13) previous studies for black patients was not significantly so in this study. Nevertheless, we again report no significant systemic hemodynamic differences between the black and white patients with respect to cardiac index or total peripheral resistance (Table 1).

A two-way covariance data analysis was used to test for differences (controlling for age and body surface area). With respect to regional blood flow determinations, there were no differences demonstrated between the two racial groups in regard to splanchnic hemodynamics (Table 1). Correlation analysis showed no relationship between mean arterial pressure or total peripheral resistance and splanchnic hemodynamic functions in the patients whether considered as a single group or as two separate racial groups. However, renal blood flow was significantly reduced ($p < 0.003$) and renal vascular resistance significantly increased ($p < 0.002$) in the black patients when considered as a homogenous group. These differences reflect changes primarily in the male black patients. Moreover, although splanchnic hemodynamics were not related to systemic hemodynamic alteration, a highly significant relationship existed between arterial pressure or total peripheral resistance and the degree of renal vasoconstriction in all patients considered as a single group (MAP, $r=0.481$, $p < 0.004$; TPR, $R=0.329$, $p < .0037$, respectively). Thus, the higher the mean arterial pressure (or total peripheral resistance) the greater was the renal vascular resistance in patients of both races when considered as a single group; but this was especially so in the blacks. Moreover, these data demonstrated that the higher the mean arterial pressure, the lesser was the renal blood flow in black patients ($r-0.322$, $p < 0.047$) and the greater their renal vascular resistance ($r=0.592$, $p < 0.0004$). This relationship was significantly different between the two racial groups ($p < 0.05$).

Table 1

Systemic hemodynamic characteristics of male and female black and white patients with essential hypertension (15 in each of the 4 groups). Each value represents the mean (± 1 standard error of the mean).

	White Patients		Black Patients	
Index	Male	Female	Male	Female
Age (years)	46 (2.5)	46 (4.0)	43 (2.8)	39 (3.1)
Body Surface Area (m^2)	1.94 (.04)	1.77 (.05)	1.96 (.04)	1.87 (.05)
Mean Arterial Pressure (mm Hg)	116 (3)	113 (2)	122 (4)	116 (3)
Heart Rate (beats/min)	73 (2)	70 (2)	69 (3)	64 (4)
Cardiac Index ($L/min/m^2$)	3.12 (.08)	3.01 (.13)	2.91 (.14)	3.19(.18)
Total Peripheral Resistance (U/m^2)	36 (2)	39 (2)	39 (3)	38 (2)
Splanchnic Blood Flow (ml/min)	821 (124)	647 (74)	763 (73)	647 (81)
Splanchnic Vascular Resistance (mmHg/ml/min)	.178 (.029)	.199 (.026)	176 (.059)	.200 (.072)
Renal Blood Flow (ml/min)	1115 (56)	947 (75)	883 (66)	922 (80)*
Renal Vascular Resistance (mm Hg/ml/mn)	.107 (.005)	.130 (.012)	.153 (.015)	.136 (.011)*

*Covariate analysis (taking into consideration differences in BSA with respect to age and sex and in age with respect to BSA) revealed a significantly lower renal blood flow ($p < 0.003$) and higher renal vascular resistance ($p < 0.002$) in the black patients.

BSA = body surface area
MAP = mean arterial pressure
TPR = total peripheral resistance

DISCUSSION

These data confirm our previous report demonstrating that at any level of pressure, cardiac output and total peripheral resistance were similar in black and white patients with essential hypertension (12). These findings lend less credence to the concept that systemic vascular disease is more severe in the black patient with essential hypertension. However, strikingly different from these observations are the disparate findings that we observed in two major regional circulations between the racial groups. Our results demonstrated similar hemodynamic findings between the races with respect to the splanchnic circulation and that in black patients renal vasoconstriction seemed to be more severe regardless of the level of mean arterial pressure.

We have already cited the epidemiological observations suggesting more severe manifestations of hypertensive vascular disease in the black patient. These observations have been variously ascribed to differences in socioeconomic as well as physical (e.g., obesity) factors compounded by possible differences in risk factors (9).

Our previous studies have shown that black patients with essential hypertension had a greater prevalence of expanded plasma volume, lower plasma renin activity (15), and slower heart rate (12), lending support to the concept of lesser adrenergic and renopressor activities and greater participation of volume-dependent mechanisms (23) in the black. Indeed, recent therapeutic studies that support this contention indicate that black patients seem to respond better to diuretic therapy and not as well to beta-adrenergic receptor inhibiting therapy than white patients (24-29).

These findings suggest that black patients with essential hypertension may be predisposed to a greater participation of volume-dependent pressor factors. Explanations may be on the basis of alterations in sodium balance (30), defects in sodium transport (31), or active sodium and water retention, but there is no evidence at present to support these concepts. Another explanation might be the presence of even slight degrees of renal

parenchymal damage secondary to renal ischemia produced by more intense renal vasoconstriciton. A previous report has indicated more severe nephrosclerosis and a reduced renal blood flow in black patients with essential hypertension who were not matched for arterial levels with white patients (10). This latter mechanism is supported by our present data. Thus, our findings demonstrated that at any level of arterial pressure renal blood flow was lower and renal vasoconstriction more intense in the black patient with otherwise uncomplicated essential hypertension. This lends pathophysiological support to the epidemiological findings and clinical impressions that, at any level of blood pressure, hypertensive renal vascular disease is more severe in the black patient.

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13. EFFECTS OF BETA-ADRENERGIC ANTAGONISTS AND DIURETICS ON KIDNEY FUNCTION IN HYPERTENSIVE PATIENTS

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ABSTRACT

Most beta-adrenergic blocking agents effectively reduce blood pressure in hypertensive patients without causing significant changes in kidney function. Only propranolol on occasion has been shown to decrease creatinine clearance in some studies. In this study, we re-evaluated the effect of four different agents with beta-blocking properties, propranolol, metoprolol, acebutolol and labetalol, on creatinine clearance and on serum concentrations of uric acid and potassium. We compared the effect of these agents when used as monotherapy with the effects observed when the beta-blockers were given in combination with a diuretic. Decreases in kidney function were encountered with equal frequency during treatment with the beta-blockers individually, the diuretic alone, or the diuretic-beta-blocker combination, even though blood pressure was lowest during the combined therapy.

Uric acid levels increased during treatment with the beta-blockers alone. Administration of a beta-blocker to diuretic treated patients decreased uric acid levels in 30 percent of patients. These decreases in uric acid levels were observed during treatment with propranolol, acebutolol or labetalol, but not when metoprolol was used in combination with the diuretic. The differing effects of the beta-blockers on uric acid metabolism deserve further study. Serum potassium concentrations increased during beta-blocker therapy both in the absence or presence of a diuretic. All four beta-blockers were equally effective in increasing the potassium levels. However, the increase in serum potassium levels might reflect a shift of potassium from the intracellular compartment into the blood rather than an increase in total body potassium.

INTRODUCTION

Beta-adrenergic antagonists are commonly used as monotherapy in patients with mild hypertension. A combination of relatively low doses of diuretics and beta-adrenergic antagonists is often prescribed in the treatment of more severe forms of hypertension. In general, beta-blockers with or without diuretics have been shown to be safe and without major side effects. However, there have been some reports of decreased kidney function during beta-blocker therapy (1-5). These adverse effects on kidney function are believed to be secondary to the treatment-induced decreases in blood pressure and cardiac output, resulting in a reduction in renal blood flow. Significant decreases in kidney function have been

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reported only during treatment with the beta-blocker propranolol and not during therapy with other beta-blockers.

In this study we have evaluated the effects of four different beta-adrenergic antagonists on blood pressure and biochemical parameters of kidney function in patients with mild or moderate forms of hypertension. Moreover, we have studied the effects of beta-blockers on kidney function in patients in whom a beta-blocker was added to a diuretic in order to control blood pressure.

METHODS

The study was designed to evaluate the effects of beta-adrenergic antagonists, diuretics and the combination of these drugs on blood pressure and biochemical parameters of kidney function in patients with mild or moderate essential hypertension. Patients with clinical or biochemical signs of secondary hypertension were excluded from the study. All patients signed an informed consent prior to the start of the study.

Eighty-seven male patients were treated with beta-adrenergic antagonists. Four different drugs were used: propranolol in doses of 80 to 320 mg daily (n=22), metoprolol in doses of 100 to 400 mg daily (n=19), acebutolol in doses of 400 to 1600 mg per day (n=31) and labetalol in doses of 400 to 1200 mg daily (n=15). The doses of these beta-adrenergic antagonists were increased in a step-wise fashion during the first weeks of the study in patients in whom blood pressure was not controlled (decrease in supine diastolic blood pressure to 90 mm Hg or less). The optimum doses of the drugs then were given for 4 to 8 weeks. The diuretic, hydrochlorothiazide 50 mg daily, was given alone to 65 of the patients for 4 to 6 weeks. The combination of one of the adrenergic blocking agents and the diuretic was given to 47 of the patients for another 4 to 6 weeks. All patients in this group had been treated with a beta-adrenergic antagonist alone prior to the start of combination therapy. Thirty-three patients were challenged with all three therapeutic modalities (beta-blocker alone, diuretic alone, and the combination).

Blood pressure was measured during placebo therapy and at the end of each active treatment period after at least 5 minutes of supine rest using a standard mercury sphygmomanometer. Blood samples for the measurement of creatinine, urea nitrogen, uric acid and potassium were also obtained at the end of each treatment period. The patients were asked to collect a urine sample for measurements of creatinine excretion during the last 24 hours prior to each visit. Serum levels and urinary excretion of creatinine were used to calculate endogenous creatinine clearance. Standard laboratory tests were used to measure

the biochemical parameters reported in this study.

The t-test for unpaired samples and the chi-square test were used in the statistical analysis of the data. The data are given as the mean and the standard deviation of the mean. As an aid in the analysis of the data, blood pressure responses induced by the antihypertensive agents used were subdivided into four categories: marked decreases in systolic or diastolic blood pressure (greater than 15 mm Hg); moderate decreases in pressure (5 to 15 mm Hg); no change in pressure (-5 to +5 mm Hg) and increases in pressure (greater than +5 mm Hg). Increases or decreases in biochemical parameters were defined as changes of 0.2 mg/dl or more for serum creatinine, 4 mg/dl or more for blood urea nitrogen, 20 ml/minute or more for creatinine clearance, 1 mg/dl or more for uric acid and 0.4 mEq/liter or more for serum potassium concentrations. The prevalence of a particular response in blood pressure or in a biochemical measurement was calculated as the percentage of patients who exhibited such a response.

RESULTS

A comparison of the clinical data obtained during administration of a placebo in patients treated with a beta-adrenergic blocking drug, hydrochlorothiazide or combination therapy is given in Table 1. The group of patients treated with a diuretic was slightly, but significantly, older than the group of patients treated with a beta-adrenergic antagonist. Moreover, the patients treated with a diuretic alone and the patients treated with combination therapy had, on average, significantly higher control blood pressure levels than those treated with a beta-adrenergic antagonist alone. Baseline values of serum creatinine, blood urea nitrogen, uric acid and potassium were not different between the three subgroups. Calculated creatinine clearance also was similar for the three groups (Table 2).

Beta-Adrenergic Antagonists as Monotherapy

The response pattern (as defined in the Methods Section) of blood pressure during treatment with a beta-adrenergic antagonist alone revealed that 59 percent of patients had a moderate or marked decrease in systolic blood pressure and 71 percent had a moderate or marked decrease in diastolic blood pressure (Figure 1, top panel). Increases in systolic blood pressure were more common than increases in diastolic blood pressure (16 percent versus 5 percent, $p<0.025$). The response pattern was similar for each of the four beta-adrenergic antagonists used.

Increases in serum creatinine levels were observed in 30 percent of patients and increases in blood urea nitrogen in 18 percent. Decreases in creatinine clearance were observed in 16 percent of the patients studied. Increases in serum

Table 1. Comparison of baseline clinical characteristics (Mean ± SD) in three groups of patients with hypertension

	Patients Treated With a Beta-Blocker n=87	P	Patients Treated With a Diuretic n=65	P	Patients Treated With a Beta-Blocker + Diuretic n=47
Age (yrs)	52.1 ± 11.3	<0.05	55.5 ± 8.3	ns	54.6 ± 7.8
White/Black Ratio	79/8	ns	55/10	ns	47/6
Systolic BP (mm Hg)	153 ± 18	<0.001	165 ± 20	ns	162 ± 18††
Diastolic BP (mm Hg)	98 ± 11	<0.001	107 ± 10	ns	105 ± 10†

††P < 0.001 versus Beta-Blocker alone
†P < 0.01 versus Beta-Blocker alone

Table 2. Comparison of baseline biochemical parameters (Mean ± SD) between three groups of patients with hypertension

	Patients Treated With a Beta-Blocker n=87	Patients Treated With a Diuretic n=65	Patients Treated With a Beta-Blocker + Diuretic n=47
Serum Creatinine Concentration (mg%)	1.2 ± 0.2	1.2 ± 0.3	1.2 ± 0.3
Blood Urea Nitrogen Concentration (mg%)	15.6 ± 3.9	16.3 ± 5.2	16.4 ± 4.5
Creatinine Clearance (ml/min)	93 ± 27	93 ± 26	90 ± 28
Serum Uric Acid Concentration (mg%)	6.6 ± 1.4	6.7 ± 1.3	6.1 ± 2.0
Serum Potassium Concentration (mEq/l)	4.21 ± 0.41	4.17 ± 0.45	4.19 ± 0.45

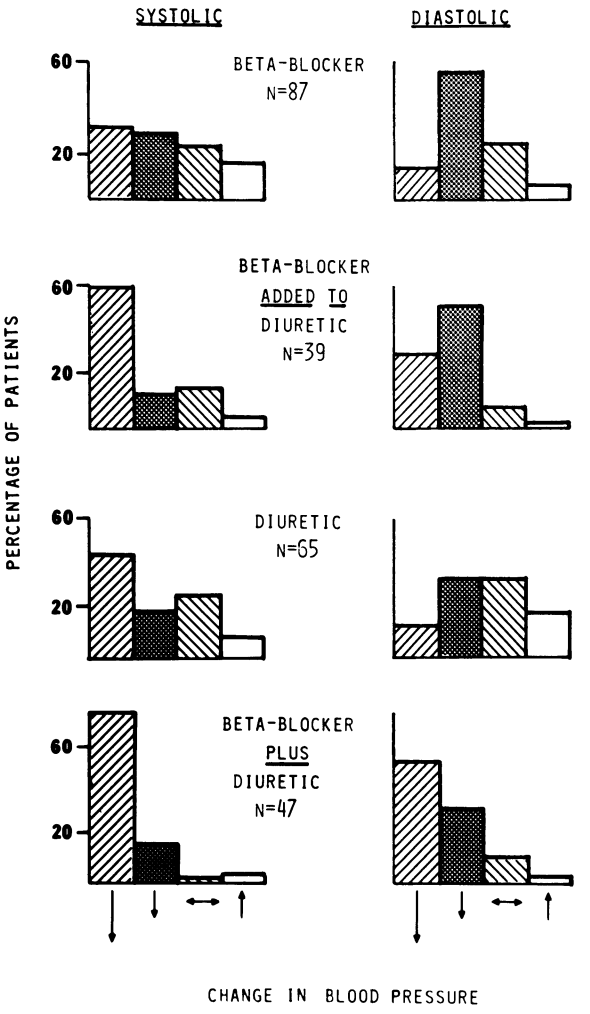

FIGURE 1. Prevalence of blood pressure responses to treatment with beta-blockers, diuretics or its combination in patients with hypertension. The arrows under the figure indicate, respectively, marked decreases, moderate decreases, no change, or increases in blood pressure (definitions of these changes are given in the text). The designation "beta-blocker added to diuretic" represents the effect of adding a beta-blocker to the diuretic" the designation "beta-blocker plus diuretic" represents the effect of combination treatment.

creatinine or in blood urea nitrogen concentrations were more common than were decreases in these measurements (Figure 2, top panel). The prevalence of these changes in kidney function was similar for each of the four beta-blockers used.

Treatment with beta-blockers increased serum potassium and uric acid levels in 26 and 21 percent of patients, respectively (Figure 3, top panel). Again, no differences in changes in uric acid were found between the various beta-blockers used. However, decreases in serum potassium levels were only observed during therapy with acebutolol (26 percent of patients) and labetalol (14 percent of patients) and not during therapy with metoprolol or propranolol.

Beta-Adrenergic Drugs in Diuretic Treated Patients

Decreases in blood pressure were more often seen when a beta-blocker was given to patients treated with a diuretic than during monotherapy with a beta-blocker. A decrease in systolic blood pressure was observed in 77 percent of patients and a decrease in diastolic blood pressure in 87 percent when a beta-blocker was given to diuretic treated patients (Figure 1).

Changes in serum creatinine, blood urea nitrogen or creatinine clearance observed after the addition of beta-blocker therapy were comparable to those observed during beta-blocker monotherapy despite the slightly more pronounced decreases in blood pressure observed during combination therapy (Figure 2). Changes in serum potassium after addition of a beta-blocker to the diuretic also were similar to those observed during beta-blocker monotherapy (Figure 3). However, decreases rather than increases in uric acid were observed when a beta-blocker was given to diuretic treated patients. Decreases in uric acid were observed in 5 percent of patients during beta-blocker monotherapy and in 30 percent of patients when a beta-blocker was added to a diuretic ($p<0.01$, Figure 3). This disparate effect on uric acid was seen after addition of propranolol, acebutolol and labetalol, but not after addition of metoprolol. When metoprolol was added in diuretic treated patients, uric acid increased in 26 percent and decreased in 11 percent of patients.

Combination therapy was more effective in lowering blood pressure than therapy with a beta-blocker alone or diuretic monotherapy ($p<0.01$, Figure 1). However, changes in parameters of kidney function observed during the diuretic-beta-blocker combination were similar to those observed during beta-blocker monotherapy or monotherapy with a diuretic (Figure 2). Serum potassium decreased rather than increased during combination therapy. However, changes in uric acid were similar during monotherapy or combination therapy (Figure 3).

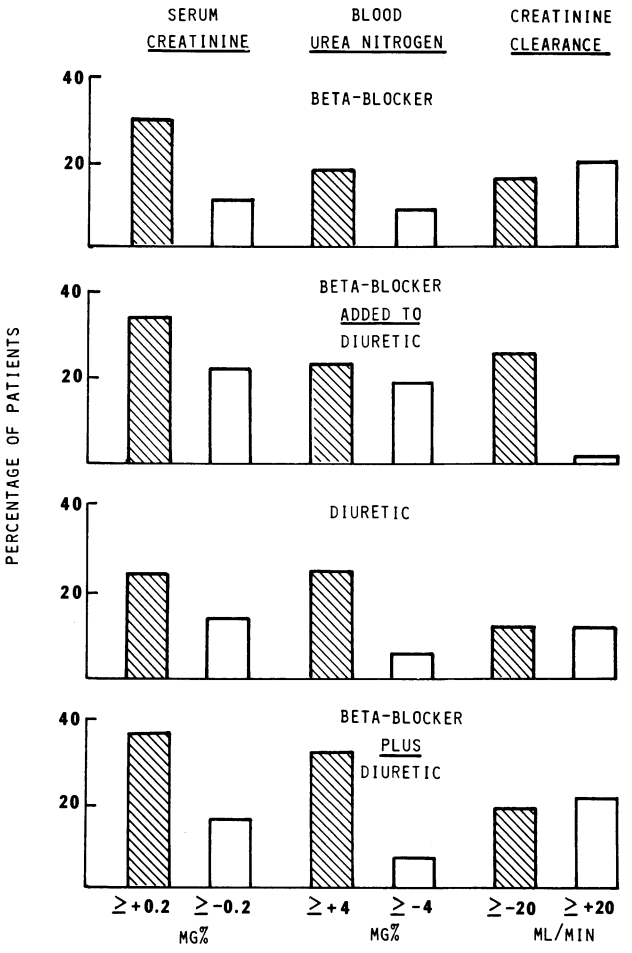

FIGURE 2. Prevalence of changes in kidney function during treatment with beta-blockers, diuretics or its combination in hypertensive patients. The designation "beta-blocker added to diuretic" represents the effect of adding a beta-blocker to the diuretic; the designation "beta-blocker plus diuretic" represents the effect of combination treatment.

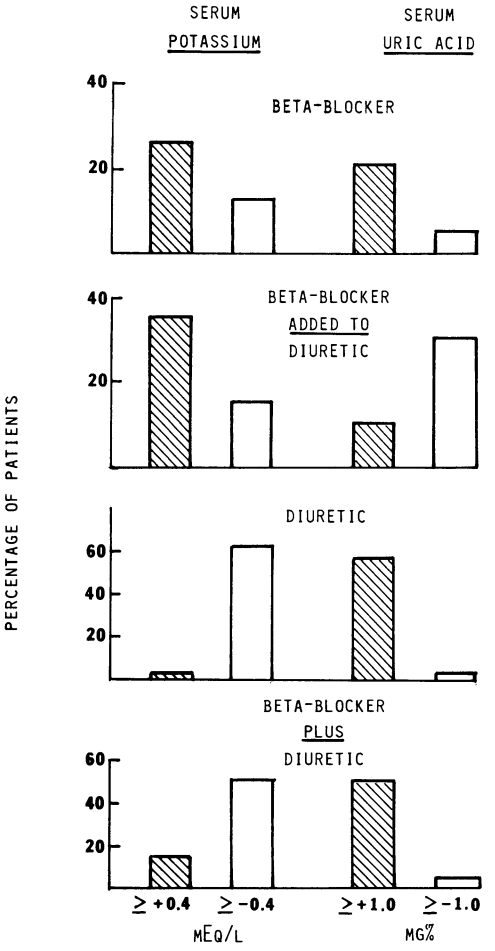

FIGURE 3. Prevalence of changes in serum potassium and uric acid concentrations during treatment with a beta-blocker, a diuretic or its combination. The designation "beta-blocker added to diuretic" represents the effect of adding a beta-blocker to the diuretic; the designation "beta-blocker plus diuretic" represents the effect of combination treatment.

Beta-Blocker Versus Diuretic Therapy

Treatment with hydrochlorothiazide resulted in changes in systolic blood pressure similar to those observed during monotherapy with a beta-adrenergic antagonist (65 and 59 percent of patients, respectively). However, diastolic blood pressure decreased less often with diuretic therapy (47 percent of patients) than during beta-blocker treatment (71 percent of patients, $p<0.01$, Figure 1). Changes in kidney function during diuretic therapy were similar to those found during beta-blocker or combined diuretic beta-blocker therapy (Figure 2). As expected, treatment with diuretics decreased serum potassium in 62 percent of patients, whereas beta-blockers tended to increase serum potassium levels. Changes observed in uric acid were similar for both types of treatment.

Abnormal Biochemical Test Results

Serum creatinine levels of greater than 1.7 mg/dl were observed in 5 patients; in one during diuretic therapy, in two during treatment with a beta-blocker, and in two during combination therapy. Blood urea nitrogen concentrations greater than 22 mg/dl were observed in 13 patients (22 percent) during diuretic therapy, in eight patients (18 percent) during combination therapy, but less often (six patients, 7 percent) during treatment with a beta-blocker ($p<0.05$). Creatinine clearance decreased to less than 80 ml per minute in 9 patients; in 4 during beta-blocker therapy, in 2 during treatment with a diuretic and in 3 during combination therapy. Serum uric acid levels of 9.0 mg/dl or more were found more often ($p<0.01$) during diuretic therapy (15 patients, 25 percent) than during treatment with a beta-blocker (5 patients, 6 percent). Increases in uric acid were found in 16 percent of patients treated with the combination of a diuretic and a beta-blocker. Serum potassium levels lower than 3.7 mEq/liter were seen most often during diuretic therapy (56 percent of patients) and less often ($p<0.01$) in 5 patients (6 percent) during treatment with a beta-blocker. Hypokalemia was found in 17 patients (39 percent) treated with the diuretic-beta-blocker combination.

DISCUSSION

Although slight decreases in creatinine clearance have been observed during treatment with various beta-adrenergic antagonists, changes in kidney function have generally not been clinically important. Significant decreases in creatinine clearance have been observed in five studies during propranolol therapy in hypertensive patients (1-5), but this effect of propranolol has not been confirmed by other investigators (6-9). The disparity between these two groups of studies cannot be explained by any differences in the clinical characteristics of the

patients treated, but it is possible that differing durations of treatment might influence renal function. There has been a tendency for renal function to decrease during short-term treatment, but to subsequently return to control values. Thus, in the recently completed report of the Veterans Administration Cooperative Study Group (7,8), increases in serum creatinine and urea nitrogen values observed after a few weeks of treatment with propranolol were no longer in evidence after 12 months. Treatment with other beta-adrenergic antagonists does not appear to significantly change creatinine clearance (2, 9–19). The data reported in our study confirm that kidney function remains essentially constant during treatment with beta-adrenergic antagonists. The prevalence of significant decreases in creatinine clearance was small and these changes occurred with the same frequency during treatment with propranolol as with the other beta-blockers we used: the cardioselective beta-blockers, metoprolol and acebutolol, and the combined alpha and beta-blocking agent, labetalol.

The effects of beta-blocker therapy on kidney function reported in our study provide further evidence that beta-blockers do not substantially alter kidney function. Decreases in creatinine clearance of greater than 20 ml per min were found in only 16 percent of patients. Moreover, creatinine clearance fell to less than 80 ml per minute in 4 of the 87 patients and serum creatinine levels increased to levels greater than 1.7 mg percent in only two patients. The possible adverse effects on kidney function induced by beta-blockers were not exaggerated by pretreatment with a diuretic. Decreases in creatinine clearance were equally as common during beta-blocker monotherapy as in patients in whom a beta-blocker was added to a diuretic. Although pretreatment with a diuretic enhanced the blood pressure-lowering effects of the beta-blockers, these more powerful antihypertensive responses did not alter the prevalence of adverse effects on kidney function. Therefore, it seems unlikely that the drug-induced decreases in blood pressure per se are responsible for any decreases in kidney function. Monotherapy with a beta-blocker or with a diuretic decreased kidney function in 16 and 12 percent of patients, respectively. The prevalence of decreases in creatinine clearance after beta-blocker-diuretic combination therapy was 18 percent. Thus, the effects of each drug on kidney function are not additive when the drugs are given in combination.

Serum uric acid levels increased during beta-blocker monotherapy in 21 percent of patients. In contrast, increases in uric acid were seen in only 10 percent of patients in whom a beta-blocker was given after pretreatment with a diuretic; in fact, decreases in uric acid were observed in 10 percent of these

patients. This apparent uric acid-lowering action of the beta-blockers when superimposed upon a diuretic helps explain why increases in uric acid were found less often during combination therapy than during treatment with a diuretic alone. It is not unlikely that the diuretic induced changes in uric acid secretion are, at least in part, attenuated during treatment with these beta-blockers. Of interest, this effect was not observed when the cardioselective drug, metoprolol, was used in combination with the diuretic. It has been reported that the increases in uric acid induced by beta-blockers are dose dependent (20). The doses of beta-blockers used in our study were relatively high but comparable for metoprolol and the other three agents. Further studies are needed to explain the disparate effects of beta-blockers on uric acid excretion in diuretic treated patients.

Serum potassium concentrations usually increase during chronic beta-blocker therapy. However, measurements of exchangeable potassium or total body potassium have been reported not to change during chronic therapy (2). In fact, potassium balance has been reported to be negative during short-term therapy with timolol, although serum potassium levels did not change (21). It has been argued that the beta-blocker induced decreases in the activity of the renin-angiotensin-aldosterone system are responsible for increases in serum potassium. In addition, other mechanisms might result in shifts of potassium from the intracellular to extracellular spaces; it has been suggested that blockade of cell membranes' beta-receptors will slightly decrease intracellular potassium but increase serum potassium levels (22,23).

We found that serum potassium increased by more than 0.4 mEq per liter in 35 percent of patients given a beta-blocker following pretreatment with a diuretic. This beneficial effect of beta-blockers on serum potassium levels helps explain why the prevalence of hypokalemia during combination therapy with a diuretic and a beta-blocker is slightly less than during diuretic monotherapy. Significant hypokalemia (serum potassium concentrations below 3.7 mEq per liter) was found in 56 percent of diuretic treated patients and in 39 percent of patients using beta-blocker diuretic combination therapy. Other investigators have also shown that potassium levels during treatment with hydrochlorothiazide and metoprolol are slightly higher than those during hydrochlorothiazide therapy alone (24). A more marked degree of hypokalemia during combination therapy has been reported in only one study (25). It should be emphasized, however, that the increases in serum potassium concentrations after addition of a beta-blocker to a diuretic do not necessarily reflect a positive potassium balance. It remains to be shown whether these beta-blocker induced changes in serum potassium

concentrations might help to reduce the possible dysrhythmogenic effect of diuretic induced hypokalemia.

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14. EFFECTS OF CENTRAL ALPHA-ADRENOCEPTOR AGONISTS AND ADRENERGIC-NEURONAL BLOCKING AGENTS ON THE KIDNEY

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ABSTRACT

The acute and chronic effects of the central alpha$_2$-adrenoceptor agonists (alpha-methyldopa, clonidine, and guanabenz) and the adrenergic-neuronal blocking agents (reserpine and guanethidine) on renal function, salt and water excretion, body fluid composition, and plasma renin activity are reviewed. The central alpha$_2$-adrenergic agonists have qualitatively similar renal effects: relative preservation of renal function despite persistent reductions in systemic blood pressure, lack of clinically relevant effects on sodium excretion or body fluid composition, and absence of sustained effects on plasma renin activity. Guanabenz may be unique in producing a water diuresis. Reserpine has no clinically relevant renal effects: renal function, salt and water excretion, body fluid composition and plasma renin activity are essentially unchanged. Guanethidine produces significant reductions in renal function and salt and water excretion, significant increases in body fluid volumes, but has no sustained effect on plasma renin activity.

1. INTRODUCTION

This review will focus on three generic classes of drugs commonly prescribed for the treatment of hypertension: 1) central alpha$_2$-adrenoceptor agonists (alpha-methyldopa, clonidine, guanabenz), 2) central and peripheral adrenergic-neuronal blocking agents (rauwolfia alkaloids and derivatives such as reserpine), and 3) peripheral adrenergic-neuronal blocking agent (guanethidine).

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Central alpha$_2$-adrenoceptor agonists have a direct effect on specific adrenergic receptors in the central nervous system vasomotor center (medulla oblongata and hypothalamus) (1-4). Stimulation of these receptors diminishes sympathetic outflow from the central nervous system, and increases parasympathetic outflow to the heart via the vagus nerve. The net effect is a decrease in peripheral vascular resistance and a slowing of the heart rate; cardiac output is either unchanged or mildly decreased.

Reserpine acts both within the central nervous system and in the peripheral sympathetic nervous system (5,6). It effectively depletes stores of norepinephrine and 5-hydroxytryptamine by competitively inhibiting the uptake of dopamine by storage granules, and by preventing the incorporation of norepinephrine into protective chromaffin granules. The net effect is a decrease in peripheral vascular resistance, heart rate, and cardiac output.

Guanethidine interferes with neuro-transmission at the adrenergic post-ganglionic nerve terminal (6,7). It is pumped into the adrenergic neuron against a concentration gradient, similar to that of norepinephrine. As a consequence, guanethidine achieves a high concentration in the adrenergic nerve terminal and disrupts the release of norepinephrine in response to an action potential. Acutely, there is a substantial reduction in cardiac output caused partly by diminished venous return (due to venodilation) and partly by the blockade of sympathetic beta effects on the heart, whereas peripheral vascular resistance is unchanged. However, following long-term therapy, peripheral vascular resistance is decreased, along with modest decreases in heart rate and cardiac output.

Each of these generic classes of drugs will be reviewed in terms of their acute and chronic effects on renal function, their effects on salt and water (including body fluids and the renal handling of sodium and water) and their effects on plasma renin activity. This review will focus only on human studies, since these data are probably most relevant for the practicing physician.

2. CENTRAL ALPHA$_2$-ADRENOCEPTOR AGONISTS

2.1. Alpha-Methyldopa

Alpha-methyldopa (L- α -methyl-3, 4-dihydroxyphenylalanine) enters the central nervous system where it is decarboxylated and beta-hydroxylated to alpha-methylnorepinephrine, the active metabolite (1,4).

2.1.1. Acute renal effects. The acute intravenous administration of 2.0 to 2.5 g alpha-methyldopa produces a maximum hypotensive response within 10 to 20 hours. Onesti et al (8,9) have measured glomerular filtration rate (GFR; by inulin clearance) and effective renal plasma flow (ERPF; by para-aminohippurate clear-ance) in ten hypertensive patients, in the supine, head-up tilt, and erect positions during the maximum hypotensive response. A 34 mm Hg decrease in the supine mean arterial pressure (from 147 to 113 mm Hg) was associated with a 13% decrease in GFR (from 69 to 60 ml/min), an 8% (insignificant) decrease in ERPF (from 404 to 373 ml/min), and a 17% decrease in renal vascular resistance (from 20.6 to 17.2 dynes/sec/cm^{-5} x 10^3). Similar results were obtained in the head-up tilt and erect positions. Grabie et al (10) have measured GFR and ERPF following the acute oral administration of 1.0 g alpha-methyldopa in ten hypertensive patients in the supine position. Although mean arterial pressure was unchanged, GFR decreased 8% (from 119 to 109 ml/min), and ERPF was unchanged.

2.1.2. Chronic renal effects. Sannerstedt et al (11) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) following the oral administration of 0.5 to 2.0 g alpha-methyldopa per day for a period of 6 to 19 days in eleven hypertensive patients in the supine position. Glomerular filtration rate and ERPF were not consistently changed, whereas renal vascular resistance decreased. Similar findings have been reported by others (10,12,13).

2.1.3. Salt and water effects. Grabie et al (10) have found that both the acute and short-term (1 week) administration of 1.0 gram alpha-methyldopa in 10 hypertensive patients were associated with decreases in the fractional sodium excretion and urine flow rate, but no change in urine osmolality or free water clearance.

Short-term administration was associated with a 0.6 kg weight gain and an average positive sodium balance of 318 mEq. Retention of salt and water with weight gain and edema, when present, appears unrelated to the degree of blood pressure reduction (14-16). It is most likely to occur in patients with severe degrees of hypertension and in patients with severe renal insufficiency. However, at least two clinical trials report that alpha-methyldopa, given as monotherapy for a period of six months, had no significant effect on body weight (17,18).

2.1.4. Renin effects. Alpha-methyldopa has no consistent effect on plasma renin activity (19,20). It does not impair plasma renin response to furosemide stimulation and upright posture (19), but has been reported to lower plasma renin activity and concentration in a subset of patients with normal renin essential hypertension of moderate to severe degree (20).

2.2. Clonidine Hydrochloride

The hypotensive action of clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline) is a result of the direct action of the unchanged drug in the central nervous system (2-4).

2.2.1. Acute renal effects. The acute oral administration of 0.45 to 0.75 mg clonidine produces a maximum hypotensive response within two to four hours. Onesti et al (21) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in seven hypertensive patients, in the supine and head-up tilt positions, during the maximum hypotensive response. A 27 mm Hg decrease in the supine mean arterial pressure (from 155 to 128 mm Hg) was associated with a 9% (insignificant) decrease in GFR (from 79 to 72 ml/min), a 7% (insignificant) decrease in ERPF (from 383 to 356 ml/min) and a 16% (insignificant) decrease in renal vascular resistance (from 23.3 to 18.8 dynes/sec/cm^{-5} x 10^3). Similar results were obtained in the head-up tilt position. Reubi et al (22) have measured GFR and ERPF in nine hypertensive patients, in the supine position, following the acute intravenous administration of 0.15 mg clonidine. An initial decrease in both the GFR (27%) and ERPF (23%) (during the first 30 minutes) was followed (90 to 120 minutes post-injection) by a

return of GFR to 87% of control values, and the ERPF to 92% of control values.

2.2.2. Chronic renal effects. A number of clinical investigators have studied the chronic oral effects of clonidine on GFR and ERPF (23-29). No consistent effect on renal function has been observed.

2.2.3. Salt and water effects. Definitive studies on the effects of clonidine on body fluids or the renal handling of sodium and water have not been reported in man. Although clonidine acutely decreases sodium and chloride excretion (21,22), its chronic administration has no consistent effect on these parameters, and salt and water balance remains unchanged (24,25,28-30). At least four clinical trials report that clonidine, given as monotherapy for periods of three or more months, had no significant effect on body weight (29-32). Indeed, Campese et al (33) have reported that six weeks of chronic clonidine therapy, in fifteen hypertensive patients, is associated with a fall in exchangeable sodium and plasma volume.

2.2.4. Renin effects. Clonidine administration produces an acute decrease in plasma renin activity in both the supine and head-up tilt positions (33-37); however, results are inconsistent following more prolonged periods of drug treatment (28,29,33). Both salt-depletion and change in posture can induce renin-secretion in clonidine-treated patients (37).

2.3. Guanabenz Acetate

The hypotensive action of guanabenz (2,6-dichlorobenzylidene amino-guanidine acetate) is a result of the direct action of the unchanged drug in the central nervous system (38,39).

2.3.1. Acute renal effects. The acute oral administration of 16 to 32 mg of guanabenz produces a maximum hypotensive response within two to four hours. Bosanac et al (40) have measured GFR (by inulin or creatinine clearance) and ERPF (by para-aminohippurate clearance) in eight hypertensive patients, in the supine position, during the maximum hypotensive response. A 12 mm Hg decrease in mean arterial pressure (from 135 to 123 mm Hg) was associated with a 21% decrease in GFR (from 129 to 102 ml/min) and

a 19% decrease in ERPF (from 417 to 337 ml/min).

2.3.2. Chronic renal effects. Bauer (41) has measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in seventeen hypertensive patients in the supine position, following the oral administration of 10±8 mg (mean ± SD) guanabenz twice daily for a period of 3-6 weeks, and then at 5-6 months (see Table Ia). Decreases in mean arterial pressure were associated with 12% and 18% decreases, respectively, in GFR and 9% and 17% decreases respectively, in ERPF. Renal vascular resistance was unchanged. The changes in both GFR and ERPF reverted to baseline values two weeks following withdrawal of drug.

2.3.3. Salt and water effects. Bosanac et al (40) have reported that guanabenz acutely decreases the fractional excretion of sodium, urine flow rate, and free water clearance. Bauer (41) has reported that guanabenz has no effect on fractional sodium excretion at either 3-6 weeks, or at 5-6 months of drug therapy (see Table Ib). However, guanabenz increased urine flow rate 30% to 36%, decreased urine osmolality 38% to 43%, and increased free water clearance 50% to 52%, respectively, at 3-6 weeks, and at 5-6 months of drug therapy. Since the ratio of free water clearance to urine flow rate increased following drug therapy (from 0.55 to 0.66 and 0.69, respectively, $p < 0.05$), he speculated that guanabenz produced either decreased circulating levels of vasopressin and/or renal resistance to its effects. Since plasma vasopressin levels were not determined, definitive proof for this hypothesis is lacking. Finally, Bauer (41) observed that guanabenz lowers blood pressure without producing salt and water retention; guanabenz had no effect on the distribution of salt and water within the plasma volume, total blood volume, interstitial fluid volume, extracellular fluid volume, intracellular fluid volume, total body water, or body weight at either 3-6 weeks, or at 5-6 months of drug therapy. Others have also reported guanabenz to be effective as monotherapy without inducing sodium retention (42,43).

2.3.4. Renin effects. The acute effect of guanabenz on plasma renin activity has not been reported in man. During chronic therapy, plasma renin activity is not altered from baseline levels (see Table Ic) (42-44).

TABLE I

	Placebo (4 wks)	Short-Term (3-6 wks)	Long-Term (5-6 mo.)	Washout (2 wks)
a. Effect of Guanabenz on Renal Function				
MAP (mm Hg)	113±2	98±2***	100±2***	110±2
GFR (ml/min/1.73 m^2)	84±7	74±4*	69±5*	91±6
ERPF (ml/min/1.73 m^2)	369±35	336±19	306±20	395±34
RVR (dyne sec cm^{-5}/1.73 m x 10^3)	11.8±1.5	10.2±0.6	11.8±1.0	11.1±1.9
b. Effect of Guanabenz on Salt and Water				
C_{Na} (ml/min/1.73 m^2)	1.34±0.63	1.50±0.20	1.30±0.14	1.48±0.18
FE_{Na} (%)	1.9±0.1	2.2±1.3	2.0±0.1	1.7±0.1
$\dot{V}$ (ml/min)	8.3±0.9	11.3±1.2***	10.8±1.3*	10.6±1.4
Uosm (mOsm/kg)	184±30	114±24***	104±19***	120±22*
Cosm (ml/min)	2.8±0.3	2.8±0.3	2.4±0.3	2.8±0.2
C_{H_2O} (ml/min/1.73 m^2)	4.6±1.0	6.9±1.0**	7.0±1.2*	6.7±1.2
c. Effect of Guanabenz on Plasma Renin Activity				
PRA (ng/ml/hr)	1.0±0.1	1.1±0.2	1.0±0.1	1.1±0.1

MAP = mean arterial pressure; GFR = glomerular filtration rate; ERPF = effective renal plasma flow; RVR = renal vascular resistance; C_{Na} = sodium clearance; FE_{Na} = fractional excretion of sodium; $\dot{V}$ = urine flow rate; Uosm = urine osmolality; Cosm = osmolar clearance; C_{H_2O} = free water clearance; PRA = plasma renin activity

mean ± SEM; N = 17 *$p<0.05$, **$p<0.025$, ***$p<0.005$ compared to placebo

2.4. Summary: Central Alpha$_2$-Adrenoceptor Agonists: see Table II

Alpha-methyldopa, clonidine, and guanabenz have similar antihypertensive mechanisms of action. They appear to have qualitatively similar renal effects: acutely, GFR and ERPF decrease, but the magnitude of the decrease is usually small; chronically, GFR and ERPF either remain mildly decreased, or return to pretreatment levels. Renal vascular resistance is either mildly decreased or unchanged. The renal effects of these drugs are probably a consequence of both a centrally-induced loss of sympathetic tone, and increased vagal tone. The result is a decrease in blood pressure, a reduction in peripheral vascular resistance, and a decrease in cardiac output (secondary to the decrease in heart rate). Reduced renal perfusion pressure leads to reduced GFR and ERPF. However, the net chronic effect appears to be relative preservation of renal function, despite persistent reductions in systemic blood pressure and/or cardiac output.

The apparent quantitative differences between these drugs on renal function probably reflect both the antihypertensive effectiveness of the dosage employed, and the hemodynamic characteristics of the patients studied. Variable acute decrease in the mean arterial pressure (from 147 to 113 mm Hg for alpha-methyldopa versus 155 to 128 mm Hg for clonidine versus 135 to 123 mm Hg for guanabenz) might be expected to have varying degrees of effect on renal function. Quantitatively more severe systemic hemodynamic alterations would be expected to produce quantitatively more severe renal hemodynamic alterations. Failure of renal glomerular filtration and renal perfusion autoregulation might even occur if renal mean arterial pressure fell below 80-100 mm Hg. Furthermore, the degree of the existing arteriolar nephrosclerosis and/or renal vascular disease, would be expected to influence the effect of these drugs on renal function. Mean pretreatment GFR and ERPF varied widely both within and between the clinical studies reported. Thus, it is probably inappropriate to characterize one drug versus another as having a greater or lesser quantitative effect on renal function. Pharmacologically, these drugs should have similar qualitative and quantitative effects on renal function, provided the patients being stud-

TABLE II

Effects of Alpha-Adrenoceptor Agonists on the Kidney

	α-methyldopa		clonidine		guanabenz	
	acute*	chronic**	acute	chronic	acute	chronic
GFR	↓	↓→	↓	↓→	↓	↓
ERPF	↓	↓→	↓	↓→	↓	↓
RVR	↓	↓→	↓	↓→	↓	→
FE_{Na}	↓	→	↓	→	↓	→
V	↓	→	↓	→	↓	↑
C_{H_2O}	→	→	?	?	↓	↑
ECF	↑	→	↑	→	↑	→
Weight	↑	→	↑	→	↑	→
PRA	↓	→	↓	→	?	→

*renal response to acute oral or intravenous administration during maximum hypotensive effect of drug

**renal response to chronic (weeks to months) oral administration of drug

GFR = glomerular filtration rate; ERPF = effective renal plasma flow; RVR = renal vascular resistance; FE_{Na} = fractional excretion of sodium, V = urine flow rate; C_{H_2O} = free water clearance, ECF = extracellular fluid, PRA = plasma renin activity

↓ = decrease; → = no change; ↑ = increase

ied have similar pre-existing renal function, similar pre-existing systemic hemodynamics, and have been treated with equivalent antihypertensive dosages.

Alpha-methyldopa, clonidine, and guanabenz generally do not chronically produce excessive salt and water retention; earlier concepts about alpha-methyldopa should be reassessed. Acute sodium retention, when it occurs, is most likely due to acute reductions in GFR and perfusion pressure, changes which do not usually persist during chronic therapy. Clinical trials for all these drugs suggest that some patients can be treated effectively for long periods without clinically apparent weight gain or edema formation. These observations are consistent with the lack of a clinically significant chronic effect of these drugs on renal function and sodium excretion. Guanabenz may be unique in producing a water diuresis via inhibition of vasopressin; however, clonidine has not been carefully studied for this effect in man.

Finally, alpha-methyldopa, clonidine, and guanabenz may acutely decrease plasma renin activity, but chronically the effect is lost. The acute inhibition of renin release may be mediated by either a peripheral alpha-adrenergic agonistic effect, or a centrally-mediated inhibition of sympathetic outflow. The contribution that renin inhibition has to the chronic antihypertensive effect of these drugs remains speculative.

3. CENTRAL AND PERIPHERAL ADRENERGIC-NEURONAL BLOCKING AGENT

3.1. Reserpine

3.1.1 Acute renal effects. The acute intravenous administration of 1-3 mg reserpine (Rauwolfia serpentina), produces a maximum hypotensive response within three hours. Moyer et al (45) have measured the GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in six hypertensive patients in the supine position during the maximum hypotensive response. A 21 mm Hg decrease in the mean arterial pressure (from 146 to 125 mm Hg) was associated with a 5% (insignificant) decrease in GFR (from 79 to 75 ml/min), a 2% (insignificant) decrease in the ERPF (from 425 to 417 ml/min), and a 10% (insignificant) decrease in the renal vascular resistance (from 0.21 to 0.19 units). The authors

concluded that reserpine had no acute effect on renal function.

3.1.2. Chronic renal effects. Moyer et al (45) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in eight hypertensive patients, in the supine position, following the oral administration of 3 to 6 mg reserpine per day, for a period of three months. A 24 mm Hg decrease in mean arterial pressure (from 152 to 128 mm Hg) was associated with a 6% (insignificant) decrease in GFR (from 109 to 102 ml/min), a 2% (insignificant) increase in ERPF (from 585 to 596 ml/min), and a 13% (insignificant) decrease in renal vascular resistance (from 0.16 to 0.14 units). Reusch (46) performed similar studies, in eight hypertensive patients, and also found no significant chronic effects of reserpine on renal function.

3.1.3. Salt and water effects. Moyer et al (45) have reported that reserpine has no effect on the renal excretion of water or electrolytes, either after intravenous or after oral administration of the drug for three months. These observations have been confirmed by Kogsgaard (47); furthermore, he was unable to demonstrate any significant effect of reserpine (2 to 4.5 mg/day x 6 days) on plasma volume, extracellular fluid volume, total body water, or body weight. Melick and McGregor (48) studied 18 hypertensive patients treated with reserpine, Rauwiloid, or Raudixin, for a period of 28 to 119 days; although the patients had an average weight gain of 2.22 kg, the authors were unable to demonstrate a significant change in the extracellular fluid space. They suggested that the weight gain was, in part, due to the increase in appetite associated with reserpine therapy. Although fluid retention, with the appearance of edema formation, can occur (49), it is unclear what the frequency or mechanism is for this potential side effect.

3.1.4. Renin effects. Reserpine appears to have no significant effect on plasma renin activity (50).

3.1.5. The effects of reserpine on the kidney are summarized in Table III.

TABLE III

Effects of Reserpine on the Kidney

	Acute*	Chronic**
Glomerular filtration rate	→	→
Effective renal plasma flow	→	→
Renal vascular resistance	→	→
Fractional excretion of sodium	→	→
Urine flow rate	→	→
Free water clearance	?	?
Extracellular fluid	→	→
Weight	→	↑ (true weight gain)
Plasma renin activity	→	→

*renal response to acute oral or intravenous administration during maximum hypotensive effect of drug

**renal response to chronic (weeks to months) oral administration of drug

↓ = decrease; → = no change; ↑ = increase

4. PERIPHERAL ADRENERGIC-NEURONAL BLOCKING AGENT

4.1. Guanethidine

Guanethidine (2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate), bioavailability is incomplete and variable among individual subjects; only 3% to 50% of an oral dose reaches the systemic circulation (51,52). The drug rapidly leaves the plasma for extravascular storage sites, including sympathetic neurons. After distribution in the body, guanethidine is eliminated with a half-life of approximately 5 days, which corresponds to the time course of its antihypertensive effects (51,52). When therapy is initiated or the dosage changed, three half-lives (15 days) are required to accumulate to 87.5% of steady-state levels (51,52). By administering loading doses of guanethidine at six-hour intervals (the nearly maximal effect from a single oral dose), blood pressure can be lowered in one to three days (51,52). Because of the delay in the maximum oral hypotensive effect of the drug, the renal effects of guanethidine will be characterized by being either short-term (1-2 weeks) or long-term (months).

4.1.1. Short-Term renal effects. Richardson and Wyso (53) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in 14 hypertensive patients, in the supine and head-up tilt positions, following loading doses of guanethidine (150-200 mg on day 1, 75-100 mg on day 2, then 25-75 mg per day for a period of 1-2 weeks). A 29 mm Hg decrease in the supine mean arterial pressure (from 158 to 129 mm Hg) was associated with an 18% decrease in the GFR (from 67 to 55 ml/min), a 9% (insignificant) decrease in the ERPF (from 254 to 230 ml/min), and a 7% (insignificant) decrease in renal vascular resistance (from 0.82 to 0.76 units). In the head-up tilt position, mean arterial pressure fell further (from 151 to 109 mm Hg), and was associated with further declines in renal function; GFR fell 26% (from 42 to 31 ml/min), ERPF fell 17% (from 169 to 140 ml/min), and renal vascular resistance fell 18% (from 1.15 to 0.94 units). Villarreal et al (54) and Novack (55) have reported similar findings in 10 and 8 hypertensive patients, respectively, 40 to 90 minutes following the intravenous administration of 15 to 30 mg guanethidine.

4.1.2. Long-term renal effects. Smith (56) has serially measured GFR (by creatinine clearance) in seven hypertensive patients at three-month intervals for one year. Pretreatment mean GFR was 92 ml/min; at six months it was 56 ml/min, and at 12 months, it was 59 ml/min. The acute, short-term and long-term reductions in renal function following guanethidine are probably a consequence of its peripheral sympatholytic action. The antihypertensive response to guanethidine is characterized by a significant reduction in cardiac output; reduced renal perfusion pressure leads to reduced GFR and ERPF. The impaired peripheral adrenergic transmission and the resulting blockade of the baroreceptor reflex magnifies these responses when the patient is in the upright position.

4.1.3. Salt and water effects. Villareal et al (54) have reported that guanethidine acutely decreases the fractional excretion of sodium, urine flow rate, and free water clearance. Fluid retention, with edema formation, occurs following short-term and long-term therapy (44-59). Increases in plasma volume, total blood volume, exchangeable sodium and body weight have been reported from as early as one week to as long as twelve months following 15 to 75 mg/day guanethidine therapy (56,58-60). These changes are probably related, in part, to removal of the sympathetic inotopic drive to the heart and/or to reductions in GFR and perfusion pressure.

4.1.4. Renin effects: Guanethidine appears to have no significant effect on plasma renin activity (19,50); this may, in part, be related to opposing effects of the drug on renin secretion: sympathetic blockade would be expected to decrease renin secretion, whereas reduced renal perfusion pressure would be expected to increase renin secretion.

4.1.5. The effects of guanethidine on the kidney are summarized in Table IV.

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TABLE IV

Effects of Guanethidine on the Kidney

	Short-Term*	Long-Term**
Glomerular filtration rate	↓↓	↓
Effective renal plasma flow	↓↓	↓
Renal vascular resistance	↓→	↓→
Fractional Excretion of sodium	↓↓	↓
Urine flow rate	↓↓	↓
Free water clearance	↓↓	?
Extracellular fluid	↑↑	↑
Weight	↑↑	↑
Plasma renin activity	→	→

*renal response to oral loading doses of guanethidine (supine and standing positions)

**renal response to chronic (months) oral administration of drug

↓ = decrease; → = no change; ↑ = increase

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15. EFFECTS OF ALPHA$_1$-ADRENOCEPTOR ANTAGONISTS AND DIRECTLY ACTING VASODILATORS ON THE KIDNEY

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ABSTRACT

The acute and chronic effects of the alpha$_1$-adrenoceptor antagonists (prazosin and indoramin) and the directly acting vasodilators (hydralazine and minoxidil) on renal function, salt and water excretion, body fluid composition, and plasma renin activity are reviewed. The alpha$_1$-adrenoceptor antagonists have qualitatively similar renal effects: preservation of renal function and reduction in renal vascular resistance despite persistent reduction in systemic blood pressure; decrease in sodium excretion and increase in body fluid volumes without the development of pseudotolerance; and probably no sustained effect on plasma renin activity. The directly acting vasodilators also have qualitatively similar renal effects: preservation of renal function and reduction in renal vascular resistance; decrease in sodium excretion and increase in body fluid volumes leading to the rapid development of pseudotolerance; and stimulation of plasma renin activity.

1. INTRODUCTION

This review will focus on two generic classes of drugs commonly prescribed for the treatment of hypertension: 1) selective post-synaptic alpha$_1$-adrenoceptor antagonists (prazosin and indoramin), and 2) directly acting vasodilators (hydralazine and minoxidil).

Alpha$_1$-adrenoceptor antagonists induce dilation of both resistance (arterial) and capacitance (venous) vessels by interfering with sympathetic constrictor tone (1,2). The net effect is a decrease in peripheral vascular resistance. Reflex tachycardia (and the attendant increase in cardiac output) does not predict-

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ably occur, presumably due to preservation of the alpha$_2$-mediated presynaptic feedback loop, preventing excessive norepinephrine release, and hence excess sympathetic activity.

Directly acting vasodilators may have an effect on both peripheral resistance and venous capacitance; however, both hydralazine and minoxidil are highly selective for the resistance vessels (2-4). Their mechanism of vascular relaxation, and reasons for selectivity, are unknown. The net effect is a decrease in peripheral vascular resistance, associated with a compensatory increase in heart rate and cardiac output. The latter is related, in part, from withdrawal of parasympathetic tone.

Each of these generic classes of drugs will be reviewed in terms of their acute and chronic effects on renal function, their effects on salt and water (including body fluids and the renal handling of sodium and water), and their effects on plasma renin activity. This review will focus only on human studies, since these data are probably most relevant for the practicing physician.

2. SELECTIVE POST-SYNAPTIC ALPHA$_1$-ADRENOCEPTOR ANTAGONISTS

2.1. Prazosin hydrochloride

Prazosin (1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine) is classified as both an arteriolar dilator and a venodilator. Although its mechanism of action is not well understood, it appears to act predominantly as an alpha$_1$-adrenergic blocking agent on vascular smooth muscle (2,5,6).

2.1.1. Acute renal effects. The acute intravenous (0.06 to 13 mg) or oral (7 to 14 mg) administration of prazosin produces a maximal hypotensive response within two to four hours. Maxwell (7) has measured glomerular filtration rate (GFR, by inulin clearance) and effective renal plasma flow (ERPF, by para-aminohippurate clearance) in four hypertensive patients (post-IV), and in three hypertensive patients (post-oral) in the supine position during the maximum hypotensive response. A decrease in the mean arterial pressure (from 136 to 121 mm Hg post-IV; from 123 to 116 mm Hg post-oral) was associated with 4% and 17% (insignificant) decreases, respectively, in GFR (from 76 to 73 ml/min post-IV;

and from 89 to 74 ml/min post-oral and 16% and 30% (insignificant) decreases, respectively, in ERPF (from 367 to 309 ml/min post-IV; and from 269 to 187 ml/min post-oral). No other studies assessing the acute effect of prazosin on renal function have been reported.

2.1.2. Chronic renal effects. Koshy et al (8) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in six hypertensive patients in the supine position, following the oral administration of 4 to 20 mg prazosin per day for eight weeks. Glomerular filtration rate and ERPF were not significantly affected. Similar findings in small series of patients have been reported by others (7,9,10). Preston et al (10) have reported that chronic (one month) prazosin therapy (3-15 mg/day) is associated with a 19% decrease in renal vascular resistance (from 7.0 to 5.7 dyne sec cm^{-5} x 10^3); these authors suggested that prazosin could act directly on the afferent arteriole to reduce afferent, and hence total, renal vascular resistance. Post-synaptic alpha blockade in the renovascular bed would be expected to diminish afferent resistance preferentially. Bauer (unpublished data) using inulin and para-aminohippurate clearance techniques, has also found that chronic (2 months) prazosin therapy (2-20 mg/day) was associated with a 14% decrease in renal vascular in renal vascular resistance in 14 hypertensive patients (see Table Ia).

2.1.3. Salt and water effects. Definitive studies on the effects of prazosin on the renal handling of sodium and water have not been previously reported in man. Bauer (unpublished data) has found that chronic prazosin therapy has no significant chronic effect on fractional sodium excretion (although it decreased 20%), urine flow rate, urine osmolality, or free water clearance (see Table Ib). Bauer (unpublished data) has also found that chronic prazosin therapy is associated with significant increases in plasma volume (as determined by ^{125}IHSA), extracellular fluid volume (as determined by $Na_2{}^{35}SO_4$), interstitial fluid volume, and total body water (as determined by ^3H_2O), but not intracellular fluid volume (see Table Ic). Koshy et al (8) and Ibsen et al (9) have also reported increases in plasma volume and extracellu-

TABLE I

Effect of Prazosin on the Kidney

	Placebo (4 weeks)	Chronic Therapy (8 weeks)
A. Renal Function		
Mean arterial pressure (mm Hg)	108±1	99±2
Glomerular filtration rate (ml/min/1.73 m^2)	85±5	85±5
Effective renal plasma flow (ml/min/1.73 m^2)	371±17	399±16
Renal vascular resistance (dyn sec cm^{-5}/1.73 m^2 x 10^3)	9.6±0.4	8.2±0.4***
B. Salt and Water		
Sodium clearance (ml/min/1.73 m^2)	1.17±0.19	1.0±0.12
Fractional excretion of sodium (%)	1.5±0.1	1.2±0.1
Urine flow rate (ml/min)	12.2±1.0	11.6±1.0
Urine osmolality (mOsm/kg)	95±16	99±26
Osmolality clearance (ml/min)	2.7±0.2	2.5±0.1
Free water clearance (ml/min/1.73 m^2)	7.7±0.8	7.2±0.9
C. Body Fluid Composition		
Plasma volume (liters)	3.22±0.11	3.39±0.11**
Extracellular fluid (liters)	15.65±0.55	17.09±0.56***
Interstitial fluid (liters)	12.43±0.46	13.71±0.50***
Intracellular fluid (liters)	25.12±0.75	25.05±0.77
Total body water (liters)	40.77±1.08	42.14±1.18**
Weight (kg)	87.40±2.7	87.9±2.7
D. Plasma Renin Activity		
Plasma renin activity (ng/ml/hr)	1.2±0.2	1.2±0.2

mean ± SEM; N = 14; *$p<0.05$, **$p<0.025$, ***$p<0.005$ compared to placebo

lar fluid volume following chronic prazosin therapy.

2.1.4. Renin effects. Chronic prazosin therapy has no consistent effect on plasma renin activity (8,10, see Table Id).

2.2. Indoramin Hydrochloride

Indoramin (3-2-(4-benzyamidopiperid-1-yl)ethyl indole) is a new alpha$_1$-adrenergic blocking agent commercially available in the United Kingdom, South Africa and Brazil, which is currently undergoing phase III clinical trials in the United States. Indoramin differs from prazosin in its capability to block histamine and 5-hydroxytryptamine receptors, and it has been shown to have myocardial membrane stabilizing and bronchodilator properties (11-13).

2.2.1. Acute renal effects. The acute intravenous or oral administration of indoramin produces a maximal hypotensive response within two to four hours. Henry et al (14) have measured GFR (by ^{51}Cr EDTA clearance) and ERPF (by ^{125}I sodium iodohippurate clearance) in eight normotensive subjects, in the supine position, during the maximal hypotensive response following the intravenous administration of 0.2 to 0.5 mg/kg indoramin. No significant changes were observed in mean arterial pressure, GFR or ERPF. No acute studies have been reported in hypertensive man.

2.2.2. Chronic renal effects. Bauer et al (15), using inulin and para-aminohippurate clearance techniques, have found that chronic (2 months) indoramin therapy (50 to 150 mg/day) in eleven hypertensive patients increased GFR 28% and ERPF 24% (insignificant), and decreased renal vascular resistance 30% while lowering mean arterial pressure from 112 to 100 mm Hg (see Table IIa).

2.2.3. Salt and water effects. Bauer et al (15) have found that chronic indoramin therapy decreases fractional sodium excretion 38%, and has no significant effect on urine flow rate, urine osmolality, or free water clearance (see Table IIb). They have also found that indoramin therapy is associated with significant increases in plasma volume (as determined by ^{125}IHSA), and body weight, but could not demonstrate significant increases in extracellular fluid volume (as determined by $Na_2{}^{35}SO_4$), interstitial

TABLE II

Effect of Indoramin on the Kidney

	Placebo (4 weeks)	Chronic Therapy (8 weeks)
A. Renal Function		
Mean arterial pressure (mm Hg)	112±3	100±2***
Glomerular filtration rate (ml/min/1.73 m^2)	71±9	91±5**
Effective renal plasma flow (ml/min/1.73 m^2)	288±37	358±26
Renal vascular resistance (dyn sec cm^{-5}/1.73 m^2 x 10^3)	14.1±1.3	9.8±1.0***
B. Salt and Water		
Sodium clearance (ml/min/1.73 m^2)	1.48±0.16	1.33±0.20
Fractional excretion of sodium (%)	2.6±0.1	1.6±0.1**
Urine flow rate (ml/min)	11.7±0.9	11.3±1.1
Urine osmolality (mOsm/kg)	88±16	100±19
Osmolar clearance (ml/min)	2.9±0.2	3.1±0.3
Free water clearance (ml/min/1.73 m^2)	7.4±0.9	6.9±0.9
C. Body Fluid Composition		
Plasma volume (liters)	3.27±0.14	3.42±0.14*
Extracellular fluid (liters)	16.31±0.68	16.67±0.55
Interstitial fluid (liters)	12.97±0.57	13.28±0.47
Intracellular fluid (liters)	25.81±0.97	25.66±1.01
Total body water (liters)	41.92±1.47	42.26±1.30
Weight (kg)	82.40±3.7	84.6±3.8***
D. Plasma Renin Activity		
Plasma renin activity (ng/ml/hr)	0.87±0.09	1.15±0.11*

mean ± SEM; N=11; *$p<0.05$, **$p<0.025$, ***$p<0.005$ compared to placebo

fluid volume, intracellular fluid volume, or total body water (as determined by $^{3}H_2O$) (see Table IIc).

2.2.4. Renin effects. Nicholls et al (14) have reported that one to four days of indoramin therapy has no effect on plasma renin activity. Bauer (unpublished data) has observed an increase in the two-hour recumbent (non-stimulated) plasma renin activity following chronic indoramin therapy (see Table IId).

2.3. Summary: alpha$_1$-adrenoceptor antagonists (see Table III)

Prazosin and indoramin have similar antihypertensive mechanisms of action. They appear to have qualitatively similar renal effects. Chronic administration of the drugs produces no change or an improvement in GFR and ERPF, and renal vascular resistance is reduced. Post-synaptic alpha adrenoceptor antagonism would be expected to diminish afferent renal arteriole resistance, and hence total renovascular resistance.

Chronic prazosin and indoramin therapy probably decrease fractional sodium excretion, leading to the retention of salt and water. Vasodilator therapy is often associated with decreased renal excretion of sodium and water, and the development of pseudotolerance. However, in spite of the retention of sodium and water, neither prazosin nor indoramin exhibited a loss of its antihypertensive effectiveness when prescribed as monotherapy for the time intervals studied. However, the addition of a diuretic to either drug alone could be expected to improve the blood pressure response.

Finally, prazosin may acutely inhibit renin release via alpha$_1$-adrenoceptor antagonism, but chronically the effect is lost; this mechanism does not significantly contribute to its antihypertensive effect. Acute indoramin therapy has no effect on plasma renin activity (14); the observation that chronic indoramin therapy produces an increase in plasma renin activity will need to be confirmed by others, and the mechanism defined.

3. DIRECT ACTING VASODILATORS

3.1. Hydralazine

Hydralazine (1-Hydralazinophthalazine) reduces blood pressure

TABLE III

Alpha$_1$-Adrenoceptor Antagonist Effects on the Kidney

	Prazosin		Indoramin	
	Acute*	Chronic**	Acute*	Chronic**
Glomerular filtration rate	↓→	→	→	↑
Effective renal plasma flow	↓→	→	→	↑
Renal vascular resistance	↓	↓	→	↓
Fractional excretion of sodium	?	↓	?	↓
Urine flow rate	?	→	?	→
Free water clearance	?	→	?	→
Extracellular fluid	?	↑	?	↑→
Weight	?	↑	?	↑ (true weight gain)
Plasma renin activity	↓	→	→	↑

*renal response to acute oral or intravenous administration during maximum hypotensive effect

**renal response to chronic (weeks to months) oral administration of drug

by decreasing total peripheral resistance through relaxation of the smooth muscle in the walls of arterioles.

3.1.1. Acute renal effects. The acute intravenous administration of 0.25 to 0.50 mg/kg hydralazine produces a maximal hypotensive response within 8 to 70 minutes. Wilkinson et al (16) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in 16 normotensive and hypertensive patients in the supine position. A 29 mm Hg decrease in mean arterial pressure (from 111 to 82 mm Hg) was associated with a 15% (insignificant) decrease in GFR (from 95 to 80 ml/min), a 14% increase in ERPF (from 521 to 596 ml/min), and a 33% decrease in renal vascular resistance (from 0.21 to 0.14 units). The increase in ERPF was more striking in the normotensive patients than in the hypertensive patients. Similar results have been reported by others (17-19).

3.1.2. Chronic renal effects. Vanderkolk et al (20) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in seven hypertensive patients, before and after 11-15 weeks of continuous treatment with hydralazine. Hydralazine (75 to 150 mg) given as a single oral dose before the beginning of the chronic treatment period had no significant effect on GFR, but increased ERPF 36% (from 385 to 523 ml/min), and decreased renal vascular resistance 40% (from 0.23 to 0.14 units). The same oral dose, given at the end of the chronic treatment period, had no significant effect on any of the parameters studied, suggesting that tolerance to the renal effects of hydralazine occurred during prolonged oral therapy.

3.1.3. Salt and water effects. Definitive studies on the effects of hydralazine on body fluid composition or the renal handling of sodium and water have not been reported in man. Hydralazine acutely decreases sodium and water excretion in patients with compensated hypertension, whereas it increases sodium and water excretion in patients with congestive heart failure (19). Although fluid retention and edema formation may be clinically observed following hydralazine therapy (21), the early studies using hydralazine alone for the treatment of hypertension uniformly failed to comment on this side effect.

3.1.4. Renin effects. Hydralazine therapy acutely increases renin activity in plasma (22,23).

3.2. Minoxidil

Minoxidil (2,6-diamino-4-piperidinopyrimidine-1-oxide) acts primarily on systemic arterioles producing arteriolar dilation; it has little effect on capacitance vessels. Following a single oral dose of minoxidil, blood pressure begins to decline within 15 minutes, reaches a nadir between two and four hours, and recovers at an arithmetically linear rate of 30% per day (24). When minoxidil is administered chronically, once or twice a day, a steady state blood pressure reduction is achieved on 10 mg per day within seven days, on 20 mg/day within five days, and on 40 mg/day within three days (24). Because of the delay in the maximum hypotensive effect of the drug, the renal effects of minoxidil will be characterized as being either short-term (1-2 weeks) or long-term (months).

3.2.1. Short-term renal effects. Gilmore et al (25) have measured GFR (by inulin clearance) and ERPF (by para-aminohippurate clearance) in six hypertensive patients, in the supine position, following the oral administration of 15 to 80 mg minoxidil for seven days. A 20 mm Hg decrease in mean arterial pressure (from 145 to 125 mm Hg) had no significant effect on GFR (from 99 to 108 ml/min) or ERPF (from 387 to 393 ml/min). The short-term addition of minoxidil to hypertensive patients receiving diuretic and beta blocker therapy also has no significant effect on GFR or ERPF (23,25).

3.2.2. Long-term renal effects. The long-term addition of minoxidil to patients with essential hypertension receiving diuretic and beta blocker therapy has no significant effect on either GFR or ERPF (26,27).

3.2.3. Salt and water effects. Short-term and long-term administration of minoxidil causes progressive retention of sodium and an increment in body weight appropriate to the degree of sodium retention (23-25). Plasma volume and total blood volume are increased. The degree of sodium and water retention correlates with the dose administered, the duration of therapy, and the pa-

tient's degree of impairment in renal function (28). Rigid salt restriction, coupled with the use of potent diuretics, is usually required to maintain body weight close to pretreatment levels (29).

3.2.4. Renin effects. Minoxidil therapy increases renin activity in plasma (23,24,30-32).

3.3. Summary: direct acting vasodilators (see Table IV)

Hydralazine and minoxidil have similar antihypertensive mechanisms of action; however, minoxidil has a substantially greater hypotensive effect (23,27). The two directly acting vasodilators have qualitatively similar renal effects: in hypertensive patients, neither hydralazine nor minoxidil alter GFR or ERPF, although renal vascular resistance probably declines.

Hydralazine and minoxidil therapy are both accompanied by retention of sodium and water, and expansion of plasma volume and extracellular fluid volume. This is particularly important when the hypotensive effect is severe, or when renal insufficiency is pronounced. Pseudotolerance rapidly develops without concomitant diuretic therapy. Since the retention of sodium and water is not related to reductions in GFR or ERPF, it has been suggested that vasodilation increases sodium reabsorption in the proximal convoluted tubule of the nephron (33).

Finally, both hydralazine and minoxidil elevate plasma renin activity. The increase is mediated both by 1) activation of the sympathetic nervous system (via activation of the carotid and aortic baroreceptor reflexes) which can be inhibited by beta blockade, and 2) activation of an intrarenal (? baroreceptor) mechanism, which is unresponsive to beta blockade (30). The increase in plasma renin activity following minoxidil therapy is not consistently associated with parallel increases in plasma aldosterone concentration; an enhanced metabolic clearance of aldosterone secondary to hepatic vasodilation is thought to be responsible for this effect (32).

TABLE IV

Direct Acting Vasodilator Effects on the Kidney

	Hydralazine		Minoxidil	
	Acute*	Chronic**	Short-term†	Long-term§
Glomerular filtration rate	→	→	→	→
Effective renal plasma flow	→	→	→	→
Renal vascular resistance	↓	↓	↓	↓
Fractional excretion of sodium	↓	↓	↓↓	↓↓
Urine flow rate	↓	↓	↓↓	↓↓
Free water clearance	?	?	?	?
Extracellular fluid	↑	↑	↑↑	↑↑
Weight	↑	↑	↑↑	↑↑
Plasma renin activity	↑	↑	↑	↑

*renal response to acute oral or intravenous administration during maximum hypotensive effect

**renal response to chronic (weeks to months) oral administration of drug

†renal response to oral loading doses (supine and standing positions)

§renal response to chronic (months) oral administration of drug

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16.
DIURETICS AND THE KIDNEY

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The remarkable development of new chemical diuretics over the last thirty years has caused an astonishing change in the clinical treatment of an array of fluid and electrolyte disorders. Diuretics successfully block the tenacious reabsorption of sodium which takes place in a variety of generalized edema states and have played a pivotal role in the treatment of patients with essential hypertension. An enormous amount of knowledge has been gained regarding the site of action of diuretics, physiological effects, value in clincal treatment, side effects and toxicities. This discussion will review some of this information. [1-6]

Comments Regarding Site Diuretic Action In The Nephron

Renal physiologists have identified up to twelve distinctive segments of the nephron which are responsible for the normal integrated tubular function of the kidney. Each one of these anatomical nephron segments has a relatively unique electrolyte transport system. Thus there is a potential for an array of chemical agents which interfere with these transport systems to be used as diuretics. Viewing the nephron, however, in simpler perspective one can, at the present time, focus on at least four anatomical sites where diuretics could have a unique action, namely the proximal convoluted tubule, the thick ascending limb of Henle's loop, the distal convoluted tubule and the collecting duct.[7]

Proximal tubule and carbonic anhydrase inhibitors. The proximal convoluted tubule is the site of bulk isotonic reabsorption of 2/3 of the glomerular filtrate which is returned to the circulation by driving forces relating to

active sodium reabsorption offset by passive backflux across the tight junctions connecting the epithelial cells. Sodium reabsorption occurs in part in exchange for hydrogen secretion even though substantial reabsorption still occurs with chloride. Overall reabsorption of salt water in the proximal tubule bears a relationship to the extracellular fluid volume so that when volume is expanded proximal reabsorption is reduced and when volume is contracted proximal tubule reabsorption is enhanced. Almost all the diuretics that operate on the proximal tubule do so by inhibiting the enzyme carbonic anhydrase. This then reduces reabsorption of sodium bicarbonate as well as sodium chloride and water because of the osmotic effects of the now non-reabsorbable sodium bicarbonate. Carbonic anhydrase inhibitors such as acetazolamide are not highly natriuretic because the loop of Henle reabsorbs most of the rejected sodium chloride delivered from the proximal tubule back into the circulation. The ascending limb of Henle's loop has a considerable capability for increasing its salt reabsorption rate in direct proportion to the load presented to it unless other factors (eg. loop diuretics) are present to interfere with this process. There may also be a small reduction in sodium bicarbonate reabsorption in the distal tubule after acetazolamide which could contribute further to natriuresis and bicarbonaturia. Significant urinary potassium losses also occur because the increased delivery of sodium bicarbonate to the distal potassium secretory site enhances potassium secretion into an alkaline urine. Effects of carbonic anhydrase inhibitors readily wear off due to the development of chronic metabolic acidosis. These drugs are now little used except in some instances where alkanizing the urine is useful and in the treatment of glaucoma. Other diuretics which operate primarily in more distal regions of the nephron have only minor effects on the proximal tubule. As regards the straight portion of the proximal tubule little precise information is presently available as to the specific effects of diuretics.

Loop diuretics. The thick ascending limb of Henle's loop is responsible for some 25% of the reabsorption of filtered salt. It is now clear that it is a secondary active chloride reabsorption followed by passive sodium reabsorption which is a mechanism of the salt transport process. The loop diuretics are effective from the luminal side of the membrane following secretion into the urinary fluid by the proximal convoluted tubule. Inhibition of chloride transport system by the loop diuretics prevents the establishment of a concentration profile within the renal medulla and interferes with the ability to concentrate and in part with the ability to dilute the urine. The inhibition of the chloride transport system also seems to be the likely explanation for the inhibition of the normally passive reabsorption of other cations such as potassium, calcium, and magnesium.[2,6-8]

There is no question that the advent of the potent loop diuretics effective orally and intravenously has been a major achievement in diuretic therapy. The availability of furosemide and ethacrynic acid decisively changed the therapeutic approach to the treatment of heart failure because of their high ceiling dose response curves. These drugs are also highly effective despite the development of various electrolyte disorders such as hyponatremia, hypokalemia and acid-base disturbances. They are by far the most potent group of diuretics which at maximal doses cause excretion of some 30% of the filtered load of salt in the urine. All loop diuretics now in use similarly reduce sodium chloride reabsorption in the thick ascending limb. Many studies have been carried out to further clarify the mechanism of action of the loop diuretics in reducing passive permeability to chloride across the luminal membrane, reducing the positive transtubular potential difference and, in turn, decreasing sodium and other cation reabsorption. It is now generally agreed that the loop diuretics work largely in the loop of Henle even though there may be minor effects in the proximal tubule at high doses. There is now an array of other loop diuretics which appear to be equally useful but reached the market at a later

time. Drugs such as bumetanide and piretanide are equally effective but have no special advantages. The loop diuretics have been of enormous value in the rapid alleviation of pulmonary edema and the chronic treatment of congestive heart failure, nephrotic syndrome with edema, cirrhosis with ascites, symptomatic hypercalcemia, drug intoxications and even as diagnostic tests of hypertension to rapidly increase the secretion rate of renin. All loop diuretics are accompanied by fluid and electrolyte complications if not carefully monitored but on balance are remarkably low in the incidence of toxicities.

Distal convoluted tubule and thiazide diuretics. The distal convoluted tubule is now known to be the site of action of the thiazide and related group of diuretics. These diuretics interfere with urinary dilution and bring about a modest natriuretic response which maximally approaches 10% of the filtered load. There is no question that agents such as hydrochlorothiazide have been among the most significant advances of our time in the treatment of mild to moderate edema and in the treatment of essential hypertension. They are, by and large, excellent drugs and are widely used by physicians throughout the world. All of the agents of the thiazide-hydrothiazide group as well as related drugs such as metolazone, chlorthalidone, clopamide and quinethazone appear to have similar sites of action and overall renal effects with differences primarily in their duration of action. Micropuncture studies have indicated that thiazide diuretics as well as metolazone may reduce reabsorption in the proximal tubule but this only makes a minor contribution to the overall natriuretic effects as any increased delivery from the proximal tubule is mostly reabsorbed in the loop of Henle. No effects have been observed in the thick ascending limb. Careful micropuncture studies have indicated that the prime natriuretic, chloruretic and diuretic responses of the thiazide diuretics occur in the distal convoluted tubule. This explains why thiazides are only moderately effective since they work at

a transport site of limited capacity. It is still uncertain whether the change in the salt transport in the distal convoluted tubules is sufficient to explain the whole diuretic response of thiazide diuretics. As thiazide diuretics are effective just prior to the potassium secretory site, they can cause significant kaliuresis. Hypokalemia has been noted with low to moderate rates of incidence resulting in potassium depletion. The addition of potassium to the urine is directly related to the rate of urine flow through the distal tubules and the collecting duct system. Alkalosis and hyperaldosteronism further enhance potassium secretion. As the natriuretic effect of thiazides (or other potassium lossing diuretics) wears off so does the potassium lossing effect of the thiazide diuretics unless there is persistent alkalosis or hyperaldosteronism.

Thiazides have interesting and unique effects on calcium excretion in that they enhance calcium reabsorption in the distal tubule and have become one of the mainstays of the treatment of patients with idiopathic hypercalcuria and recurrent renal calculi.(8) Most important thiazide diuretics play a major role in the first step of antihypertensive therapy and it is hard to imagine the daily practice of a physician without access to one of the thiazide-like drugs.

In comparing the two most useful groups of clinical diuretics, it would appear that the loop diuretics are more potent, have fewer depressant effects on the renal hemodynamics, maintain their effectiveness later in renal failure, are effective in symptomatic hypercalcemia and may have a somewhat lesser tendency to lose urinary potassium. The thiazide diuretics probably have better antihypertensive effects and are highly effective for hypercalcuria.

Distal convoluted tubule and natriuretic potassium sparing diuretics. The distal convoluted tubule and the cortical collecting ducts are the sites within the nephron for sodium-potassium exchange. Spironolactone is a well

established anti-aldosterone agent which competes directly with the action of aldosterone for sodium retention and enhances potassium loss. Triamterene and amiloride inhibit the sodium-potassium exchange as well but not through direct anti-aldosterone action. This group of agents represents another major advance in diuretic therapy. These agents are all very mild natriuretic agents resulting in the excretion of 1-2% of the filtered load of sodium at maximum doses and are valuable in situations requiring mild diuresis. A principle advantage is the inhibition of potassium secretion and the prevention of hypokalemia. They are particularly valuable in clinical situations which are accompanied by secondary hyperaldosteronism such as cirrhosis with ascites where a slow gentle diuresis is required in order to prevent electrolyte disorders and not to trigger encephalopathy. Needless to say the natriuretic potassium sparing diuretics have their largest use in combination with more proximally acting diuretics such as thiazides or loop diuretics that tend to produce hypokalemia. On the other hand their use can lead to significant hyperkalemia in the presence of a high potassium intake and blunted renal ability to excrete potassium as in chronic renal failure. Mild metabolic acidosis frequently ensues as these agents also inhibit sodium-hydrogen exchange. The natriuretic potassium sparing agents used primarily with other diuretics have also become a mainstay in antihypertensive therapy with small additive effects in reducing blood pressure and preventing potassium losses. Each one of these agents is similarly effective and present usage is largely limited by their special toxic effects.

Miscellaneous diuretics. Osmotic diuretics such as mannitol by virtue of its nonreabsorbability exerts an osmotic effect which retards the reabsorption of water and in turn inhibits reabsorption of all electolytes. The overall renal response to osmotic diuretics with progressively increasing plasma osmolality is a marked increase in water excretion with lesser increases in salt excretion. Recent studies have

indicated that the action of mannitol begins in the proximal tubule with a lowering of the concentration of sodium chloride relative to the plasma concentration. The overall decrease in proximal tubule reabsorption of salt and water is, however, much less than the decrease in reabsorption that occurs within the loop of Henle. During maximum mannitol diuresis up to 30% or more of reabsorption of the filtered salt and water can be inhibited in the loop of Henle. It would appear that osmotic diuretics retard the passive reabsorption of water in the descending limb and limit the overall salt reabsorption by the ascending limb perhaps by reducing the positive transtubular potential difference. In any case, the combination of the osmotic effects of mannitol in the proximal tubule and the loop of Henle delivers increasing amounts of salt and water to the distal tubule where some of the salt is retrieved back into the circulation. In addition to significant losses of salt and water, significant urinary losses of potassium, calcium, and magnesium may occur with marked osmotic diuresis. Mannitol has had some use as a preventive measure for situations in which the development of acute renal failure is likely. It has also been of value in drug intoxications by increasing the rate of urine flow when the excretion of an intoxicant drug is flow dependent. Urea diuresis mimics mannitol diuresis closely except that the losses of potassium are much greater with urea, an effect which occurs in the straight proximal tubule.(1,2,4)

Compounds designed to improve filtration rates such as aminophillin have been used for years to improve diuretic effects. Renal vasodilators such as dopamine and related compounds have similar effects.

Determinants of Diuretic Action

The effectiveness of any diuretic is highly dependent on the adequacy of the glomerular filtration rate, the volume status of the patient, the integrity of the secretory pathways in the proximal tubule as well as various electrolyte and acid-base disturbances which may affect diuretic action. Any

time GFR is reduced because of low perfusion pressure, one would expect to observe a lower diuretic response. This is not an infrequent situation when a patient appears in hospital with low blood pressure and concurrent pulmonary edema. A potent loop diuretic may be administered intravenously and the response may be less than had been anticipated. If renal blood flow and glomerular filtration rates are low, the delivery of drug to the tubule and overall absolute tubular transport capacity will be greatly reduced with a lesser diuretic effect. Chronic reduction of GFR as occurs in chronic renal disease will similarly reduce the capacity of the electrolyte transport system that can be inhibited by diuretics, and the absolute diuretic response is reduced even though the fraction of the filtered load that is excreted may be higher than normal. Uremia appears also to reduce the secretion of diuretics into the proximal tubule requiring a higher dose to reach an equally effective urinary concentration. The most important determinant in diuretic action relates to the extracellular fluid volume status. First when extracellular fluid volume is expanded in a normal person the diuretic response is enhanced since salt reabsorption is reduced in the proximal tubule leading to enhanced reabsorption in the loop of Henle. The loop diuretics will then produce a greater effect since there is a greater capacity of the transport site within the loop of Henle which can be inhibited. Generally speaking in congestive heart failure with greatly expanded extracellular fluid volume due to heart failure the nephron is very sensitive to inhibition by diuretics operating in the loop of Henle and the distal tubule. Conversely during any situation of volume contraction the diuretic response is less which is advantageous under normal circumstances as the diuretic response will wear off appropriately and tend to produce the desired goal of treatment. This has been called the "braking" effect on diuretic action. However, the powerful loop diuretics may continue to work to a modest extent despite volume contraction and serious further volume contraction can occur. It is now

also clear that factors which alter the secretion of the diuretics into the proximal tubule and into the luminal fluid will reduce diuretic action. Probenecid can interfere with the entry of furosemide into the urinary fluid, and prostaglandin inhibitors reduce the effect of furosemide.

Indications for Diuretic Use

The various edema states served initially as the primary indication for the use of diuretics. This was true for the mecurial diuretics and the carbonic anhydrase inhibitors. With the advent of the thiazide group of diuretics and later the loop diuretics the possible uses were extended with great success and better chronic control. Very early in the development of diuretic therapy it was recognized that these drugs played a successful role in the treatment of hypertension. Until very recently most experts in the treatment of hypertension recommended diuretic therapy as the initial step in antihypertensive treatment. In fact diuretics are currently used more extensively in the treatment of hypertension than for the relief of edema. A role for diuretic therapy which could not have been predicted has been in the field of calcium disorders where the loop diuretics play a key role in the treatment of acute symptomatic hypercalcemia and the thiazide diuretics in the treatment of hypercalcuria in patients with recurrent renal calculi. A host of other indications have been present for diuretic therapy including the still controversial use of loop diuretics in impending acute tubular necrosis, the use of loop diuretics in certain drug intoxications, the use of thiazide diuretics in nephrogenic diabetes insipidus, the use of carbonic anhydrase inhibitors in glaucoma and various situations in which urinary alkalinization is required, and the specific use of spironolactones or related drugs in primary hyperaldosteronism.(2)

Diuretics and Hypertension

Whereas the cause of essential hypertension remains elusive, it is clear that hypertension can generally be

effectively treated and the treatment leads overall to significant reduction in morbidity and mortality. The introduction of thiazide diuretics for the treatment of hypertension in the late 1950's was a very significant advance in the therapy of hypertension. Thirty years later thiazide-like diuretics remain a drug of initial choice to many physicians in the treatment of essential hypertension even though a note of caution has been inserted recently by some suggestions that an increased long-term risk of cardiovascular deaths in hypertensive patients may result. The rationale for diuretics in hypertension relates to the underlying premise that there is an altered pressure natriuresis response curve in hypertension reflecting a higher set point of extracellular fluid volume to renal salt excretion. Whether this relates to a genetic renal defect in salt excretion or a defect in the volume sensing mechanism is unknown. However, diuretics pharmacologically appear to reset the relationship between extracellular fluid volume and renal salt excretion. The nature of the antihypertensive effects due to diuretics have not been entirely clarified but vary between acute and the chronic administration. Acutely a decrease in blood pressure occurs over 2-4 days with a sodium loss of approximately 200-300 ml and a weight loss of 1-3 kilos. Extracellular fluid volume diminishes by 1-2 litres. This effect can be sustained by a low salt diet and abrogated by a high salt diet. Basically all diuretics reduce blood pressure acutely in this manner and roughly in proportion to their overall potency and salt loss. All the thiazide groups and loop diuretics are effective as well as the potassium sparing diuretics. Accompanying the natriuresis and descreased extracellular fluid and plasma volume is a considerable decrease in venous return and cardiac output. Total peripheral resistance may actually increase initially. With the development of new steady state of salt balance over succeeding months blood pressure shows a slow but further decline. At this point one observes a sustained decrease in total peripheral resistance while cardiac

output may have returned to normal. A number of mechanisms of action have been postulated to account for the sustained decrease in total peripheral resistance due to chronic diuretic therapy. These include direct vasodilatation, local structural changes, and perhaps most likely due to local changes in microvascular autoregulation due to initial decreased cardiac output. It is estimated that approximately 50% or more of the hypertensive population will respond to diuretics with a greater than 10% reduction in main arterial pressure. The average reduction in blood pressure in a patient treated with diuretics is approximately 17-18% for systolic and 12-14% for diastolic pressures. The most responsive patients are those with highest initial blood pressure; as a rule, diuretics do not lower the blood pressure in normotensive patients. At normal therapeutic doses, diuretics do not usually produce signficant orthostatic blood pressure, even though it can occur. Diuretics clearly exaggerate orthostatic hypotension in patients receiving other antihypertensive drugs. Benzothiadiazine diuretics have been the primary choice in the diuretic treatment of essential hypertension. More recently amiloride or triamterene alone or with hydrochlorothiazide have been effectively used. Loop diuretics are no more effective antihypertensive agents than thiazides and may have a greater incidence of adverse side effects, resulting in less frequent use. Diuretic therapy is a well established initiative in the step care approach to the treatment of hypertension. Diuretics, when added to almost any antihypertensive regime, significantly increase the antihypertensive effect and this permits a reduction in diuretic drug dosage. Refractoriness to diuretic therapy results from patient non-compliance, from volume depletion, high plasma renin patients, and patients with renal failure.(1,9)

The Use of Diuretics in Edema States

Ideally in all edema states treatment is directed at primary disorder. In congestive heart failure, improvement in cardiac contractility with cardiac glycosides or reducing

afterload may shift the Frank-Starling curve into a more effective state. Diuretic therapy plays a critical and successful role in severe congestive heart failure by reducing the level of extracellular fluid volume expansion, thereby relieving symptoms of circulatory congestion especially in the lungs and generally improving local tissue perfusion. Chronic diuretic usage then helps to maintain a more optimal extracellular fluid volume. At times metolazone has been found to play a useful adjunct role with the loop diuretics because of its distal and proximal effects and because of its continuing effectiveness in renal failure. In acute pulmonary edema, the loop diuretics - particularly furosemide have been used extensively in treatment because of their rapid action. These agents seem to manifest a therapeutic effect prior to the increase in urine flow and this appears to be due to dilatation of the pulmonary venous capacitance vessels. The loop diuretics can be administered intravenously and the dose can rapidly be escalated and may attain values as high as 500 mgs or more. However, overvigorous diuresis may lead to significant volume contraction and impairment of cardiac output. In cirrhosis with ascites primary treatment is usually not successful and diuretic therapy only partially alleviates ascites. Slow diuresis not exceeding 900 mls/24 hours seems to give the most beneficial results and avoids sudden intravascular volume contraction. When accompanied by salt restriction, the use of distal natriuretic potassium sparing diuretics resulting in a daily weight loss of 0.5 to 1 kilogram may bring about optimal therapy. However with more refractory cirrhosis and ascites, more potent thiazides or particularly loop diuretics may be required but increase the hazard of electrolyte disturbances and possible development of portal encephalopathy as well as hepato-renal failure. In the nephrotic syndrome primary treatment is directed to the leaky glomerular membrane usually with steroids and/or immunosuppressives. The value of diuretic is more limited as hypoproteinemia hinders the return of interstitial fluid back

into the vascular space. A massive diuresis can quickly lead to hypotension due to contraction of plasma volume despite obvious clinical interstitial edema. Finally in idiopathic cyclical edema in women, diuretic therapy may be of transient benefit and sometimes may not overcome the marked sodium retaining stimulus making the edema worse because of plasma volume contraction.[1-3]

Complications Resulting from Diuretic Therapy

It would be surprising not to anticipate major electrolyte complications from drugs that can so profoundly affect renal tubular electrolyte transport. Generally speaking many patients may have mild symptoms of volume depletion such as fatigue and malaise. Eventually postural hypotension may occur with further volume depletion. Aggravation of heart failure may occur if the venous pressure is reduced too quickly. Renal function may also be aggravated as reflected by increasing azotemia. Hyponatremia is perhaps most commonly caused in the setting of diuretics that blunt urinary diluting ability and continuing oral or intravenous water intake. A number of factors are at play in the genesis of the hyponatremia due to diuretic therapy including volume depletion, reduction in glomerular filtration rate, compensatory increases in salt reabsorption in the proximal tubule due to volume depletion or edema states, release of antidiuretic hormone and interference with the ability to separate salt from water reabsorption in the loop of Henle and distal tubule. Usually stopping the diuretic and allowing correction of extracellular fluid volume losses will be sufficient to correct the hyponatremia. For very severe hyponatremia of less than 120 mEq/l, additional hypertonic saline may be required to correct the hyponatremia and sometimes the remaining diluting ability of loop diuretics can then be an advantage. By contrast hypernatremia may occur when salt depletion is so excessive.

The most familiar complication of diuretic therapy is hypokalemia and potassium depletion. The literature is replete

with extensive discussion on this issue.[1,2,9,11] The rate of potassium loss bears a direct relationship to the urine flow through the distal tubule and is exaggerated by alkalosis and hyperaldosteronism. Any loop or thiazide diuretic can bring about excessive loss of potassium particularly during the rapid diuretic phase. There may be an actual tendency for thiazide diuretics to be slightly more kaliuretic. When carefully evaluated, the actual degree of potassium depletion in the body following diuretic therapy in patients with hypertension has ranged from values that are normal or marginally low to values that may be as high as 25-30% reduction. Hypokalemia is most obvious in patients with previously low potassium intakes, with brisk diuretic responses or who have alkalosis or hyperaldosteronism. Hypokalemia can be avoided with intermittent diuretic therapy and if nutritional advice is given re ingestion of foods with higher potassium intake. Particularly important are those patients who are at risk for hypokalemia such as those on digitalis compounds, or those being treated with high doses of steroids. Many physicians feel that serum potassium levels as low as 3 mEq are satisfactory unless the patient has specific complaints or is at risk for toxic effects from hypokalemia. Below a serum potassium of 3 mEq a number of physiolgical disturbances relating to cardiac arrhythmias and function occur as well as increased neuromuscular irritability and muscle weakness. Many physicians use a combination of distal potassium sparing diuretics with thiazides or furosemide. Such combinations are usually effective and uneventful but hyperkalemia can occur with distal natriuretic potassium sparing agents. In fact, this may be more serious hazard to life than hypokalemia as cardiac arrhythmias and neurological signs may result.

Hyperkalemia associated with diuretics is usually mild and is related to continuing overzealous use of the distal potassium-bearing natriuretics. This may be observed in a setting in which potassium intake is high, usually when supplemented orally, during rapid cellular catabolism and

especially when renal function is reduced. A particular example is the elderly patient with modest chronic renal failure, often a diabetic who may have hyporeninemic hypoaldosteronism and may also be on anti-inflammatory agents.

Calcium disorders may occur in diuretic therapy. Hypercalcemia is observed due to excessive diuresis or unmasking of hyperparathyroidism. Conversely, hypocalcemia can result from rapid massive diuresis. Excessive diuresis can also lead to hypomagnesemia and magnesium deficiency. Diuretic therapy can induce acid-base disorders including metabolic alkalosis with the loop and thiazide diuretics and metabolic acidosis with the potassium-sparing diuretics and carbonic anhydrase inhibitors. Hyperuricemia may occur with the loop and thiazide diuretics. Some believe that the long-term effects on uric acid metabolism and lipid metabolism may play an atherogenic role in patients undergoing chronic diuretic therapy.

A number of specific toxicities may occur with diuretics including hypersensitivity reactions involving the skin, blood, and kidney. An allergic interstitial nephritis may occur with thiazide-like diuretics and furosemide leading to a decline in renal function in the presence of no other offending cause but is usually reversible. Thiazide-like diuretics may be associated with pancreatitis. Loop diuretics can cause a variety of gastrointestinal symptoms such as nausea, vomiting and sometimes bleeding. Deafness may be associated with loop diuretics usually transient with furosemide. Renal stones may return with acetazolamide causing calcium phosphate stones and Triamterene with "triamterene" stones. Spironolactone has endocrine side effects such as impotence, diminished libido, gynecomastia and menstrual disorders. Liver toxicity has been reported with thiazide diuretics, furosemide, and the uricosuric diuretic tienilic acid.

Refractoriness to Diuretic Therapy

Despite the splendid array of potent diuretics, there are a number of situations in which patients are refractory to

diuretic therapy and include non-compliance by the patient particularly when poorly informed by the physician as to the rationale of his drug therapy. Very often there may be inadequate treatment of the primary disorders such as cardiac glycosides in heart failure. There may be no curtailment of the salt intake in the patients with edema and hypertension. Conversely, volume contraction may have occurred and diuretic action has ceased. There may be limited response to diuretic therapy in patients with cirrhosis and hypoproteinemia since plasma volume may be rapidly contracted. Renal failure may have ensued. Finally the patient's overall condition with very severe heart failure, cirrhosis with ascites or end-stage renal failure may have reached a degree of severity reflecting a devastation of tissue pathology which even the best drugs cannot reverse.

SUMMARY

Extraordinary progress has been made by the pharmaceutical industry in providing physicians and their patients with highly effective and relatively non-toxic drugs. The development of the loop, thiazide-like, and distal potassium-sparing diuretics has given physicians the capability of treating even severe forms of edema and has provided him with pharmaceutical tools for treating a number of other disorders, particularly hypertension. Much responsibility rests with the physician, the patient, and the drug industry for the proper utilization and the marketing of these drugs. A continued attempt to gain understanding of the basic mechanism of the action of these drugs can only lead to further excitement and optimism regarding further developments in improved diuretic therapy. The physician should continue to make every effort to optimize the diuretic of choice, to use the lowest dose possible, to consider the function of the kidney and the circulation and to carefully monitor and deal with electrolyte and toxic disturbances.

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17. CONVERTING ENZYME INHIBITION AND THE KIDNEY: EFFECT ON POTASSIUM HOMEOSTASIS AND RENAL FUNCTION

E.L. BRAVO, S.C. TEXTOR, L. TADENA-THOME

Angiotensin II regulates the production of aldosterone, an electrolyte-active adrenal cortical steroid that contributes importantly to the kidney's ability to handle potassium. Other studies (1-3) also indicate that angiotensin II plays a critical role in the autoregulation of renal blood flow and glomerular filtration rate. Since angiotensin converting enzyme inhibitors inhibit angiotensin II generation, we studied the possible adverse consequences of acute and long-term converting enzyme inhibition (CEI) on potassium homeostasis and on renal function in hypertensive subjects with a wide range of renal function.

In a first study (4) 33 hypertensive patients were studied over a relatively short period after initiation of CEI therapy. Patients were given an isocaloric diet of known sodium (110 mEq/day) and potassium (80 mEq/day) content throughout the study period. A 3-5 day equilibration period was allowed before starting therapy. A 24-hour urine sample for sodium, potassium and creatinine levels and aldosterone excretion rate (AER) was collected daily. Plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were measured before and 4-7 days after initiation of captopril given in average doses of 575 mg/day (range: 100-1000 mg).

Of the 33, twenty-one showed significant reductions in AER and constitute the basis of this review. Individual changes in AER and in serum potassium are shown in Figure 1. During treatment, PRA increased from 11.4 ± 2.7 (normal: 1.18 ± 0.37, SD) to 26.8 ± 3.6 (SE) ng/ml/hr suggesting decreased circulating angiotensin II resulting in uninhibited release of renal renin. In these patients, AER was reduced from 16.7 ± 1.7 (normal:

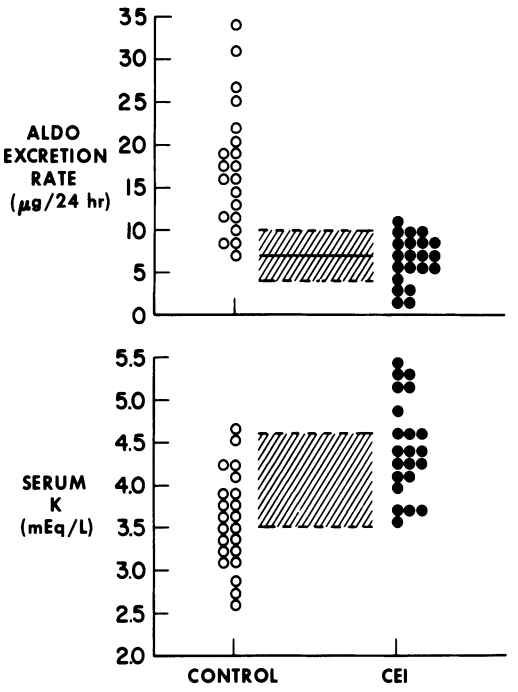

FIGURE 1. Aldosterone excretion rate and concomitant increases in serum potassium concentration during short-term (4-7 days) captopril treatment.

6.5 ± 1.5, SD) to 5.9 ± 0.7 (SE) μg/24 hours. At the same time serum potassium concentration increased from 3.4 ± 0.2 (normal range: 3.5 - 4.6) to 4.4 ± 0.2 (SE) mEq/L. Six patients exhibited clearly hyperkalemic values. Despite the rising serum potassium concentrations AER remained subnormal in 9, and 4 clearly had hypoaldosteronism. For these 9 patients, the basal serum potassium concentration averaged 3.7 mEq/L before treatment and rose to 4.7 mEq/L 4-7 days after initiating therapy. Although the correlation between percent changes in serum potassium concentration and AER was significant, hyperkalemia was infrequently associated with low AER values but appeared better related to altered renal function.

The relationship between initial and subsequent serum potassium values over the range of creatinine clearance in patients with subnormal AER values is shown in Figure 2. Although pretreatment serum potassium values were either normal or low regardless of the glomerular filtration rate (GFR), the serum potassium values achieved during CEI and the rise from baseline were inversely related to the basal GFR. Serum potassium values

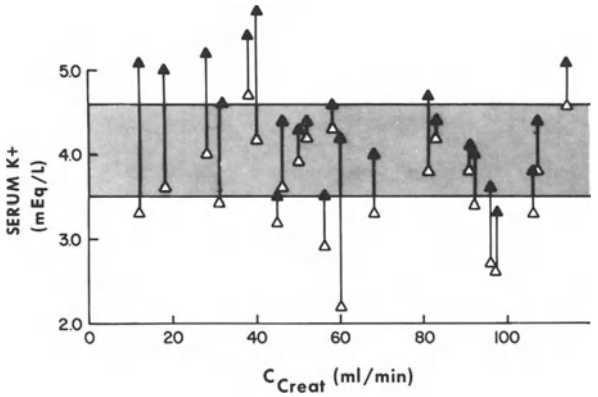

FIGURE 2. Relationship of serum potassium values to glomerular filtration rates before (Δ) and during (▲) administration of captopril. Final serum potassium values correlated inversely with glomerular filtration rate ($r = -0.58$, $p < 0.01$).

above 4.6 mEq/L were more common in those patients with GFR levels lower than 40 ml/min. This observation was independent of the absolute levels of aldosterone in urine or blood during CEI.

A clearer illustration of this observation is portrayed in Figure 3. It shows the daily serum potassium values in three subjects with differing GFR levels, but with similar PAC values during CEI. Although all three exhibited increased serum potassium values, only the patient with a GFR less than 40 ml/min showed a sustained rise in serum potassium concentration to hyperkalemic levels.

To assess the effect of chronic suppression of aldosterone production during CEI on potassium homeostasis, additional studies were performed in eleven patients who had been on continuous CEI therapy for an average of 33.5 months (5). All had normal renal function and had sustained reductions in AER despite significant increases in serum potassium concentrations from pretreatment values. Our objective was to assess the ability of these patients to excrete an acute potassium load.

The patients were studied during therapy and 36 hours after cessation of therapy. Return of serum ACE and PRA to normal values and increases of arterial blood pressure to pretreatment levels

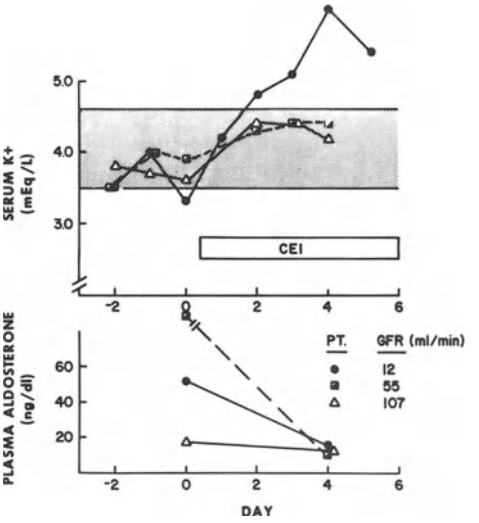

FIGURE 3. Aldosterone - glomerular filtration rate - serum potassium values interrelationship during captopril treatment. Hyperkalemia developed only in the patient with a GFR of 12 ml/min despite having plasma aldosterone values as the others.

gave some assurance that functional ACE inhibition had been reversed. Patients were on an isocaloric diet containing 110 mEq sodium and 80 mEq potassium per day during the studies. Studies were performed after an overnight fast, in the morning, under maximum water diuresis. Serum and urinary potassium, and PAC were determined before and at 30 min intervals during infusion of KCl (0.75 mEq/kg) in 500 ml of 0.2% NaCl solution over 90 minutes. To assure early detection of potassium cardiotoxicity, the patients were placed on continuous EKG monitoring.

Table 1 summarizes the results of these studies. Responses were similar whether patients were on or off captopril. Serum potassium concentrations increased significantly during KCl infusion. However, this was associated with increases in both aldosterone production and renal secretion of potassium, both tending to blunt further increases in serum potassium concentration.

These studies suggest that acute and long-term inhibition of ACE invariably lead to sustained suppression of aldosterone production and retention of potassium. However, gross hyperkalemia is a rare occurrence. When hyperkalemia does occur, it is usually seen primarily in patients with significant impairment

Table 1. Responses to acute infusion of KCl in 11 hypertensive patients on long-term converting enzyme inhibition.

Measurements	On Captopril		Off Captopril	
	Basal	KCl*	Basal	KCl*
Serum K (mEq/L)	4.01±0.13	4.7±0.15†	4.04±0.10	4.7±0.11†
Urinary K (μEq/min)	72±8	146±6.2†	74±12	145±20†
Plasma Aldosterone (ng/dl)	14±6	27±13†	11±4	21±8†

All values expressed as mean ± SEM. *Intravenously administered over 90 minutes as KCl (0.75 mEq/kg) in 500 ml 0.2% NaCl. †Significantly different from control.

of renal function (GFR < 40 ml/min). In addition, although long-term CEI therapy produces sustained suppression of aldosterone production, the ability of the kidney to respond to an acute load of potassium does not appear to be seriously compromised. The effect of chronic potassium loading was not studied.

Acute renal failure has been reported with CEI therapy (6-8). Mechanisms postulated to account for these observations have included direct drug nephrotoxicity (6), hypersensitivity (7), and renal ischemia (8) due to rapid reductions in systemic blood pressure.

Our experience (9) in seven patients is shown in Figure 4.

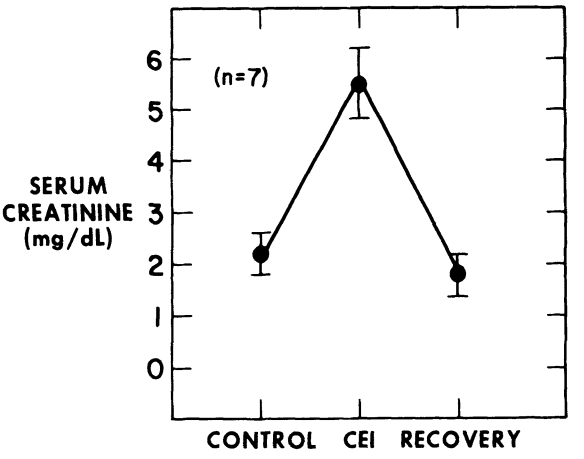

FIGURE 4. Acute renal failure during captopril treatment in some patients with renovascular hypertension.

Before CEI therapy serum creatinine averaged 2.3 mg/dl (range: 4.1-9.1). The onset of acute renal failure varied from 1-18 days (mean: 8 ± 3). Serum creatinine fell promptly to pretreatment values upon withdrawal of CEI therapy. Of the seven, one had unchanged arterial blood pressure while experiencing acute renal failure. None of the patients had evidence of nephrotoxicity or of hypersensitivity.

Clinically, these patients had in common several features that appeared to be predisposing factors. They were all older than 50 years (range: 52-69); all had generalized atherosclerosis and impairment of renal function; all had either bilateral renal arterial stenosis or renal artery stenosis in a sole remaining kidney. At the time of CEI administration, all were taking relatively large amounts of diuretic drugs.

Our observations are similar to the findings of others. Hricik and coworkers (10) recently reported similar findings in eleven patients receiving captopril for treatment of hypertension associated with stenosis involving either both renal arteries or of an artery to a solitary kidney. In this particular report, it was clearly shown that equivalent reductions in blood pressure with drugs other than CEI did not lead to acute renal failure and that both captopril and enalapril were equally effective in producing the same clinical disturbance. Additional corroborating evidence was provided by Curtis et al (11) who reported identical clinical course in four patients treated with captopril for hypertension associated with stenosis of the transplanted renal artery.

The studies of Hall and associates (3) are germane to these clinical observations. These investigators have shown in dogs that when renin is chronically suppressed, reduction of renal perfusion pressure to low levels leads to decreases in GFR while autoregulation of renal blood flow is maintained. On the other hand, when renin is chronically elevated and the same experiments are performed, both GFR and autoregulation of renal blood flow remain unchanged. If during these studies captopril is infused, autoregulation of renal blood flow persists, but GFR falls progressively. These experiments provide evidence that the

renin-angiotensin system plays a crucial role in regulating GFR when renal perfusion is low.

Taken together, these studies suggest that CEI-induced renal insufficiency results from a disturbance in the autoregulation of GFR, and that this disturbance is a consequence of blockade of the renin-angiotensin system. In view of this evidence, angiotensin converting enzyme inhibitors should be used with caution in patients in whom the risk of a critically low level of renal perfusion pressure is increased by the drug. This group includes, at the very least, patients with bilateral renal artery stenosis and those with renal-artery stenosis in a solitary kidney. Whether or not the group at risk should be enlarged to include other patients in whom perfusion pressure may be low, remains to be determined.

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18. SYSTEMIC AND RENAL HEMODYNAMIC EFFECTS OF ENALAPRIL IN PATIENTS WITH ESSENTIAL HYPERTENSION

FRANCIS G. DUNN, WILLE OIGMAN, HECTOR O. VENTURA, FRANZ H. MESSERLI, ISAAC KOBRIN, EDWARD D. FROHLICH

ABSTRACT

Enalapril, a new angiotensin converting enzyme inhibitor, has been shown to be an effective antihypertensive agent both in renovascular and in essential hypertension. It is structurally different from captopril in that it does not possess the sulfhydril group. We have studied the systemic and renal hemodynamic, biochemical, and cardiac adaptive changes induced by this agent in eight patients with essential hypertension before and after 12 weeks of therapy. Mean arterial pressure fell from 110 mm Hg to 90 mm Hg (p 0.001) and this was mediated through a fall in total peripheral resistance from 42 $\pm$ 3 units to 32 $\pm$ 3 units (p 0.001). Cardiac index and heart rate remained unchanged. Renal plasma flow rose in six of the eight patients checked. Renal vascular resistance fell in all patients ($p < 0.001$). Left ventricular mass index fell from a mean of 166 $\pm$ 29 gm/M^2 to 117 $\pm$ 8 gm/M^2 ($p < 0.05$) without impaired myocardial contractility. Thus, enalapril lowers arterial pressure by reducing total peripheral resistance without reflexive cardiac effects. In addition, it also has favorable hemodynamic effects on the kidney and produces a reduction in left ventricular mass within three months of the start of therapy.

INTRODUCTION

Enalapril (MK 421) is a converting enzyme inhibitor (CEI) of angiotensin II generation from angiotensin I that differs structurally from captopril by having no attached sulfhydryl group. Preliminary studies in experimental animal models of hypertension (1-3) and in patients (4-6) have confirmed its antihypertensive

Messerli, F.H. (ed.), Kidney in Essential Hypertension.

efficacy, although, as with captopril, its mechanism of action may not be mediated solely through converting enzyme inhibition (2,6). To date, there have been no studies that delineate the hemodynamic, cardiac, and reflexive effects of this agent with prolonged therapy. This report details the alterations produced by enalapril on the above indices in patients with essential hypertension.

MATERIALS AND METHODS

Patients

Eight patients (six white men and two black women) with established essential hypertension are the subjects of this report. Their mean age was 48 with a range of 34 to 65. All had either never received antihypertensive therapy or had all therapy discontinued at least 4 weeks before entering into the study. Funduscopic appearances were normal in four patients and showed grade I changes in four. No patient was in cardiac failure, but one had left ventricular hypertrophy by ECG criteria and four by echocardiographic criteria. Detailed clinical evaluation did not reveal any secondary cause for the hypertension, and no significant abnormalities of hepatic or renal function were found.

Study Design

The patients were included in the study if, on the day prior to starting therapy, they had a supine diastolic pressure between 95 and 110 mm Hg, determined at hourly intervals for 3 hours and showing a variation of less than 10 mm Hg. Pretreatment clinical evaluation on that day included an electrocardiogram, chest x-ray, a laboratory screen (including complete blood count; serum electrolytes, indices of renal and hepatic function, uric acid, and lipid levels; urinalysis; 24-hr urine for protein, and creatinine), and measurement of converting enzyme activity (7). In addition, baseline systemic and renal hemodynamics were determined, and an M-mode echocardiogram was recorded. Each patient was started thereafter on enalapril (5 mg) taken in the morning and was observed for 4 hours with hourly blood pressure checks.

Patients who demonstrated a 20% fall in diastolic pressure or a reduction in diastolic pressure to less than 90 mg Hg 24 hours after therapy were regarded as responders and were maintained on that dose. Those who did not respond to the 5 mg dose had weekly increments in dosage as follows until response occurred: 10 mg/day; 20 mg/day, 40 mg/day, 20 mg b.i.d and finally 20 mg b.i.d + 50 mg hydrochlorothiazide with the morning dose. Once the optimum antihypertensive dose had been established, patients remained on therapy for 12 weeks when all laboratory, hemodynamic and echocardiographic studies were repeated.

Hemodynamic Assessment

Systemic and renal hemodynamics were determined by methods that have been reported previously in detail (8). In brief, baseline studies were performed in the morning with the patient in the fasting, unpremedicated state, and the subsequent study was performed 24 hours after administration of the last dose of enalapril. Using a modified Seldinger method, the brachial artery and median antecubital vein were cannulated with polyethylene tubing advanced to shoulder level, and continuous recordings of arterial and venous pressures were made simultaneously with the electrocardiogram (lead II). Cardiac output was measured in triplicate using the dye dilution method (indocyanine green), and the following hemodynamic indices were calculated using standard hemodynamic formulae: mean arterial pressure, cardiac index, total peripheral resistance index, and left ventricular ejection rate index. After these supine measurements were obtained in triplicate, hemodynamic responses were made to 45^{o} head-up tilt and isometric exercise (8). Arterial pressure and heart rate responses were also measured during the Valsalva maneuver (9).

Renal plasma flow was determined by the single injection clearance of ^{131}iodinated para-amino hippurate (^{131}I-PAH) (8), and renal vascular resistance was calculated by dividing mean arterial pressure by renal blood flow. Plasma volume was determined from the decline in plasma radioactivity after 15 and 30 minutes of equilibration after injection of ^{125}I-human serum albumin (8).

Echocardiogram

M-mode echocardiograms were recorded in all eight patients. In only six were they regarded as having technical quality high enough to be analyzed. The techniques for visualization of the left ventricle were described previously (10). Measurements were made of posterior wall thickness, septal wall thickness, systolic dimension, and diastolic dimension (11). From these data fractional fiber shortening, velocity of circumferential fiber shortening (12), left ventricular volumes (13), and left ventricular mass index (14) were derived. The method of recording the echocardiograms was standardized, and subsequently each tracing was coded and read in a "blinded" manner by two of us (15).

Statistics

Statistical comparisons before and 12 weeks after enalapril therapy were made using a paired student's t-test (16) with the exception of the echocardiographic data which were analyzed using Wilcoxon's sign ranking test.

RESULTS

All eight patients completed the trial and demonstrated satisfactory control of arterial pressure. Outpatient supine systolic and diastolic pressures fell from 148±6 mm Hg to 120±3 mm Hg ($p < 0.001$) and from 100±2 mm Hg to 83±2 mm Hg ($p < 0.01$), respectively. A small, but significant, decrease in outpatient supine heart rate also occurred (from 75±6 to 71±6 beats/min; $p < 0.01$). The doses of enalapril required were 5 mg, one patient; 10 mg, three patients; and 40 mg, four patients. Three of the four patients on the highest dose also received 50 mg hydrochlorothiazide per day.

Directly measured systolic and diastolic pressures fell (Fig. 1) ($p < 0.02$) and this was due to a reduction in total peripheral resistance (Fig. 2)($p < 0.01$); cardiac index (Fig. 2) and heart rate (Fig. 1) remained unchanged. Renal plasma flow rose in six patients. Renal vascular resistance fell in all patients (Fig. 3)($p < 0.001$). Plasma volume and other hemodynamic indices were not altered significantly (Table 1).

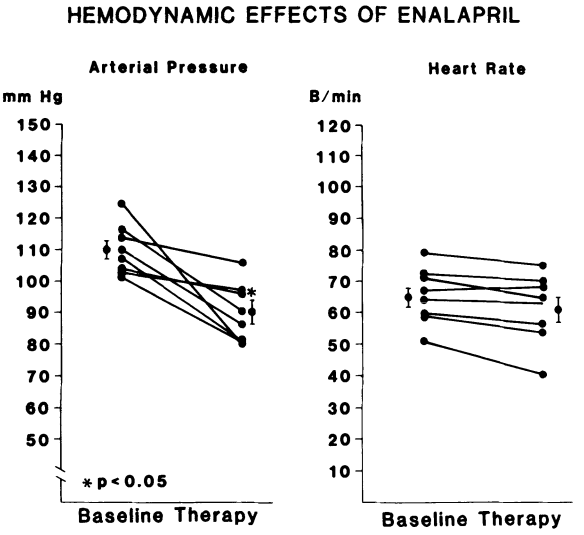

FIGURE 1. Alterations in systolic pressure, diastolic pressure, and heart rate induced by enalapril.

No difference was observed in the response to tilt following enalapril and no significant orthostatic hypotension was seen. The percent rise in arterial pressure during isometric exercise was similar before and during treatment although the height of the pressure rise was less with enalapril. No changes in Valsalva response were noted apart from a decrease in the absolute height of pressure during the overshoot.

TABLE 1. STROKE INDEX, EJECTION RATE AND INTRAVASCULAR VOLUME BEFORE AND AFTER ENALAPRIL

		Enalapril	
	Baseline	Week 12	p Value <
Stroke index ($ml/beat/M^2$)	42±2	50±4	N.S.
Left ventricular ejection rate index ($ml/sec/M^2$)	135±8	150±11	N.S.
Plasma volume (ml/cm)	16.9±2	16.9±2	N.S.
Total blood volume (ml)	4846±318	4803±387	N.S.

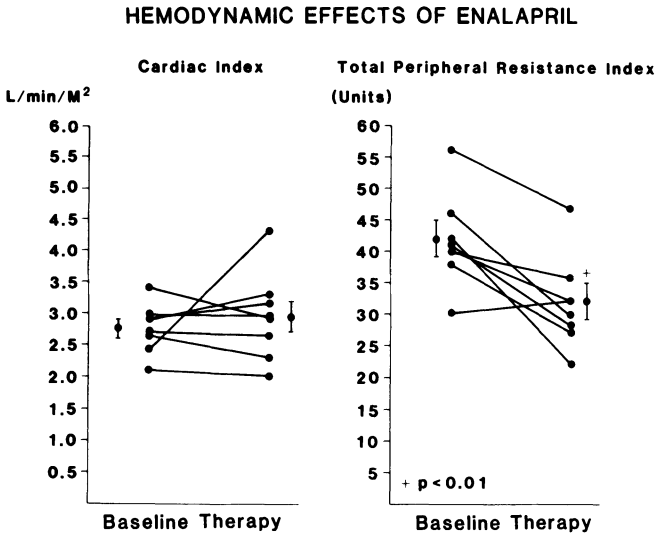

FIGURE 2. Alterations in cardiac index and total peripheral resistance induced by enalapril.

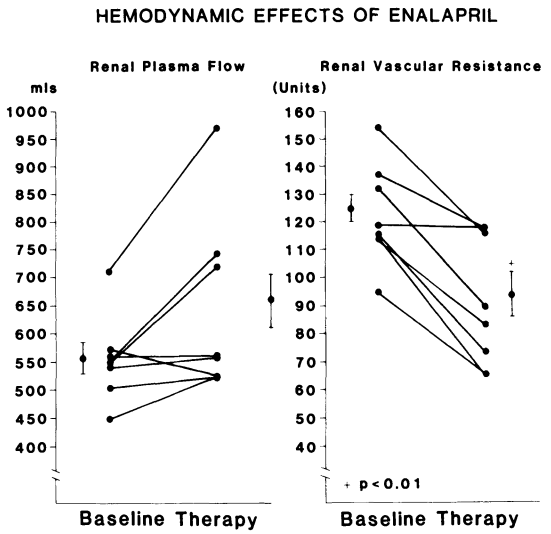

FIGURE 3 Alterations in renal plasma flow and renal vascular resistance induced by enalapril.

Left ventricular mass decreased in the six patients studied ($p < 0.05$; Table 2). This was due to both a reduction in volume and in wall thickness. Septal and posterior wall thicknesses both decreased (Table 2) though neither reached levels of statistical significance. The electrocardiographic voltages (Table 2) showed a highly significant reduction regardless of the precordial voltage combination used ($p < 0.001$). No alterations in the indices of left ventricular performance were determined (Table 2). Angiotensin converting enzyme levels fell in all seven patients in whom it was measured from a mean of 48±0.7(units) to undetectable levels.

TABLE 2. CARDIAC STRUCTURAL AND FUNCTIONAL ALTERATIONS INDUCED BY ENALAPRIL

Echocardiographic Indices	Baseline	Enalapril
Systolic dimension (cm)	3.31 ± 0.2	3.13 ± 0.16
Diastolic dimension (cm)	5.56 ± 0.35	5.0 ± 0.2*
Posterior wall thickness (mm)	11.2 ± 0.9	9.8 ± 0.4
Septal wall thickness (mm)	13.0 ± 1.4	11.1 ± 0.9
Left ventricular mass index (gm/M^2)	166 ± 29	117 ± 8*
Velocity of circumferential fiber shortening (circ/sec)	1.31 ± 0.06	1.19 ± 0.06
Fractional fiber shortening (%)	41 ± 3	38 ± 2
Electrocardiogram		
$SV_1 + RV_5$ (mm)	28 ± 2.3	24.5 ± 2.2+
Deepest S + tallest R (mm) in precordial leads	35.5 ± 2.3	29.5 ± 1.7+

Mean ± SEM; *$p < 0.05$; +$p < 0.001$

The systemic hemodynamic responses of the three patients who received a diuretic in addition to enalapril were similar to those who received enalapril. Renal vascular resistance was lowered to a similar degree although the consistent rise in renal plasma flow seen with enalapril alone was not observed in the patients

receiving both drugs. While a slight increase in plasma volume was seen during therapy in the patients receiving enalapril alone, baseline plasma volume was higher as would be expected and fell with therapy in the three patients who received hydrochlorothiazide in addition.

DISCUSSION

The results of the study confirm that enalapril is an effective antihypertensive agent: all patients demonstrated a significant and sustained fall in outpatient systolic and diastolic pressures that was confirmed by intra-arterial pressure measurements. Since the patients all had essential hypertension, it is clear that the use of this agent need not be confined to angiotensin-mediated hypertension. The drug was well tolerated, and no adverse signs or symptoms were observed. The previously described adverse effects of captopril (namely proteinuria, dysgeusia and leukopenia) thought to be related to the presence of sulfhydryl group were not seen with enalapril.

The fall in arterial pressure was clearly related to a reduction in total peripheral resistance while heart rate and cardiac output remained unchanged. There are several possible explanations for the failure of heart rate to increase in response to the pressure fall. First, it could be due to decreased adrenergic outflow as a result of inhibition of angiotensin II production with less angiotension available for central or peripheral neuronal interaction (17,18). Another, though less likely, explanation is a general modulating effect of enalapril on cardiovascular reflexive responses. Against this possibility is the fact that the other reflex responses were not qualitatively modified. A third explanation relates to the observation that angiotensin II previously has been shown to have a positive chronotrophic (19,20) and inotropic (21) effect upon the myocardium, and inhibition of this may have contributed to the failure of heart rate to rise in a reflex manner.

Renal plasma flow increased in six patients. Renal vascular resistance fell after prolonged administration of enalapril, a

finding also recently reported by others (22). The improved flow suggests that regional changes in flow are not wholly dependent on systemic flow. Furthermore, since an increase in renal vascular resistance may be a fundamental pathophysiological abnormality in patients with essential hypertension (23), reversing that abnormality may be of great therapeutic importance.

Left ventricular mass was reduced in all six patients in whom it could be measured reproducibly. This resulted from a fall in both systolic and diastolic dimensions and in wall thickness. This supports the findings of regression of left ventricular mass by converting enzyme inhibition in experimental animal studies (24) and is the first report of reduction in left ventricular mass by enalapril. The mechanism of the regression in cardiac mass is still speculative. It could result from the reduced ventricular afterload that was seen in all patients; and this factor is clearly important in the development and progression of ventricular hypertrophy (10). Alternatively, it may have been due to the inhibition of angiotensin II production that is known to increase myocardial protein synthesis (25). A third explanation is that it may have been due to a reduction in angiotensin-mediated adrenergic outflow. Reduced cardiac adrenergic input is a feature of several agents previously noted to regress hypertrophy in animals (26) and in man (27). The highly significant fall in electrocardiographic voltages lends some support to our echocardiographic findings, although these voltage changes could also be explained on the basis of the reduced arterial pressure (28).

In conclusion, enalapril is an effective antihypertensive agent when given alone or in combination with a diuretic. The fall in arterial pressure is mediated through a reduction in total peripheral resistance and a maintenance of systemic flow. Two further important characteristics of the agent are the significant fall in renal vascular resistance and the reduction in left ventricular mass.

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19. ANTIHYPERTENSIVE TREATMENT IN RENAL FAILURE

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ABSTRACT

Renal failure may alter the disposition of antihypertensive drugs. The half-life of methyldopa, guanethidine, clonidine captopril and the lipid-insoluble beta blockers may be prolonged. However, the best guide to adequate dosage is the blood pressure response. Furosemide has definite advantages over current thiazid diuretics. Potassium-sparing agents may cause hyperkalemia and should be avoided.

The effects of antihypertensive drugs on renal function vary with time. The initial fall in GFR, responsible for a transient rise in serum creatinine, is followed by a progressive readjustment towards pretreatment values. After years of sustained treatment the drug-specific effects have become negligible, and effective control of hypertension often produces stabilization or improvement of renal function.

Drug combinations including furosemide, a beta blocker and a vasodilator, are generally adequate for long-term treatment. For initiating therapy preference may be given to agents which do not depress markedly GFR. In emergency situations any potent drug may be given. If necessary, transient uremia should be treated by hemodialysis.

INTRODUCTION

The treatment of hypertension in renal-insufficient patients raises two main problems. The first is that renal failure may alter the disposition of drugs which are normally excreted by the kidney. Accumulation of antihypertensive compounds could enhance their effectiveness and result in an excessive fall in blood pressure. This would call for a reduction of the doses.

The second problem is that the acute reduction of blood pressure is usually accompanied by a decrease in glomerular filtration rate (GFR). Whereas a 33% decrease from 120 to 80 ml/min has no consequences, a drop from 12 to 8 ml/min may raise serum creatinine from 8 to 12 mg/dl and make hemodialysis necessary. Fortunately, this initial response to the fall in mean blood pressure (mBP) is followed by a compensatory readjustment of the renal vascular tone. GFR tends to rise again after a few weeks, despite maintenance of the antihypertensive effect (1).

In this presentation we shall first review the pharmacokinetics of antihypertensive drugs and their effects on renal function. A second part shall serve as guidelines for the antihypertensive treatment of renal-insufficient patients.

DISPOSITION AND DOSAGE OF ANTIHYPERTENSIVE DRUGS IN RENAL FAILURE

Whereas pharmacokinetics of most antihypertensive drugs have been well studied in subjects with normal kidneys, only fragmentary information is available concerning their disposition in renal failure. It should also be emphasized that the plasma half-life not always reflects tissue concentrations and that the biological half-life may exceed the plasma half-life. Metabolites may accumulate in the body, even when the half-life of the parent drug is not prolonged, and may display toxic effects or retain antihypertensive properties. In addition, bioavailability, enteral resorption and protein binding may be altered in renal failure. Finally, the plasma concentrations which must be achieved in order to decrease the blood pressure vary greatly among individual patients. For these reasons, it is a better policy to adjust the doses to the patient's requirements rather than according to pharmacokinetic considerations. The blood pressure is the best guide to adequate dosage.

Diuretics

Thiazide and furosemide are eliminated in part by the renal route (2, 3). Their half-life is prolonged in renal failure, and normal doses may result in elevated plasma concentrations (2). However, provided no toxic reaction occurs, even

higher plasma concentrations are needed in patients with impaired renal function in order to achieve a saluretic and antihypertensive effect. Thiazide diuretics have a flat dose-response curve (4), and increasing their plasma concentration is of little advantage. In contrast, loop diuretics have a steep dose-response curve and are still effective in renal failure (5). Therefore, patients with reduced renal function usually require higher doses of furosemide than subjects with normal GFR.

Ethacrynic acid, spironolactone and triamterene are excreted predominantly by the liver (6). However, potassium-sparing diuretics should not be administered in renal failure, since they may produce hyperkalemia, and ethacrynic acid has been reported to cause ototoxicity (7).

Beta-blockers

There are large differences in the bioavailability and disposition of beta-blockers (8). The lipid-soluble compounds such as propranolol, oxprenolol, metoprolol, alprenolol, acebutolol and timolol are largely metabolized by the liver. Only inactive metabolites are normally excreted in the urine. Patients with renal failure do not require adjustment of the dosage (8, 9, 10). The same holds true for labetalol, a combined alpha- and beta-blocking agent (11) and also for pindolol (12), despite a 30% excretion by the normal kidney.

In contrast, the lipid-insoluble compounds atenolol, sotalol and nadolol are excreted mainly by the kidney. Their already long plasma half-life is prolonged in renal failure, and in these cases reduced doses may suffice to control hypertension (10, 13).

Other sympathicolytic drugs

Patients with impaired renal function may show increased sensitivity to alpha-methyldopa and guanethidine (14). In the case of alpha-methyldopa, the active 3-O-sulfate conjugate accumulates in the serum (15). Therefore, reduction of the dosage is advisable. The available data concerning guanethidine are conflicting (16). Renal failure produces an accumulation

of metabolites, but the variability of both enteral resorption and blood pressure response is more important. The half-life of clonidine may also be prolonged in renal falure (17). The doses should be reduced when side effects occur.

Vasodilating drugs

Hydralazine, prazosin, verapamil, minoxidil and sodium nitroprusside are largely metabolized by the liver and do not accumulate as active compounds in uremic patients (18-21). Nevertheless, in the case of prolonged nitroprusside infusions, there may be a retention of the toxic metabolite thiocyanate, which is normally excreted by the kidney (22). In contrast, captopril is eliminated to a significant extent by the kidney (23), and it has been observed that side effects occur mainly in patients with impaired renal function receiving high doses (24). Thus, the maximum dosage should not exceed 200-300 mg a day.

Diazoxide is excreted in part by the kidney, but since it is administered almost exclusively as a single bolus injection, a prolonged half-life has no practical consequence. However, decreased plasma protein binding may enhance its short-term effectiveness in uremia (25).

EFFECTS OF ANTIHYPERTENSIVE DRUGS ON RENAL FUNCTION

I. Short-term effects (Table 1)

Antihypertensive agents usually decrease renal resistance. In most instances the decrease in resistance only partially compensates for the fall in mBP, so that the effective renal plasma flow (ERPF) measured by the PAH clearance (C_{PAH}) decreases slightly. In contrast, some vasodilators, such as captopril and hydralazine, may actually increase ERPF (26).

Changes in GFR are determined largely by those in ERPF and mBP. We have analyzed the pooled data from acute experiments performed in our department with 7 different drugs (27), supplemented with data on alpha-methyldopa published by Onesti et al (26). This analysis reveals that the mean changes in GFR can be predicted from the changes in mBP and C_{PAH}, according to the equation:

$$GFR = 1.7 + 0.475 \ mBP + 0.47 \ C_{PAH} \qquad (1)$$

Table 1. Changes in mean blood pressure, PAH-clearance and glomerular filtration rate induced in hypertensive patients by a single dose of various antihypertensive agents.

Drug	Number of clearance periods	Hemodynamic changes Percent of control (mean ± SE) mBP	C_{PAH}	GFR
Alpha-Methyldopa*	20	72.1 ± 11.7	97.9 ± 18.1	90.0 ± 16.7
Clonidine	18	77.4 ± 11.9	93.8 ± 14.5	88.4 ± 14.5
Guanethidine	24	92.3 ± 6.8	87.2 ± 9.7	90.5 ± 10.3
Chlorisondamine	13	78.9 ± 12.2	85.9 ± 14.5	70.3 ± 11.8
Hydralazine	40	87.7 ± 10.9	120.8 ± 21.4	101.5 ± 15.2
Endralazine	19	82.8 ± 14.0	94.6 ± 40.3	66.6 ± 23.9
Pyrogen	32	76.8 ± 15.5	115.3 ± 28.9	96.7 ± 17.3
Phenotolamine	16	89.0 ± 8.3	93.6 ± 21.6	85.2 ± 19.5
All data	182	82.7 ± 13.4	102.6 ± 26.4	89.3 ± 19.6

Correlations (all data)

C_{PAH} vs mBP NS

GFR vs mBP $p < 0.001$

GFR vs C_{PAH} $p < 0.001$

$GFR = 1.7 + 0.475\ mBP + 0.47\ C_{PAH}$

* Data of Onesti et al. (27)

GFR correlates significantly ($p < 0.001$) with both mBP and C_{PAH}. The average changes produced by the 8 drugs listed in Table 1 consist of a marked decrease in mBP, a small increase in ERPF and a moderate decrease in GFR. Thus, changes in GFR are intermediate between those in mBP and ERPF.

Admittedly, the data exhibit a large splay related to the variability of individual responses. In addition, endralazine and chlorisondamine depress GFR more than do other drugs, suggesting a direct effect on the flomerular ultrafiltration coefficient Kf or a relaxation of the efferent arteriolar tone. Nevertheless, equation (1) permits one to predict the average changes in GFR elicited by other drugs. In a series of 8 patients

the changes recorded after a few days of captopril therapy were mBP - 16.6 ± 8.5%, C_{PAH} + 2.7 ± 21.0% and GFR - 8.4 ± 27.4%. According to equation (1) the predicted fall in GFR would be -10.4%.

Unlike current thiazide diuretics, which reduce renal function, the loop diuretics often produce an increase in ERPF and GFR (5). The effect is more pronounced in patients with reduced GFR, a clinically important advantage (5).

The acute administration of most antihypertensive drugs also results in a reduction of the fractional excretion of water and sodium. However, some increase in water and salt output may occur when ERPF increases significantly (26).

II. Long-term effects after weeks or months of sustained treatment (Table 2)

Under sustained antihypertensive treatment GFR tends to increase again towards pretreatment values and to depend less on mBP than under short-term conditions. Accordingly, there is a significant correlation between GFR and ERPF, but not between these 2 variables and mBP. The mean values of the renal parameters depart only slightly from the pretreatment data, but there are some differences between individual drugs. When we consider together the magnitude of the blood pressure response and the pattern of renal changes, it would seem that captopril, minoxidil, nadolol, methyldopa, clonidine and perhaps endralazine were especially valuable compounds. However, methyldopa and clonidine may reduce renal function in erect position. The antihypertensive effect of endralazine tends to diminish with time. Captopril may reduce renal function when a nephrotic syndrome develops under therapy. Finally, there is a great individual variability of response to every drug, so that the renal changes in a given patient can hardly be predicted. Clinical evidence indicates that sustained antihypertensive treatment may produce fluid and salt retention, but we are not aware of comparative long-term balance studies.

Table 2. Changes in mean blood pressure and renal hemodynamics under sustained treatment with a single drug. Where no reference is given, experiments were performed in our laboratories.

Drug	No. of cases	Duration of therapy (days)	Changes (in percent of control) mBP	GFR	C_{PAH}
Captopril	5	180	88.7±6.3	110 ±37.3	112.2±12.7
Minoxidil (28)*	6	7	85.5	109 ±14	101.5±38.5
Endralazine	8	13	90.5±15.2	127 ±54.5	145.7±54.8
Hydralazine	10	28	95.2± 8.7	102.1±13.3	97.9± 6.9
Propranolol (29)*	7	35	82.0	93.1	100.3
Oxprenolol	7	14	93.4±11.5	95.3±13.3	108.7±15.0
Nadolol (29)*	7	35	84.4	100	118.1
Labetalol	9	40	89.3± 7.5	83.4±19.2	79 ±21.7
Methyldopa	5	177	74.4± 4.6	98 ±17.5	107.8±27.4
Clonidine (30)*	7	50	79.4±10.5	94 ± 8.2	114.4±17.2
Reserpine	10	28	97.2± 8.9	96.3±12.3	94.4±18.4
Chlorothiazide	10	28	90.2± 9.3	95.2±16.6	100 ±13.5
Guanethidine (31)*	12	14	84.5±11.5	93.5±18.4	91.7±16.1
Chlorisondamine	7	24	90.5± 9.2	95.7±30.5	102.3±18.4
Mecamylamine	10	28	93.9± 5.5	86.5±17.9	90.2±12.1
Mean values			87.9± 6.2	98.6±10.5	104.3±15.3

Correlations GFR vs C_{PAH} r = 0.82 $p < 0.001$
GFR vs mBP NS
$GFR = 9.9 + 0.311\ mBP + 0.588\ C_{PAH}$

*Reference numbers
**An additional case with captopril-induced nehprotic syndrome and consecutive deterioration of renal function is not included.

III. Long-term effects after several years

Even benign essential hypertension, if untreated, is accompanied by a slow, progressive impairment of renal function due to arteriolar sclerosis. Effective, long-term treatment may oppose this tendency (32,33) and even result in an actual increase in the clearance values (1, 33). The effects of therapy are also very conspicuous in malignant hypertension. In untreated patients there is a rapid decrease in GFR (-28.6% per year) and C_{PAH} (-36% per year) (33). Further impairment can be slowed down or arrested by effective antihypertensive treatment (33, 34).

This means that under any treatment extending over years the drug-specific effects on the kidney have become negligible. They are obscured by intrinsic changes in renal function related to the progression and, in favorable cases, to the reversibility of organic lesions.

GUIDELINES FOR TREATMENT

Since in essential hypertension previous deterioration of renal function may be arrested by antihypertensive treatment, all hypertensive patients, regardless of their level of renal function, need effective and even aggressive therapy. Even in primary renal disease, it is hoped that the development of superimposed arteriolar sclerosis or necrosis will be prevented by lowering the blood pressure. Thus, if renal failure is due to malignant essential hypertension, renal function may remain stabilized for years. In patients with primary parenchymatous nephropathy, the rate of functional deterioration will reflect the activity of the tissue lesions.

In patients with chronic renal failure, elevation of the blood pressure is determined in part by sodium (or volume) retention and activation of the renin-angiotensin system (35). Thus, a logical and often successful therapeutic approach is to combine diuretics with angiotensin inhibitors, such as captopril or certain beta-blockers. However, many patients need a three- or four-drug combination. There is no convincing evidence that they do better under certain regimens than under others. Thus, the choice of drugs remains largely empirical.

The application of stringent pharmacokinetic criteria in determining the adequate dosage of antihypertensive agents in renal failure is not always mandatory, provided the blood pressure is monitored carefully and the administered amounts are continuously adjusted to the patient's response. Nevertheless, we should remember that alpha-methyldopa, guanethidine, clonidine, captopril and the lipid-insoluble beta-blockers (or their metabolites) may accumulate and cause side effects not necessarily related to the drop in blood pressure (for instance, accumulation of thiocyanate under sodium nitroprusside therapy). It is also

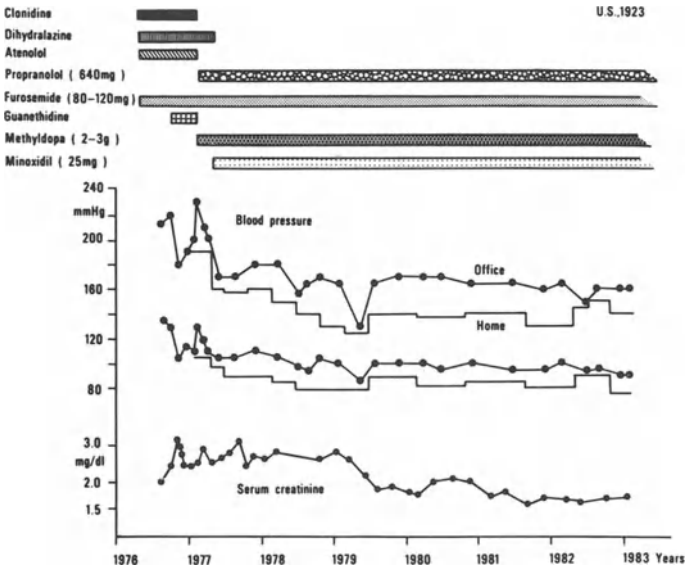

Figure 1. Slow decrease in serum creatinine under sustained antihypertensive treatment in a patient with severe essential hypertension. The drug combination includes propranolol.

very important to avoid potassium-sparing diuretics in order to prevent hyperkalemia. It has been claimed that long-term therapy with propranolol would produce deleterious effects on the kidney (36-38), but this is a controversial issue. In contrast, some investigators believe that minoxidil might be especially advantageous (39). More probably, any effective treatment may produce during the first few months a slight reduction of GFR but will eventually prove to be beneficial to the patient. Figure 1 illustrates the slow decrease in serum creatinine observed under long-term therapy with a drug combination including high doses of propranolol in a patient with essential hypertension.

Unfortunately, we may occasionally observe the late development of terminal renal failure in patients with previous malignant essential hypertension, in whom progression had been arrested for many years by therapy (Figure 2). The reason may be that the arteriolar necrosis accompanying malignant hypertension

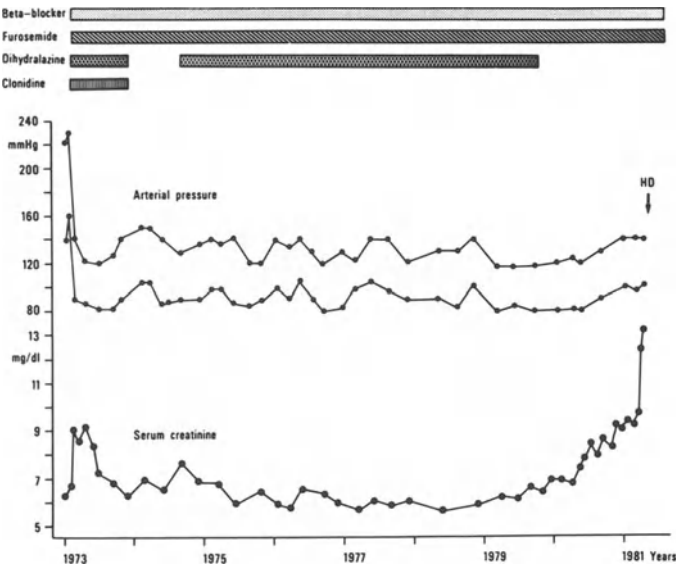

Figure 2. Unexpected terminal renal failure occurring after years of excellent blood pressure control and functional stabilization in a patient presenting initially with malignant essential hypertension.

leads to the formation of antibodies directed against the arteriolar wall and that an immune mechanism induces new vascular lesions (40). An increased T-lymphocyte reactivity against arterial antigen has been shown in certain cases (41).

One problem of long-term treatment in patients with reduced renal function is water and salt retention. Except for the diuretics, this has been observed with almost every antihypertensive drug, but patients receiving minoxidil are especially prone to develop extensive edema. In many subjects, only the combination of metolazone with furosemide is capable of overcoming the fluid retention.

Most hemodialysis patients also need some antihypertensive treatment, especially when their fluid balance cannot be controlled adequately between dialytic treatments. As long as residual diuresis can be increased by diuretics, it is probably advantageous to administer furosemide, 250-500 mg daily. Among the other antihypertensive drugs, preference should be given to

short-acting compounds, so that therapy can be discontinued at the time of dialysis and resumed as soon as the blood pressure lowering effect of fluid removal is wearing off.

The last point is how to initiate treatment, since during the first days of administration there may be a transient rise in serum creatinine, especially when a very high diastolic pressure falls rapidly. This rise may be alleviated by reducing the blood pressure more slowly, so as to attain normal values within a week or so. It is also advisable to choose drugs which do not produce a severe depression of GFR, such as furosemide, nadolol, hydralazine, captopril, nifedipine, or verapamil. However, in emergency situations, i.e., pulmonary edema or hypertensive encephalopathy, it is necessary to reduce the blood pressure within hours, using any drug combination, regardless of its effects on GFR. Under such circumstances the rapid control of blood pressure is more important than the level of serum creatinine. Should renal failure become critical, one should not hesitate to perform hemodialysis or peritoneal dialysis, until renal function begins to improve again.

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