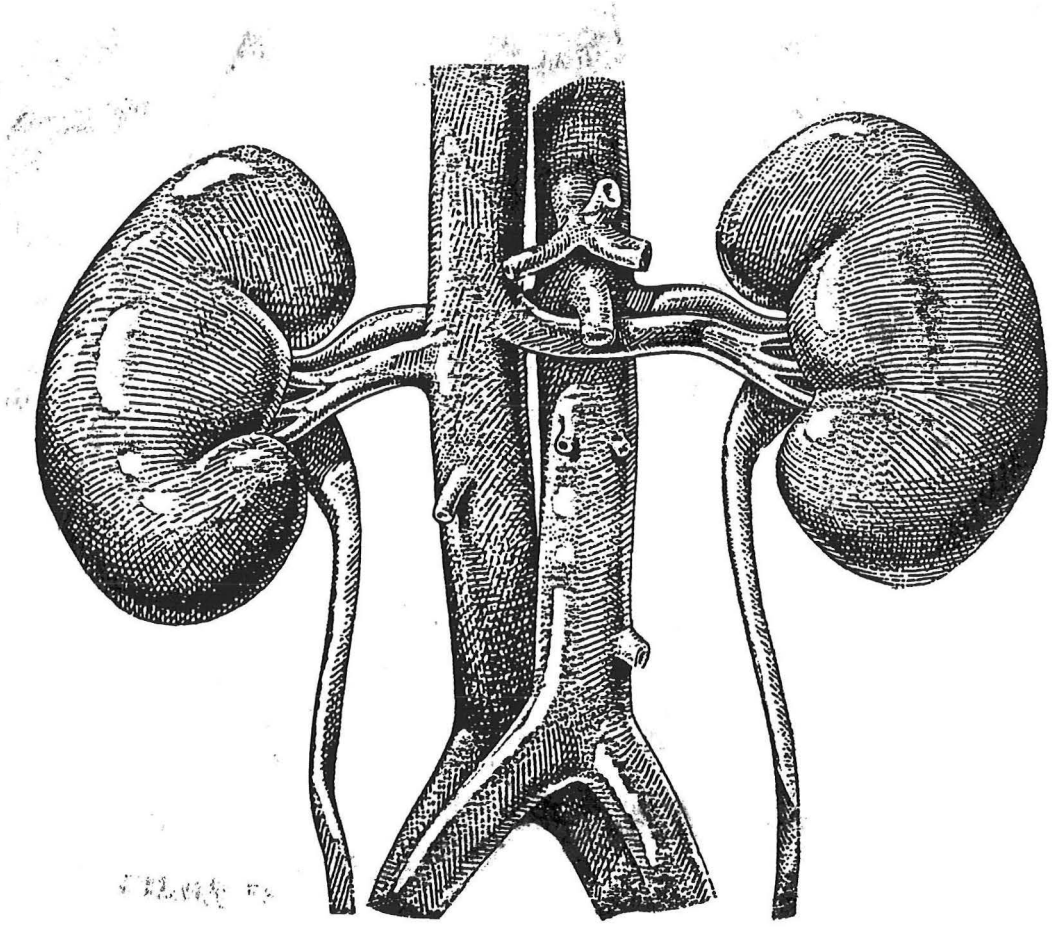
AN ANALYSIS OF THE RENAL PROTECTION AFFORDED BY CALCIUM CHANNEL BLOCKERS



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I. INTRODUCTION.

Calcium channel blockers (CCB's) constitute an important part of today's approach to the treatment of vascular disease. These agents are potent vasodilators, which in comparison with nonspecific vasodilators such as hydralazine and minoxidil generally induce less reflex tachycardia and fluid retention. As such, CCB's have proven to be very useful in the management of ischemic coronary artery disease and diverse forms of hypertension. Recently it has been suggested that CCB's also exert salutary effects on the kidney by improving renal perfusion, by ameliorating chronic progressive renal failure, and by attenuating the degree of acute renal failure in a variety of situations (Kazda 1987; Schrier 1987; Eliahou 1988; Loutzenhiser 1988; Bauer 1989; Reams 1989). The purposes of this review are 1) to provide a brief overview of CCB's and their effects on vascular calcium physiology; 2) to examine how CCB's affect the normal and diseased kidney and 3) to analyze the evidence that CCB's protect the kidney.

II. OVERVIEW OF VASCULAR CALCIUM PHYSIOLOGY AND CALCIUM CHANNEL BLOCKERS.

A. Vascular calcium physiology. The generation of tension by contractile proteins in vascular smooth muscle cells critically depends on the concentration of ionized calcium ($[Ca^{++}]$) in the cytosol. The vasorelaxant effects of CCB's appear to depend on their ability to reduce vascular cytosolic $[Ca^{++}]$ (Loutzenhiser 1985; van Breeman 1987). In resting vascular smooth cells, cytosolic calcium concentrations are normally kept near 0.1 uM (Rasmussen 1984; Loutzenhiser 1985), a remarkably low level compared to the average extracellular concentration of approximately 1200 uM. Basal cytosolic calcium concentrations are kept low by relative impermeability of the unstimulated cell membrane to calcium, by intracellular sequestration (in or on organelles such as the sarcoplasmic reticulum and plasma membrane), and by extrusion into the extracellular space (Figure 1).

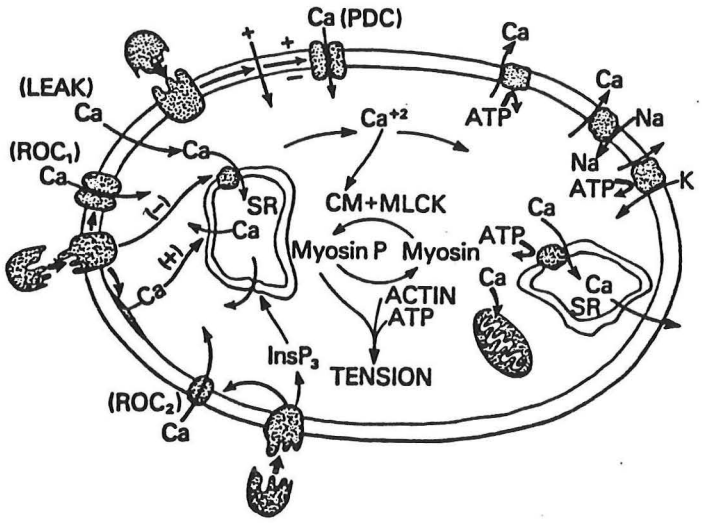


Figure 1.

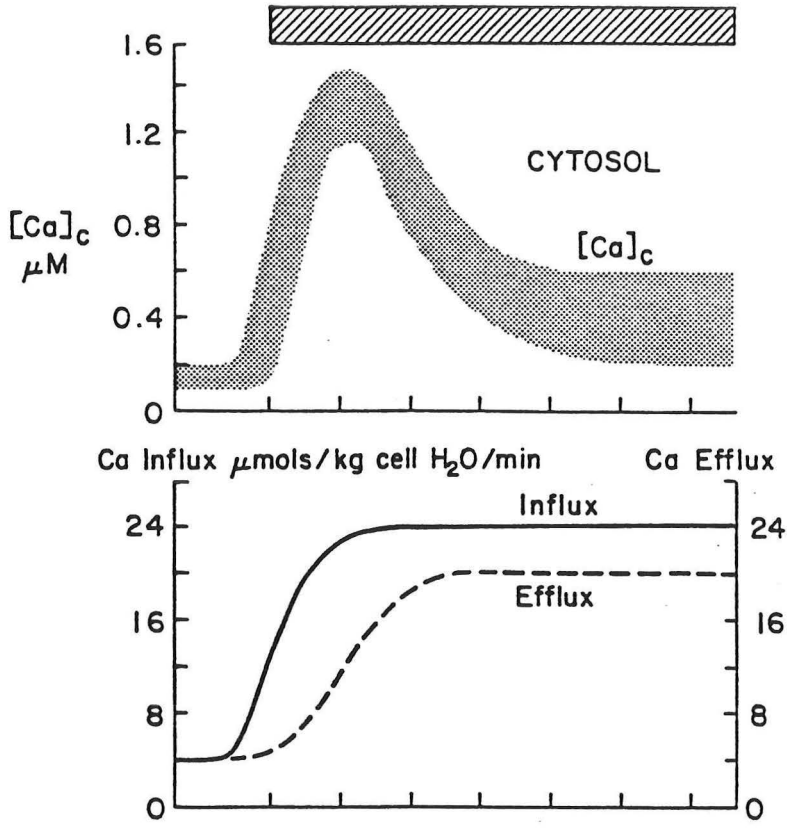
Ca^{2+} mobilization in vascular smooth muscle. Smooth muscle stimulants increase Ca^{2+} entry by depolarization-induced activation of potential-dependent Ca^{2+} channels (PDC), by activating Ca^{2+} channels directly coupled to receptors (ROC_1), or by increasing Ca^{2+} entry through alterations in membrane lipids (ROC_2). Receptor-activated mechanisms also increase myoplasmic Ca^{2+} by inhibiting Ca^{2+} sequestration and releasing internal Ca^{2+} stores. These Ca^{2+} delivery systems are counterbalanced by the removal of myoplasmic Ca^{2+} via Ca-ATPase in the sarcolemma and sarcoplasmic reticulum (SR) and by Na-Ca exchange transport. Resultant level of myoplasmic Ca^{2+} regulates phosphorylation of myosin through a calmodulin- (CM) activated myosin light-chain kinase (MLCK) and thereby regulates smooth muscle tone.

From Loutzenhiser (1985).

When vascular smooth muscle cells are stimulated by stretch or by receptor agonists (e.g., angiotensin II and norepinephrine), however, their cytosolic [Ca^{++}] increases severalfold. Such increments in cytosolic [Ca^{++}] directly or indirectly activate a number of calcium-dependent proteins including myosin light chain kinase, which facilitates the interaction of myosin and actin, and potently stimulate cell contraction.

Once a vascular smooth muscle cell is stimulated, a complex series of events ensues (Rasmussen 1984; Mene 1989). First, cytosolic [Ca^{++}] increases rapidly owing to the release of calcium from storage sites (and perhaps also due to the influx of extracellular calcium) (Figure 2).

Figure 2.



Representation of changes in cytosolic [Ca^{++}] and calcium fluxes as a function of time during sustained activation of a hypothetical cell by the presence of a hormone (shaded bar). Top panel depicts change in cytosolic [Ca^{++}], shaded curve. Lower panel depicts calcium influx and efflux across plasma membrane. From Rasmussen (1984).

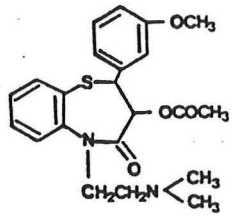
Correspondingly, the tension of the cell's contractile proteins increases. However, the bulk of the initial increment in cytosolic [Ca^{++}] is transient due to subsequent acceleration of 1) calcium efflux into the extracellular space and 2) sequestration in mitochondria. During continued stimulation of the cell, the cytosolic [Ca^{++}] declines to a level still slightly higher than in the basal state. This phase, which is characterized by maintenance of tonic cell contraction despite dissipation of the early calcium transient, is usually sustained until stimulation ceases. Persistence of the more modest elevation of cytosolic [Ca^{++}] in this phase appears to depend on a sustained increment in the rate of calcium influx from the extracellular space. When cell stimulation ceases, extracellular calcium influx also ceases, extrusion of cytosolic calcium continues, and sequestration by nonmitochondrial organelles resumes. Cytosolic [Ca^{++}] is thereby returned to normal. Many hormones that stimulate vascular smooth muscle cells do so by activating phospholipase C (PLC). At least two products of PLC-driven reactions, including inositol 1,4,5-trisphosphate (IP_3) and diacylglyercol (DAG), serve as important modulators of cytosolic [Ca^{++}] and calcium-dependent muscle contraction. IP_3 stimulates the release of calcium from the sarcoplasmic reticulum; it may also directly or indirectly enhance calcium influx from the extracellular space. DAG activates protein kinase C, which phosphorylates myosin and cytoskeletal regulatory proteins, and helps maintain tonic cell contraction. Notably, the activation of protein kinase C by DAG is also calcium-dependent, further emphasizing the central role of cytosolic calcium in the regulation of vascular muscle tone.

B. Effects of CCB's on vascular calcium. There are several ways in which calcium can enter the cytosol of vascular smooth muscle cells from the extracellular space (Figure 1). One of the most important of these is evident when the plasma membrane of a stimulated cell depolarizes. Depolarization of vascular smooth muscle cells opens a variety of voltage-dependent channels in the plasma membrane and allows sustained, passive entry of calcium into the cytosol. CCB's stabilize one class of these channels in the "closed" position at relatively low (clinically relevant) concentrations, thereby blocking the voltage-dependent component of calcium flux into stimulated cells (Loutzenhiser 1985; Schwartz 1988). Therefore, CCB's suppress the ability of smooth muscle cells to develop and maintain tonic contraction. CCB's do not appear to affect calcium influx into resting cells, but slightly higher concentrations of some of these drugs inhibit the intracellular release of calcium, inhibit the flux of calcium through receptor-operated voltage-independent channels in the cell membrane, or both (Loutzenhiser 1985). At very high concentrations (not likely to be achieved in vivo) many "CCB's" also act as calmodulin inhibitors. Accordingly, a variety of names have been applied to these drugs: calcium antagonists, calcium entry blockers, calcium channel blockers/antagonists/inhibitors, and "slow channel" blockers. The term "calcium channel blocker" will be used in this review with recognition that these agents may have multiple effects, including effects that might not be fully characterized.

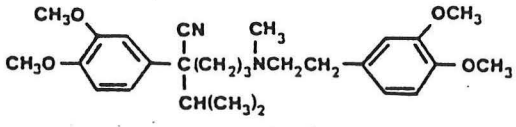
C. Classification of CCB's. The family of organic CCB's comprises a chemically heterogeneous group of drugs. Although CCB's have been classified in several ways, they are often classified according to the scheme shown in the following Table:

Table 1: Organic Calcium Channel Blockers

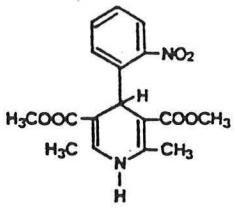
Phenylalkylamines	Benzothiazepines	Dihydropyridines	Misc.
Verapamil	Diltiazem	Amlodipine	Bepridil
		Isradipine	Chlorcyclizine
		Nicardipine	Cinnarizine
		Nifedipine	Flunarizine
		Nimodipine	
		Nisoldipine	
		Nitrendipine	



Diltiazem



Verapamil



Nifedipine

Certain inorganic species (including the cations of lanthanum, cadmium, manganese and cobalt) also serve as calcium channel blockers. However, they do so in a nonspecific way and will not be considered further.

It is also possible to classify CCB's according to their physiologic properties. All CCB's exert vasodilating effects. However, some (particularly verapamil and to a lesser extent diltiazem) suppress the conduction of the atrioventricular node, an effect that is clinically useful in certain patients with supraventricular arrhythmias but problematic when AV nodal effects are not desired. Some CCB's (chiefly verapamil and diltiazem) exert negative inotropic effects that may limit their usefulness in patients with congestive heart failure. In contrast, the newer dihydropyridines generally exert more selective effects on vascular smooth muscle than on the AV node or cardiac myocytes. But with regard to the kidney, the biologic effects of the organic CCB's appear to be sufficiently similar that they will be considered collectively for purposes of this discussion unless specific exception is noted.

D. CCB's as vasodilators and antihypertensives. As noted earlier, CCB's do not appear to affect the cytosolic $[Ca^{++}]$ of resting vascular smooth muscle cells, probably because voltage-dependent calcium channels in such cells are normally closed. It would be expected, therefore, that the vasodilating action of CCB's on a given blood vessel is dependent on the pre-existing state of that blood vessel. This is the case. Laboratory studies show that blood vessels constricted by KCl, calcium salts, various receptor agonists (such as angiotensin II and norepinephrine) or sympathetic nerve stimulation are much more responsive to CCB's than dilated vessels (Loutzenhiser 1985). Furthermore, both clinical and laboratory evidence shows that the blood pressure reduction effected by CCB's

is significantly greater in hypertensive patients than in normotensive controls (Loutzenhiser 1985; Kiowski 1987; Romero 1987).

It is of interest that at least some patients with essential hypertension may have supranormal intracellular calcium concentrations. Three groups have reported that cytosolic calcium concentrations in platelets from patients with essential hypertension are increased (Erne 1984, Bruschi 1985; Lindner 1987). Furthermore, at least one group has shown that cytosolic calcium concentrations in platelets correlate positively with blood pressure as shown below.

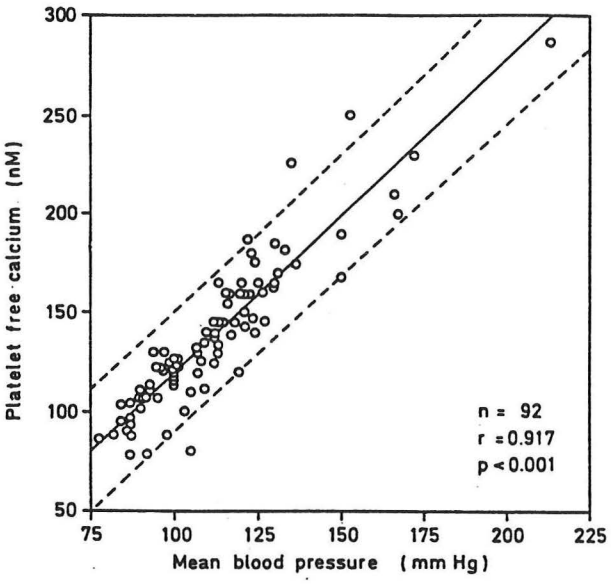


Figure 3.
(Erne 1984).

Correlation between Mean Blood Pressure and Intracellular Free-Calcium Concentrations in Platelets of 38 Normotensive Subjects, 9 Patients with Borderline Hypertension, and 45 Patients with Established Essential Hypertension.
Broken lines indicate 95 per cent confidence limits.

Although it would be more useful to know cytosolic [Ca^{++}] in vascular smooth muscle cells, this is not easily measured without significant perturbation of these cells. Platelets, on the other hand, are readily accessible and resemble vascular smooth muscle cells in several ways (including the fact that they contain calcium-dependent contractile proteins). Inferentially, therefore, it may be that similar increments in cytosolic [Ca^{++}] occur in the vascular smooth muscle of patients with essential hypertension, thus promoting inappropriate vasoconstriction. One group has not been able to find a good correlation between platelet [Ca^{++}] and the degree of hypertension in patients (Hvarfner 1988), but it has been possible to show that spontaneously hypertensive rats have elevated platelet [Ca^{++}] (Bruschi 1985). Perhaps CCB's serve to reverse a basic cellular defect in at least some forms of hypertension.

In addition to the above considerations, CCB's are now used with considerable frequency in the management of hypertension for more practical reasons. First, it appears that CCB's are generally less likely to induce major side effects than diuretics, beta blockers, and vasodilators. Second, it is suspected that CCB's are likely to be effective in a broad variety of hypertensive patients including those with diabetes, "low renin hypertension", and hypertensive crises (Working Group on Hypertension in Diabetes 1987; Kiowski

1987; Herlitz 1987; Buhler 1989; Kaplan 1989). Current evidence supports most of these perceptions. However, increasing evidence indicates that hypertensive blacks, who generally have lower plasma renin activities (PRA's) than hypertensive whites, are somewhat less responsive to the blood pressure lowering effects of CCB's than whites (Cruickshank 1988; Kaplan 1989). Although it does not follow that PRA measurements necessarily provide a useful index of local angiotensin II and aldosterone concentrations, it does follow that at least one population of hypertensive patients is probably less responsive to the antihypertensive effects of CCB's than originally suspected. This conclusion notwithstanding, CCB's are frequently very effective antihypertensives that may have special advantages in hypertensive patients with coronary artery disease and certain other forms of vascular disease.

III. RENAL EFFECTS OF CCB'S: PHYSIOLOGY.

CCB's can affect both hemodynamics and epithelial transport processes in the kidney. These effects are not completely characterized. In a general sense, however, it is clear that CCB's have the potential to vasodilate the kidney, increase renal plasma flow (RPF), increase GFR, and stimulate natriuresis and diuresis. They also have the potential to inhibit renal autoregulation and urinary concentration.

A. Renal hemodynamics and GFR. CCB's clearly reduce total renal vascular resistance and increase GFR in some situations, particularly when infused directly into the renal artery in doses that avoid changes in systemic blood pressure (Loutzenhiser 1985; Romero 1987). However, as in nonrenal vascular systems, the extent of these effects is quite dependent on the pre-existing state of the organ. The unperturbed, normal kidney with low to moderate vascular tone is not likely to manifest major changes in renal blood flow or GFR during CCB administration. The same is true of the kidney vasodilated by aortic constriction or ganglionic blockade. However, the kidney vasoconstricted by angiotensin II, norepinephrine, general anesthesia, or other means is likely to manifest large increments in renal blood flow and GFR during CCB administration. Figure 4 shows an example of the dose-dependent effect of nifedipine on GFR and RPF in the isolated perfused rat kidney pretreated with norepinephrine.

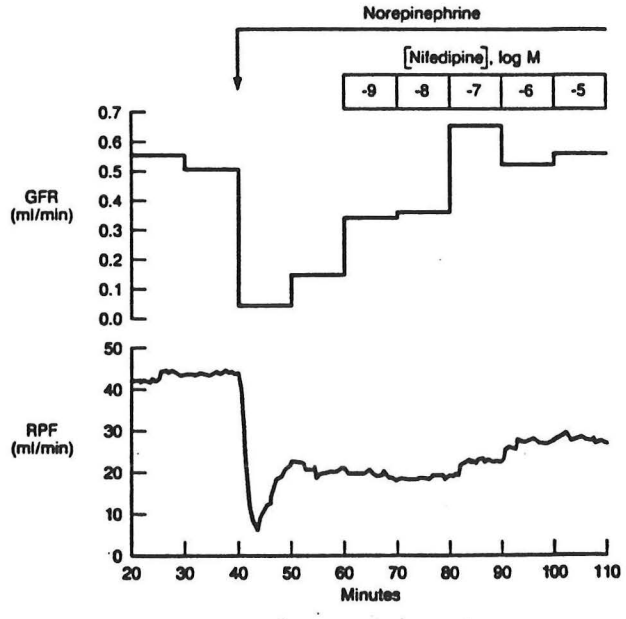


Figure 4. Reversal by nifedipine of the decrement in GFR and renal plasma flow rate induced by administration of 0.3 uM norepinephrine to the isolated perfused rat kidney. From Loutzenhiser (1988).

There is considerable evidence that hypertension is a common and important factor associated with enhancement of renovascular and glomerular responsiveness to the effects of CCB's (Loutzenhiser 1985; MacLaughlin 1985; Steele 1985, 1987; Romero 1987; Isshiki 1988; Wilson 1989). Figure 5 illustrates the effects of CCB's on GFR in isolated perfused kidneys from rats genetically predisposed to develop hypertension while on a high salt diet.

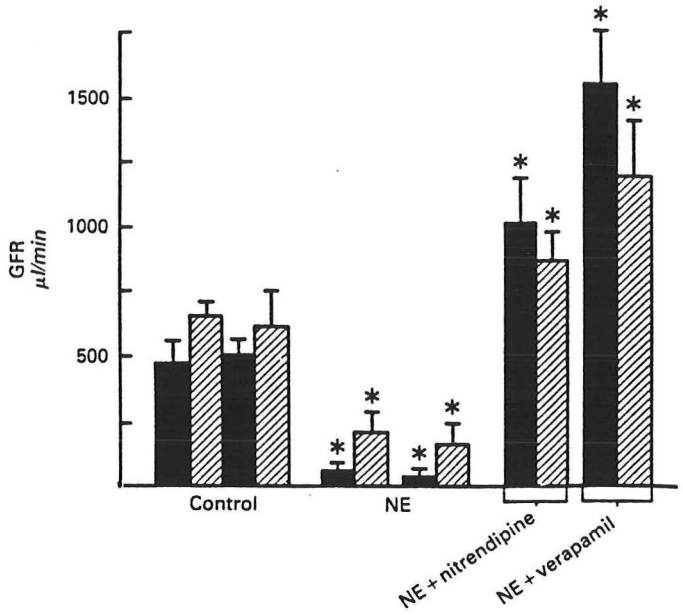


Figure 5. Greater effect of CCB's on the GFR of isolated perfused kidneys from prehypertensive "salt-sensitive" Dahl rats (black bars) compared to kidneys from normotensive "salt-resistant" Dahl rats (hatched bars). NE = norepinephrine. * indicates $P < 0.05$ compared to control. Effects on renal vascular resistance were similar. From Steele (1987).

There are several potential reasons why the kidney exposed to systemic hypertension is particularly responsive to CCB's. The simplest is that the renal vasculature tends to constrict in response to increased systemic pressure, particularly at the afferent arteriolar level (Arendshorst 1979; S. Azar 1979; Olson 1986). It is likely, therefore, that the high renovascular tone characteristic of the hypertensive state predisposes more exuberant vasodilation in response to CCB administration. However, it cannot be excluded at the present time that other factors (e.g, increased sympathetic tone, high local levels of vasoconstrictors, high cytosolic [Ca^{++}]) also predispose greater responses to CCB's.

The effects of CCB's on the determinants of GFR are both complex and controversial. There is no doubt that these agents often reduce total renal vascular resistance, thereby increasing RPF and GFR. However, because CCB-induced increments in GFR are frequently greater than could be expected on the basis of increased RPF alone (Sterzel 1987; Loutzenhiser 1988), it is likely that factors other than blood flow also contribute to GFR changes during CCB administration. There is general agreement that CCB's can increase the glomerular ultrafiltration coefficient, K_f, presumably by relaxing glomerular mesangial cells whose structural and contractile properties and intracellular [Ca^{++}] closely resemble those of vascular smooth muscle cells (Ichikawa 1979; Pelayo 1988; Yoshioka 1988; Mene 1989). Thus, GFR increments during CCB administration are probably driven at least partially by increments in K_f.

It is also possible that changes in glomerular arteriolar resistance and glomerular capillary pressure could contribute to changes in GFR during CCB administration. However, the specific effects of CCB's on these determinants of GFR are less straightforward. Several lines of evidence suggest that the afferent arteriole is more responsive to the vasodilating action of CCB's than the efferent arteriole. Indeed, a predominance of preglomerular vasodilation has been observed by direct microscopy of the hydronephrotic kidney treated in vivo or in vitro with nitrendipine or nifedipine (Fleming 1987; Loutzenhiser 1988; Hayashi 1989) and juxtamedullary glomeruli of the isolated, perfused kidney treated with verapamil or diltiazem (Carmines 1989). Data from Carmines are illustrated in Figure 6.

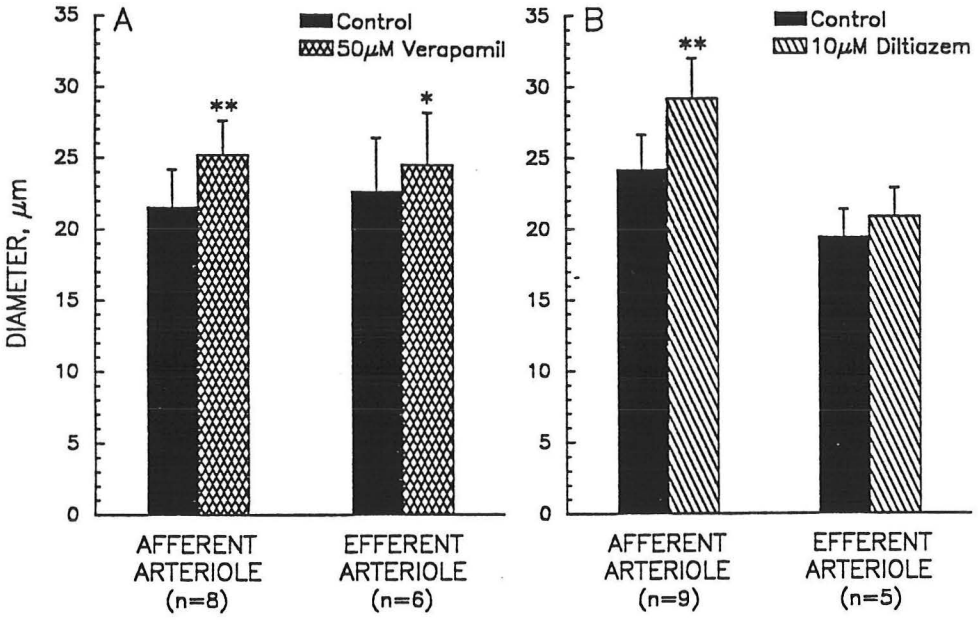


Figure 6.

Responses of captopril-treated afferent and efferent arterioles to calcium antagonists. Vessel inside diameters were measured before and during topical administration of either 50 μM verapamil HCl (*A*) or 10 μM diltiazem HCl (*B*). * $P < 0.05$ and ** $P < 0.01$ vs. control diameter.

Micropuncture studies, on the other hand, provide less consistent evidence that CCB's act selectively on the afferent arteriole. Examining rats with markedly reduced renal mass, Brunner et al (1987) found that proximal tubule stop-flow pressure (an index of glomerular capillary pressure) rose 8 mm Hg during acute, systemic administration of verapamil even though systemic blood pressure fell from 144 to 118 mm Hg. This suggests that afferent resistance declined more than efferent resistance in this particular model. Other micropuncture studies have confirmed that systemic administration of CCB's can elicit afferent vasodilation. However, these studies have also shown that CCB administration can lead to significant efferent dilation in at least some situations. Table 2 summarizes the available micropuncture data on this issue.

Table 2: Micropuncture Analysis of Renal CCB Effects.

Reference	Rat Model	CCB	CCB Effect on:			
			MAP	R-aff	R-eff	P-gc
Ichikawa (1979)	Normal	Verapamil (acute)	-8%	-18%	-18%*	NC
Pelayo (1987)	Normal	Verap/Nif (acute)	-7%	-29%	NC	NC
Brunner (1987)	5/6 RA	Verapamil (acute)	-18%			+8 mmHg
Pelayo (1988)	5/6 RA	Verapamil (chronic)	+9%	NC	-26%*	NC
Yoshioka (1988)	5/6 RA	Verapamil (acute)	-36%	-53%	-55%	-31%
Anderson (1988)	5/6 RA	Verap/Dilt (acute)	-27/34%			-25/29%
Dworkin (1988)	UNX + DOCA/salt	Nifedipine (chronic)	-24%	-33%		NC

* Not statistically significant. MAP, mean arterial pressure; R-aff and R-eff, afferent and efferent arteriolar resistances; P-gc, glomerular capillary pressure. NC, no change. RA, renal ablation. UNX, uninephrectomy. DOCA, deoxycorticosterone.

Considered together, these seemingly disparate results do not clearly show that systemic CCB administration selectively dilates the afferent arteriole. Several points must be kept in mind, however. First, single nephron GFR was shown to rise in only one of these studies (Ichikawa 1979). It actually fell 31-33% in one (Anderson 1988) and was not reported in another (Brunner 1987). Thus, the results of most of these studies are probably not applicable to circumstances in which CCB administration increases GFR. Second, the models examined in these studies varied considerably. Because the renal response to CCB's is clearly dependent on pre-existing conditions, it is quite possible that afferent dilation could predominate in one situation but not in another. Third, it is possible that the choice of drug, dose or route of administration partly determined the manner in which CCB treatment affected renal hemodynamics. It seems unlikely, however, that the choice of drug was important in this respect since two groups (Pelayo 1987; Anderson 1988) found that chemically dissimilar CCB's had comparable effects. Fourth and very importantly, changes in systemic blood pressure were present in all of these studies; it is possible that changes in systemic hemodynamics were more closely related to the observed renovascular changes than any direct action of CCB's on renal arterioles. The renal perfusion studies described earlier (Fleming 1987; Loutzenhiser 1988; Carmines 1989;

Hayashi 1989) circumvented the problem of systemic hemodynamic changes and therefore may have provided more meaningful information concerning the effects of CCB's on arteriolar resistances. However, significant other forms of artifact are inherent in the currently available methods of in vitro perfusion of the kidney. It must be concluded that the precise ways in which CCB's affect renal hemodynamics and GFR are not fully defined.

B. Autoregulation. Renal autoregulation, the ability of the kidney to maintain constant renal blood flow despite changes in perfusion pressure, is an important aspect of renal function. The normal kidney is able to maintain a nearly constant blood flow (and GFR) when it is exposed to perfusion pressures ranging from approximately 90 to 150 mm Hg. The precise mechanisms that underlie renal autoregulation are not completely understood. However, current evidence suggests that at least two processes are important in this respect. One is the tubuloglomerular feedback (TGF) mechanism, as shown by Navar et al (1974). The TGF mechanism utilizes a negative feedback loop at the individual nephron level to help to maintain constancy of afferent arteriolar resistance, glomerular capillary pressure, glomerular plasma flow rate rate, and K_f. It relies on the juxtaposition of the later part of the loop of Henle, where flow-dependent signals are sensed, and the vascular pole of the glomerulus of the same nephron, where adjustments are made to minimize variations in GFR. It has been shown that verapamil inhibits the operation of the TGF system (Muller-Suur 1976). The other likely autoregulatory process involves the ability of the afferent arteriole to resist changes in ambient pressure actively, a finding taken to mean that the afferent arteriole possesses a "myogenic" autoregulatory system (Gilmore 1980). The effects of CCB's on this system are not yet known.

The work of several groups has clearly shown that CCB's can significantly inhibit renal autoregulation (Navar 1986; Ogawa 1986; Hayashi 1989). This is illustrated in Figure 7 and 8.

Figure 7.

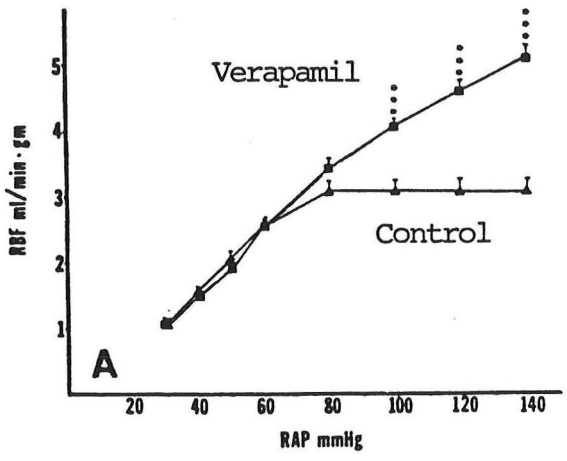
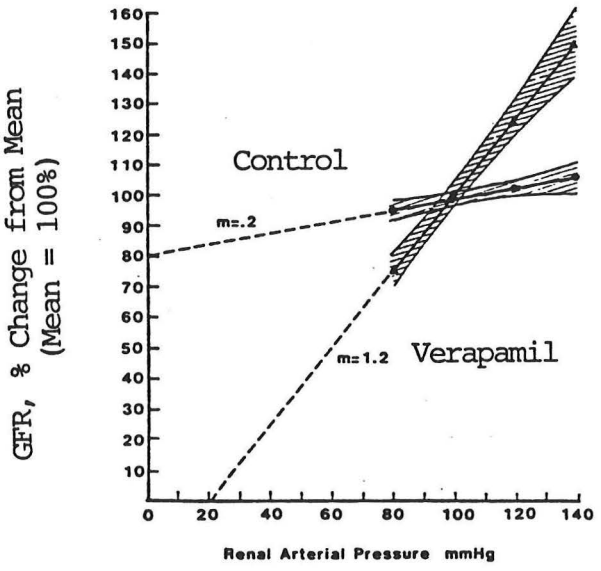


Figure 8.



Impairment of autoregulation in anesthetized dogs given verapamil systemically. RAP, renal artery perfusion pressure adjusted by aortic clamping. RBF, renal blood flow. From Navar (1986).

Owing to impairment of renal autoregulation by CCB's, it can be predicted on theoretical grounds that CCB's could have a major impact on renal blood flow and GFR when the renal perfusion pressure falls or increases. For example, if systemic blood pressure were to decrease significantly during inhibition of renal autoregulation, it is possible that renal blood flow and GFR would fall. This is precisely what Anderson et al observed after intravenous administration of two different CCB's (1988). In extreme cases, major degrees of acute renal failure could ensue. Second, if a CCB were to inhibit renal autoregulation in the face of pre-existing hypertension without significantly correcting this hypertension, it is possible that renal blood flow and GFR would rise, perhaps significantly. This possibility may explain some of the increment in GFR observed in hypertensive patients placed on CCB's.

C. Salt and water transport. Many studies have documented mild diuretic and natriuretic properties of CCB's, which differ significantly from nonspecific vasodilators in this respect (Loutzenhiser 1985; Barrett 1987). Although increases in GFR may facilitate these processes, it is clear that elevation of GFR is not required. Therefore, it is argued that CCB's can act directly on renal epithelia. This is likely to be true. Currently, evidence is clearest that CCB's inhibit salt and water reabsorption in the distal tubule and collecting duct (DiBona 1984; Giebisch 1987; Kauker 1987), but certain evidence suggests that CCB's might also inhibit reabsorptive processes in the proximal tubule and loop of Henle (MacLaughlin 1985; Takeda 1986; Haberle 1987). It should be noted, however, that the diuretic and natriuretic properties of these drugs tend to be acute; studies of the effects of chronic administration usually do not show their persistence. CCB's also appear to inhibit maximal urinary concentrating ability (Okaniwa 1989), perhaps because they increase medullary blood flow (Hansell 1988) and "wash out" medullary solutes.

IV. PROTECTION AGAINST PROGRESSION OF CHRONIC RENAL DISEASE.

A. Overview of proposed mechanisms. Increasing attention is now being focused on the possibility that CCB's exert long-term renal protective properties. Theoretically, they could do so in several ways. They could reduce systemic hypertension, thereby minimizing hypertensive renal damage. Studies have shown that life-long administration of CCB's to spontaneously hypertensive rats effectively controls hypertension, mitigates cardiac damage, and increases survival (Kazda 1987; Scriabine 1989). Chronic CCB administration also tends to reduces PRA in these animals unlike nonspecific vasodilators, which consistently increase PRA. [Note that in contradistinction to chronic CCB administration, acute CCB administration usually increases PRA.] However, proof that CCB's mitigate human nephrosclerosis is not available. Alternatively, it is possible that CCB's could reverse "glomerular hypertension", a proposed factor contributing to the progression of renal disease in the face of reduced renal mass or diabetes (Brenner 1985). As shown in Table 2, however, it is not clear that CCB's consistently reduce glomerular capillary pressure. Indeed, Brunner et al (1987) believe that CCB's increase glomerular capillary pressure in their rat model of reduced renal mass.

It has been suggested that CCB's could also protect the kidney through nonhemodynamic means. Laboratory studies show that CCB's can suppress renal nephrocalcinosis, which some investigators believe is an important factor

accelerating progressive renal disease (Harris 1987; Kazda 1987; Schrier 1987). Another possibility is that CCB's suppress renal inflammation or thrombosis. CCB's have been shown to inhibit the activation of macrophages, granulocytes and platelets (Sterzel 1987) and the proliferation of glomerular mesangial cells in vitro (Schultz 1990). Moreover, they have been shown to improve GFR, reduce proteinuria, and lessen glomerular changes in a model of anti-glomerular basement membrane nephritis (Sterzel 1989). Yet another possibility is that CCB's suppress renal hypertrophy (Dworkin 1988, 1989), which some investigators believe contributes to the progression of chronic renal disease (Yoshida 1989).

Nevertheless, the question remains whether CCB's commonly protect the chronically diseased kidney. The next portion of this review will examine available information concerning the effects of CCB's on two commonly studied animal models of chronic renal disease, renal ablation and streptozotocin-induced diabetes. Then patients with chronic renal disease will be considered.

B. Animal models: reduced renal mass and diabetes. Rats with substantially reduced renal mass develop hypertension, proteinuria, renal failure and glomerulosclerosis. Several groups have now examined the short and long-term effects of systemic CCB treatment on these animals. These studies are summarized in Tables 3 and 4.

Table 3. Favorable CCB Effects on Renal Function/Histology in Rats with Reduced Renal Mass.

Reference	Model	Drug/BP Effect	Duration of Rx	Renal Effects
Harris (1987)	5/6 RA	Verap/None	15 wks	Reduced serum creat and nephrocalcinosis; improved renal histology.
Eliahou (1988)	5/6 RA	Nisold/Decr Dihydral/Decr	20 wks	Nisold improved serum creat proteinuria and renal histol more than dihydral.
Yoshioka (1988)	5/6 RA	Verap/Decr	Acute	Reduced proteinuria and improved glom permselectivity.
Dworkin (1988)	UNX + DOCA/salt	Nifed/Decr	8 wks	Reduced proteinuria and glomerulosclerosis despite high P-gc.
Dworkin (1989)	5/6 RA	Nifed/Decr Enal/Decr	8 wks	Both reduced proteinuria and glomerulosclerosis. Only nifed prevented increase in glom volume.
Dworkin (1990)	UNX/SHR	Nifed/Decr Enal/Decr	30 wks	Both reduced proteinuria, glomerulosclerosis and kidney weight.

Table 4.

Neutral or Unfavorable CCB Effects on Renal Function/Histology in Rats with Reduced Renal Mass

Reference	Model	Drug/BP Effect	Duration of RX	Renal Effects
Pelayo (1988)	5/6 RA	Verap/None	4 wks	No change in proteinuria or renal histology.
Jackson (1988)	15/16 RA	Felod/Decr Enal/Decr	6 wks	Enal reduced but felod increased proteinuria. Only enal reduced glomerulosclerosis.
Brunner (1989)	5/6 RA	Verap/None Enal/Decr	15 wks	Enal reduced proteinuria and glomerulosclerosis. Verap increased both.

Legend for Tables 3 and 4. RA, renal ablation; UNX, uninephrectomy; SHR, spontaneously hypertensive rat. Verap, verapamil; nisold, nisoldipine; dihydral, dihydralazine; enal, enalapril; felod, felodipine. Decr, decreased.

CCB treatment reduced renal functional and/or structural damage in 6 of 9 studies. The study of Harris et al suggested that the beneficial effects of CCB therapy are not strictly dependent on blood pressure. The study of Eliahou showed that CCB treatment is more effective in protecting the kidney than a nonspecific vasodilator despite comparable degrees of blood pressure reduction, further indicating that the benefits of CCB's on the kidney are not entirely dependent on a reduction of blood pressure. The work of Dworkin (1988, 1989) suggests (a) that the renal protection afforded by CCB's does not strictly depend on reduction of glomerular capillary pressure and (b) that the renal protection afforded by at least one agent, enalapril, does not strictly depend on reduction of either glomerular capillary pressure or glomerular hypertrophy.

Three of nine studies failed to show a renal protective action of CCB's; 2/9 studies showed that CCB treatment actually worsened renal outcome. In addition, the studies of Dworkin, Jackson and Brunner showed that enalapril is equally or more effective in preventing proteinuria and glomerulosclerosis than CCB's. Therefore, it is not at all clear from these studies that CCB treatment of rats with reduced renal mass consistently effects a satisfactory outcome.

Similar uncertainty concerning the renal effects of CCB's is found in studies of rats with streptozotocin-induced diabetes. Sato et al (1987) found that CCB's but not hydralazine reduced proteinuria in such animals. However, Jackson et al (1987) found that enalapril rather than verapamil reduced proteinuria in diabetic animals. As in the renal ablation studies, therefore, two preliminary conclusions are suggested. First, CCB's probably protect the kidney more effectively than nonspecific vasodilators in at least some conditions. Second, it is possible that angiotensin converting enzyme inhibitors protect the kidney more effectively than CCB's.

C. Patients with chronic renal disease. There are instances in which the results of rat studies may not be clinically relevant. Unfortunately, however, relatively little information is available in an area of extreme clinical interest: does long-term CCB treatment of hypertensive (or normotensive) patients with established renal disease prevent or slow progression? A number of studies have shown that short-term (< 6 months) CCB therapy tends to maintain or slightly increase renal blood flow and GFR in hypertensive patients with chronic renal failure (Del Rio 1986; Romero 1987; Bauer 1989; Krishna 1989; Reams 1989). However, one group has found that nisoldipine administration for 6 weeks reduces hippurate clearance 12% (without affecting GFR) in patients with chronic renal failure (Wilson 1989). Another group has concluded that nifedipine administration for two weeks can worsen fractional urinary albumin excretion in patients with pre-existing proteinuria (Mickisch 1988).

Few long-term (> 6 month) studies of the effects of CCB's on chronic renal disease have been completed. Herlitz et al (1985) gave felodipine to a small number of patients with "renoparenchymatous" hypertension and chronic renal insufficiency, finding that GFR remained nearly constant during approximately one year of treatment. The same group found in another study (1988) that felodipine slowed the loss of renal function in patients with progressive renal insufficiency. However, the interpretation of these studies is clouded by small numbers of patients and the lack of controls. Ambroso et al (1988) were unable to find that nifedipine altered the progression of chronic renal insufficiency in a small, uncontrolled study. Eliahou et al, on the other hand, performed a prospective, randomized, placebo-controlled study examining the effects of nisoldipine on patients with progressive, chronic renal failure (1988). They followed a total of 34 patients divided equally between nisoldipine and placebo-treated groups for 6-30 months (mean 17). Diastolic but not systolic blood pressure was slightly lower in nisoldipine-treated patients compared to placebo-treated patients. They found that the rate of renal deterioration (judged by the inverse of serum creatinine) was not altered by placebo whereas nisoldipine reduced the rate of renal deterioration by 35% (Figure 9).

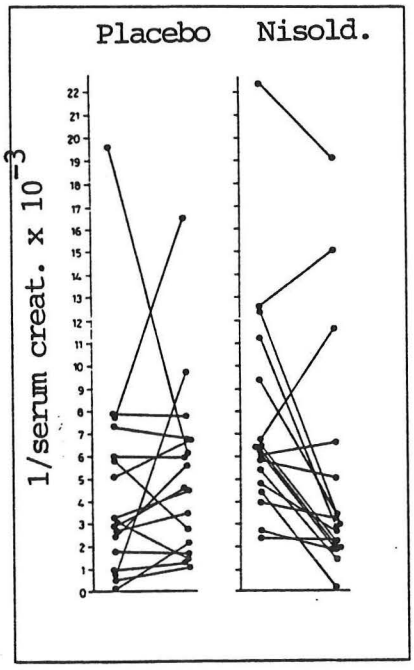
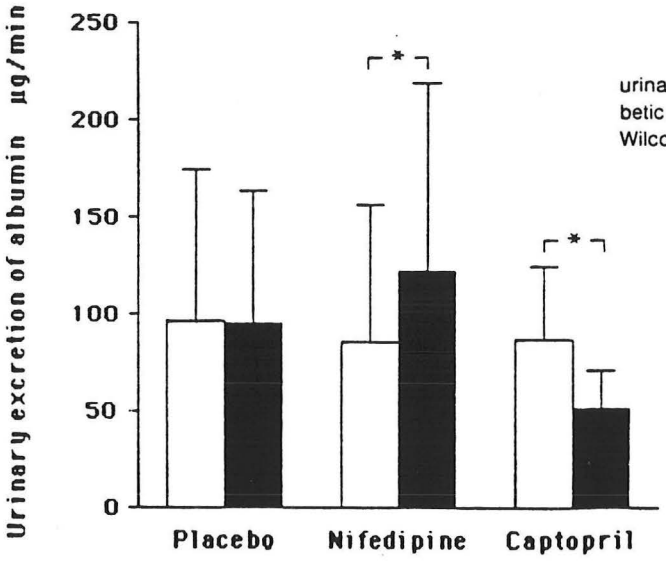


Figure 9. Effect of nisoldipine on progression of chronic renal failure in individual patients. Data shown as inverse of serum creat (L/uM creat) x 10^{-3}. (Eliahou, 1988).

Although this study was well designed, it must be noted that patients randomized to CCB treatment appeared to have more rapid pretreatment deterioration of renal function than patients randomized to placebo treatment. Furthermore, comparison of 1/serum creatinine values during the treatment phase of this study does not appear to show statistically significant differences between the CCB and placebo-treated groups. Thus, the conclusion of this study that CCB treatment slowed the rate of progressive renal disease needs confirmation.

Uncertainty of the benefits in diabetic patients is also apparent. Stornello et al (1987) and Baba et al (1989) reported that CCB's and angiotensin converting enzyme inhibitors, given for 4 weeks to type II diabetics, lowered blood pressure and urinary albumin excretion. However, Mimran et al (1988) found that 6 weeks of captopril treatment reduced microalbuminuria in type I diabetics whereas nifedipine increased it (Figure 10).



Effect of treatment by placebo, nifedipine and captopril on the urinary excretion of albumin in insulin-dependent normotensive diabetic patients. □ , Control; ■ , treatment. *$P < 0.05$ using paired Wilcoxon signed rank test.

Figure 10.
(Mimran, 1988).

Long-term studies of CCB effects on proteinuria, GFR and morphology in diabetic patients are not yet available, but these preliminary data do not make it clear that CCB's consistently exert a positive influence on the diabetic kidney.

Turning to another clinical issue, there are reports of at least 8 patients who have developed acute renal failure while taking CCB's (Diamond 1984; Ter Wee 1984; R. Azar 1987; Eicher 1988; Cacoub 1988). Most of these patients had moderate to severe pre-existing renal failure; all had significant other problems including diffuse atherosclerotic vascular disease, coronary artery disease, congestive heart failure and/or hypertension; and all were older (ranging in age from 61-82). Interestingly, none experienced a large drop in blood pressure during CCB administration. In each case, CCB-related renal dysfunction appeared to be functional since factors such as obstruction, acute tubular necrosis, and interstitial nephritis could not be detected, and all recovered renal function upon withdrawal of the CCB. Exactly why these patients developed acute renal failure, however, is not clear. It is likely that pretreatment renal perfusion was poor in all of these patients due to cardiac dysfunction and diffuse vascular

disease. Therefore, these patients probably depended heavily on compensatory adjustments in renovascular tone to maintain GFR. CCB's may have interfered with compensation effected by renal autoregulation (see Section IIIB), hormonal modulators of vascular tone (e.g., angiotensin II and prostaglandins), or renal nerve activity. Moreover, considering the extent of vascular disease in these patients, it is possible that some or all had renal artery stenosis, which predisposes acute renal failure in a small subset of patients receiving angiotensin converting enzyme inhibitors (Franklin 1985). At least one patient did have renal artery stenosis (Diamond 1984), but no specific comments were made for the others. Preliminary information suggests that CCB's are less likely than angiotensin converting enzyme inhibitors to reduce GFR in the face of renal artery stenosis (Miyamori 1988; Ribstein 1988; Mourad 1989). However, studies of two-kidney, one-clip Goldblatt hypertensive rats show that CCB's can markedly reduce the rate of filtration in kidneys served by clipped arteries (Huang 1986; Ploth 1987).

D. Summary. It seems that there are both advantages and disadvantages associated with the use of CCB's when chronic renal disease is present. A substantial body of literature shows that CCB's usually (but not always) maintain or even enhance renal function in the short-term. CCB's appear to be superior to nonspecific vasodilators in this sense. A few studies also show that CCB's have the potential to mitigate progressive renal disease. On the other hand, several studies show that CCB's do not consistently improve long-term renal outcome. Indeed, roughly one fourth of currently available studies show that CCB's **promote** chronic renal damage. It is far too soon to conclude that CCB's exert long-term "salutary" effects. We must continue to be as careful with CCB's as all other antihypertensive medications in treating our patients with renal disease.

V. PROTECTION AGAINST ACUTE RENAL FAILURE.

There is also substantial interest in the possibility that CCB's can lessen acute renal failure in various circumstances. It is possible that CCB's could help offset the vasoconstriction and decrements in renal blood flow that are commonly present in acute renal failure. Laboratory studies show that this is likely to be true, particularly when CCB's are given prior to ischemic or nephrotoxic insults (Bakris 1985; Schrier 1987; Russell 1989). As in the studies of chronic renal disease, however, laboratory studies also suggest that CCB's protect against acute renal failure through nonhemodynamic mechanisms. Schrier and colleagues (1987) note that the brush border membrane of the proximal tubule is particularly susceptible to damage in models of acute renal failure. They believe that the proximal tubule cell membrane becomes abnormally permeable to calcium early in the course of acute renal failure, thus permitting cytosolic [Ca^{++}] and intramitochondrial [Ca^{++}] to rise (Burke 1984; Schrier 1987). In view of evidence that very high intracellular [Ca^{++}] can be cytotoxic (Burke 1984; Rasmussen 1984), they have proposed that CCB's mitigate acute renal failure by suppressing excessive cell membrane permeability to calcium, thereby preventing toxic increments in cytosolic and intramitochondrial [Ca^{++}]. It can be argued that increases in intracellular [Ca^{++}] are more directly the result of cell injury than the cause of it, but increasing evidence supports the view that high intracellular [Ca^{++}] is at least partially responsible for the functional and metabolic derangements in acute renal failure (Schrier 1987). Irrespective of

mechanistic considerations, however, it is clear that CCB's can reduce the severity of acute renal failure in laboratory models (Schrier 1987; Russell 1989).

Studies of the protective effects of CCB's against human acute renal failure have been limited to renal transplant recipients. Work done by several groups including Dawidson et al at this institution clearly shows that CCB treatment of the recipient (before and after transplantation) and of the graft (during extracorporeal perfusion) reduces the amount of post-transplant acute renal failure (Dawidson 1989; Russell 1989; Finn 1990). There is not a consensus that such treatment improves long-term organ function (Russell 1989), but there is a consensus that the need for post-operative dialysis is significantly reduced. Why CCB's prevent post-transplant acute renal failure is not fully resolved. One possibility is that CCB's suppress cyclosporine and/or calcium uptake by proximal tubule cells in vitro (Nagineni 1988). However, the significance of these findings is uncertain since very high CCB concentrations were studied. A better possibility is that CCB's help reverse cyclosporine-induced renal vasoconstriction (Barros 1987; Dawidson 1989).

VI. CONCLUSIONS.

It is clear that calcium channel blockers can serve a very useful role in the management of coronary artery disease and hypertension. In the short-term, it is also clear that CCB's usually maintain or increase GFR when hypertension and/or chronic renal disease are present. This property may (or may not) prove to be a further advantage of this class of drugs. In the long-term, however, preliminary studies fail to show convincingly that CCB's exert a positive effect on the function and histology of the diseased kidney. It is possible that CCB's actually worsen long-term renal outcome in some situations. Therefore, caution must be exercised when these drugs are given to patients with renal disease. Little information concerning the use of CCB's for the prevention of acute renal failure in patients is available. However, there is good evidence that CCB's can mitigate the severity of acute renal failure in renal transplant recipients. Although a promising start has been made toward the understanding of the renal effects of calcium channel blockers, much further work is needed to understand their effects on the normal and diseased kidney.

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