CONVERTING ENZYME INHIBITORS AND THE KIDNEY

by

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INTRODUCTION

Recent advances in our understanding of the renin-angiotensin system (RAS) and its importance in regulation of renal function and body fluid composition in both normal and abnormal circumstances provided the impetus for this Medical Grand Rounds. A major contribution to our current understanding of the RAS in human physiology was sparked by the discovery and application of converting enzyme inhibitors (CEIs). Over the past 15 years the CEIs, especially the first orally active CEI, captopril, have proven to be extremely effective antihypertensive agents in common and uncommon causes of human hypertension. More recently, these agents have been effectively employed in the management of chronic congestive heart failure and are now being tested in humans with chronic renal insufficiency in hopes that they may effectively slow the progression to end stage renal disease. Thus, a spectrum of indications for these agents is evolving and the patient populations these drugs subserve is rapidly growing. Many diseases in which these agents are particularly useful are commonly managed by the general internist. This Grand Rounds will focus on the beneficial hemodynamic effects of CEIs in several commonly encountered clinical disorders wherein the kidney is directly or indirectly involved in the pathogenesis up-to-date review of the clinical utilities of these agents with an emphasis on These will include chronic renal insufficiency with hypertension, congestive heart failure, diabetes mellitus and renovascular hypertension. Hopefully this review will provide the clinician an up-to-date analysis of the clinical use of CEIs in these situations and allow one to make intelligent decisions about how and when to employ these agents safely.

HISTORICAL ASPECTS

Renin-Angiotensin System -

The concept that an anti-renin system is central to the pathogenesis of hypertension stemmed from the classic experiments of Goldblatt in which chronic hypertension was induced in dogs by: 1) clamping one renal artery in association with contralateral nephrectomy, or 2) clamping both renal arteries (1). It was established that hypertension could not be abolished by complete sympathectomy, spinal cord destruction or transplantation of the clamped denervated kidney in the neck but could be abolished by bilateral renal vein ligation (2). The subsequent search for a humoral mediator was based on the earlier findings of Tigestedt and Bergmann (3) who had shown that extracts of normal kidney injected into the circulation of normal animals induced acute hypertension. Thus, in 1939 Helmer and Page (4) found that this extract (later proven to be renin) was highly active when injected into intact animals but produced no vasoconstriction when perfused through dogtail or rabbit ear in vitro. Kohlstaedt, Page and Helmer (5) then found that this substances pressor activity could be reconstituted by a plasma protein fraction which they designated renin activator. The subsequent discovery of the pressor substance, then termed angiotensin by Page and Helmer (6) and hypertensin by Braun-Menendez et al. (7) in 1939 ushered in an era of intensive investigation into the humoral system we now call the renin-angiotension system. After the discovery that angiotensin was present in the plasma of animals with experimental hypertension by Skeggs et al. (8), isolation and identification of angiotensin I and angtiotensin II was carried out by Skeggs et al. (9). Soon thereafter it was

determined that a chloride activated enzyme was responsible for cleaving two amino acids from angiotensin I to form angiotensin II: the converting enzyme (10). Although the pressor functions of AII had been investigated for many years, it was not until Davis et al. (11) postulated that a humoral factor was responsible for the release of aldosterone that Laragh et al. (12) and subsequently later Biron et al. (13) showed that the humoral factor was indeed angiotensin II. These and other subsequent studies laid the groundwork to further characterize the pathogenetic importance of the renin-angiotensin system in human hypertension and develop strategies designed to control blood pressure by inhibitors of the system.

Discovery of Converting Enzyme Inhibitors -

The development of the CEIs evolved from the seminal observation of Ferreira in 1964 (14), who partially purified a bradykinin-potentiating factor (BPF) from the venom of the South African pit viper Bothrops Jararaca. Ferreira demonstrated that this bradykinin-potentiating factor (BPF) enhanced bradykinin-induced hypotension in cats in vivo and bradykinin-induced contraction of guinea pig ileum in vitro. His preliminary work suggested that the BPF was a polypeptide. In subsequent work Ferreira (15) and Ferreira and Vane (16) demonstrated that BPF action correlated with an inhibition of kinin-destroying enzymes. In 1968, Bakhle utilizing cell-free extracts from dog lung demonstrated that BPF inhibited pulmonary angiotensin converting enyzme in vitro (17). Taken together with the previous studies of Ng and Vane (18,19) showing that the lung was the predominant circulation responsible for conversion of angiotensin I to angiotensin II, in 1970, Ferreira and Vane reported that BPF was capable of inhibiting bradykinin metabolism and angiotensin I converting enzymes in vivo (20). Then in 1971 Ondetti et al. (21) successfully purified BPF and were able to synthesize several polypeptides derived from BPF in active forms. One of these compounds, termed teprotide, was subsequently tested in humans with high-renin essential hypertension and was shown to be a potent vasodepressor. After several years of experimental studies demonstrating the blood pressure lowering effects of teprotide, in 1977, Ondetti and Cushman (22) reported the synthesis and activity of the first orally active CEI: captopril. More recently, Patchett et al. (23) synthesized a non-sulfhydryl converting enzyme inhibitor, enalapril. These two agents are the most widely used converting enzyme inhibitors currently available.

PHYSIOLOGY OF THE RENIN-ANGIOTENSIN SYSTEM

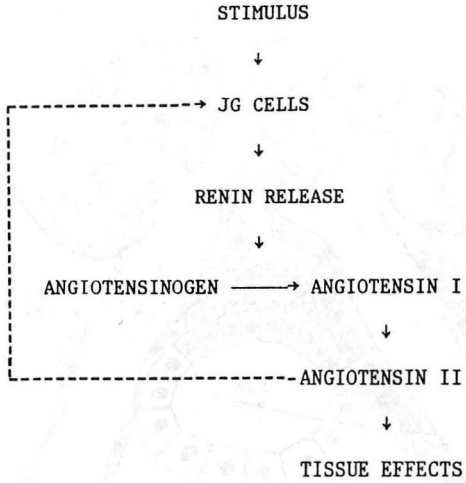
General Scheme -

The renin-angiotensin system is extremely important in the regulation of blood pressure and body fluid and electrolyte composition. The general scheme for this system is shown below in figure 1. As shown in the figure, renin is released from the JG cells into the systemic circulation where it enzymatically generates angiotensin I from its precursor angiotensinogen. Angiotensin I is cleaved by converting enzyme in the lung to form angiotensin II. Angiotensin II is the main effector of this system since it acts on many tissues including blood vessels, the adrenal gland, brain, renal tubule and other tissues. Feedback regulation of renin secretion is mediated in part by a direct effect of angiotensin II on the JG cells. In addition, angiotensin II mediated alterations in renal perfusion pressure may also cause a feedback reduction in renin release (see below). In general, an increase in renin release can be equated with an increase in

angiotensin II production, therefore, high renin states are usually accompanied by high angiotensin II states.

Figure 1

RENIN-ANGIOTENSIN SYSTEM OVERVIEW



Anatomy of the Juxtaglomerular Apparatus -

As shown in figure 2, in the wall of the afferent arteriole immediately proximal to the glomerular capillary are the specialized myoepithelial cells or juxtaglomerular cells which are responsible for synthesis and secretion of renin. Adjacent to this region of the afferent arteriole is a button of tubular epithelial cells known as the macula densa which are located in the transition zone between the early portion of the distal tubule and the cortical thick ascending limb of the Henle's loop. The macula densa cells have a polarity opposite that of cortical thick limb and distal tubules epithelial cells. The reversed polarity is thought to be important in their specialized function. The apposition of the macula densa to the afferent arteriole is intruded on by the interdigitation of cellular elements contiguous with the glomerular mesangium. This unique morphological arrangement is felt to be important in the regulation of renin secretion and in the feedback regulation of glomerular filtration.

Renin Physiology

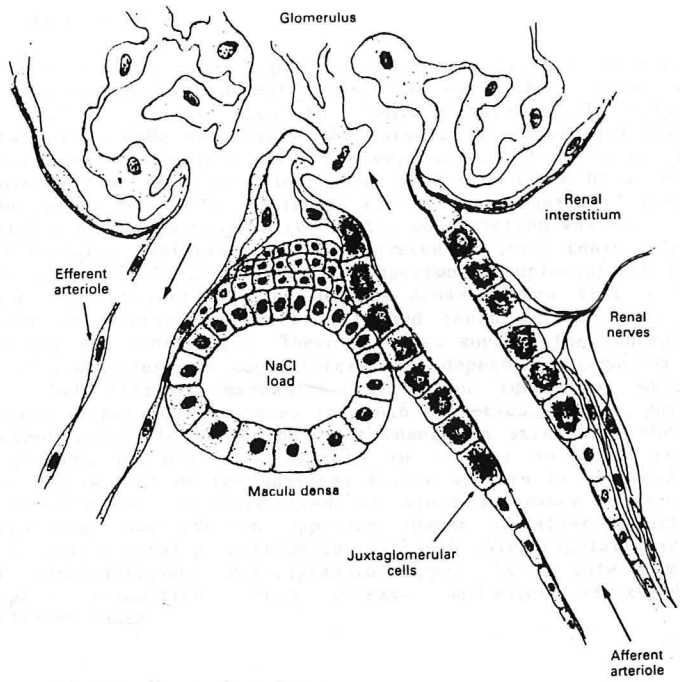
A. Synthesis and Secretion -

Renin is a highly specific aspartyl protease glycoprotein that mediates the first and rate limiting step in the generation of angiotensin II. The juxta-

glomerular cells (or JG cells) contain large amounts of intracellular granules which store renin. Renin containing granules have also been found in the afferent arteriole upstream from the juxtaglomerular apparatus, in the media of

Figure 2

Anatomy of the Juxtaglomerular Apparatus



From Reference 167.

interlobular arteries and in efferent arterioles. Renin is synthesized in the rough endoplasmic reticulum and packaged in golgi apparatus. Renin containing "proto-renin" granules are elaborated from the golgi apparatus in the formation of these storage granules. Renin secretion is thought to occur by exocytosis: the renin granules fuse with the plasma membrane and renin is extruded into the extracellular space. It appears that renin is synthesized in a prepro-form and then converted to pro-renin and subsequently to active renin. Cells can release either pro-renin or active renin into the extracellular space, however, the factor(s) regulating the secretion ratio of these two forms and the enzymatic machinery responsible for the conversion of pro-renin to renin have not yet been elucidated.

B. Physiology of Renal Renin Release -

Physiologic control of renin release involves a complex interaction between neural, humoral, baroreceptor and ionic stimuli. There are at least five basic mechanisms that are important in renal renin release including 1) intrarenal baroreceptor; 2) the amount of sodium (or chloride) reaching the macula densa; 3) the sympathetic nervous system; 4) humoral mediators including prostaglandins and angiotensin II; and 5) certain electrolytes including K^{+} and Ca^{++} (24).

1. Baroreceptor -

Elevated renal perfusion pressure decreases renin release whereas decreased renal perfusion pressure increases renin release. The stimulus-response curve of pressure and renin release shows that renin release is relatively unresponsive to the inital 10-20 mmHg reduction from normal. Threshold pressure is 80-90 mmHg below which renin release follows a steep curve. Tobian et al. first postulated that renin release from the kidney could be stimulated by a reduction in renal perfusion pressure (25). Skinner et al. subsequently showed that renal hypotension produced by progressive aortic constriction was associated with a fall in renal vascular resistance and an increase in renal renin release (26). Then Blaine et al., (27,28) in a series of experiments employing non-filtering kidneys to remove any effects of the macula densa showed that either hemorrhagic hypotension or aortic constriction evoked renin release even after bilateral adrenalectomy and denervation. These findings support the concept that a fall in renal perfusion pressure constitutes an independent mechanism of renal renin release. Two possible mechanism have been identified which may mediate baroreceptor associated increases in renin secretion. First, physical changes in the afferent arteriole perceived as a change in stretch of the presumed sensor site have been postulated to result in changes in renin release. The most important determinant of the physical factor appears to be intraluminal pressure or the transluminal pressure gradient since increases or decreases in these parameters can supercede an opposing change in afferent arteriolar radius. Second, increased renal prostaglandin synthesis which regularly accompanies states of renal hypoperfusion. Prostaglandins appear to mediate a major portion of baroreceptor stimulated renin release mechanism especially within the autoregulatory range.

2. Autonomic Nervous System -

The juxtaglomerular cells are innervated directly by non-myelinated sympathetic afferents (29). Barajas et al. have shown that noradrenergic fiber terminals are separated from granular JG cells by 1000-2000 A with an intervening basement membrane (30). Direct stimulation of renal nerves causes a marked increase in renin release which is not blocked by papaverine or ureteral occlusion (31). Reflex stimulation of sympathetic afferents by central and cardiopulmonary receptors may also regulate renin release. These effects appear to be primarily related to β-adrenergic mediated stimuli. In addition, α_2 receptor stimuli have been reported to modulate renin release under some circumstances. Catecholamines including nonepinephrine and epinephrine also directly stimulate renin release from the JG cells independent of renal vasoconstriction or renal nerve activity (32).

3. Macula Densa

Based on the unique anatomical relationship between the macula densa and the afferent arteriole and glomerulus it has long been suspended that a relationship exists between tubular factors and glomerular filtration (33). It is now well appreciated that alterations in the ionic composition of fluid in the macula densa can modulate renin release. It has been postulated that an increase in luminal sodium (or chloride or osmolality) concentration or delivery is associated with an increase in renin secretion (i.e. renin release is universely related to tubular soidum load). The release of renin by this mechanism may be mediated by renal postaglandins consistent with the observations made during periods of sodium depletion and sodium loading (34).

4. Humoral agents

It is well recognized that angiotensin II has a direct negative feedback effect on the JG cells to reduce renin release. Specific localization of AII to these cells have been shown by immunohistochemical techniques. Angiotensin II inhibition of renin release is dependent upon extracellular calcium and is probably mediated by causing an increase in cell Ca^{++} which in turn inhibits degranulation of the cell. In contrast, prostaglandins including I_2 and E_2 directly stimulate renin release from JG cells by increasing intracellular cyclic AMP. Serotonin has also been shown to stimulate renin release. Adenosine suppresses renin release.

5. Calcium

Elevated levels of calcium in the renal circulation as well as in vitro appear to inhibit renin release from the kidney. In contrast, a minimun level of calcium may be necessary for basal renin secretion. Thus, prolonged calcium depletion may prevent renin release induced by various stimuli including catecholamines. Calcium appears to have direct effects on JG cells in vitro and perhaps blocks catecholamine-mediated renin release by increasing intracellular calcium and hyperpolarizing the JG cell membrane. Although calcium has direct effects in vitro, in vivo elevated calcium may have indirect effects on renin release. For example, increased renal plasma calcium concentration evokes an increase in renal vasodilator prostaglandins which can in turn increase renin release. Thus, calcium may have opposing effects on renin release depending upon the extent to which its direct and indirect effects are operative in vivo.

6. Potassium

Numerous studies have shown that hyperkalemia increases renin release in experimental animals in vivo. Conversely, hypokalemia is associated with increase renin and angiotensin II levels. It should be noted, however, that perturbations in potassium balance are also associated with alterations in renal hemodynamics and tubular sodium transport changes which may in turn affect renin release.

C. Renin-Sodium Interactions -

The most physiologically important and clinically relevant regulator of renal renin release and thereby the synthesis of angiotensin II is the state of the

"effective arterial blood volume". "Effective arterial blood volume" may be conceptualized as the relative filling of the arterial tree that maintains renal perfusion pressure within normal limits. Numerous factors are important in determining the state of the effective arterial volume including the blood volume itself, the cardiac output, distribution of arterial blood flow, the autonomic nervous system and various humoral substances (e.g. angiotensin II, prostaglandins). Dietary sodium intake plays a pivotal role in renin release by altering effective arterial volume. For example, when dietary sodium is markedly increased effective arterial blood volume tends to increase causing a reduction in renal renin release and a reduction in circulating angiotensin II and aldosterone levels. Conversely, when dietary sodium is severely restricted effective arterial blood volume decreases resulting in an increase in renal renin release. Changes in renin secretion brought about by alterations in effective arterial volume may be mediated by a macula densa mechanism (when NaCl delivery to the MD is decreased, increased renin secretion by the JG cells takes place) by increased β-adrenergic reflexes and by the baroreceptor mechanism. The renin response to these alterations in dietary sodium intake provides a feedback loop that tends to preserve a "normal" effective arterial blood volume. Thus, the renin-angiotensin system plays a critical role in volume homeostasis particularly under conditions of severely reduced effective arterial blood volume such as in hypotensive states. Activation of the system results in increased angiotensin II which buffers the fall in blood pressure. Figure 3 illustrates the relationship between renal renin release and effective arterial blood volume at three different levels of sodium intake.

The relationship between dietary sodium intake and the status of the renin angiotensin system in humans has been studied in detail by Laragh et al. (35). In normal subjects on diets of varing sodium intake they measured plasma renin activity after sodium balance was achieved. Under these conditions, the urinary sodium excretion rate is equal to the net dietary sodium load. A low dietary sodium intake corresponds to reduced EABV and a high dietary sodium intake vice versa. As shown in figure 4, a curvilinear inverse relationship exists between dietary sodium intake and plasma renin activity. At high sodium intakes, plasma renin activity is low, whereas at low dietary sodium intakes, plasma renin activity is very high. These renin-sodium interactions accord with studies demonstrating that alterations in sodium intake are paralleled by morphologic changes in the JG apparatus. For example, a low sodium diet in a pre-renal state (e.g. cirrhosis) is associated with enlargement of the JG cells. On the other hand, JG cells become less conspicious after sodium loading. Thus, there exists anatomical correlate to the physiologic expression of altered renin release and renin activity. These relationships must be kept in mind when discussing disease states involving the renin angiotensin system, and particularly when assessing the impact of angiotensin converting inhibitors.

D. Importance of Angiotensin II in Regulation of Blood Pressure and Volume Status -

As depicted in figure 5, angiotensin II has direct effects on multiple organ systems involved in blood pressure and volume regulation. Two major biologic effects of angiotensin II with respect to its role in blood pressure and volume regulation have been appreciated for many years: first, angiotensin II is a very potent direct vasocontrictor in peripheral vascular beds thereby increasing peripheral resistance. In addition to its direct effect on vascular tone, angiotensin II also acts indirectly by enhancing CNS sympathetic outflow and by potentiating sympathetic activity at peripheral neuroeffector junctions (36,37).

EFFECT OF DIETARY SODIUM ON RENAL RENIN RELEASE AND ANGIOTENSIN II PRODUCTION

NORMAL DIETARY SODIUM

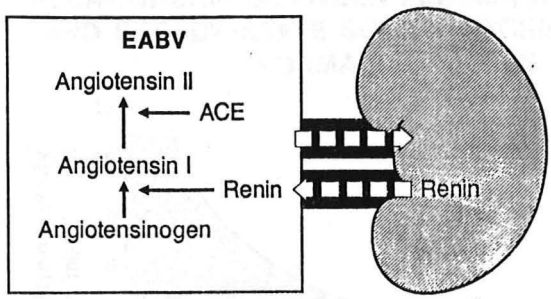


Figure 3a

DIETARY SODIUM EXCESS

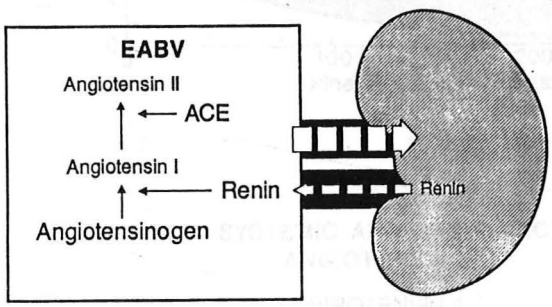


Figure 3b

DIETARY SODIUM RESTRICTION

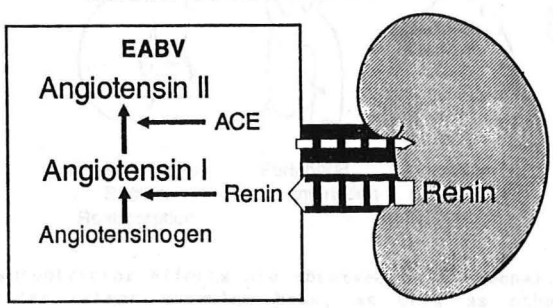
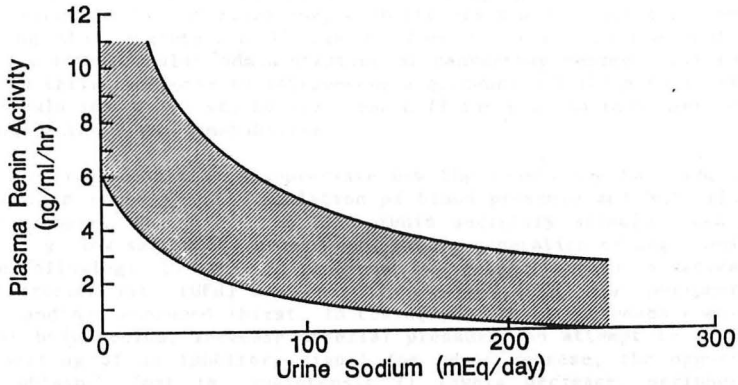


Figure 3c

Figure 4

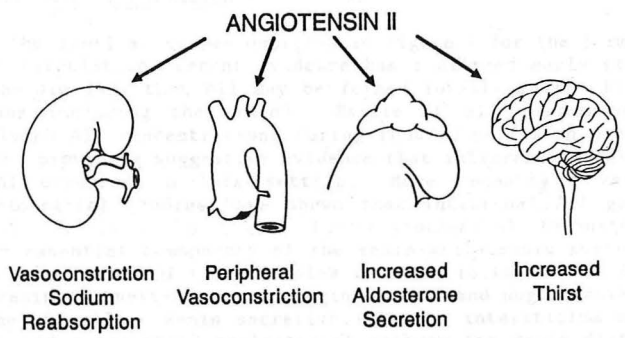
RELATIONSHIP BETWEEN PLASMA RENIN ACTIVITY AND STEADY-STATE SODIUM EXCRETION RATE IN NORMAL SUBJECTS



Adapted from Reference 35.

Figure 5

RENAL SYSTEMIC AND CNS EFFECTS OF ANGIOTENSIN II



These vasocontrictor effects are observed in the renal, splanchnic, cerebral and to a lesser extent muscular beds, as well as other circulations. Second, angiotensin II plays an important role in modulating renal sodium reabsorption by at least three mechanisms. First, angiotensin II is a potent aldosterone secretagogue, directly stimulating aldosterone release from the adrenal zona glomerulosa. By increasing aldosterone secretion AII can indirectly enhance

sodium reabsorption in the distal nephron. Second, recent evidence accumulated from several studies indicates that angiotensin II directly stimulates proximal tubular sodium reabsorption (38,39). Third, AII decreases glomerular filtration rate and renal blood flow in a manner that results in an increase in filtration fraction which in turn (vide infra) enhances proximal sodium absorption.

A more recently and less well appreciated effect of angiotensin II is its ability to stimulate thirst (40). Recent studies employing immunocytochemistry have detected the presence of converting enzyme in the brain and evidence has been accumulated showing that angiotensin II can be formed locally in the rostral pontine region. Intraventricular administration of converting enzyme inhibitors blocks the enhanced thrist response to intravenous angiotension I infusion in rats (41,42). Thus, regulation of thirst, by angiotensin II may play an important role in clinical derangements of water metabolism.

Taken together one can begin to appreciate how the renal, systemic and CNS effects of AII act in concert in a regulation of blood pressure and body fluid composition. For example, when subjected to a renin secretory stimulus such as volume depletion (e.g. low salt diet, hemorrhage, etc.), generation of angiotensin II results in the following: 1) enhanced renal sodium reabsorption 2) a decrease in glomerular filtration rate (GFR) and renal blood flow (RBF), 3) peripheral vasoconstriction, and 4) enhanced thirst. In consequence these phenomena combine to conserve total body sodium, increase arterial pressure and attempt to expand volume. In the setting of an inhbitory signal for renin release, the opposite situation would obtain. That is, angiotensin II levels decrease, peripheral resistance falls, GFR and RBF increase, renal sodium reabsorption decreases and hypodysia occurs. This sequence of events engenders fluid and electrolyte excretion and lowering of the blood pressure. Thus, the renin angiotensin system plays homeostatic role in day-to-day regulation of volume and blood pressure regulation.

E. Intrarenal Angiotensin II Formation -

In addition to the familiar scheme depicted in figure 1 for the formation of AII in the systemic circulation, recent evidence has confirmed early studies by Bailie, Rector and Seldin (43) that AII may be formed locally in the kidney (as well as other organs including the brain). Bailie et al. documented marked increases in renal lymph AII concentrations during reduced perfusion pressure in anesthelized dogs thus providing suggestive evidence that intrarenal generation of AII from infused AI occurred in this setting. More recently a variety of anatomical and physiological studies have shown that intrarenal AII generation takes place in vivo and in vitro (44). Immunocytochemical techniques have localized all of the essential components of the renin-angiotensin system within the kidney (45). A compliation of these studies is shown in figure 6. As can be seen, angiotensin, renin, converting enzyme angiotensin I and angiotensin II have been detected in the JG cells. Renin secretion into the interstitium may occur with various stimuli and a potential periarterial pathway for renin distribution in the kidney has recently been identified by Kriz (46). In addition, it has been estimated from in vivo studies that approximately 20% of circulating AI is converted to AII by the kidney. Furthermore, numerous physiological studies have raised the intriguing possibility that locally formed angiotensin II may be important in regulation of renal function. In this regard in a recent study Ingelfinger et al. furnished further evidence that intrarenal angiotensin forma-

tion may be an important physiologic regulator of local vascular and tubular function pathway (47). They found that rat renal cortical and medullary angiotensinogen mRNA synthesis is modulated by extremes of dietary sodium intake suggesting that locally formed angiotensin II is regulated by dietary means through an as yet unidentified mechanism. Although these studies are of great interest at the present time the importance and precise role of intrarenal AII formation in normal or pathophysiological states will require further investigation.

In summary, the renin-angiotensin system acts as a homeostatic mechanism for regulating arterial blood pressure and fluid and electrolyte balance. Angiotensin II is formed in the circulation as well as locally in the kidney and has effects on a wide variety of tissues. Let us now look more closely at the effects of this important hormonal system on the kidney.

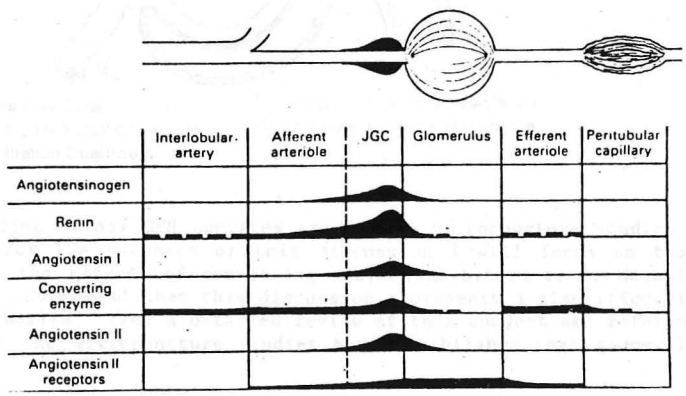
ANGIOTENSIN II AND RENAL HEMODYNAMICS

A. Renal Blood Flow -

Angiotensin II plays a major role in regulation of renal blood flow (RBF) and glomerular filtration rate (GFR) under normal circumstances and in various disease states. In experimental animals, acute intrarenal infusion of angiotensin II in subpressor doses results in a fall in both renal plasma flow (RPF) and glomerular filtration rate (GFR). However, it should be noted that due to the relatively larger reduction in renal blood flow relative to glomerular filtration rate, filtration fraction rises (Filtration Fraction = GFR/RPF) after angiotensin II infusion. The fall in renal plasma flow after angiotensin II infusion is due to a marked increase in renal vascular resistance. The site(s) of increased resistance are a subject of much discussion, however, the arterioles and in particular the efferent arteriole appears to be a major site of the increased renal resistance.

Figure 6

Localization of Components of the Renin-Angiotensin System Within the Renal Vasculature



From Reference 61.

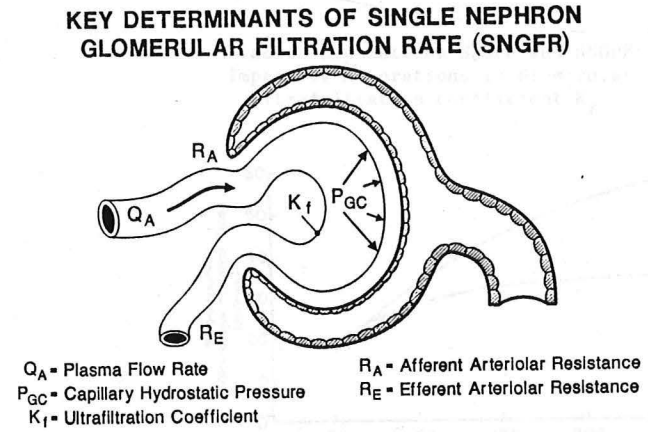
Based on these infusion studies in experimental animals it is not surprising that endogenous angiotensin II plays an important regulatory role in determining steady-state renal blood flow. Thus, placing dogs on a low sodium diet to induce a high renin, high angiotensin II state, results in a fall in steady-state renal blood flow (and glomerular filtration rates) as compared to dogs on high salt diets (48). Moreover, infusion of sodium depleted dogs with angiotensin II synthesis blockers results in an increase in renal blood flow (and glomerular filtration rate) to levels similar to those observed in animals on high salt diets. Similar studies on dietary sodium intake in rats (49,50), rabbits (51) and humans (52,53) have further demonstrated that RBF and GFR are reduced during sodium restriction-induced activation of the renin-angiotensin system.

B. Glomerular Filtration Rate -

1. General -

Angiotensin II also plays an important role in regulation of GFR. The effects of AII on the glomerular circulation are quite complex. To better understand how angiotensin II affects GFR regulation a review of the normal determinants of GFR is in order. Figure 7 depicts the major determinants of glomerular filtration rate at the single nephron level: Q_A, the glomerular plasma flow rate, P_{GC}, the intracapillary hydrostatic pressure, and K_f, the glomerular capillary ultrafiltration coefficient.

Figure 7



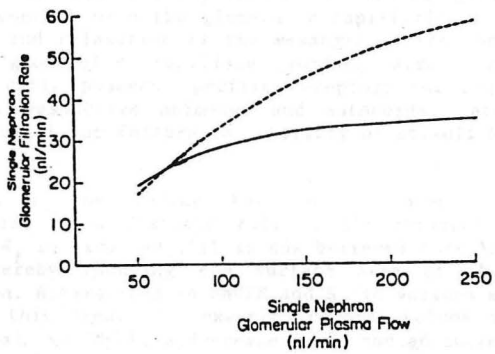
Our modern understanding of how GFR operates comes from micropuncture studies of single nephrons. For the purposes of this discussion I will focus on those factors pertinent to the effects of converting enzyme inhibitors to be detailed later. It should be understood that this discussion represents a simplified view of ultrafiltration dynamics. (For a detailed review of this subject see reference 54.) The results of the micropuncture studies have established that glomerular

plasma flow rate is the most important determinant of single nephron GFR (or SNGFR). SNGFR varies directly with plasma flow rate. Thus, a fall in glomerular plasma flow tends to be associated with a fall in GFR whereas a rise in plasma flow rate tends to increase GFR. Brenner et al. (54) have demonstrated the critical dependence of SNGFR on Q_A and have pointed out the importance of changes in afferent (R_a) and efferent (R_e) arteriolar resistances in regulating this variable. Another imporant determinant of filtration rate is the intracapillary hydrostatic pressure which is in turn dependent upon the glomerular plasma flow rate and the afferent and efferent resistances. The P_{GC} is the major physical driving force favoring filtration across the capillary wall and is opposed by the oncotic pressure in the plasma (π_a) and the hydrostatic pressure in Bowman's space (P_T). The difference between these variables ($P_{GC}-P_T-\pi_a$) determines the net ultrafiltration pressure. In general increasing P_{GC} increases SNGFR and decreasing P_{GC} decrease SNGFR.

A third and very important variable is the glomerular capillary ultrafiltration coefficient which represents the product of the glomerular capillary surface area (A) and the intrinsic hydraulic permeability of the capillary wall (L_p). SNGFR also varies directly with K_f so that factors which increase K_f tend to cause an increase in SNGFR and vice versa. Dynamic interplay among these variables in vivo determines the SNGFR on a minute-to-minute basis. It is important to mention that pertubations in SNGFR may come about as a result of changes in one or more of these determinants. An example of the effects of K_f on the flow dependence of SNGFR is depicted in figure 8.

Figure 8

Relationship Between SNGFR and SNGPF:
Impact of Alterations in Glomerular
Ultrafiltration Coefficient K_f



Ref: Arendshorst and Gottschalk, AJP 248:F163, 1985.

—— low K_f, as in hypovolemia
--- high K_f, as in euvolemia

As shown in the figure, increasing glomerular plasma flow at a low K_f (bottom curve) is associated with a slight but definite increase in glomerular filtration rate. At a higher K_f (upper curve) the curve shifts upward indicating that GFR is higher at any plasma flow rate within the range of 75-250 ml/min. One possible explanation for this effect of K_f is that an increase in capillary surface results when K_f is increased. However, either an increase in surface area or an increase in hydraulic permeability or both may be responsible for this phenomenon.

2. Effects of Angiotensin II-Induced Alterations in Afferent and Efferent Arteriolar Tone -

The net effect of angiotensin II on glomerular hemodynamics is the result of a combination of alterations in both afferent and efferent arteriolar tone as well as effects on K_f. Numerous studies have clearly demonstrated that angiotensin II directly constricts the efferent arteriole (38). There is a heated debate regarding whether it has a direct or indirect effect on afferent arteriolar resistance. Angiotensin II infusion increases with afferent and efferent resistances but the increase in efferent resistance is proportionately larger (55). It is important to mention that the effects on afferent arteriolar tone may result from changes in renal perfusion pressure attending the systemic effects of angiotensin II. Moreover, in vitro studies employing isolated renal microvessels Edwards (56) has shown that angiotensin II stimulates efferent arteriolar tone directly but does not alter afferent arteriolar tone directly. Furthermore, as we shall see, many alterations in renal hemodynamics in patients treated with CEIs can be explained on the basis of effects exerted by angiotensin II on the efferent arteriole.

3. Effects of Angiotensin II-Induced Alterations of the K_f -

The glomerular capillary network is supported by a specialized group of cells known collectively as the mesangium. Mesangial cells have contractile elements in their cytoplasm and they are are anatomically situated within the glomerulus such that they are in intimate contact with the glomerular capillaries. It has been postulated that contraction and relaxation of the mesangial cells (or mesangium) results in changes the glomerular capillary surface area available for ultrafiltration. Mesangial cells possess specific receptors for angiotensin II (57) as well as for other vasoactive hormones and autocoids. Activation of mesangial cell contraction in tissue culture to a variety of stimuli has recently been demonstrated (58).

Based on these studies and the finding that acute intravenous infusion of angiotensin II is accompanied by a dramatic fall in the glomerular capillary ultrafiltration coefficient K_f in vivo (49), it is now believed that AII modulates mesangial contractility thereby changing the surface area of the capillary available for ultrafiltration. Alterations in SNGFR and K_f in various experimental models are consistent with this view. For example, chronic volume depletion in rats is associated with a fall in SNGFR, a decrease in K_f and an increase in both afferent and efferent arteriolar resistances and an increase in P_{GC} (49,59). Moreover, these effects can be blocked by simultaneous infusion of AII receptor blockers or synthesis inhibitors (e.g. captopril). Figure 9 depicts glomerular hemodynamic parameters in vivo during normal conditions, and during AII excess before and after AII plus converting enzyme inhibition. As shown in figure 9b,

Figure 9a

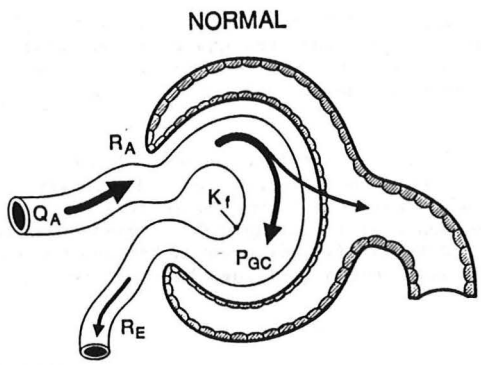


Figure 9b

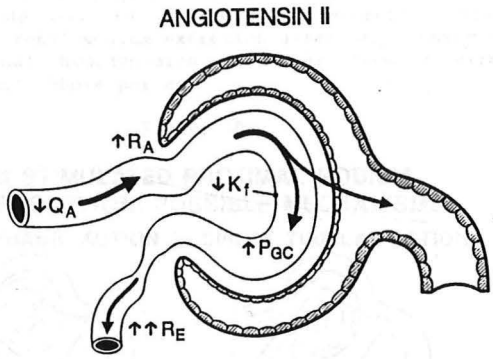
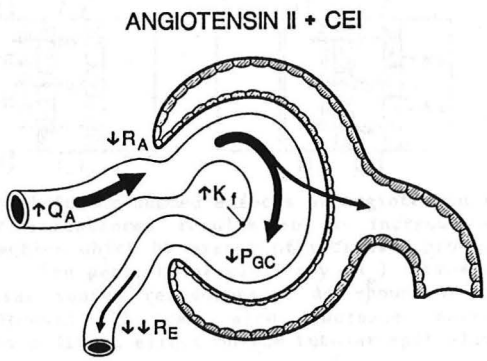


Figure 9c



angiotensin II decreases Q_A and K_f in association with increases in R_e and P_{GC}. Since SNGFR falls in this situation it is apparent that the decreases in Q_A and K_f exceed the effect of increased P_{GC}. When AII is inhbited by CEIs, Q_A and K_f increase and P_{GC} and R_e decrease. This combination of effects leads to an increase in SNGFR.

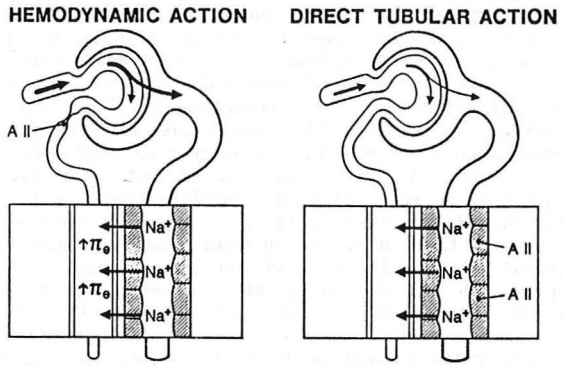
The enhancement of the RAS in sodium depletion is part of a homeostatic mechanism that serves to limit the loss of sodium from the body. By decreasing plasma flow rate and glomerular filtration rate while simultaneously increasing filtration fraction sodium is conserved. Disruption of this homeostatic mechanism in the setting of severe volume depletion could actually cause GFR to fall further particularly if glomerular plasma flow and capillary hydrostatic pressure decrease substantially.

C. Tubular Sodium Reabsorption -

The generation of incresed angiotensin II or direct infusion of angiotensin II is associated with a decrease in urinary sodium excretion (61). As shown in figure 10, a decrease in renal sodium excretion after angiotensin II could result from alterations in renal hemodynamics alone or from a direct effect of angiotensin II on the renal tubule per se.

Figure 10

AII STIMULATED PROXIMAL SODIUM REABSORPTION: POSSIBLE MECHANISMS



As shown on the left the summed effects of angiotensin II on arteriolar resistances results in an increase in filtration fraction which by virtue of increased protein concentration in the peritubular capillary (π_e) increases proximal tubular sodium reabsorption. As shown on the right, angiotensin II can also increase sodium reabsorption by a direct effect on the tubular epithelium per se.

It is now clear from recent studies that angiotensin II directly stimulates proximal tubular sodium reabsorption in vitro. In addition, specific reversible binding sites for AII in renal tubules have been demonstrated on both the basolateral and brush border membranes. Moreover, low doses of angiotensin II infused in vivo can reduce fractional sodium excretion without noticeably altering renal hemodynamics. These data suggest that natriuresis observed with acute administration CEIs may in part be due to inhibition of direct tubular action of angiotensin II.

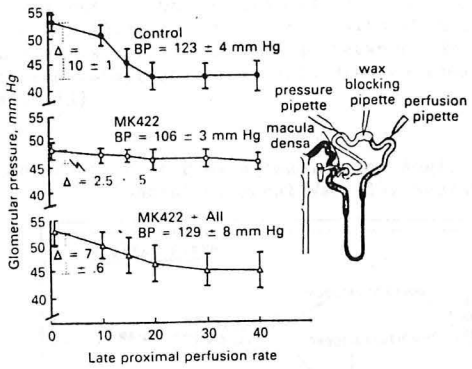
In addition to these effects in the proximal tubule, clearance and micropuncture studies have shown that angiotensin II may inhibit sodium transport at distal nephron segments corresponding to the distal convoluted tubule and/or collecting duct (61).

D. Effects on the Tubuloglomerular Feedback Mechanism -

Each nephron possesses an internal feedback mechanism designed to adjust its own glomerular filtration rate. This so-called "tubuloglomerular feedback" mechanism plays an important role in regulating glomerular filtration rate under normal and abnormal circumstances (62). The mechanism involves a feedback loop as follows: As GFR increases, proximal flow rate and subsequently distal tubular flow rate increases. The increase in distal fluid flow rate is "sensed" by the macula densa portion of the distal tubule. Upon sensing the change in flow rate, the macula densa sends a "signal" to the glomerular circulation causing a decrease in GFR. Conversely, a decrease in distal Na^+ (or Cl^-) delivery causes a reciprocal increase in glomerular filtration rate. This "tubuloglomerular" feedback mechanism thus represents an internal homeostatic control mechanism of the individual nephron filtration rate. At the present time most authorities believe that an alteration in afferent arteriolar tone which in turn alters glomerular plasma flow rate is the mechanism responsible for the efferent limb of the feedback mechanism. Numerous studies indicate that AII can modify the tubuloglomerular feedback mechanism (63). Furthermore, both ACE inhibitors and saralasin attenuate the angiotensin II effects on TG feedback responsiveness in intact rats. As shown in figure 11, in the top panel, under normal circumstances in intact rats subjected to micropuncture, as distal tubular flow rate to the macula densa of a single nephron increases above 10 nl/min, a sharp fall in single nephron glomerular pressure (or glomerular filtration rate) is observed. In contrast, as shown in the center panel, when a CEI is infused systemically in the same animal, no significant decrease in glomerular pressure is observed as in distal flow rate increases. As shown in the bottom panel simultaneous CEI administration with superimposed angiotensin II infusion partially restores the normal tubuloglomerular feedback response (as shown in the top panel). This observed blockade of the TG feedback mechanism after CEI administration may have clinical relevance. For example, if we imagine that elevated angiotensin II tonically enhances proximal sodium reaborption (for example, in hypertension), it is expected that distal flow rate would be reduced and TG feedback would increase SNGFR tending to restore normal tubular flow. This increase in SNGFR would increase the filtered load and proximal flow rate thereby offsetting the effect of elevated angiotensin II. Administration of CEIs in this situation could simultaneously inhibit angiotensin II-mediated proximal sodium reabsorption and block the AII-dependent component of TG feedback. In the clinical arena this could translate into a sustained natriuresis in response to CEI administration

Figure 11

Tubuloglomerular Feedback Mechanism:
Effects of Converting Enzyme Inhibitors



Ref: Navar G., KI 30(20):S86, 1987.

E. Other Effects of Angiotensin II in the Kidney -

Medullary Hemodynamics -

In addition to the above effects of AII there is evidence that AII has effects on renal medullary blood flow. Receptor for AII have been demonstrated in the renal medulla (64) and effects of altered sodium balance can modulate inner medullary blood flow in part by an angiotensin II dependent mechanism (65).

Proteinuria -

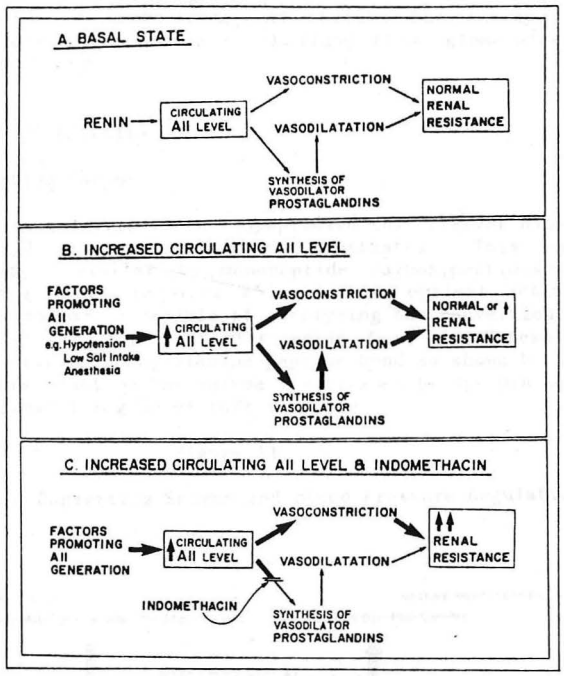
Acute angiotensin II infusion in rats has been shown to cause marked proteinuria (66). The mechanism of AII-induced proteinuria appears to involve an increase in the transcapillary hydrostatic pressure gradient. In addition, increased permeability to macromolecules in rat glomeruli has been induced by AII infusion (67). Furthermore, in rare instances renovascular hypertension due to renal artery stenosis is associated with nephrotic syndrome that is cured by nephrectomy of the stenotic kidney (68-70).

INTEGRATED ACTIONS ANGIOTENSIN II AND VASODILATOR SUBSTANCES

Under circumstances of decreased effective arterial blood volume such as sodium depletion, angiotensin II activity is increased. Renal vascular resistance rises and renal perfusion pressure increases in this setting in part owing to increased angiotensin II as well as increased renal nerve traffic (71).

Simultaneously the kidney synthesizes increased amounts of vasodilator prostaglandins, especially PGE_2. The rise in PGE_2 production offsets the effects of angiotensin II and other vasoconstrictor stimuli thereby maintaining renal blood and glomerular filtration rate (72). The importance of vasodilator prostaglandins in this circumstance has been documented in both experimental and clinical observations in which administration of non-steroidal anti-inflammatory agents to animals, subjects or patients with high plasma angiotensin II levels. Figure 12 summarizes the relationship between the counterbalancing effects of angiotensin II and vasodilator prostaglandins on renal hemodynamics as reviewed by Levenson et al. (73).

Figure 12
Interaction of Prostaglandins and Angiotensin II in the Control of Renal Vascular Resistance



Ref: Levenson et al., Am. J. Med. 72:354, 1982.

As shown in the top panel, under normal circumstances renal blood flow is maintained at normal levels of angiotensin II and renal prostaglandin production is low. In the middle panel, a pathophysiological disturbance occurs resulting in a tonic increase in angiotensin II. Increased angiotensin II causes renal vasoconstriction, a fall in renal blood flow and glomerular filtration rate and stimulates renal prostaglandin production which antagonzies the effects of angiotensin II on renal blood vessels and the glomerular mesangial cells. The counterbalancing effect of prostaglandins tends to restore renal hemodynamics

toward normal levels. Thus, a balance of vasoconstrictor and vasodilator forces is achieved in a new steady-state. As shown in the bottom panel, when renal prostaglandin production is inhibited by a NSAID, vasodilator forces are reduced and vasoconstriction predominates resulting in a sudden decrease in renal blood flow and glomerular filtration rate. This hypothetical model can be applied to a variety of clinical derangements including congestive heart failure, cirrhosis with ascites, the nephrotic syndrome, chronic renal disease, and atherosclerotic cardiovascular disease.

It seems logical that under conditions of altered renal hemodynamics such as those just described that blockade of angiotensin II receptors or angiotensin II production would lead to an increase in renal blood flow and glomerular filtration rate. In this regard some studies have clearly shown that CEIs do increase renal blood flow both acutely and chronically even in the presence of a reduction in renal arterial pressure. This finding has been borne out in some patients with congestive heart failure in whom acute and chronic CEI therapy results in significant and sustained increases in renal flood flow, glomerular filtration rate and sodium excretion (74).

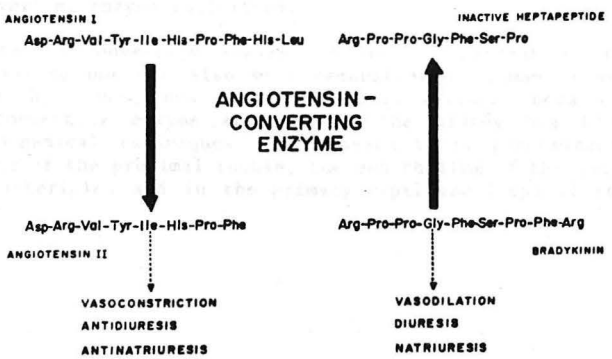
CONVERTING ENZYME INHIBITORS (CEIs)

A. Angiotensin Converting Enzyme -

Angiotensin converting enzyme is an exopeptidase that cleaves dipeptides from the carboxyterminal end of various peptide substrates. This enzyme bears structural characteristics similar to monopeptide carboxypeptidases. It is a metalloenzyme containing zinc, requires chloride for optimal activity and is inhibited by EDTA. The enzyme is capable of catalyzing the convertion angiotensin I to angiotensin II by cleaving two amino acids from the C-terminal end of angiotensin I at the histidine-phenylalanine peptide bond as shown below in figure 13. In addition to this reaction the enzyme inactivates bradykinin by cleaving a dipeptide from the C-terminal region of this molecule.

Figure 13

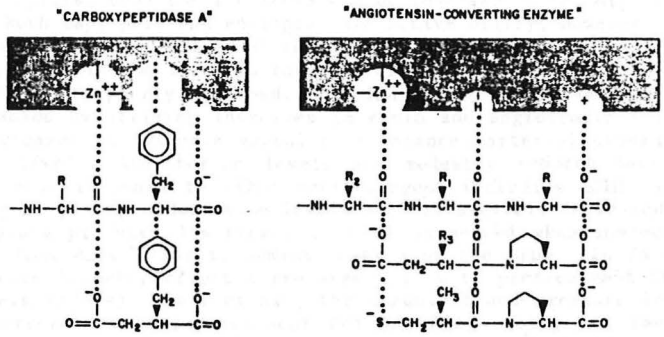
Angiotensin Converting Enzyme and Blood Pressure Regulation



From Reference 79.

Figure 14

Schematic Representation of Substrate and Inhibitor Binding Sites for Carboxypeptidase A and Angiotensin-Converting Enzyme



Ref: Ondetti et al., Science 196:441, 1977.

A diagram of the hypothetical active site of angiotensin converting enzyme as proposed by Ondetti et al. is shown in figure 14. As shown in the figure, a positively charged residue at the active site is postulated to interact with a negatively charged moiety on the substrate. The zinc ion present in the active site must be located so as to polarize the carbonyl group of the scissile amide bonds making them more susceptible to hydrolysis. Note that in comparison to the model illustrated for carboxypeptidase A that the active site of the converting enzyme is separated from the Zn^{++} site by the distance of a dipeptide residue. Based on these hypothetical models a number of enzyme inhibitors of the reversible competitive type have been synthesized (23). The structure activity relationship profile of the inhibitors suggests that optimal activity is achieved by synthesis of inhibitors containing a succinyl-L-proline moiety at the positively charged (far right) active site. The addition of the sulfhydryl group to the Zn^{++} associated binding site was shown to enhance the inhibiting activity of the orally active converting enzyme inhibitors.

Angiotensin converting enzyme activity is present in large quantities in pulmonary tissue but has also been demonstrated in many other organs including kidney, brain, liver, and most peripheral vascular beds (75). As mentioned earlier, converting enzyme activity in the kidney has been demonstrated by immunohistochemical techniques. It appears to be predominantly located in the brush border of the proximal tubule, the endothelium of the juxtaglomerular cells, arteries, arterioles and in the primary capillary loops of the glomerular stalk (76).

B. Pharmacology, Metabolism and Potency OF CEIs -

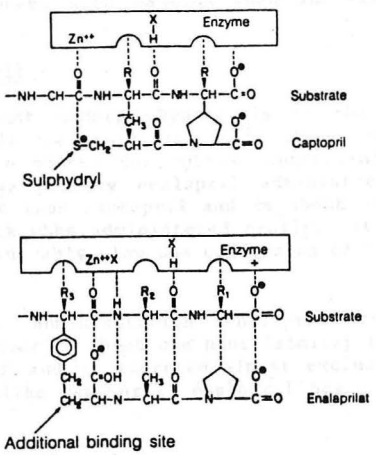
1. General-

The essential action of these agents is of course inhibition of converting enzyme activity which catalyzes the conversion of angiotensin I to angiotensin II and the degradation of bradykinin. These agents are specific and do not interact with angiotensin receptors, thus their effects can be reversed by coadministration of angiotensin II. Both captopril and enalapril are active orally, however, in the case of enalapril the drug is prepared as the monoethyl ester of enalaprilic acid (which requires oxidation in the liver to form the biologically active form) since enalaprilic acid itself is poorly absorbed. The inhibition of converting enzyme activity is accompanied by striking increases in renin and angiotensin I levels, and significant decreases in systemic vascular resistance, arterial pressure and plasma aldosterone levels. Aldosterone levels are modestly reduced during ACE inhibition: The adrenal response to other secretagogues including ACTH, and K^+, remains intact so that plasma aldosterone levels are not severely decreased. The magnitude of the blood pressure lowering effect is augmented when subjects are placed on a low sodium diet prior to administration of the drug. In fact, the initial blood pressure lowering effect correlates well with pretreatment PRA and angiotensin II levels (77-79). In contrast, the chronic blood pressure lowering effect does not correlate with pretreatment PRA and AII levels. An important feature of the pharmacologic effect of CEIs, in contrast to the β blocking agents, is the maintenance of baroreceptor function and cardiovascular reflexes which remain uncompromised.

There are important structural similarities and differences between captopril and enalapril as depicted in figure 15. Both agents contain a succinyl-proline moiety which interacts with the hydrolytic site of converting enzyme. Captopril contains the well known -SH group whereas enalapril has a benzyl function in the corresponding region of its structure.

Figure 15

Comparison of CEI Structures and Their Interactions with Converting Enzyme



Enalapril contains an ester linkage which is necessary to facillitate its absorption from the Gl tract. From a functional standpoint both of agents are potent converting enzyme inhibitors. However, enalapril, when converted from its prodrug form to its active form enalaprilic acid, is about one order of magnitude more potent than captopril. Captopril, unlike enalapril, has the additional feature of stimulating prostaglandin synthesis in the kidney as shown by Zusman et al. (80). This difference may in part explain the ability of captopril to lower blood pressure in patients with low plasma renin levels and the observation that its hypotensive effects can be attenuated in some patients taking NSAIDs.

2. Captopril -

Captropril is rapidly absorbed after oral administration and has a bioavailability of about 65%. Because bioavailability is substantially reduced by food, the drug should not be given with meals. Peak plasma concentrations occur after about an hour and the drug is largely excreted in the urine. The elimination half-half life ($t_{\frac{1}{2}}$) is about 4 hours. Approximately 50% of the parent compound is excreted in the urine unchanged whereas the remainder is excreted as the disulfide dimer and several uncharacterized polar metabolites (81). Although the terminal $t_{\frac{1}{2}}$ for captopril is approximately 2 hours in normal subjects the drug is effective at lowering blood pressure when given on TID, BID, and even QD dose schedules (82). The reason for this is not clear, however, kinetic studies in humans reveal that the drug appears to fit a three compartment model. It has been hypothesized that captopril may form disulfide linkages with ubiquitous -SH groups. It has been suggested that such linkages may provide a reservoir from which the drug is slowly released (83).

The elimination and plasma half life of captopril are closely correlated to renal function as expected from drug disposition studies. Thus, in patients with renal insufficiency the total daily dose should reduced in accordance with the severity of renal impairment. In patients with moderate to severe renal insufficiency, for example an initial dose of 6.25 to 12.5 mg/day should be employed and then the dose may be upward slowly depending on the clinical response while the patient is carefully monitoried for side effects (84). Adverse side effects are more commonly encountered in azotemic patients therefore it is advisable to proceed with caution when increasing dosages in these patients.

3. Enalapril -

Enalapril must undergo hydrolysis in the liver to form the active acid moiety. The molecule requires both the carboxy and amino groups of the carboxymethylamino moiety for optimal converting enzyme inhibitor activity. In terms of relative potency enalapril administered intravenously is two to five times more potent than captopril and is about one order of magnitude more potent on a weight basis when administered orally. It is important to note that liver disease may considerably slow the conversion of the enalapril ester to enalaprilic acid.

After oral administration enalapril is well absorbed, peak plasma concentrations occur in about one hour (similar to captopril). The drug undergoes rapid esterolysis and is excreted almost exclusively in the urine as the parent acid moiety. Unlike captopril, enalapril has a long half life and is detectable

in normal plasma up to 96 hours after a single oral dose. Brunner et al. (85) have shown that plasma converting enzyme activity is inhibited for up to 72 hours in normal subjects after oral administration which is about 3 times longer than that observed after captopril. The conversion of orally administered enalapril maleate to its acid derivative is complete in about 6 hours in normal subjects (86).

In patients with renal insufficiency elimination of enalapril is prolonged. After a 10 mg oral dose patients with mild (GFR>30<100 ml/min) and moderate (GFR<15>30 ml/min) renal insufficiency generally achieve higher peak serum concentrations and they maintain elevated levels for prolonged periods of time (87,88). The cummulative urinary excretion of enalaprilic acid is similar in these two patient groups up to 50 hours after ingestion of the dose. Thus, in patients with GFRs of less than 30 ml/min there is a tendency to develop and maintain high plasma levels of the active drug for up to 48 hours. In addition, the time to peak plasma levels in renal failure is prolonged which further tends to maintain high steady-state plasma levels of the drug. These principles should be kept in mind when prescribing enalapril in patients with impaired renal function. A dose of 2.5 to 5 mg is a reasonable starting dose in patients with moderate to severe renal insufficiency. As with captopirl careful dose and titration according to patient tolerance is indicated since adverse reactions of all types, particularly those involving the kidney, are much more likely to occur in patients with pre-existing azotemia.

ANGIOTENSIN CONVERTING ENZYME INHIBITION AND THE KIDNEY

A. Renal Effects on Hemodynamics and Electrolyte Excretion in the Normal Kidney -

1. Renal Blood Flow -

Administration of CEIs to normal subjects or normal animals particularly during sodium depletion is associated with an increase in renal blood flow and to a lesser extent glomerular filtration rate (89-94). During suppression of angiotensin II by high sodium diets, however, the administration of CEIs is not uniformly associated with significant alterations in renal hemodynamics. Some normal subjects do, however, demonstrate an increase in renal blood flow when on high sodium intake but to a lesser extent as compared to subjects on low sodium intakes (95). The mechanism of this increase in renal blood flow in the sodium replete organism (where in PRA and AII levels are low) still appears to be due to inhibition of angiotensin II effect on renal vascular tone (96). Thus, intrarenal administration of captopril in sodium replete rats at doses that selectively inhibit the renal vasocontrictor action of intrarenally infused exogenous angiotensin I have no effect on renal vascular resistance but intravenous captopril causes an increase in renal blood flow (96). Furthermore, NSAIDs do not alter the renal vasodilator response to captopril in sodium replete dogs which excludes a role for captopril-induced increases in renal prostaglandin as a possible explanation (97).

2. Glomerular Filtration Rate -

Glomerular filtration rate has been reported to remain unchanged, increase and decrease after CEI administration to normal subjects. Changes in GFR may be

Figure 16a.
Effects of CEI and CEI + AII on RBF and GFR During Reduced Renal Perfusion Pressure

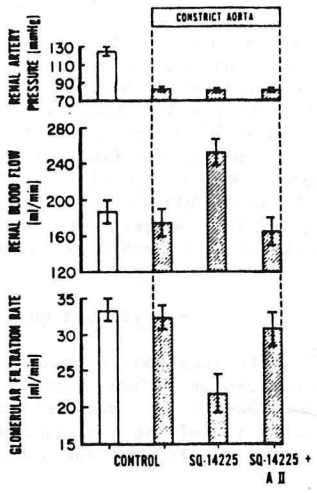
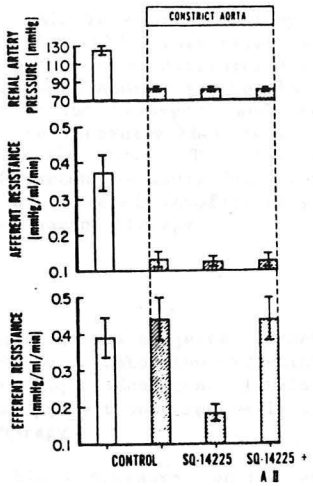


Figure 16b.
Effects of CEI and CEI + AII on Afferent + Efferent Arteriolar Resistances During Reduced Renal Perfusion Pressure



Ref: Hall, Fed. Proc. 45:1433, 1986.

the result of relative changes in afferent and efferent vascular resistances as well as the reduction in mean arterial pressure that accompanies CEI inhibition. As in the case with renal blood flow changes in GFR are most prominent when the RAS is activated. Furthermore, CEI effects on kinin metabolism have not provided convincing evidence that elevated kinin levels play any role. In most instances, renal blood flow increases and glomerular filtration rate remains constant resulting in a decrease in filtration fraction so long as renal perfusion pressure is not critically lowered. A simple explanation for this response is that CEI causes a relatively greater fall in efferent arteriolar tone. The contribution of the tonic influence of angiotensin II to efferent resistance and glomerular filtration rate in the setting of reduced renal perfusion pressure has been demonstrated by Hall et al. as shown in figure 16 (98). In anesthetized dogs previously maintained on a low sodium diet to stimulate the RAS, autoregulation of glomerular filtration rate is attenuated by administration of converting enzyme inhibition. As shown in the left hand side of the figure, during reduction of renal artery pressure to 70 mm Hg, GFR and RBF are stable. After captopril (SQ-14225) administration renal blood flow increases but GFR falls sharply.

Subsequent angiotensin II infusion in the face of continued CEI restores GFR. As shown on the right afferent resistance is constant but efferent resistance falls markedly after captopril then returns to baseline after angiotensin II infusion. Taken together these findings suggest that AII plays an important role in renal autoregulation under circumstances of impaired renal perfusion and that converting enzyme inhibitors can disrupt this homeostatic response.

3. Sodium Excretion -

In normal human subjects acute administration of CEIs is accompanined by a prompt and significant increase in urinary sodium excretion (95). This effect is independent of altered aldosterone activity (99). The mechanism of natriuresis is presumably due to blockade of AII effects on intrarenal hemodynamics and possibly to antagonism of angiotensin II effects on tubular sodium transport and the tubuloglomerular feedback mechanism. It is important to recognize that even in sodium deprivation CEIs can cause a prolonged natriuresis (100). This effect makes these agents particularly valuable in managing hypertensive individuals but at the same time may play a role in precipitating acute renal insufficiency, especially if arterial pressure is substantially reduced during therapy.

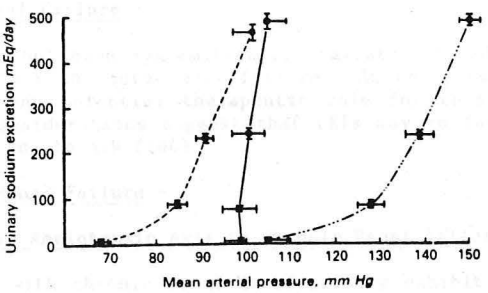
4. Potassium Excretion -

Potassium excretion decreases after CEI inhibition in normal subjects. Frank hyperkalemia does not usually occur, however, the decrease in potassium excretion is thought to be due to a decrease in circulating aldosterone levels. Hyperkalemia can and does develop if volume depletion is present and especially if renal insufficiency develops after initiation of CEI therapy.

The impact of converting enzyme inhibitors on blood pressure control as related to dietary sodium is depicted in figure 17.

Figure 17

Steady-State Relationship Between
Mean Arterial Pressure and
Urinary Sodium Excretion: Normal ●——●,
Captopril ●----●, Angiotensin II ●----●



Ref: Hall et al., Am. J. Phys. 239:F271, 1980.

The relationship between mean arterial pressure and urinary sodium excretion in three instances: 1) during normal conditions (solid line); 2) during increased angiotensin II (dotted line); and 3) during inhibition of AII production by CEIs (dashed line). It is clear that when CEI activity is inhibited the normal pressure-sodium excretion rate relationship is shifted to the left indicating that sodium balance (excretion) is achieved at the expense of lowered mean arterial pressure. In contrast, under circumstances of exaggerated angiotensin-II activity sodium balance is achieved only at higher mean arterial pressures (101).

B. Effects on Renal Hemodynamics and Electrolyte in Essential Hypertension -

1. Renal Blood Flow and Glomerular Filtration Rate -

Renal blood flow increases and GFR remains unchanged in essential hypertensive patients with normal renal function after acute and chronic CEI therapy. In hypertensives with renal insufficiency, however, both RBF and GFR increase. These increases may be sustained for several months in some cases (94,95,100,101).

2. Sodium and Potassium Excretion -

As in normal subjects sodium excretion and potassium excretion is increased and potassium excretion is decreased by CEIs in hypertensive patients. The most instances, as in normals hyperkalemia is not present or is very mild.

In summary, under normal circumstances angiotensin II converting enzyme inhibitors enhance renal blood flow without altering GFR and they enhance sodium excretion at normal (or low) mean arterial pressures. At severe reductions in renal perfusion pressure autoregulation of glomerular filtration rate is markedly impaired by CEIs. This impairment may be sufficient to result in acute renal failure. In patients with essential hypertension renal blood flow, and sodium excretion are increased after CEIs. In some hypertensive patients with reduced renal function GFR is also increased.

CONVERTING ENZYME INHIBITORS AND RENAL DISORDERS

A. Acute Renal Failure -

CEIs have not been systematically evaluated in models of acute renal failure nor in patients with acute renal failure. At the present time no information is available on any potential therapeutic role for these agents in this setting. Theoretical considerations suggest that CEIs may in fact be detrimental in acute renal failure due to ATN (104).

B. Chronic Renal Failure -

1. Renin Angiotensin Axis in Chronic Renal Failure -

Patients with chronic renal insufficiency exhibit variable levels of plasma renin activity and plasma angiotensin II levels ranging from very low to very high

(105-±08). In many patients with glomerulonephritis, particularly those with volume expansion, renin levels are generally normal or low. Renin levels are also often low in patients with diabetic nephropathy and those with primary tubulointerstitial nephritides (109). Most patients with chronic renal insufficiency have an intact RAS and respond physiologically to perturbations in sodium balance and postural changes. However, whether alterations in intrarenal angiotensin-II formation and action are present is unknown since plasma levels of renin, angiotensin I and angiotensin II may not reflect intrarenal levels.

2. Hemodynamics in Chronic Renal Failure -

It is well appreciated that the rate of progression of renal failure to end stage is a major focus of intense investigation in Medicine and Nephrology today. Control of systemic hypertension is very important in slowing progression in diabetic nephropathy (110) and in the benign as well as malignant phases of hypertensive nephrosclerosis (111) in man. The potential pathophysiologic role of the renin-angiotensin system in mediating the alterations in glomerular hemodynamics and the progression of glomerulosclerosis in a number of experimental models of chronic renal failure has recently been studied by several independent investigators. These models include chronic renal failure induced by renal ablation (112-114), diabetic nephropathy engendered by stretozotocin administration (115-117), glomerulonephritis (118,119) and chronic DOCA-induced hypertension (120). Based on these studies it has been hypothesized that a pathological increase in intraglomerular capillary hydrostatic pressure in remnant nephrons of diseased kidneys is at least in part responsible for the development and persistence of proteinuria and glomerular pathologic changes.

In an effort to better understand the genesis of the progression of renal failure in these models the role of the RAS has been probed by administering CEIs to rats in vivo (112-114). In experimental chronic renal insufficiency with hypertension induced by 5/6 nephrectomy, Anderson et al. (114) has demonstrated that chronic administration of CEIs lowers blood pressure, limits glomerular capillary hypertension, reduces proteinuria and attenuates the magnitude of glomerulosclerosis in remnant nephrons as compared to untreated rats. Similarly, in rats with diabetic nephropathy (from streptozotocin-induced diabetes mellitus) chronic administration of enalapril is associated with a reduction in glomerular capillary hypertension, proteinuria and glomerulosclerosis (116,117).

Interestingly, in experimental nephrotoxic serum-induced glomerulonephritis accompanied by systemic hypertension abnormal glomerular hemodynamics and progressive nephron loss are ameliorated in association with control of systemic blood pressure. In this study CEIs were not employed, rather a triple drug regimen consisting of reserpine, hydrolazine and hydrochlorothiazide was used.

Table 1 summarizes the essential systemic and renal hemodynamics, renal functional and morphologic alterations in these three models. As can be seen in all three models treatment with CEIs (in the first two) and with triple drug antihypertensive regimen (third study) effectively reduce blood pressure, glomerular capillary pressure (P_{GC}), and glomerular plasma flow rate (Q_A) compared to untreated controls. In addition, proteinuria and glomerular sclerosis are ameliorated. The essential abnormalities in glomerular hemodynamics common to all three of these experimental models of chronic renal insufficiency is the

presence of a sustained increase in glomerular capillary hydraulic pressure and an increase in glomerular plasma flow rate. Both of these determinants of SNGFR are altered by chronic antihypertensive therapy. It should be noted that these findings are consistent with a decrease in afferent arterioloar resistance relative to efferent arteriolar resistance. If the progression to renal failure in some or all forms of glomerulonephritis is mediated by glomerular capillary hypertension in the setting of a reduced afferent arteriolar resistance relative to efferent arteriolar resistance then it is possible that the CEIs could provide a therapeutic advantage over other antihypertensive regimens. The study by Neugarten (118) in Table 1 suggests that conventional therapy is equally successful. It is possible these two models differ and in fact as will be discussed below in the renal ablation model a standard triple drug regimen is not as efficious as are CEIs.

TABLE 1. Summary of Effects of Antihypertensive Therapy on Blood Pressure and Renal Functional and Morphologic Finding in Three Experimental Models of Chronic Renal Insufficiency

Experimental Model		Systemic BP	SNGFR	P_{GC}	Q_A	Proteinuria	Abnormal Morphology
Renal ablation* N=28	CEI Treated	NL	↑	↑	↑	↑	1+
	Untreated	↑	↑↑↑	↑↑↑	↑↑	↑↑↑	4+
Diabetic nephropathy† N=39	CEI Treated	↓	↑	NL	↑	NL	-
	Untreated	NL	↑↑	↑	↑↑	↑↑↑	4+
Nephrotoxic serum-induced glomerulonephritis†† N=15	Triple Drug	NL	NL	NL	NL	↑	2+
	Untreated	↑	↑	↑	↑	↑↑↑	4+

Compiled From: *Anderson et al., JCI 76:612, 1985; †Zatz et al., JCI 77:1925, 1986; and ††Neugaren et al., KI 28:135, 1985.

One might expect that if angiotensin II mediated efferent arteriolar vasoconstriction is important in sustaining the increases in P_{GC} and SNGFR in animal models, then inhibition of this effect may be responsible for the "protective effect" observed in the models of renal insufficiency described above. To investigate this possibility Anderson et al. (112) studied the effects of enalapril versus a triple drug regimen (TDR) consisting of hydralazine, reserpine and hydrochlorothiazide in rats with 5/6 renal ablation. Table 2 shows the essential findings in these animals after 4 weeks of therapy. As can be seen in both the enalapril and triple drug regimen treated rats systemic blood pressure was normal and SNGFR were only slightly elevated compared to 5/6 ablated untreated animals. However, P_{GC} was normalized by enalapril therapy, but not by the TDR. It is also noteworthy that efferent arteriolar resistance although lower in untreated and TDR groups as compared to normal rats was <u>much</u> lower in the enalapril treated group. In addition, as shown in the far right column K_f was increased in the enalapril group and decreased in the untreated and TDR groups. As expected, the untreated and TDR groups went on to develop progressive nephrosclerosis and marked proteinuria as compared to the enalapril treated groups. These data strongly suggest that control of glomerular capillary hypertension is paramount in preservation of renal function and morphology in this experimental model.

Preservation of renal function during antihypertensive therapy in these models is in keeping with the observations made in man. In humans with hypertension Jenkins et al. have reported that CEI therapy is short term follow up (i.e. 12 months) is accompanied by a slight decrease in serum creatinine in those patients with elevated creatinine levels between (>3.0 and 3.5 mg/dl) but not in patients with normal serum creatinine levels (≤ 1.5 mg/dl) (121). In addition, in a short-term study enalapril has recently been shown to preserve renal function in diabetic patients with microalbuminuria (122).

TABLE 2. Renal and Systemic Hemodynamic Effects of CEIs vs Conventional Antihypertensive Therapy in Experimental Chronic Renal Insufficiency

	Systemic BP	SNGFR	P_{GC}	Q_A	R_A	R_E	K_f
Untreated Control	↑	↑↑	↑↑	↑	↓	↓	↓
CEI	NL	↑	NL	↑	↓↓	↓↓↓	↑
TDR	NL	↑	↑↑	↑	↓↓	↓	↓

Adapted from: Anderson et al., JCI 77:1993, 1986.
CEI = converting enzyme inhibitor
TDR = triple drug therapy

Further studies in humans are needed to better define the role and scope of CEI therapy in patients with chronic renal insufficiency.

In summary, converting enzyme inhibitors are extremely helpful in investigating the renal functional and morphologic alterations in some animals models of chronic renal disease and may offer a therapeutic advantage over other antihypertensive regimen in certain forms of glomerular disease. In addition, inasmuch as they are excellent antihypertensive they afford excellent therapy for controlling hypertension and in turn may slow progession of various forms of chronic renal disease. However, at the present time, there is not enough information available to determine whether these agents offer a definite therapeutic advantage for over conventional regimens controlling blood pressure in humans with renal failure. This remains an important question. Further human studies will be necessary to warrant specific conclusions regarding the privacy of CEIs in patients with chronic renal insufficiency. Clinical trials are now ongoing in attempt to answer this question.

C. Renal Artery Stenosis -

This section will focus on renal hemodynamics with an emphasis on the effects of CEI in the setting of renal artery steonisis. The pathogenesis, pathology and treatment of renovascular hypertension have been extensively reviewed in a recent Medical Grand Rounds by Dr. C.V.S. Ram (123). The following discussion will be brief and the reader is referred to reference 123 for a detailed discussion.

1. Pathophysiology of Altered Renal Hemodynamics in Renal Artery Stenosis -

Unilateral Renal Artery Stenosis -

Renal hemodynamic alterations in renal artery stenosis result from a complex interaction between the RAS, systemic blood pressure and renal ischemia. In experimental unilateral renal artery stenosis in which one renal artery is partially occluded, the 2 kidney 1 clip model, is characterized by a high renin-angiotensin state in the early phase. As blood pressure rises volume expansion occurs, renin secretion is suppressed and hypertension is maintained by non-angiotensin II dependent mechanism (124,125). During the early chronic phase, in the rat model, PRA is supranormal and renal blood flow and glomerular filtration rate tend to be increased in the non-stenotic kidney as compared to the stenotic kidney. Furthermore, autoregulation of renal blood flow is impaired in the non-stenotic kidney when compared to normal kidneys of non-hypertensive animals. At this stage acute blockade of angiotensin II production or AII receptors is associated with a significant fall in blood pressure and marked increases in RBF, GFR and sodium excretion in the non-stenotic kidney. In contrast, RBF, GFR and sodium excretion are markedly reduced in the stenotic kidney (126,127). These findings support a role for circulating AII-mediated functional adaptation in the stenotic kidney whereby GFR is supported by efferent arteriolar constriction which bolsters glomerular capillary hydrostatic pressure under circumstances of reduced renal perfusion pressure. In addition it appears that AII also alters the function of the non-stenotic kidney by increasing renal resistance and enhancing renal sodium reabsorption, possibly by hemodynamic and tubular actions, which may be important in sustaining hypertension in this phase. Glomerular hemodynamics changes in non-stenotic kidneys are consistent with the view that pre-glomerular resistance is largely responsible for the increase in total renal vascular resistance (125). It should be noted that additional mechanisms besides angiotensin II may be operative in these experiments including peripheral and central renal nervous system effects. Furthermore, during the chronic phase ischemic damage in the non-stenotic kidney may play an important role in sustained hypertension in this model since at this point peripheral renin and angiotensin II levels are suppressed (128).

Bilateral Renal Artery Stenosis -

In experimental and clinical bilateral renal artery stenosis renin is chronically elevated. RBF and GFR may be normal or decreased depending upon the severity and duration of the stenosis. If critical stenosis is present administration of CEIs results in a fall in blood pressure, no change or decreases in renal blood flow and a severe reduction in GFR. These changes can be accounted for on the basis of a decrease in efferent resistance which critically regulates GFR in this condition.

In summary, CEI administration during the renin dependent phase of unilateral renal artery stenosis decreases blood pressure in association with a decrease in GFR, RBF and excretory function in the non-stenosed kidney. During the chronic or renin independent phase CEI administration has little or no effect on blood pressure, but decreases GFR and renal excretory function in the stenotic kidney is unchanged. In the non-stenotic kidney GFR, RBF and excretory function either increase or remain unchanged. In bilateral renal artery stenosis CEIs lower blood pressure and may severely impair GFR if critical stenosis is present.

2. Effect of CEIs in Humans With Renal Artery Stenosis -

CEIs lower blood pressure in most (about 95%) patients with renovascular hypertension. In patients with unilateral renal artery stenosis renal blood flow and glomerular filtration rate responses in the contralateral (non-stenotic) kidney are variable with increases or no change being reported. In contrast, the renal blood flow and glomerular filtration rate in the stenotic kidney is often decreased (129). The net effect is that overall blood flow and filtration rate may be unchanged or slightly improved in patients with unilateral renal artery stenosis after treatment with CEIs. However, in several clinical studies CEI administration in patients with unilateral renal artery stenosis is associated with a decline in renal function but not with frank acute renal failure (130). Acute renal failure has been associated with CEI therapy in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney (131-136). The mechanism of the fall in GFR may be the consequence of both a critical decrease in renal perfusion pressure and an inhibition of intrarenal angiotensin II activity (130). In bilateral stenosis where a chronic reduction in renal artery perfusion pressure obtains, maximal afferent arteriolar vasodilatation takes place in order to maintain the glomerular plasma flow rate. Angiotensin II levels are increased owing to both enhanced systemic and intrarenal formation. The elevated angiotensin II produces a tonic increase in efferent arteriolar tone which engenders a compensatory increase in glomerular capillary hydraulic pressure in the face of a reduced afferent perfusion pressure. When angiotensin II formation is interrupted by a CEI this compensatory effect is abolished, capillary hydraulic pressure falls and glomerular filtration rate is reduced. Figure 18 depicts this hypothetical mechanism.

Figure 18

BILATERAL RENAL ARTERY STENOSIS

Panel A →

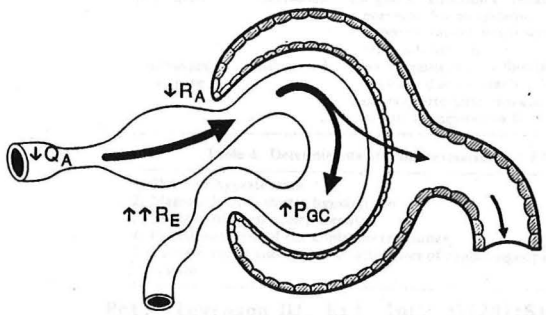
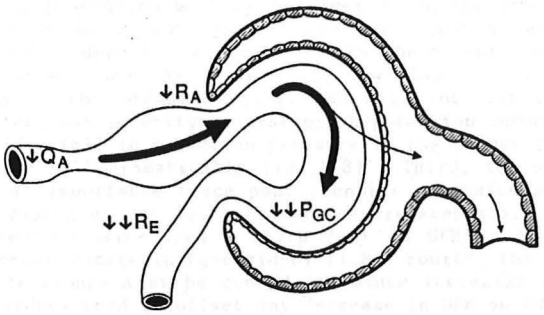


Figure 18

BILATERAL RENAL ARTERY STENOSIS + CEI

Panel B →



In bilateral renal artery stenosis GFR is maintained by an increase in AII-mediated efferent arteriolar resistance in the setting of maximal afferent arteriolar dilatation (Panel A). When AII inhibition is induced by CEI efferent resistance falls dramatically, resuling in a fall in glomerular capillary hydrostatic pressure and consequently a dramatic decline in GFR (Panel B).

It is important to emphasize that most patients with unilateral renal artery stenosis do not develop renal compromise when treated with CEIs (135). Thus, variation in the renal response depends upon the severity of the stenosis and whether it is unilateral or bilateral. Table 3 summarizes the potential patterns of renal hemodynamic responses to CEIs in patients with renal artery stenosis reported in a recent review (130).

Table 3. Patterns of renal hemodynamic changes during converting enzyme inhibition

RBF	GFR	Mechanism
Increased	Increased	Release from renal vasocontrictor effects of angiotensin II
Decreased	Decreased	Excessive reduction of renal perfusion pressure due to systemic hypotension combined with severe renal arterial stenosis
Unchanged or increase	Decreased	Loss of transcapillary filtration pressure due to selective loss of efferent arteriolar vasoconstrictor action of angiotensin II

Table 4. Determinants of renal responses to CEI

1. Phase of hypertension
2. Magnitude of systemic hypotension
3. Severity of renal artery stenosis
4. Functional state of the contralateral kidney
5. Volume status and degree of activation of renin-angiotensin system

Ref: Levenson DJ, Kid. Int. 31(20):S173, 1987.

Since renal failure occurs in only a small fraction of patients it seems likely that most patients do not have severe enough stenosis to predispose them to this adverse effects of CEIs. Several factors must be considered in evaluating the likelihood of an adverse renal response to CEIs as shown in Table 4. First, the phase of the renovascular hypertension must be considered. In the acute phase of unilateral RVH an inhibition of angiotensin-II activity would be expected to decrease GFR in the stenotic kidney but increase GFR in the non-stenotic kidney. In the chronic phase, however, when AII levels are low CEIs will cause no or little change in the GFR of the stenotic kidney and will increase GFR in the non-stenotic kidney. Second, the severity of systemic hypotension induced by CEIs is important since a critical fall in perfusion pressure in the stenotic kidney in particular may cause GFR to fall dramatically (137,138). Third, the severity of the stenosis is of critical importance since post stenotic perfusion pressure is maintained by efferent resistance. In cases of more severe stenosis, CEI therapy is likely to be associated not only with a sharp fall in GFR in the stenotic kidney but also with ischemic damage in that kidney (128). Fourth, the functional state of the contralateral kidney must be considered since increases in RBF and GFR in the contralateral kidney tend to offset any decrease in GFR on the stenotic side. On the other hand, it is possible that nephrosclerosis in the contralateral kidney may impair any vasodilatory response to CEIs. Finally, the volume status and degree of activation of the RAS is important. Thus, CEI administration in patients with volume depletion and renovascular hypertension is more likely to be associated with an acute impairment in renal function.

In summary, converting enzyme inhibitors lower blood pressure significantly in patients with unilateral and bilateral renal artery stenosis. Moreover, in most patients impaired renal function does not occur. A spectrum of renal hemodynamic responses may be exhibitied in this CEI treated group of patients. In most instances of unilateral stenosis the CEIs are safe. In either unilateral or bilateral stenosis CEIs can cause a reduction in glomerular filtration rate. Impaired renal function in much more likely to occur in bilateral renal artery stenosis particularly if systemic blood pressure is markedly lowered. CEIs should be used with extreme caution in this circumstance particularly if critical stenosis is known to be present in both renal arteries. In unilateral renal artery stenosis CEIs are generally very safe, however, if a substantial reduction in creatinine clearance is present before CEIs are administered acute deterioration in renal function may result and should be watched for. Finally, attention to dietary sodium intake is important when administering CEIs in renovascular hypertension and extreme sodium restriction (<10-20 meq/d) should be avoided.

D. Effect of CEIs on Renal Function In Congestive Heart Failure (CHF) -

1. Renal Hemodynamics and Sodium Metabolism in CHF -

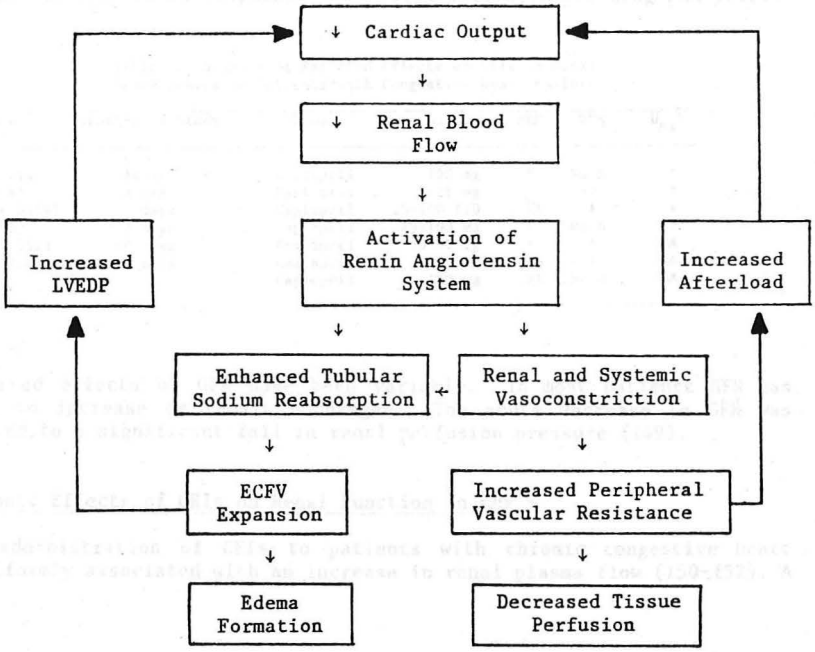
The renin-angiotensin system plays an important role in sodium retention associated with congestive heart failure as evidenced from experimental and clinical studies (139-142). The major stimulus to the RAS appears to be a fall in renal perfusion owing to a decrease in cardiac output. In addition, neurohumoral factors probably also play a role (143-144). As a consequence of RAS activation plasma renin activity, angiotensin II and aldosterone levels increase thereby contributing to increased systemic and renal vascular resistances. Renal plasma

flow, glomerular filtration rate and renal sodium excretion decrease. Subsequently tissue perfusion is impaired and ECFV expansion and edema formation develop. The increases in ECFV and vascular resistance further aggravate impaired cardiac function. Figure 19 summarizes the cardiorenal interactions in the pathogenesis of low output CHF.

Ickikawa et al. have measured microcirculatory parameters in rats with chronic congestive heart failure induced by coronary artery ligation (145). They have shown that glomerular plasma flow and SNGFR are significantly reduced, efferent arteriolar resistance is markedly increased, glomerualr capillary pressure is high and filtration fraction is increased. In addition, the glomerular ultrafiltration coefficient was suppressed and fractional proximal volume absorption was increased. These abnormal glomerular hemodynamics are comparable to those observed in high AII states such as volume depletion. Acute administration of the CEI teprotide promptly reversed these hemodynamic and functional changes indicating that they are at least in part mediated by increased angiotensin II activity. However, it must be remembered that inhibition of angiotensin II activity may also reduce sympathetic outflow. Since norepinephrine can also cause renal vasoconstriction it is possible that othr indirect effects of CEI at extrarenal sites are also important in this model. Nevertheless, CEI ameliorates the altered intrarenal hemodynamics in CHF in a manner that tends to restore normal renal function.

Figure 19

Cardiorenal Interactions and the RAS in Low Output Congestive Heart Failure



Although increases in PRA, angiotensin II and aldosterone levels are commonly observed in patients with CHF, not all clinical syndromes of congestive heart failure are accompanied by an elevated PRA. Furthermore, other factors including elevated catecholamines and the symptathetic nervous system are important in the pathogenesis of abnormal hemodynamics and sodium metabolism in these patients. However, as emphasized by Dzau et al. (140), reported differences in the relationship between CHF and the RAS may be explained by differences in clinical status of the patients. In particular, the RAS is markedly activated in patients with decompensated CHF but not in patients with stable CHF even though PCW and CI are similar in both groups. The importance of increased AII in decompensated CHF is underscored by observation that a beneficial hemodynamic response to CEIs is observed most often in those heart failure patients with elevated PRA levels. This notwithstanding some investigators have reported no consistent relationship between pre-drug PRA levels and the beneficial effects of CEIs in patients with clinically symptomatic CHF (146).

2. Acute Effects of CEIs on Renal Function In Congestive Heart Failure -

Few studies have addressed the acute effects of CEIs on renal function. Table 5 presents the salient features of the renal hemodynamic and sodium excretion effects of CEIs in recent studies which have addressed this issue. Acute intravenous administration of CEIs in humans with congestive heart failure is associated with a fall in mean arterial pressure, reductions in pulmonary capillary wedge pressure, heart rate and systemic vascular resistance and increase in cardiac index. Renal blood flow and urinary sodium excretion uniformly increase despite the fall in mean arterial pressure and renal vascular resistance decreases (74,147,148). These responses correlated well with pre-drug PRA levels.

Table 5. Summary of Reported Effects of CEIs on Renal Hemodynamics in Patients with Congestive Heart Failure

Reference	Duration of Study	Drug	Dose	RBF	GFR	$U_{Na}V$
Creager (147)	Acute	Captopril	100 mg	↑	No Δ	↑
Dzau (148)	Acute	Captopril	5-25 mg	↑	↑	↑
Pierpont (149)	3 days	Captopril	25-100 TID	NA	↓	↓
Kubo (150)	7 days	Captopril	25-100 mg	↑	No Δ	↑
Cleland (152)	60 days	Enalapril	10-40 mg	↑	↓	NA
Packer (151)	10-90 days	Enalapril	40 mg	NA	↓	NA
		Captopril	150 mg	NA	No Δ	NA

However, reported effects on GFR have been variable. In most patients GFR has been reported to increase or remain unchanged. The acute decrease in GFR was probably related to a significant fall in renal perfusion pressure (149).

3. Chronic Effects of CEIs on Renal Function in CHF -

Chronic administration of CEIs to patients with chronic congestive heart failure is uniformly associated with an increase in renal plasma flow (150-152). A

natriuresis and diuresis occurs as a result of improved renal hemodynamics, inhibition of AII activity and a decline in aldosterone levels. Most patients treated with either captopril or enalapril exhibit an improvement in overall fluid and electrolyte balance. An additional benefit is improvement of CHF associated hyponatremia reflecting an improvement in free water clearance in these patients. It is noteworthy that the addition of loop diuretics enhances natriuresis and augments free water clearance (148). Table 6 summarizes the beneificial effects of CEIs in CHF. Although some investigators have reported increases or stability of GFR (74,146,147,150-152), others have found that GFR declines and BUN and creatinine increase during chronic CEI therapy (151,152). There is a rough correlation between pretreatment PRA and the decreases in GFR reported in these patients (149) . In a double blind control study by Cleland et al., in stable patients, long-term high dose (up to 36.5 mg/day) enalapril therapy while improving systemic hemodynamics and exercise performance was associated with a decrement in mean GFR and an increase in mean RBF (152).

Table 6. Summary of Renal Effects of ACE Inhibition in CHF

Increases renal blood flow and GFR (dependent on renal perfusion pressure)
Blocks production of aldosterone
Corrects hyponatremia
Spares potassium
Without diuretic, causes little or no fluid retention
With diuretics, induces synergistic effects

It was postulated that a disruption in GFR but not RBF autoregulation occurs in these patients, presumably as a result of a decrease in efferent arteriolar resistance. Packer et al. have shown that in azotemic patients with CHF, captopril improves renal function, whereas enalapril worsens it (151). In this study enalapril caused a greater fall in blood pressure than captopril which in the setting of azotemia may predispose to toxicity (see above). Unfortunately, it is not possible to predict the renal response to CEIs based on the degree of CHF (using subjective historical data or hemodynamic parameters), PRA or serum sodium concentrations after long-term therapy particularly when concomitant drug therapy is used. In this regard, it is noteworthy that Cleland's patients were taking diuretics and digoxin which complicates matters since diuretics tend to increase PRA and angiotensin II levels, whereas digoxin tends to decrease them. Furthermore, in the enalapril group, very large doses (36.5 mg/d) were employed and the patients all had mild azotemia. Recalling that enalapril has a prolonged half-life in this setting and since drug levels were not measured it is not possible to determine whether drug toxicity played an important role in their studies.

In summary, the renin angiotensin system is activated in acute and chronic congestive heart failure particularly when acute or subacute decompensation is present. The precise mechanism for the increase in renin release is unknown but is probably multifactorial involving both a fall in renal perfusion pressure and activation of the sympathetic nervous system. Interruption of angiotensin II formation by CEIs in patients with CHF and mild to moderate azotemia improves renal blood flow, cardiovasular hemodynamics and increases sodium excretion and GFR in some cases increases. However, in some patients GFR may decrease perhaps owing to a fall in systemic arterial pressure which in turn reduces renal

perfusion pressure. "Afterload reduction of the glomerulus" by inhibiting angiotensin II effects in this situation may be the cause for the observed decrease in GFR. Although GFR may decrease in some instances, frank oliguric acute renal failure has not yet been reported in this setting. Whether patients with more severe azotemia (GFR<30 ml/min) and heart failure will demonstrate increases or decreases in GFR after CEI administration remains to be determined. At the present time it appears safe to administer these agents to patients with chronic heart failure providing that renal function is followed closely. In most patients improved cardiac function in the absence of severe, symptomatic hypotension after institution of CEI therapy may be quite beneficial. Attention to the doses of drugs used is important since high doses of CEIs, particularly of enalapril (>20 mg/d), have been associated with decreased renal function. Finally, since some patients with high circulating aldosterone levels who are on low sodium diets are prone to hyperkalemia when CEIs are administered, serum K^+ should be followed closely as well.

E. Toxicity of CEIs -

Many side effects of CEIs have been reported. The reported renal fluid and electrolyte side effects are shown below in Table 7.

Table 7. Adverse Effects of CEIs on Renal, Fluid and Electrolyte Status

1. Hemodynamic acute renal failure
2. Acute interstitial nephritis
3. Proteinuria
4. Hyperkalemia
5. Hyponatremia
6. Renal glycosuria

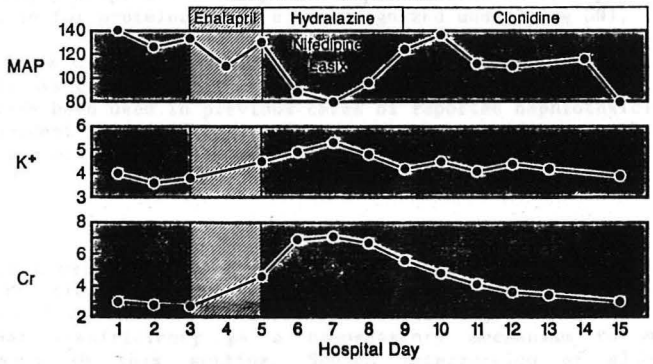
1. Acute Renal Failure-

Acute renal failure occurs most commonly after CEI in patients with bilateral renal artery stenosis. As discussed above, the renal failure in this setting is functional in the sense that it represents a pre-renal form of acute renal failure. This effect results from a fall in glomerular ultrafiltration pressure. It is reversible with discontinuation of the drug. A typical case of a patient with CEI induced acute renal failure is depicted in figure 20 below. The patient was a 58 y/o white man with severe peripheral and coronary atherosclerosis who was azotemic. His exam included bilateral carotid, epigastric abdominal and bilateral femoral artery bruit. Bilateral renal artery stenosis was confirmed by renal angiography. The urine sediment was normal and the fractional excretion of sodium was low. Within 24 hours of administration of enalapril mean arterial pressure decreased in association with a rise in serum creatinine and serum potassium levels. Upon discontinuation of the drug renal function slowly improved. The continued rise in serum creatinine for the first few days after stopping the drug was probably in part due to the prolonged half life of enalaprilic acid in renal failure. In addition because systemic pressure fell further, renal perfusion pressure was further decreased. The patient was managed conservatively and did

not require dialysis. These findings are characteristic of CEI induced functional renal failure as previously reported (131-135). The peak impairment in renal function varies widely from a few days to several months in some series; however, it is most often observed within a day or two after initiation of the drug. In most if not all cases, renal function improves within one week after discontinuation of the CEI. The possible mechanisms for acute renal failure in the patient with renal artery stenosis has been reviewed (vide supra). It should be emphasized that most all patients recover renal function promptly after discontinuation of CEI therapy. Hyperkalemia should be anticipated because of the potential reduction in aldosterone production in association with renal failure. As a corollary the development of acute renal failure in a hypertensive patient treated with a CEI should raise the possibility of renal artery stenosis. Both nonoliguric and oliguric forms of functional (or hemodynamic) acute renal failure may occur with CEIs.

Figure 20

EFFECT OF ENALAPRIL ON BLOOD PRESSURE SERUM K⁺ AND RENAL FUNCTION IN A PATIENT WITH BILATERAL RENAL ARTERIAL STENOSIS



Acute interstitial nephritis has been reported in a few patients receiving captopril therapy. Although these were biopsy proven cases, in many cases concomitant diuretic therapy was administered raising the possibility that other agents may have been responsible (154-156). In a few but by no means all of these cases, rash and/or eosinophilia has been recognized. The main feature distinguishing this form of CEI-associated acute renal failure from that reported in renal vascular hypertension was the absence of a significant fall in mean arterial pressure. In patients with functional renal failure, in every case, a significant and often substantial reduction in blood pressure occurs.

CEIs and Glomerular Disorders -

Several cases of proteinuria and frank nephrotic syndrome have been reported in patients with hypertension treated with captopril. Membranous GN has been most

frequently identified on renal biopsy specimens and is reversible after discontinuation of the drug (157-159). One case of irreversible renal failure associated with mebranous GN and unilateral renal artery stenosis has been reported. Membranous changes were only detected on the nonstenosed kidney (160). The mechanism of captopril-induced MGN appears is unknown. It has been speculated that it may be due to an immunoregulatory disturbance, rather than a hapten-associated disorder, similar to that observed in drug-associated autoimmune disturbances (161). In this regard a serum sickness-like syndrome developed in 2 patients with MGN during captopril therapy (160,162). Three potentially important predisposing factors have emerged from analysis of these reports. First, many patients had underlying nephrosclerosis which can itself be associated with proteinuria (even to nephrotic levels). Second, high doses of captopril were generally employed. Third, most patients had pre-drug azotemia to begin with.

Non-nephrotic proteinuria due to captopril has been reported in less than 1% of patients in large series (161). In most instances proteinuria is mild and reversible. This side effect is relatively rare, particularly in patients treated with less than 150 mg daily. Due to difficulty in establishing a casual link between CEI therapy and proteinuria in many instances it is difficult to be certain of the true incidence of this side effect. It does seem possible, however, that CEIs may precipitate development of proteinuria in some patients who may have a predilectin for proteinuria (i.e. unrecognized underlying GN).

In all these forms of nephrotoxicity the doses of captopril were relatively high compared to what is currently recommended for hypertension management. Doses up to 450 mg/day have been used in previous cases of reported nephrotoxicity. If there is a dose-dependent effect it is likely that these side effects will decline in the future as lower doses generally are employed now.

Hyperkalemia -

Hyperkalemia is a well recognized complication of CEI therapy. The incidence of hyperkalemia in CEI treated patients is unknown. It appears that most often in patients with pre-existing azotemia. Aldosterone levels may be elevated in some patients with renal insufficiency as a compensatory mechanism to maintain potassium homeostasis in this setting. Sudden interruption of aldosterone secretion would be expected to trigger predispose hyperkalemia. Furthermore, if acute renal failure develops in patients taking CEIs, hyperkalemia is very likely to occur.

Hyponatremia has been reported in a patient treated with captopril for congestive heart failure by Al-Mufti and Arieff (163). These authors postulated that a combination of captopril-induced polydipsia, and volume depletion-induced ADH excess was responsible for the development and persistence of hyponatremia. The dipsogenic effect of captopril is presumed to be due to the fact that whereas captopril does not cross the blood-brain barrier, angiotensin I does. Since the brain can metabolize AI to AII it is possible that local generation of AII in the brain directly stimulated thirst in this patient.

In addition to these effects, renal glycosuria has been reported with both captopril and enalapril (164).

In summary, CEI therapy may be associated with a variety of renal, fluid and electrolyte disturbances. Most of these aberrations are more likely to occur with high doses of these agents and in patients with renal insufficiency. Most importantly, in nearly every case the lesions are completely reversible after discontinuation of the drug.

Effect of CEIs in Proteinuric Renal Diseases -

Recent clinical studies have called attention to the fact that CEI may be beneficial in reducing proteinuria in some forms of glomerular disease. As already discussed proteinuria in disease models of chronic renal insufficiency can be attenuated by CEI therapy. Taguma and colleagues have recently reported that proteinuria in diabetic patients with nephrotic syndrome can be substantially reduced by CEI therapy without any adverse effect on renal function (165). Heeg et al. have also recently demonstrated that lisinopril, a new CEI, administered orally for 12 weeks in 13 patients with a variety of proteinuria glomerular diseases and impaired renal function, significantly reduced proteinuria (166). Unfortunately, GFR also declined in these patients. The authors suggested that these effects due to a reduction in intraglomerular capillary pressure. They also argued that the reduction in proteinuria was disproportinately greater than the decrease in GFR. Marre et al (122) have recently reported that administration of enalapril significantly reduced microalbuminia in normotensive diabetic patients with normal renal function in association with a decrease in blood pressure, and increases in GFR and RPF (see Table 8). Taken together with the fact that excess angiotensin II states promote proteinuria it is likely that CEI therapy reduces proteinuria by inhibiting angiotensin II. These studies are intriguing since they provide us with another potential future therapeutic strategy for ameliorating protein loss in glomerular diseases.

Table 8. Effects of Chronic Oral Enalapril on Renal Function in Patients with Diabetes Mellitus and Micro Albuminuria

	GFR		RPF		RVR		Fx ALB CL	
	E	P	E	P	E	P	E	P
	ml/min·1.73m^2		ml/min·1.73m^2					
Control	130±23	133±26	526±113	597±124	0.23±.01	0.22±.09	2.25±1.79	1.67±1.34
Experimental	141±24	127±25	581±128	602± 15	0.18±.04	0.23±.10	1.25±1.40	2.58±1.50
	p<.05	NS	p<.05	NS	p<.05	NS	p<.05	p<.01

E = enalapril
P = placebo

Ref: Marre et al., Brit. Med. J. 294:1448, 1987.

CONCLUSIONS AND RECOMMENDATIONS

Converting enzyme inhibitors represent an important breakthrough in the therapeutic management of a variety of cardiovascular disorders. Their known and potential beneificial effects are applicable to a large segment of patients in a general medical practice. These agents are generally safe, quite effective and

have reasonably few untoward side effects. In the kidney these agents show great promise for slowing progression of chronic renal insufficiency in experimental models of renal failure. Clinical trials are now being conducted in an attempt to define a possible role for these agents in ameliorating the progression of renal failure in patients with renal disease. The treatment of essential hypertension, renovascular hypertension and hypertension associated with chronic renal insufficiency as well as severe congestive heart failure with CEIs is now commonplace. Important adverse side effects on renal function including acute renal failure and proteinuria glomerular lesions may develop in any of these patient groups; however, these effects are almost always completely reversible upon discontinuation of the drug. Therefore, close monitoring of renal function by measuring BUN and serum creatinine as well as routine qualitative urinary protein testing should be carefully considered when administering CEIs. In addition, one should pay careful attention to dosage when administering CEIs to patients with underlying renal insufficiency of any cause because of the prolongation of the half life of these agents, especially enalapril. With these considerations in mind CEIs may be used safely in most patients.

REFERENCES

1. Goldblatt H., et al., J Exp Med 59:347, 1934.
2. Goldblatt H., Physiol Rev 27:120, 1947.
3. Tigerstedt and Bergmann, Skand Arch Physiol 8:223, 1898.
4. Helmer O.M., Page I.H., J Biol Chem 127:757, 1939.
5. Kohlstaedt K.G., et al, Proc Soc Exp Biol and Med 39:214, 1938.
6. Page I.H., Helmer O.M., J Exp Med 71:29, 1940.
7. Braun-Menendez et al, J Physiol (London) 98:283, 1940.
8. Skeggs et al, Circulation 3:384, 1951.
9. Skeggs et al, J Exp Med 100:363, 1964.
10. Lentz et al, J Exp Med 183:104, 1956.
11. Davis, In: Hormones and the Kidney: (Williams PC, ed.) New York, Academic Press, p. 325, 1963.
12. Laragh et al, J Amer Med Assoc 174(3):96, 1960.
13. Biron et al, J Clin Invest 40:330, 1961.
14. Ferreira, Brit J Pharmacol 24:163, 1965.
15. Ferreira and Silva, Experientia 21:347, 1965.
16. Ferreira and Vane, Br J Pharmac Chemother 29:367, 1967.
17. Bakhle, Nature 220:919, 1968.
18. Ng and Vane, Nature 216:762, 1967.
19. Ng and Vane, Nature 218:144, 1968.
20. Ferreira et al, Nature 225:379, 1970.
21. Ondetti et al, Biochem 10(22):4035, 1971.
22. Ondetti et al, Science 196:441, 1977.
23. Patchett et al, Nature 288:280, 1980.
24. Keeton T.K., Campbell W.R., Pharmacol Rev 32:2, 1980.
25. Tobian L., et al, J Clin Invest 38:605, 1959.
26. Skinner S.L., et al., Circ Res 15:64, 1964.
27. Blaine E.H., et al., Amer J Physiol 220:1593, 1971.
28. Blaine E.H., et al., Circ Res 27:1081, 1970.
29. Barajas L., Lab Invest 13:916, 1964.
30. Barajas L. and Muller J., J. Ultrastruct Res 43107, 1973.
31. Vander A.J., Amer J Physiol 209:659, 1965.
32. Ueda H., et al., Circ Res 26/27(1):195, 1970.
33. Goormaghtigh N., Proc Soc Exp Biol Med 42:688, 1939.
34. Olson, Adv Prostagl Thrombox Res 7:1135, 1980.
35. Laragh J., et al., Amer J Med 52:633, 1972.
36. Bickerton R.K. and Buckley J.P., Proc Soc Exp Bio Med 106:834, 1961.
37. Campbell W.B. and Jackson E.K., Amer J Physiol 236:H211, 1979.
38. Hall J., Fed Proc 45:1431, 1986.
39. Schuster V., Fed Proc 45:1444, 1986.
40. Reid I.A., Fed Proc 38:2255, 1979.
41. Schiffin E.L. and Genest J., Amer J Physiol 242:R136, 1982.
42. Robinson M.M. and Evered M.D., Eur J Pharmacol 90:343, 1983.
43. Bailie M.D., Rector F.C., and Seldin D.W., J Clin Invest 50:119, 1971.
44. Navar G., Fed Proc 45:1411, 1986.
45. Inagami T., et al., Fed Proc 45:1414, 1986.
46. Kriz W., Kidney Int Suppl 20:551, 1987
47. Ingelfinger J.R., et al, J Clin Invest 78:1311, 1986.

48. Hall J., et al., Amer J Physiol 233(5):F366, 1977.
49. Steiner R.W., et al., J Clin Invest 64:503, 1979.
50. Tucker B.J. and Blantz R.C., Amer J Physiol 244:F11, 1983.
51. Mimman A. et al., Kidney Int 5:348, 1974.
52. Luft F.C., et al., Circulation 60:697, 1979.
53. Kirkendall W.M., J Lab Clin Med 87:418, 1976.
54. Dworkin L.D. and Brenner B.M., in The Kidney, Raven Press, 1985, p. 397.
55. Blantz R., Kidney Int 31(20):S108, 1987.
56. Edwards R.M., Amer J Physiol 244:F526, 1983.
57. Ardaillou R., et al., Kidney Int 31(20):S75, 1987.
58. Dunn M.J. and Scharschmidt L.A., Kidney Int 31(20):S95, 1987.
59. Schor N., et al., Amer J Physiol 238:F428, 1980.
60. Hall, Amer J Physiol 237:F424, 1979.
61. Navar G., Kidney Int 31(20):S81, 1987.
62. Schnermann J. and Briggs J., In: The Kidney. (Seldin & Giebisch, eds), Chap 28, p. 669, 1985.
63. Schnermann J. and Briggs J., Fed Proc 45:1426, 1986.
64. Mendelsohn, Fed Proc 45:1421, 1986.
65. Chou et al, Fed Proc 45:1438, 1986.
66. Bohrer M.P., et al., Amer J Physiol 233:F13, 1977.
67. Blantz R., Amer J Kidney Dis 10(1):2, 1987.
68. Kumar, Arch Int Med 140:1631, 1980.
69. Berlyne G.M., et al., Q J Med 33(131):325, 1964.
70. Eiser A.R., et al., Nephron 30:374, 1982.
71. Tucker B.J. and Blantz R.C., Amer J Physiol 1986.
72. Dworkin L., et al., Amer J Physiol 244:F95, 1983.
73. Levenson et al, Am J Med 72:354, 1982.
74. Dzau V., et al., New Engl J Med 302:1373, 1980.
75. Dzau V. and Pratt R.E., In: Physiology and Pharmacology in the Heart and Cardiovascular System (Fozzard et al, eds), Raven Press, New York, p. 1631, 1986.
76. Hockenthal et al, Kidney Int 30(20):54, 1987.
77. Brunner H. et al., Ann Int Med 90:19, 1979.
78. Aldiger J.C. et al., Am J Cardiol 49:1447, 1987.
79. MacGregor et al, In: Angiotensin Converting Enzyme Inhibitors (Horowitz, ed) Urbant Schwagenberg, Baltimore Munich, p. 329, 1981.
80. Zusman R., Am J Kid Dis 10:13, 1987.
81. Kripalani K. et al, Clin Pharm Ther 77(5):636, 1980.
82. Weber, Amer J Kidney Dis 10:45, 1987.
83. Duchin K.L., et al, Clin Pharm Ther 31(4):452, 1982.
84. Duchin K.L., et al, Kidney Int 25:942, 1984.
85. Brunner D.R., et al, Brit J Pharmacol 11:461, 1981.
86. Till A.E., et al, Biopharm Drug Disp 5:273, 1984.
87. Kelly J.G., et al., Brit J Pharmacol 21:63, 1986.
88. Unger, et al., J Cardiol Pharm 7:36, 1985.
89. Hollenberg N.K., et al., Kidney Int 12:285, 1977.
90. Hollenberg N.K., Am J Cardiol 49:1425, 1982.
91. Hall J., et al, Am J Physiol 239:F271, 1980.
92. Vetter, et al., Klin Wochenschi 62:731, 1984.
93. Zimmerman, Am J Physiol 243:H277, 1982.
94. Dunn et al, Am J Cardiol 53:105, 1984.
95. Hollenberg et al, KI 20:240, 1981.

96. Wong and Zimmerman, Life Sci 27:1291, 1980.
97. Deforrest et al, Am J Physiol 243:F543, 1982.
98. Hall et al, Am J Physiol 241:R190, 1981.
99. Hall et al, Am J Physiol 237:F424, 1979.
100. Mimran et al Am J Med 76(5B):14, 1984.
101. Hall et al, Am J Physiol 239:F271, 1980.
102. Zimmerman and Wong, In Angiotensin Converting Enzyme Inhibitors (Horowitz, ed) Urban and Schwazenberg Baltimore-Munich, p 235, 1981.
103. Baun and Gaddy, Am J Kidney Dis 6:222, 1985.
104. Burke and Schrier, Kidney Int 31(20):S143, 1987.
105. Brown et al, Nephron 6:329, 1969.
106. Davies et al, Lancet 1:683, 1973.
107. McGrath and Ledingham, Clin Sci Mol Med 54:305, 1978.
108. Wilkinson et al, Q J Med 39L377, 1970.
109. Schambelan et al, Kidney Int 17:89, 1980.
110. Parving et al, Diabetes 32(2):83, 1983.
111. Woods et al, New Engl J Med 241(1):10, 1974.
112. Anderson et al, J Clin Invest 77:1993, 1986.
113. Dworkin and Feiner, J Clin Invest 77:797, 1986.
114. Anderson et al, J Clin Invest 76:612, 1985.
115. Hostetter et al, Kidney Int 19:410, 1981.
116. Zatz et al, Proc Natl Acad Sci 82:5963, 1985.
117. Zatz et al, J Clin Invest 77:1925, 1986.
118. Neugarten et al, Kidney Int 28:135, 1985.
119. Raij et al, Hypertension 7:398, 1985.
120. Dworkin et al, J Clin Invest 73:1448, 1984.
121. Jenkins et al, J Cardiovasc Pharmacol 7:596, 1985.
122. Marre M., et al., Brit Med J 294:1448, 1987.
123. Ram CVS, Medical Grand Rounds, UTHSCD, 1987.
124. Anderson, Kidney Int 31(20):S157, 1987.
125. Ploth, Am J Physiol 245:F131, 1983.
126. Huang et al, Hypertension 3:285, 1981.
127. Huang et al, Clin Sci 62:573, 1982.
128. Michel et al, Kidney Int 29:1011, 1986.
129. Wenting et al, Brit Med J 288:886, 1984.
130. Levenson D.J. and Dzau V.J., Kidney Int 31(Suppl 20):S173, 1987.
131. Hricik et al., New Engl J Med 308:373, 1983.
132. Curtis et al, New Engl J Med 308:377, 1983.
133. Bender et al, Hypertension 6:I193, 1984.
134. Silas et al., Brit Met J 286:1702, 1983.
135. Hollenberg N.K., Caardiovasc Rev Rpt 4(6):852, 1983.
136. Franklin and Smith, Am J Med 79:19, 1985.
137. Textor et al, Ann Int Med 102:308, 1985.
138. Hollenberg N.K., Amer J Kidney Dis 10(Suppl):52, 1987.
139. Curtis C., et al., Circulation 58:363, 1978.
140. Dzau V., et al., Circulation 63(3):645, 1981.
141. Chonko A.M., et al., Amer J Med 63:881, 1977.
142. Hostetter T.H., et al., Amer J Physiol 245:H98, 1983.
143. Cohn J.N., et al., New Engl J Med 311:819, 1984.
144. Cleland J., et al., Amer J Med 77:880, 1984.
145. Ichikawa I., et al., Circ Res 55(5):669, 1984.
146. Awan N.A., et al., Amer Heart J 101:22, 1981.

147. Creager M.A., et al., Circulation 64(3):483, 1981.
148. Dzau V.J., and Hollenberg N.K., Ann Intern Med 100:777, 1984.
149. Pierpont G.L., et al., Brit Heart J 46:522, 1981.
150. Kubo S., et al., J Cardiovasc Pharm 7:753, 1985.
151. Packer M., et al., New Engl J Med 315:847, 1986.
152. Cleland J.G., et al., Brit Heart J 54:305, 1985.
153. Fotino S., and Sporn P., Arch Intern Med 143:1252, 1983.
154. Cahan D.H., Kidney Int 25:160, 1984.
155. Hoake D., et al., Brit Med J 285:1538, 1982.
156. Fassett R.G., et al., Brit Med J 286:648, 1983.
157. Captopril Collaborative Study Group, Lancet 1:988, 1982.
158. Hoorntje S.J., et al., Acta Med Scand 208:325, 1980.
159. Prins, E.J.L., et al., Lancet II:306, 1979.
160. Smit A.J., et al., Neth J Med 28:23, 1985.
161. Lewis E., Amer J Kidney Dis 10(1) suppl 1:30, 1987.
162. Hoorntje S.J., Lancet 2:1297, 1979.
163. Al-Mufti H.I., and Arieff A.I., Amer J Med 79:769, 1985.
164. Cressman M.D., et al., Lancet 2:440, 1982.
165. Taguna Y., et al., New Engl J Med 313:1617, 1985.
166. Heeg, et al., Kidney Int 32:78, 1987.
167. Stella A., and Zanchetti A., Kidney Int 31(Suppl 20):S89, 1987.