INTRODUCTION

Calcium channel blockers

Calcium channel blockers are a heterogenous group of drugs with widely variable effects on heart muscle, atrioventricular conduction, blood vessels and coronary circulation (Weiner 1988). The concept of calcium channel inhibition originated when it was noticed that prenylamine, a coronary dilator, depressed cardiac performance in canine heart lung preparation (Lindner 1960). In 1962 Hass and Hartfelder reported that verapamil, a coronary vasodilator, possessed negative inotropic and chronotropic effects that were not seen with other vasodilator agents such as nitroglycerin. Fleckenstein et al (1967) suggested that the negative inotropic effect of ipraveratril and prenylamine resulted from inhibition of excitation-contraction coupling and that the mechanism involved is reduction of movement of calcium into cardiac myocyte.

Most calcium channel antagonists belong to 3 distinct chemical class as namely = phenylalkylamines (e.g. verapamil), benzothiazepines (e.g. diltiazem) and dihydropyridines (e.g. nifedipine). Receptors specific for each of these 3 major classes have been identified in L-type voltage dependent calcium channels (Schwartz et al 1992).

Diltiazem is initially developed in Japan. In clinical practice diltiazem and verapamil have some what similar therapeutic spectra and contraindications, so that these agents are combined in some classifications of calcium antagonists. Diltiazem seems more

active on sinus node, so that it is more likely to decrease the heart rate than verapamil, whereas verapamil may be more active on the A-V node (Opie 1991).

Struyker Baudier et al. (1989) stated that for verapamil, diltiazem and related drugs, the negative chronotropic and dromotropic activity may be expected to contribute to the beneficial effects of these drugs in ischaemia. The dihydropyridines, however, cause modest reflex tachycardia and their beneficial effects in ischaemia are caused by vasodilatation in the appropriate vascular bed.

Van Zwieten (1993) stated that in addition to the hemodynamic changes, a direct cytoprotective, energy-conserving, and antiischemic effects of calcium antagonists have been identified. However, clinicians have had great difficulty in finding evidence for this cytoprotective activity but organ protective activity of certain calcium antagonists has now been observed in a few controlled trials of sufficient size.

In addition to the antiischemic and cytoprotective activity of calcium antagonists, the anti atherogenic potency of calcium antagonists so far established only in animal models, is potential contributor to the protective effects of calcium antagonists (Chobanian 1987).

Despite numerous animal studies, it has been very difficult to demonstrate cardioprotective activity of calcium antagonists in spite of their beneficial effects in hypertension, angina, and supraventricular arrhythmia. Results are at best inconclusive

for a beneficial effect of calcium antagonists in the management of acute myocardial infarction (Hinstridge and Speight 1991).

Pfaffendarf et al. (1993) stated that numerous reports are available on the relative degree of selectivity of different dihydropyridines for specific vascular bed although it should be realized that tissue selectivity is merely a matter of the concentration used. Nisoldipine, for example, has been claimed to have selectivity for coronary vessels. Similarly nimodipine has been claimed to be selective for cerebral vasculature. Also, manidipine have a certain degree of selectivity for the renal vascular bed.

Diltiazem hydrochloride:

Diltiazem is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration, but undergo extensive first-pass hepatic metabolism. The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentration. Diltiazem is about 80% bound to plasma proteins. It is extensively metabolized in the liver; one of the metabolites desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compounds. The half life is reported to be about 3-4 hours. Approximately 60% of the dose is excreted in the bile and 35-40% in the urine 2-4% as unchanged diltiazem (Chaffman and Brogden 1985).

Treatment with diltiazem is generally well tolerated. Adverse effects are associated with a depression of cardiac conduction including atrioventricular block, bradycardia, and, rarely, sinus arrest. Patients with sick sinus syndrome, preexisting atrioventricular

block, or bradycardia or those taking B-blocking agents or digitalis may be at particular risk of developing these reactions. Diltiazem can also cause headache, ankle oedema, hypotension and flushing. Diltiazem should be administered with caution to patients with preexisting hypotension and probably also to those with impaired left ventricular function due to the potential negative inotropic properties of diltiazem. Diltiazem may also cause nausea and gastrointestinal discomfort. There have been reports of hyperactivity sometimes with associated psychiatric symptoms. Gynecomastia has also been reported (Chaffman and Brogden 1985)

Diltiazem appears to be an effective agent in the treatment of variant angina due to coronary spasm. Substantial efficacy has been demonstrated in the prophylaxis of stable exertion angina and unstable angina. Diltiazem has shown some efficacy in the treatment of mild to moderate hypertension and in the control or prophylaxis of supraventricular tachyrhythmia, although the exact role of diltiazem in these conditions remains to be defined. Comparative studies between diltiazem and nifedipine or verapamil have been limited, but diltiazem appears to be of similar efficacy to these drugs in the treatment of angina pectoris while causing some what less frequent or severe adverse effect (Chaffman and Brogden 1985).

Calcium channel blockers and kidney

Since the introduction of calcium antagonists over two decades ago, attention has focused on their beneficial effects in the management of symptomatic coronary artery disease, and on their ability to lower blood pressure other than the effects on the kidney (Epstein 1991).

Calcium may be pivotal in tubular as well as vascular injury associated with renal ischemic injury. For example, calcium is involved in the increased conversion of xanthine dehydrogenase to xanthine oxidase that occurs with renal ischaemia. During reflow, this calcium dependent conversion would lead to the generation of oxygen radicals, which further enhance membrane damage, resulting in additional cellular calcium overload and inhibition of repair of the membrane which is the primary gate keeper against calcium influx. With renal ischaemia, Adenosine triphosphate (ATP) decrease, cellular sodium concentration rises, and cell swelling occurs. Such cell swelling may also increase permeability to calcium (Schrier et al. 1987).

Initially, the mitochondria are able to buffer and protect against the rise in cytosolic calcium and activation of degradation enzymes. Eventually, however, the mitochondria become overburdened with calcium and lose their ability to synthesize ATP, which results in cell death. Cellular debris then causes distal tubular obstruction which is the major factor in the maintenance phase of acute renal failure. To enhance the repair

of cellular membrane, it may be necessary to scavenge oxygen radicals and inhibit phospholipase that may be activated by increase cellular calcium. The use of calcium antagonists to protect against increase influx of calcium would also allow more time for restoration of membrane integrity (Schrier 1991).

In acute renal failure, calcium antagonists reduce an inordinately high rate of calcium uptake, thus lessening renal vascular and tubular injury by calcium activated phospholipases, mitochondrial calcium overload and other potential mechanisms. In chronic renal failure, on the other hand, these drugs appear to slow the state of metabolism toward more normal level. This reduction in the hyper-metabolic states of the remnant nephrons may slow the progression of renal disease by reducing the work of transport at a time when cellular energy stores are at risk and solute transport requirements per nephron are markedly increased (Harrise et al. 1987).

The first evidence that calcium antagonists might be important in renal failure was provided by (Bruke et al. 1984) who used the norepinephrine model of ischemic acute renal failure in dogs. Without treatment, the glomerular filtration rate (G.F.R.) was negligible at 24 hours. Intrarenal infusion of verapamil 30 minutes before the administration of norepinephrine provided total protection against the fall in G.F.R. Even when verapamil was given after total cessation of renal blood flow for 40 minutes, it provided 50% protection.

Further evidence for the protective effect of verapamil was found in studies of a second model, the isolated perfused rat kidney, done by Shapiro et al (1985) who concluded that the increasing doses of verapamil significantly improved inulin clearance in the hour of reperfusion following 8 hours of cold ischaemia in this model; progressive restoration of cortical ATP levels at increasing verapamil concentration was also observed after 40 minutes of warm ischaemia.

But Van Zwieten (1993) stated that the final common pathway leading to death of ischemic reperfused cells is excessive calcium influx associated with a breakdown of cellular calcium homeostatic mechanisms and intracellular calcium overloading. The calcium influx that takes place during reperfusion after ischaemia occurs not only by way of L-type voltage operated channels, but also by way of alternate pathways such as passive diffusion (leak) and in exchange for sodium. Because calcium antagonists are selective potential operated channels (POC), theoretically these compounds will be unable to prevent the calcium influx that occurs by non-POC routes during ischaemia perfusion. In terms of direct cytoprotective effects, the calcium antagonists are therefore poor calcium overload blockers and should be considered, at least theoretically, as therapeutically suboptimal antischemic drugs.

New calcium antagonists were developed to block calcium ion influx by way of POCs and other routes. At present it is not possible to identify the intracellular site of

action of these compounds. The calcium overload blockers e.g. lidoflazine, flunarizine, are weak calcium antagonists in the classic sense, although a specific interaction with T.type channels in the central nervous system has recently been demonstrated for flunarizine (Peter et al 1991).

Epstein (1991) stated that calcium antagonists reverse afferent arteriolar vasoconstriction induced by widely divergent stimuli, including putative mediators of deranged renal hemodynamics such as endothelin. Such observations suggest that the activation of potential operated calcium channels constitute a final common mechanism of afferent arteriolar vasoconstriction by diverse agonists. In contrast, the efferent arterioles appear to be highly refractory to the vasodilator effects of calcium antagonists, indicating a remarkable intra-organ heterogenicity of mechanisms that activate smooth muscle within the renal microcirculation.

Calcium antagonists have additional properties that may contribute to their ability to afford renal protection under diverse experimental conditions and perhaps in clinical disorders. These include the ability of calcium antagonists to retard renal hypertrophy (Dworkin et al 1990), to attenuate the mitogenic effect of platelet derived growth factor and platelet activating factor and to act as free radical scavenger (Sweeney et al 1990).

Dwarkin et al (1991) concluded that renal protective effect of calcium antagonists is thought to be related to its systemic blood pressure lowering effect. Anderson (1991)

stated that reduction in systemic pressure should lead to a reduction in the pressure transmitted to the glomerular capillary bed, reducing barotrauma to the endothelium. Moreover, suppressed mesangial cell growth, proliferation, and matrix function could result from either the reduction in shear stress (Floege et al 1992) or from a direct anti mitogenic effect of the calcium antagonist (Shultz and Raij (1990). Also, Reams et al (1993) suggested that attenuation of compensatory glomerular hypertrophy may participate in the protection of the uninephrectomized spontaneous hypertensive rat (SHR) kidney from injury.

An additional renal protective mechanisms may relate to the proposal that calcium antagonists may attenuate mesangial entrapment of macromolecules (Epstein 1991). Keane and Raij (1985) demonstrated that Angiotensin II (Ang II) influence the transport of blood borne macromolecules into the mesangium. Raij and Keane (1985) have demonstrated that Ang II, when given to rats in subpressor doses, can both increase the uptake and decrease the disappearance rate of macromolecules such as radio labeled IgG in the mesangium. Also, they stated that entrapment of macromolecules in the mesangium may lead to mesangial cell and/or matrix expansion with subsequent progression to glomerular sclerosis. Epstein (1991) concluded that the demonstration that calcium antagonists can antagonize these mesangial effect of Ang II suggests an additional mechanism where by the drug may attenuate or retard the development of glomerular sclerosis.

Mesangial cells release platelet derived growth factor in response to certain injuries (Shultz et al 1988). The release of platelet derived growth factor is further enhanced in the presence of thrombin, suggesting an additional link between the coagulation system and glomerular injury (Shultz et al 1989). Shultz and Raij (1990) noted that calcium antagonists inhibit mitogenic effect of platelet-derived growth factor and of thrombin on mesangial cells. In addition calcium antagonists have also been shown to inhibit thrombin-induced stimulation of platelet activating factor production by endothelial cells. This may constitute another mechanism whereby calcium antagonists could attenuate glomerular injury induced by platelet activating factor (Epstein 1991).

Bauer and Reams (1985) concluded that calcium antagonists, in particular the dihydropyridines causes a short term loss of sodium and water in hypertensive animals and humans. The dose dependent effect appears to occur without any change in glomerular filtration rate. The natriuresis is associated with an increase in renal blood flow. However, this cannot be the sole cause of the natriuresis, because during long-term therapy with dihydropyridine calcium antagonists, sodium excretion returns to normal levels, whereas renal blood flow remains elevated.

Van Zwieten (1993) stated that it has been proposed that the natriuresis caused by calcium antagonists involves a direct tubular effect on the reabsorption of sodium. Serum electrolytes and plasma volume however, remains unchanged. The natriuretic effect of

the dihydropyridine, although modest and transient explain why these potent vasodilators do not cause fluid retention even in the long-term treatment of essential hypertension.

Takabataka et al (1993) stated that the intrinsic control of renal hemodynamics depend on the tubule glomerular feed back (TGF) mechanism as well as the myogenic mechanism. The former mechanism alters blood flow and glomerular filtration of a single nephron by changing afferent arteriolar resistance in response to the sodium chloride concentration at the macula densa. The (TGF) mechanism is believed to play an important role in the regulation of water and electrolytes. Calcium antagonists inhibit the (TGF) response by dilating the afferent arteriole, the effector site of the (TGF) mechanism.

Van Zwieten (1993) stated that the following renal disorders are now being explored as potential targets for calcium antagonists: renal insufficiency caused by radio contrast agents and cancer chemotherapy, and cyclosporine and aminoglycoside nephrotoxicity. Limited clinical evidence shows that verapamil, diltiazem, and nitrendipine may protect against radiocontrast-induced nephrotoxicity. Also, both diltiazem and verapamil have demonstrated an ability to protect against the development of tubular necrosis after transplantation of cadaveric kidneys (Wagner et al 1987 & Dawidson and Rooth 1990).

Takabataka et al (1993) stated that because the protective effects of antihypertensives on the kidney may be related to a reduction in glomerular hypertension as well as systemic blood pressure, the nephroprotective effect of individual calcium antagonists should be assessed separately.

Van Zwieten (1993) concluded that in various experimental models, calcium antagonists display potent antagonistic activity against the effect of different types of vasoconstrictors in the renal vascular bed, in particularly at the preglomerular level. In the absence of vasoconstriction provoked by catecholamines, angiotensin II, or endothelin, the calcium antagonists show little or no vasodilator activity in the renal vascular bed. The antivasoconstrictor effect is probably a major mechanism in the renal protective activity of these agents. In addition, counteracting calcium overload provoked by ischemic damage can be thought of as a potentially beneficial mechanism of calcium antagonists.

Angiotensin Converting Enzyme Inhibitors

The renin angiotensin system is now regarded as both a circulating hormonal system and a local endocrine system (Johnston 1990). The last step in the renin angiotensin enzymatic cascade is the conversion of Angiotensin I (AngI) into angiotensin II (AngII) by specific substance, angiotensin converting enzyme (ACE). This enzyme is widely distributed in the body and has many other peptide substrates, including bradykinin substance P, enkepalins, neurotensin and luteinizing hormone releasing hormone (Johnston et al 1992).

Ondetti (1988) concluded that the key to the action of ACE inhibitors on the renin-angiotensin system is their affinity for the zinc ion binding site on ACE. ACE inhibitors can be placed into three chemical classes based on their zinc ligand. Fosinoprilate (a metabolite of fosinopril) binds to the zinc binding site via phosphatinic acid group other ACE inhibitors bind via a carboxylic acid group (enalapril, lisinopril, and ramipril) or a sulfhydryl containing group (captopril).

Johnston et al (1992) stated that the function of ACE differs in individual tissues. This particularly applies to the brain where it may be responsible for processing other neuropeptides aside from AngI or bradykinins. Similarly in the testis, the function of the enzymes are not known but presumably are related to reproductive function, as the enzyme is known to be in germinal cells and spermatids. It's high concentration in

epithelial ion transporting cells, such as choroid plexus, gastrointestinal tract, seminal vesicles and submandibular gland, suggests that the enzyme and its peptide substrates may be responsible for ion transport in these tissues. Moreover, ACE may be important in the local regulation of regional blood flow, as the enzyme is localized in high concentration in blood vessels, both in endothelial cells and in vascular smooth muscle. It also modulate local sympathetic activity particularly in the heart.

Shelling et al (1991) suggested that local AngII may be a stimulus for hyperplasia and hypertrophy in both heart and the vasculature through direct action, stimulation of growth factors.

Sica (1992) stated that almost 80 new compounds belonging to the class of angiotensin-converting enzyme (ACE) inhibitors are under investigation, and that at least 11 newer ACE inhibitors should shortly become available for clinical use.

Salvetti (1990) stated that despite an abundance of ACE inhibitors and a range of interesting pharmacokinetics and biochemical features that distinguish them, two primary means remain by which ACE inhibitors will be considered separable. First, tissue activation and subsequent localized binding features that take advantage of multiple loci for tissue-based elements of the renin-angiotensin system (RAS) may vary among the various ACE inhibitors second, differential route of clearance may exist that then distinguish ACE inhibitors metabolically.

Cushman et al (1989) stated that the relationship between the circulatory and tissue based RAS is complex, and it remains unclear whether there are genuine differences as a consequence of tissue specificity.

On the other hand, considerable information exists relative to metabolic disposition of ACE inhibitors and there in the clearest distinction exists. Virtually all ACE inhibitors undergo a predominant renal mode of elimination, relying on both drug filtration and tubular secretion for their disposition (Kelly and O'Mallley 1990).

Sica (1992) stated that the elimination mode for an ACE inhibitor resides in the fact that agents within this drug class are extensively utilized in patients with differing degrees of renal insufficiency due to their effectiveness in the control of blood pressure and for their ability to retard the rate of progression of renal insufficiency. Moreover, the frequent use of ACE inhibitors in hypertensive renal failure population though proves problematic for several reasons. First, precise renal functional assement, beyond that which might be obtained by serum creatinine determinations, is required to ascertain the extent of renal functional improvement afforded by ACE inhibitor therapy. Second, as virtually all ACE inhibitors are renal eliminated, the accurate assessment of renal function is pivotal in the determination of ACE inhibitor dosage reduction to prevent drug accumulation.

Shulman et al (1989) concluded that the additional significance of accurate assessment of renal function resides in the fact that the weight of clinical evidence now supports the involvement of the kidney in most, if not all, forms of hypertension. This involvement is complicated by the clinically "silent" nature of the condition with progressing renal failure often going undetected for long periods of time.

Walker et al (1990) by analyzing the results of Multiple Risk Factor intervention trial (MRFIT)found that a decline in renal function was identified in 46% of participants. Also, they stated that there is evidences that loss of renal function is augmented with increasing levels of blood pressure (systolic, diastolic, and mean arterial) at entry of the trial. Rosnasky et al (1990) found that patients with essential hypertension had a greater rate of decline in renal function than did non hypertensives. Moreover, Grossman and Messerli (1992) concluded that a progressively steeper decline in renal blood flow supply with increasing severity of hypertension.

Benetas et al (1992) stated that in spontaneously hypertensive rats, acute treatment with ACE inhibitors Quinapril is able to improve compliance by decreasing distending pressure and by shifting the pressure / volume curve to the left (vasorelaxation). However, compliance remains lower compared with normotensive animals, chronic treatment seems to be able to normalize the compliance values. This action should be related to the effect of the drug in the arterial structure as well.

Johnston et al (1992) stated that in the vascular tree, ACE is not uniformly distributed and appears to be highest in mesenteric resistance vessels. In some forms of vascular and cardiac hypertrophy, ACE concentration are increased. Whether the beneficial cardiac and vascular effects of ACE inhibitors is due to suppression of the local renin - angiotensin system or their beneficial hemodynamic effects is fruitful area for further investigation.

Townend and Davies (1992) stated that treatment with quinapril resulted in lymphocyte B-receptor upregulation in patients with severe heart failure. There was an associated improvement in the cardiac responses to exercise and dobutamine stimulation. This would be consistent with functional myocardial B-receptor up regulation. They suggested that restoration of myocardial response to sympathetic nervous stimulation may be an important mechanism contributing to the improved symptomatic status of patients with heart failure during treatment with ACE inhibitors.

Schön et al (1992) stated that the ACE inhibition-induced effects of a smaller ventricular volume, decreased regurgitant fraction, and lowered ventricular work load would seem beneficial in delaying development of ventricular dysfunction in asymptomatic patients with severe, chronic aortic regurgitation. Further prospective studies are mandatory to establish if these beneficial effects of ACE inhibition are maintained for the long term, and if they may delay timing for aortic valve replacement in patients with severe, chronic aortic regurgitation.

Many experimental (Raya et al 1989) and clinical (Pfeffer et al 1988 & Sharp et al 1988) studies supported the use of ACE inhibitors in presenting an increase in decreasing left ventricular size post infarction by unloading the left ventricle and decreasing left ventricular chamber size. They may improve left ventricular ejection fraction and do so better than furosemide in patients with overt heart failure.

Benazepril

Benazepril is a non sulfhydral ACE inhibitor that is hydrolysed in vivo to the carboxylic metabolite, Benazeprilat. Oral benazepril is about 30% bioavilable and is primarily eliminated metabolically whereas renal elimination dominates the disposition of its primary metabolite, benazeprilat. The kinetics of benazepril are not significantly influenced by the kidney function, as might be anticipated for a compound mainly cleared from plasma by biotransformation. Alternatively, the kinetics of its metabolite benazeprilat are significantly affected by renal impairment, in that elimination is significantly slowed (Kaiser et al 1989).

Benazepril has shown a sustained antihypertensive effect (treatment up to 28 days) in both spontaneously hypertensive rats and renal hypertensive rats and dogs (Watkins and Weiss 1983 & Ogaw and Ono 1987). In DOCA / salt hypertensive rats, benazepril was only marginally effective in reducing blood pressure. This animal model has a low renin dependence and much experimental evidence suggests that it is the least sensitive model for testing ACE inhibitors (Miller 1988).

Wood et al (1987) stated that, although benazepril, or more accurately its metabolite benazeprilat, has been clearly shown to be a potent ACE inhibitor. In longer term studies a clear antihypertensive effect is seen which persists after serum ACE activity has returned to pretreatment levels. The significance of this finding is not clear, however, since it is likely that the inhibition of tissue bound ACE is of much greater significance than inhibition of the circulating enzyme. In common with other ACE inhibitors, benazepril potentiates the blood pressure lowering effect of bradykinin, an expected finding since ACE is also involved in degradation of bradykinins. However, animal studies suggested that at least with one week treatment, the blood pressure reduction induced by benazeprilat is mainly due to reduced angiotensin II formation.

Benazepril is used in hypertension (the usual maintenance dose is 20 mg once daily), heart failure. This agent appears well tolerated there is no evidence for an incidence of side effect any different that of other ACE inhibitors (hypotension, angioedema, dry irritating cough and hyperkalemia (Opie 1994).

correlation existed for their long-term antihypertensive effect. Thus, Wilson (1992) suggested that mechanisms other than inhibition of circulating ACE might cause this long-term effect. One of such mechanisms could be changes in renal prostaglandin synthesis.

It seems likely that all cells having cyclooxygenase can synthesize prostaglandins, although there may be regional differences in relative amounts. Thus, endothelial cells of afferent arteriole produce prostaglandin I_2 (PGI_2), glomeruli produce prostaglandin E_2 (PGE_2), PGI_2 and TXA_2, while interstitial cells yield PGE_2, These prostaglandins can be released from their origin and stimulate several types of receptors (Hallushka et al 1989).

Fray et al (1983) stated that for practical purposes, there are two types of classes: a prostacycline receptor recognizing PGI_2 and prostaglandin E_1 and a thomboxane receptor recognizing Tx A_2, prostaglandin H_2 (PGH_2), and possibly (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Prostacycline receptors activate adenyl cyclase, elevating intracellular c. AMP, which in turn leads to vasodilation and renin release while Tx A_2/PGH_2 receptors elevate intracellular free calcium via the inositol phosphate cycle, which causes vasoconstriction and inhibition of renin release. Moreover, Wilson (1992) stated that both classes of receptors are found on vascular smooth muscle cells, juxta glomerular cells and glomerular mesangial cells. All of these have receptors for other vasoactive agents such as angiotensin II, so that the overall effect of such peptides in the intact animal will be variable and the sum of a number of interactions.

Also, Wilson (1992) concluded that when the renal perfusion pressure is reduced more vasoconstrictors such as AngII and norepinephrine perfuse the kidney, prostaglandins (mainly PGI_2) are formed, modulate the vasoconstriction, and maintain the glomerular filtration rate (GFR).

Benjamin et al (1989) stated that if the vasoconstriction due to T x A_2 were primarily at the efferent arterioles, the GFR would be preserved and would be physiologically consistent with a role for arachidonate products in maintaining the GFR. Bradykinin, a vasodilator peptide can also release arachidonic acid from its esterified form in cell membrane and increase vasodilator prostaglandin synthesis. This effect is more marked in the kidney than other vascular bed so that cyclooxygenase inhibitors are able to prevent bradykinin-induced renal vasodilation but not forearm muscle vasodilation.

Romero and Knax (1988) stated that Besides maintaining renal blood flow and G.F.R, prostaglandins, affect other aspects of renal function. Their effects on renin secretion have been mentioned. Two other groups of actions in which there is general agreement are pressure natriuresis and modulation of the effects of vasopressin on water reabsorption. Medullary PGE_2 synthesis is increased when renal perfusion pressure is raised and may reduce sodium reabsorption in the thick ascending limb of loop of henle. Preventing the increase in PGE_2 synthesis reduces pressure natriuresis.

Wilson (1992) concluded that ACE inhibitors might reduce prostaglandins synthesis by reducing AngII formation while they might increase it by preventing bradykinin inactivation. In addition, the ACE inhibitor might have a direct stimulatory or inhibitory effect on PGs formation. Thus it should not be surprising that increase or decrease in prostaglandins synthesis have been reported during treatment with ACE inhibitors.

Diabetic nephropathy is the single most important cause of end stage renal disease accounting for more than 25% of all end stage renal disease in adults (Eggers 1988). The diabetic state is characterized by enhanced GFR, hyperperfusion, raised filtration fraction and nephromegaly. These abnormalities are particularly prominent in patient with poor metabolic control (Christiansen et al. 1982). These hemodynamic changes are due to a more pronounced dilation of the preglomerular or afferent arterioles compared with the postglomerular or efferent arterioles (Jensen et al 1986). Moreover, renal autoregulation is preserved in incipient diabetic nephropathy (Hommel et al 1986) whereas autoregulation is impaired or sometimes completely lacking in overt diabetic nephropathy (Parving et al 1984).

Jackson et al (1986) demonstrated the beneficial effect of ACE inhibition in uninephrectomized rats made diabetic by streptozocin. In contrast, they found that treatment with calcium antagonist verapamil, although producing equivalent falls in the systolic blood pressure did not alter intra renal hemodynamics, nor did it influence the

progressive increase in proteinuria in diabetic rats. Also, Anderson et al (1989) have demonstrated that antihypertensive therapy slow diabetic glomerulopathy, but that ACE inhibition afford superior long term protection compared with triple therapy with reserpine, hydralazine, and hydrochlorothiazide. Finally, Parving (1992) mentioned that ACE inhibition retard the development of glomerular basement membrane thickening and albuminuria in diabetic rats in presence or absence of hypertension.

Morre et al (1988) showed the effectiveness of ACE inhibitors in preventing diabetic nephropathy in normotensive diabetic patients with incipient nephropathy (persistent microalbuminuria). Later, Mathiesen et al (1990) confirmed the above finding and demonstrated that progression to clinical, overt, diabetic nephropathy was prevented in the group receiving ACE inhibition.

In a randomized, controlled trial comparing ACE inhibitors with Nifedipine, the former reduced albuminuria in normotensive microabluminuric diabetic patients treated for 6 weeks (Insua et al 1988).

Bjarck et al (1990) have demonstrated that antihypertensive treatment with an ACE inhibition reduces albuminuria in patients with diabetic nephropathy more than an equally effective treatment with metoprolol. They stated that the specific antiproteinuric effects of ACE inhibitors is independent of the effects of systemic blood pressure. Reduced

glomerular hypertension is likely a candidate mechanism since ACE inhibitors have a specific effect on intraglomerular hemodynamics independent of their effect on systemic blood pressure. Moreover, Marelli et al (1990) concluded that inhibition of ACE in patients with established diabetic nephropathy may reduce glomerular permeability to proteins by enhancing barrier size selectivity.

Holdaas et al (1990) have compared ACE inhibition with calcium channel blocker in a randomized, double-blind study of hypertensive insulin dependent diabetes mellitus patients with nephropathy. The ACE inhibitor reduced albuminuria, while albuminuria remained unchanged during treatment with the calcium channel blocker in spite of an equal reduction in systemic blood pressure. They stated that calcium channel blockers act predominantly on the preglomerular arterioles, while ACE inhibitors induce vasodilation of the postglomerular arterioles. Consequently, the glomerular capillary pressure is not reduced and renal blood flow autoregulatory efficiency markedly attenuated during calcium channel blockade, in contrast to the finding during ACE inhibition.

Parving (1992) suggested a more beneficial effect (renoprotective) of ACE inhibitors compared with conventional antihypertensive treatment and concluded that inhibition of angiotensin converting enzyme arrests the progressive rise in albuminuria in normotensive IDDM patients with diabetic nephropathy.

Beaufils (1992) stated that in various animal experiments, ACE inhibitors were able to prevent proteinuria and glomerular sclerosis, presumably by lowering transglomerular capillary pressure. In the diabetic human, ACE inhibitors are powerful antihypertensive drugs and devoid of metabolic side effects. Clinical studies indicate that ACE inhibitors reduce proteinuria and possibly slow the rate of decline in renal function. Such effect is not observed with B blockers. Large scale studies are needed to confirm this very important hypothesis.

On the contrary, de Jong et al (1992) concluded that although ACE inhibitors may induce symptomatic improvement by lowering urinary protein loss. These agents do not cure the underlying disease causing the increased passage of protein through the glomerular basement membrane.

On the contrary, Dworkin et al (1990) stated that nifedipine prevent DOCA-salt rats from becoming hypertensive and protect them from proteinuria and morphological evidence of glomerular injury, whereas enalapril is ineffective.

On the other hand, Apperlao et al (1991) concluded that enalapril lowers proteinuria more than atenolol in patients with non diabetic renal disease despite a similar blood pressure lowering effect of both drugs, and its antiproteinuric effect seems to be associated with the characteristic renal hemodynamic effect of ACE inhibitors by lowering

of intraglomerular capillary pressure. Also, Kamper et al (1992) stated that enalapril is superior to conventional antihypertensive therapy for slowing the deterioration of renal function in patients who have chronic nephropathy although there were no significant differences between the two groups in blood pressure or plasma lipid levels.

Weder (1990) stated that consistent and convincing experimental data have demonstrated that angiotensin II plays many roles in the control of renal function and the kidney response to injury. The intrarenal effects of angiotensin II include 1) increase in the efferent arteriolar tone resulting in increased glomerular capillary pressure 2) Promotion of mesangial cell contraction 3) Stimulation of proximal tubular Na^+ reabsorption, and 4) Possible growth hormone like effects leading to hypertrophy or hyperplasia of vascular smooth muscle. Because of their favorable intrarenal hemodynamic effects (particularly reduction of glomerular capillary pressure), ACE inhibitors may provide a renal protective effect in addition to their systemic antihypertensive effects.

Also, Sanchez et al (1991) stated that ACE inhibitors may exert a protective effect on the renal function of patients with severe hypertension as well as in those with renal impairment, by lowering systemic and, probably, intraglomerular pressure, reducing proteinuria and slowing the progression of renal failure.

Experimental models of acute renal failure

Brady and Singer (1995) stated that for purposes of differential diagnosis and management, acute renal failure is conveniently subclassified as: (1) prerenal (about 70%), a physiological response to renal hypoperfusion in which the integrity of the renal tissue is preserved; (2) intrinsic renal failure (about 25%) in which acute renal failure is caused by diseases of renal parenchyma and (3) Post renal acute renal failure (about 5%) due to acute obstruction of the urinary tract. Most acute intrinsic renal failure is induced by ischaemia and/or nephrotoxins and is classically associated with necrosis of renal tubule epithelial cells. Ischemic acute renal failure differ from prerenal type in that renal hypoperfusion has been severe enough to injure renal parenchymal cells, particularly tubule epithelium and the acute renal failure does not resolve immediately after restoration of renal blood flow.

Studies in experimental models have provided considerable insight into some of the pathophysiological events that initiate and maintain acute renal failure. The pathogenesis of acute renal failure is multifactorial and the involvement of responsible mechanisms differs between the various experimental models. These models generally rely on one of two initiating events: (1) renal ischaemia, as evoked by arterial occlusion, infusion of noradrenaline or the intermuscular injection of glycerol or 2) a nephrotoxic injury following the administration of mercuric chloride or nephrotoxic aminoglycoside antibiotics (Gattone et al 1983).

Venkatachalam et al (1976) stated that the prompt vasoconstriction, which appears to involve both preglomerular and post glomerular arterioles provides avascular basis for the initiation of myohemoglobinuric acute renal failure in glycerol treated rates. The acute renal failure in this model has two phases, the first dependent on blood flow and the second appearing to rely on other factors. Ayer et al 1971 stated that although incomplete tubular obstruction in the distal nephron may also be present. Obstruction does not seem to be the total explanation for the maintenance of renal functional impairment in this model (Ayer et al 1971).

Zhang (1991) stated that, in glycerol induced renal failure, the impaired glomerular microcirculation and reduced glomerular filtration rate were the main factors accountable for the acute renal failure. Moreover Gatton et al (1983) observed that after glycerol administration there was prompt constriction of afferent arterioles of both inner and outer cortical glomeruli. This constriction was no longer observed at 3 days despite the presence of acute renal failure. However by that time the endothelial finesteral area of the glomerular filtration barrier was significantly diminished. The same authors stated that this observations are consistent with the notion that in ischemic acute renal failure, an initiating vascular constrictive event is followed by sustaining renal mechanism that may include damage to the filtration barrier.

Bowmer et al (1983) concluded that, in glycerol induced acute renal failure, several abnormalities of cardiovascular responses have been demonstrated 48 hours after the induction of acute renal failure. These are similar to those occurring in patients and rats with chronic renal failure. Examples of these abnormalities were reduction of chronotropic response to sympathetic and vagal stimulation, elevated circulating nor-adrenaline with reduction in it's pressor response, and reduction in basal heart rate.