THE CALCIUM ANTAGONISTS --
NEW THERAPY FOR ISCHEMIC HEART DISEASE

MEDICAL GRAND ROUNDS

June 19, 1980

Peter G. Roan, M.D.

TABLE OF CONTENTS

I. INTRODUCTION

The calcium-antagonists are an interesting and important new class of drugs with a variety of potent cardiovascular effects. These agents may provide a new and unique mode of therapy of ischemic heart disease. They may provide some insight into the pathophysiologic role of the calcium ion and coronary vasospasm in ischemic heart disease.

Physicians have become increasingly aware that coronary artery bypass surgery is, essentially, a palliative procedure. Five years after surgery only about 40% of patients remain asymptomatic (Tecklenberg et al, 1975). Such deterioration is seen even in patients with "complete revascularization" documented angiographically at 1 year who were followed for 6 years thereafter (Robert et al, 1978). Worsening, or recurrence, of angina in these patients is usually a result of progression of atherosclerotic disease in the native circulation; this occurs in approximately 88% of such patients. In 1976, between 70,000 and 100,000 patients underwent coronary artery bypass surgery at an average cost of $11,000 per patient (Stoney et al, 1978). Given the costs involved in performing large numbers of bypass operations, new and effective means of medical treatment of coronary artery disease are becoming increasingly essential.

Two calcium antagonists have been used extensively abroad over the past 10 years and will probably be released for general clinical use here in the next 6 months to 1 year. Verapamil was first introduced 18 years ago as a smooth muscle relaxant with potent peripheral as well as coronary vasodilating effects. Subsequently it has found use as an antiarrhythmic agent as well.

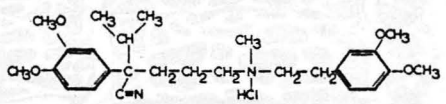

Figure 1. *Structural formula of verapamil.*

Nifedipine is a 1,4 dihydropyridine compound which is claimed to be the most potent coronary vasodilator ever synthesized (Taira et al; 1975). This drug is devoid of antiarrthymic qualities.

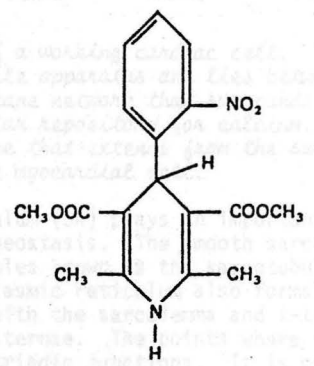

Figure 2. *Chemical structure of nifedipine.*

II. CARDIAC PHYSIOLOGY AND PATHOPHYSIOLOGY OF CALCIUM

A. Role of Calcium in Excitation-Contraction Coupling

In order to understand how the calcium antagonists produce their physiologic effects it is first necessary to review the role of calcium in mediating (1) excitation contraction coupling; (2) membrane depolarization; (3) ischemic cellular injury.

The calcium ion has two major roles in excitation-contraction coupling. It acts as a trigger substance to initiate contraction and as a regulating substance in the modulation of cardiac contractility. Calcium enters the cell during phase 2, or the plateau phase of the action potential (Reuter, 1974). Although calcium flux predominates during phase 2, sodium ion flux also contributes. The action potential spreads from the cell membrane down an extensive tubular system which is formed of invaginations of the cell membrane and is known as the transverse (t) tubular system. Importantly, the t-system is much larger in diameter in mammalian cardiac muscle than in skeletal muscle. This difference reflects the importance of extracellular calcium flux in cardiac muscle, as opposed to skeletal muscle. In addition to the sarcolemma and membranes of the t-tubular system other membrane systems divide the cell interior into various compartments.

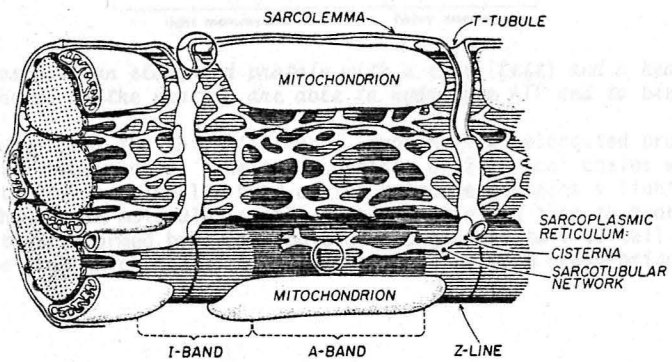

Figure 3. *Ultrastructure of a working cardiac cell. The sarcomere is the functional unit of the contractile apparatus and lies between two Z-lines. The sarcoplasmic reticulum, a membrane network that surrounds the contractile proteins, is the principal intracellular repository for calcium. The transverse t-tubular system is lined by a membrane that extends from the sarcolemma and carries the extracellular space into the myocardial cell.*

The sarcoplasmic reticulum (SR) plays an important role in the regulation of intracellular calcium homeostasis. The smooth sarcoplasmic reticulum forms a series of intracellular tubules known as the sarcotubular network and surrounds the myofibrils. The sarcoplasmic reticulum also forms specialized structures when it comes into contact with the sarcolemma and t-tubules; the SR flattens and forms subsarcolemmal cisternae. The points where the SR and t-tubes are in close contact are known as triadic junctions. It is currently felt that the t-tubular system is able to depolarize the sarcoplasmic reticulum resulting in the

release of free calcium ions which then mediate the intiation of muscular contraction. Calcium ions are primarily released from the terminal cisternae of the SR. Alternatively, some authors feel that the small amount of calcium which crosses the sarcolemma is able to trigger a massive calcium release from the sarcoplasmic reticulum (Katz, 1977).

Following release from the SR, calcium ions are bound to the protein, calmodulin. Calmodulin is known to bind to and activate various enzymes in the presence of calcium (Adelstein and Hathaway, 1979). In the myocardium the calcium-calmodulin complex results in the phosphorylation of myosin.

There are 4 principal proteins that form the basis for myocardial contraction:

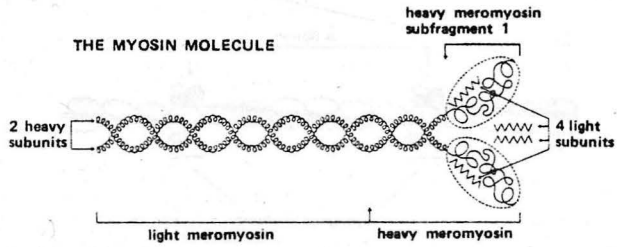

Figure 4. *Myosin is an elongated protain with a tail (left) and a head (right). The globular heads of the protein are able to hydrolyze ATP and to bind actin.*

(1) myosin forms the thick filament. Myosin is an elongated protein consisting of a tail and a head. The tail consists of 2-helical chains wound around each other. The globular head of the molecule contains 4 light subunits. The head of the myosin molecule is able to bind actin and also to hydrolyze ATP. Thick filaments are formed by myosin molecules organized tail to tail forming a rigid backbone from which the myosin heads project to form cross-bridges.

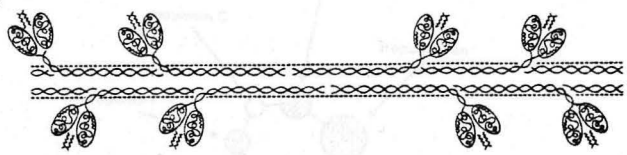

Figure 5. *Myosin molecules are arranged in a "tail to tail" configuration to form thick filaments. The myosin heads project at right angles to the backbone of the thick filament.*

(2) actin is a polymer, forms the thin filaments, and exists in the myocardium in the form of a double-stranded helix.

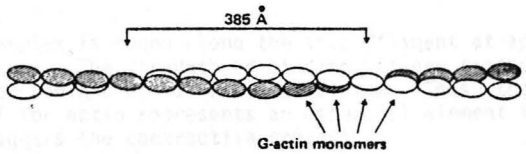

Figure 6. *Actin exists as a polymer with the basic structure of a double-stranded helix.*

(3) tropomyosin plays an important role in modulating the interactions between actin and myosin. Tropomyosin, in conjunction with troponin, serves as the calcium receptor mechanism of the contractile process. Tropomyosin lies in each of the 2 grooves that run longitudinally between the 2 strands of actin.

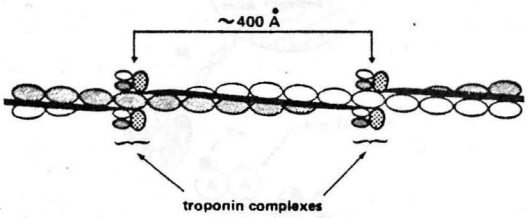

Figure 7. *Tropomyosin lies in the groove between actin polymers. Troponin complexes are bound to tropomyosin at 400-Å (Angstrom) intervals along the thin filament.*

(4) troponin is actually composed of 3 discrete proteins. Troponin I regulates interactions between actin and myosin principally in an inhibitory manner. Troponin T binds the troponin complex to tropomyosin and troponin C contains 2 high and 2 low affinity binding sites for the calcium ion. There is an interaction between calcium binding sites in troponin C such that when one binding site is occupied the affinity of the remaining sites is enhanced; this results in an amplification phenomena.

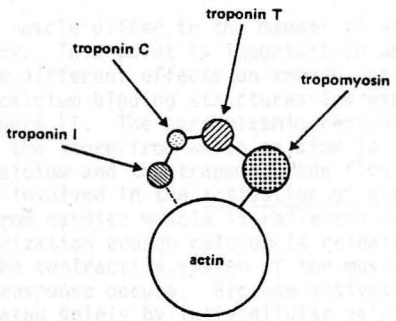

Figure 8. *Cross-section of the troponin complex. The dashed line between troponin I and actin represents a bond postulated to vary in strength depending on the binding of calcium to troponin C.*

The troponin complex is found along the thin filament at approximately 400 Angstrom unit intervals. The strength of binding between troponin I and actin depends on whether troponin C contains bound calcium. Thus, the variable affinity of troponin I for actin represents an essential element in the mechanism by which calcium triggers the contractile process.

In the absence of free calcium ion tropomyosin is oriented in such a way as to inhibit interactions between actin and myosin. When calcium ion becomes bound to troponin C the filamentous tropomyosin molecule shifts in position allowing cross-bridge formation to occur (Katz, 1977; Gergely, 1976), see Figures 9 and 10.

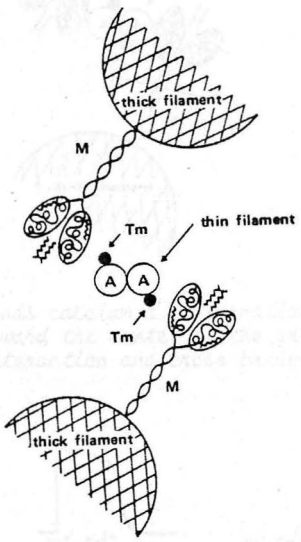

Figure 9. *Cross-section of a resting sarcomere. The tropomyosin molecule (TM) lies in such a way as to prevent actin (A)-myosin (M) interaction and cross-bridge formation.*

Different types of muscle differ in the manner in which calcium activates the contractile machinery. This point is important in understanding why the calcium antagonists have different effects on smooth, cardiac and skeletal muscle. Intracellular calcium binding structures are especially important in skeletal muscle, see Figure 11. The sarcoplasmic reticulum is well developed and is considered to be the store from which calcium is released and taken up again. Extracellular calcium and the transmembrane flow of calcium are not thought to be primarily involved in the activation of skeletal muscle. An additional difference from cardiac muscle is reflected by the fact that at the time of membrane depolarization enough calcium is released from the sarcoplasmic reticulum to saturate the contractile system of the muscle -- thus, in skeletal muscle, an all-or-none response occurs. Because activation and relaxation of skeletal muscle is mediated solely by intracellular calcium, with little or no dependence on extracellular calcium, the calcium antagonists have no effect on skeletal muscle excitation or contraction. Thus, Andersson (1978) noted that verapamil did not affect the twitch tension developed by isolated skeletal muscle fibers.

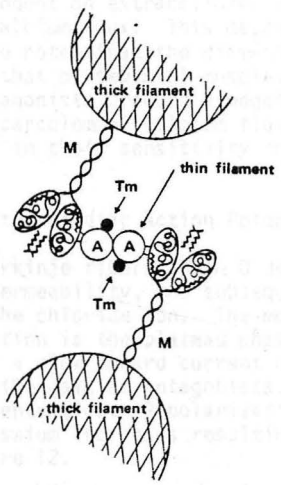

Figure 10. As troponin C binds calcium a conformation change occurs allowing tropomyosin (Tm) to shift toward the center of the groove between actin strands (A) allowing actin-myosin interaction and cross-bridge formation to occur.

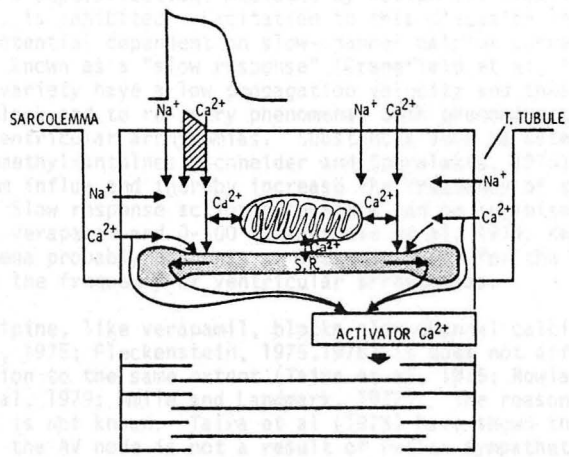

Figure 11. Calcium flux across the sarcolemma and t-tubular system occurs principally during the plateau phase of the actin potential. This calcium influx triggers further calcium release from the sarcoplasmic reticulum (SR) or is taken up and stored in the SR.

In marked contrast to skeletal muscle both cardiac muscle and especially smooth muscle are highly dependent on extracellular calcium concentration and on the extent of transmembrane calcium flux. This dependence is reflected by morphologic differences. We have noted that the diameter of the t-tubular system in cardiac muscle is 5 times that of skeletal muscle. Thus, in both cardiac and smooth muscle the calcium antagonists produce a negative inotropic effect or relaxation by limiting trans-sarcolemmal calcium flux. Different types of smooth muscle differ somewhat in their sensitivity to the calcium antagonists (Massingham, 1973).

B. Role of Calcium in the Cardiac Action Potential

In cardiac muscle and Purkinje fibers phase 0 depolarization is mediated by a sudden increase in sodium permeability, the subsequent phase 1 of repolarization is probably carried by the chloride ion. The most distinctive portion of cardiac electrical depolarization is the plateau phase. This phase of the action potential is produced by a slow inward current of calcium ions. The slow inward current is reduced by the calcium antagonists, as well as by a reduction in extracellular calcium concentration. Repolarization, or phase 3, occurs when membrane permeability to potassium increases resulting in a repolarizing current (Rosen et al, 1974), see Figure 12.

It is important to note that in the sinoatrial, and more prominently in the atrioventricular nodes, the slow calcium channels play a much more important role than in myocardial cells or Purkinje fibers in the production of phase 0 depolarization (Zipes and Fischer, 1974). This explains the ability of some calcium antagonists, such as verapamil, to produce high-degree A-V block (Zipes and Troup, 1978), see Figure 13. Furthermore, in the presence of ischemia or hypoxia rapid phase 0 depolarization, mediated by sodium ion flux in ventricular and Purkinje fibers, is inhibited. Excitation in this situation leads to a propagated action potential dependent on slow-channel calcium current -- such an action potential is known as a "slow response" (Cranefield et al, 1972). Action potentials of this variety have a low propagation velocity and thus contribute to unidirectional block and to re-entry phenomena; both phenomena are important in the genesis of ventricular arrhythmias. Substances such as catecholamines (Reuter, 1967) and methylxanthines (Schneider and Sperelakis, 1975) increase slow channel calcium influx and thereby increase the frequency of slow response action potentials. Slow response action potentials can be inhibited by the calcium antagonists verapamil and D-600 (Cranefield et al, 1974; Kass and Tsien, 1975). This phenomena probably accounts at least in part, for the ability of verapamil to reduce the frequency of ventricular arrhythmias.

Although nifedipine, like verapamil, blocks slow-channel calcium influx (Fleckenstein et al, 1975; Fleckenstein, 1975,1976) it does not affect atrioventricular conduction to the same extent (Taira et al, 1975; Rowland et al, 1979; Podeletti et al, 1979; Amlie and Landmark, 1977). The reason for this differential effect is not known. Taira et al (1975) have shown that the differential effect on the AV node is not a result of reflex sympathetic stimulation. The slow calcium channels of the A-V node may have different characteristics from those of the ventricular myocardium or Purkinje fibers. Although verapamil prolonged A-V node induction time and increases the duration of the effective and functional A-V nodal refractory periods, it does not change intraatrial conduction times or QRS, H-V and Q-T intervals (Mangiardi et al, 1978). The A-V node is more sensitive to the depressant effects of calcium antagonists than the SA node -- effects are dose related, see Figure 14.

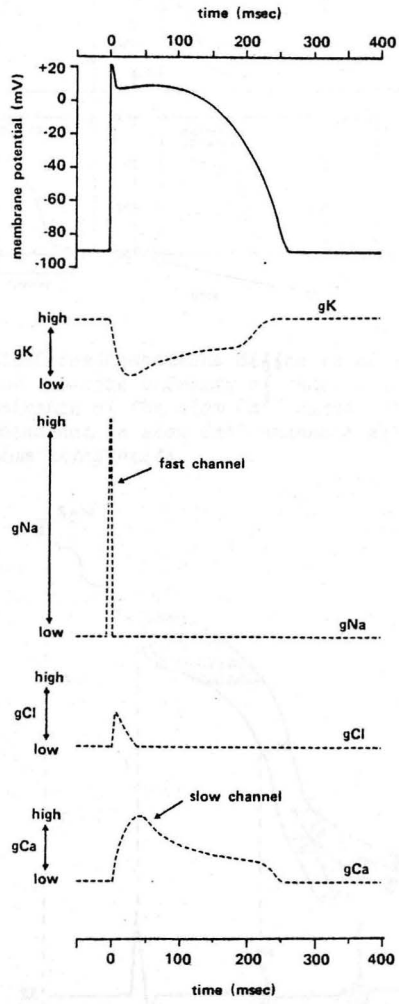

Figure 12. *Changes in ionic conductances during the action potential in a Purkinje fiber. Note the typical action potential (top) and, reading from top to bottom, the accompanying changes in conductance for potassium (gK), sodium (gNa), chloride (gCl), and calcium (gCa). An increase in gNa or gCa augments inward current flow, whereas increasing gK or gCl augments outward current flow.*

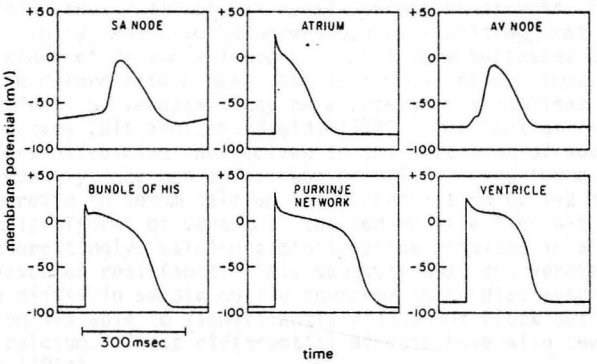

Figure 13. *Action potential configurations differ in different regions of the mammalian heart. The slow upstroke velocity of phase 0 in the SA and AV nodes is a result of the predominance of the slow Ca^{2+} rather than the rapid Na+ inward current. This dependence on slow Ca^{2+} channels explains the sensitivity of these regions to calcium antagonists.*

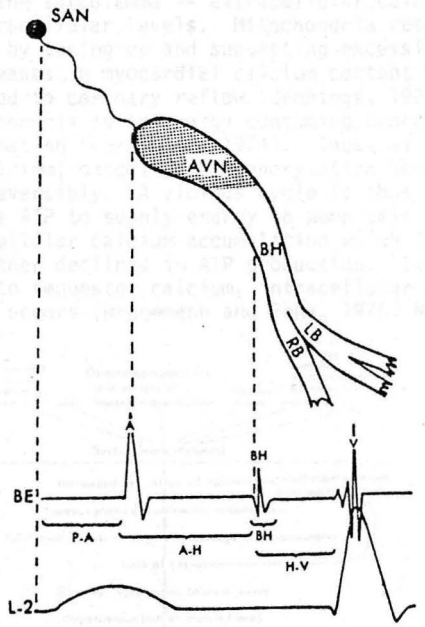

Figure 14. *The A-V conduction system in relationship to an intracardiac electrical recording. Verapamil produces a prolongation of the A-H interval with little effect on the P-A or H-V interval.*

Alternatively, the prominent A-V nodal depressant effects of verapamil, in contrast to nifedipine, may also be understood by realizing that verapamil exists as a racemic mixture of d- and l-isomers. The l-form possesses calcium-blocking effects while the d-form also blocks fast sodium channels. Thus, the proximal A-V node blocking effects of verapamil may be a result of a combined sodium and calcium channel blockade (Wit and Cranefield, 1974). The lack of A-V nodal blocking properties renders nifedipine ineffective in the treatment of supraventricular arrhythmias. Recently, Hariman and co-workers (1979) have found in open chest dogs that an increase in serum calcium ion concentration by 1-2 meq/L reverses the negative inotropic effects of verapamil but had no effect on A-V conduction or sinus rate. Interestingly, calcium administration resulted in a further decrease in peripheral vascular resistance. This suggests that the verapamil-calcium interaction may differ in smooth muscle compared to cardiac muscle. A sodium chloride infusion was able to significantly reduce A-V block but only after pretreatment with calcium. These differential effects have also been noted by Shigenobu et al (1974).

C. Role of Calcium in the Mediation of Ischemic Cellular Necrosis

In ischemic cardiac damage, as well as human muscular dystrophies, there is good evidence for a generalized plasma membrane defect (Wrogemenn and Pena, 1976; Burton, 1977). Such defects apparently allow for an increased net influx of calcium ions into the cell. Calcium influx is favored by the large concentration gradient across the sarcolemma -- extracellular calcium concentration is 10,000 times that of intracellular levels. Mitochondria respond to an increase in intracellular calcium by taking up and sequesting excessive amounts of this ion. Up to 50-fold increases in myocardial calcium content have been found in ischemic regions subjected to coronary reflow (Jennings, 1976). Massive uptake of calcium ions by mitochondria is an energy consuming process and occurs even in preference to ATP formation (Lehninger, 1974). Thus, as mitochondria become massively loaded with calcium, oxidative phosphorylation becomes progressively impaired, eventually irreversibly. A vicious cycle is thus initiated where mitochondria produce less ATP to supply energy to pump calcium out of the cell resulting in more intracellular calcium accumulation which in turn is taken up by mitochondria with further declines in ATP production. Eventually mitochondria are no longer able to sequester calcium, intracellular cytosolic calcium begins to rise and rigor occurs (Wrogemenn and Pena, 1976; Hearse et al, 1977).

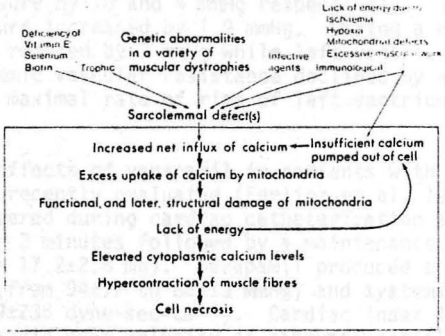

Figure 15. *Hypothetical sequence of events leading to cell necrosis through a vicious cycle of mitochondrial calcium overload.*

Calcium antagonists such as verapamil and D-600 have been found to retard such contracture or rigor formation (Hearse et al, 1977; Henry et al, 1977) and to retard mitochondrial calcium accumulation (Fleckenstein et al, 1975; Henry et al, 1977). For reasons enumerated above, this limitation in mitochondrial calcium accumulation may result in a decrease in myocardial necrosis (Henry et al, 1977; Henry et al, 1978; Fleckenstein et al, 1975). In an ischemic reflow model functional or mechanical abnormalities have been noted to be closely correlated with mitochondrial calcium accumulation and potentially reversible with nifedipine administration (Henry et al, 1977). Other non-organic calcium antagonists such as potassium or magnesium have also found to be effective (Rosenberger and Triggle, 1978). Thus the calcium ion plays an important role not only in activating muscular contraction (Gergely, 1976), but also in modulating glycolytic flux (Mayer, 1974), in regulating oxidative phosphorylation in mitochondria (Lehninger, 1974) as well as modulating adrenergic effects on the myocardium (Reuter, 1974).

III. HEMODYNAMIC EFFECTS OF THE CALCIUM ANTAGONISTS

The hemodynamic effects of the calcium antagonists are largely predictable on the basis of their known pharmacological effects.

(1) Peripheral arteriolar vasodilatation occurs as a result of smooth muscle relaxation. Relaxation occurs because calcium is known to play an important role in the maintenance of peripheral vascular tone (Bevan et al, 1976).

(2) A negative cardiac inotropic effect occurs as trans-sarcolemmal calcium flux is decreased.

(3) Atrioventricular (A-V), and to a lesser degree, sinoatrial (SA) depression occur.

The hemodynamic effects of verapamil have been investigated in 8 normal middle-aged men by Atterhög and Ekelund (1975). Verapamil was administered as an initial dose of 0.1 mg/kg over 2 minutes followed by a constant infusion at a rate of 0.007 mg/kg/min (average total dose = 21.4 mg). These investigators noted an increase in heart rate by 9 beats/min with a decrease in systolic and diastolic aortic pressure by 10 and 4 mmHg respectively. The mean pulmonary capillary wedge pressure increased by 1.9 mmHg. During a mild level of exercise systolic pressure was reduced by 7 mmHg while left ventricular and stroke volumes were unchanged. Systemic vascular resistance declined by about 10% but maximum peak dp/dt (i.e., the maximal rate of rise of left ventricular pressure) did not change.

The hemodynamic effects of verapamil in patients with coronary artery disease has also been recently evaluated (Ferlinz et al, 1979). In this study verapamil was administered during cardiac catheterization as an initial loading dose of 0.1 mg/kg over 2 minutes followed by a maintenance infusion of 0.005 mg/kg/min (mean dose = 17.2±2.8 mg). Verapamil produced a substantial drop in mean aortic pressure (from 94±17 to 82±13 mmHg) and systemic vascular resistance (from 1413±429 to 1069±235 dyne-sec-cm^{-5}). Cardiac index increased from 2.8±0.6 to 3.1±0.7 L/min/m^2 as did mean velocity of circumferential fiber shortening and ejection fraction (which increased from 55±16 to 61±18%). Heart rate did not change significantly, nor did ischemic wall motion abnormalities as qualitatively

assessed by ventriculography. It is of interest that at the lower dosage levels verapamil did not induce a reflex tachycardia despite a significant drop in aortic pressure. The absence of a reflex tachycardia is probably a result of the depressant, or negative chronotropic, effects of verapamil on the SA and AV nodes (Mangiardi et al, 1978; Roy et al, 1974). In isolated heart preparations verapamil produces a bradycardia (Naylor et al, 1968). Thus, in vivo a cancellation of effects occurs in which increased sympathetic outflow resulting from baroreceptor activation is counter-balanced by a direct depressant effect on the cardiac conduction system, see Figures 16 and 17.

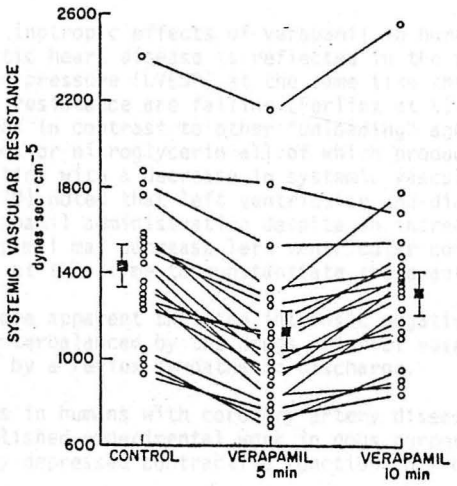

Figure 16. *Effect of verapamil administration on systemic vascular resistance in 20 patients given 10 mg of verapamil intravenously.*

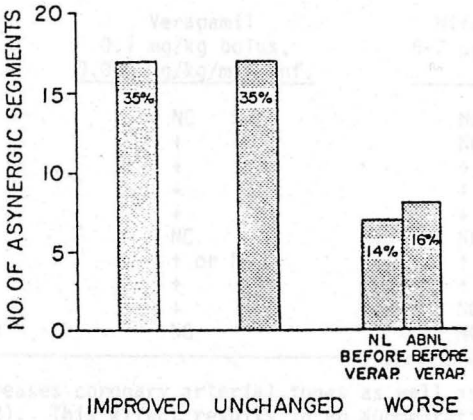

Figure 17. *Changes in left ventricular contractility after administration of verapamil in patients with coronary artery disease, determined by contrast ventriculography.*

The apparent improvement observed in left ventricular function with verapamil administration at first seems somewhat surprising in view of its known negative inotropic effects in isolated systems (Magnussen and Kudsk, 1974; Naylor and Szeto, 1972). The explanation for this seeming disparity lies in the realization that ejection fraction, velocity of circumferential fiber shortening, and dp/dt are "afterload dependent". This means that these measures of cardiac function may show an apparent improvement as aortic pressure or "afterload" is lowered in the absence of any real changes in cardiac contractility (Mahler et al, 1975).

The negative inotropic effects of verapamil in humans with coronary artery disease or rheumatic heart disease is reflected in the rise in the left ventricular end diastolic pressure (LVEDP) at the same time that aortic pressure and systemic vascular resistance are falling (Ferlinz et al, 1979; Singh and Roche, 1977). This stands in contrast to other "unloading" agents such as nitroprusside, phentolamine, or nitroglycerin all of which produce an increase in stroke volume in conjunction with a decrease in systemic vascular resistance and LVEDP. Ferlinz et al (1979) noted that left ventricular end-diastolic volume was unchanged after verapamil administration despite an increase in LVEDP; the authors suggest that verapamil may decrease left ventricular compliance. Inadequate data is available at this time to substantiate these authors' impressions.

It is therefore apparent that the intrinsic negative inotropic effects of verapamil are counterbalanced by the drugs arterial vasodilating or "unloading" effect as well as by a reflex sympathetic discharge.

These results in humans with coronary artery disease are reassuring in view of previously published experimental work in dogs purporting to show that verapamil selectively depressed contractile function in ischemic myocardium (Smith et al, 1976).

TABLE 1.

Parameter	Verapamil 0.1 mg/kg bolus, 0.005 mg/kg/min inf.	Nifedipine 5-7 µg/kg bolus
HR	NC	NC or ↑
LVEDP	↑	NC
SYST AP	↓	↓
DIAST AP	↓	↓
SVR	↓	↓
PVR	NC	NC
SVI	↑ or NC	↑
EF	↑	↑
LV dp/dt	↓	NC or ↑
Seg LV Fx	NC	NC

Verapamil decreases coronary arterial tones as well as peripheral vasomotor tone (Ekelund, 1978). This effect results in an augmentation of coronary flow. After coronary occlusion in dogs verapamil increased flow to normal myocardium but not ischemic myocardium in both awake (Karlsberg et al, 1977) and anesthetized animals (Smith et al, 1976). Although they did not measure regional flow Reimer et al (1977) did document a reduction in myocardial necrosis when verapamil

was administered prior to coronary occlusion and reflow. Naylor et al (1976) have noted in vitro that verapamil provides a protective effect against some consequences of hypoxia: loss of myocellular potassium, rate of creatine kinase release, depletion of ATP, mitochondrial swelling and membrane disruption.

Although Karlsberg et al (1977) failed to find a protective effect with verapamil. However, in their study the drug was not administered until 7 hours after coronary occlusion. A more recent study (daLuz et al, 1980) found a significant increase in retrograde flow and decrease in regional coronary resistance in ischemic zones. This apparent increase in collateral blood flow occurred with a reduction in heart rate and the heart rate-blood pressure product. Smith et al (1975) found that verapamil reduced myocardial infarct size following experimental coronary occlusion in dogs. Thus, verapamil in some studies appears to improve regional coronary flow to ischemic myocardium while at the same time reducing myocardial oxygen demand. It has been shown in an experimental setting to be effective in limiting myocardial necrosis and hypoxic myocardial cellular injury.

Nifedipine has also been shown in experimental animals to limit the development of ischemic contracture and abnormal mitochondrial calcium uptake in isolated rabbit hearts (Henry et al, 1977). Nifedipine exerts a protective effect on globally ischemic canine hearts during cardiopulmonary bypass (Clark et al, 1979). Nifedipine has been shown in awake dogs to improve collateral flow development to ischemic myocardium and to limit ischemic injury (Henry et al, 1978). Segmental function is improved in open chested dogs after coronary occlusion when nifedipine is given (Henry et al, 1979).

The antianginal efficacy of the calcium antagonists can be understood in light of their hemodynamic effects. Nifedipine has some hemodynamic effects which are dissimilar to those of verapamil. For example, when nifedipine was given as a 20 mg sublingual dose to 20 patients with coronary artery disease, a reflex tachycardia occurred (with a 17% increase in heart rate) with a 12% increase in dp/dt. While systolic and diastolic pressures decreased by 28% and 23% respectively, left ventricular end diastolic fell by 14% (d'Oliveira et al, 1976). In other studies (Lydtin et al, 1975) the reflex tachycardia was short-lived, whereas decreases in peripheral vascular resistance and cardiac output were more prolonged (at least 3 hours). Nifedipine does not appear to reduce left ventricular end diastolic pressure or volume ("preload") to the same extent as nitroglycerin (Lichtlen, 1975). The tachycardia seen with nifedipine is a result of autonomic mechanisms -- but 80% of the decrease in coronary vascular resistance is a result of a direct effect of the drugs and only 20% is attributable to autonomic mechanisms (White et al, 1974). Nifedipine has actually been used in the acute treatment of pulmonary edema in patients with hypertensive cardiovascular disease, valvular heart disease and cardiomyopathy (Polese et al, 1979). After a 10 mg sublingual dose nifedipine significantly reduced left ventricular end diastolic presure and echocardiographically determined end diastolic volume and end systolic volume. Symptomatic improvement occurred in all patients; the predominant hemodynamic effect was a reduction in systemic vascular resistance. The effectiveness of nifedipine in this situation attests to its lack of significant in vivo negative inotropic effects as well as to its profound peripheral vasodilatory effect.

In the treatment of exertional angina pectoris the hemodynamic effects of the calcium antagonists during exercise may be more relevant than resting changes.

Thus Kurita and colleagues (1976) studied the hemodynamic effects of nifedipine and propranolol during exercise in 17 patients with angina pectoris. Previous studies have demonstrated a striking hemodynamic response to exercise in patients with ischemic heart disease -- a marked rise in left ventricular end-diastolic pressure. In contrast, those patients who received nifedipine (5-7 μg/kg) experienced a decrease in the magnitude of rise in LVEDP during exercise. Propranolol did not alter the rise in LVEDP, but rather acted to decrease the heart rate-blood pressure product and dP/dt (or LV contractility).

TABLE 2. Effect of nifedipine and propranolol on hemodynamic response to exercise

	Effect of exercise n = 17	Nifedipine n = 9	Propranolol n = 8
HR	↑	→	↓
BAm	↑	→	→
LVEDP	↑	↓	→
dp/dt	↑	→	↓
TTI	↑	→	↓
CI	↑	→	→
LVSWI	↑	→	→

BAm=Brachial artery mean pressure; LVEDP=Left ventricular end-diastolic pressure; dp/dt=1st derivative of LV pressure; TTI=tension-time index; CI=cardiac index; LVSWI=LV stroke work index

Nifedipine has also found use as a cardioplegic and protective agent during cardiopulmonary bypass (Magee et al, 1979; Clark et al, 1979). However, available data suggests nifedipine may not be superior to potassium cardioplegia in this situation (Magee et al, 1979).

Thus, we can summarize the significant hemodynamic effects of calcium antagonists in the setting of acute myocardial ischemia as follows:

(1) An increase in collateral blood flow to ischemic zones;

(2) A reduction in myocardial oxygen demand in experimental animals primarily mediated by a combination of "afterload reduction" and, with verapamil, a mild negative inotropic effect;

(3) A protective effect on ischemic myocardium measured by creatine kinase depletion, by the extent of histologic necrosis, or by mitochondrial calcium accumulation;

(4) In some instances, apparent improvement in ischemic segmental function.

IV. CLINICAL USE OF THE CALCIUM ANTAGONISTS

A. Clinical Studies -- Stable Angina Pectoris

There are several published clinical studies, adequately designed and controlled, which demonstrate the efficacy of verapamil in the treatment of stable classic angina pectoris (angina of effort). Sandler (1970), for example, examined the use of a two-step exercise test to assess the efficacy of low (40 mg tid) and high (120 mg tid) doses of verapamil compared in a double-blind manner to propranolol (100 mg tid) and placebo. After placebo for 1 month each drug was given in a double-blind fashion for a month. The low dose of verapamil, although reducing the number of anginal attacks and quantity of nitroglycerin consumed, was not statistically superior to placebo. Neither did exercise parameters improve with the low dose. At the higher dose however, verapamil significantly improved exercise duration and reduced the extent of ST segment depression. Verapamil was comparable to propranolol in efficacy.

Livesley et al (1973) used a double blind cross-over design to evaluate verapamil in a low (80 mg tid) and a high (120 mg tid) dose; comparisons were made to propranolol 100 mg tid and isosorbide dinitrate 20 mg tid. Active drugs were administered for 4 weeks. The antianginal efficacy of propranolol and verapamil (120 mg tid) did not differ but both were superior to placebo. Isosorbide dinitrate therapy was not superior to placebo. Both propranolol and the higher dose of verapamil reduced resting heart rate, blunted exercised induced tachycardia, decreased diastolic blood pressure, prolonged exercise duration and increased maximum workload. The lower dose of verapamil (80 mg tid) did reduce consumption of nitroglycerin and diastolic pressure at rest.

Another double-blind randomized placebo-controlled study (Andreasen et al, 1975) examined the effect of verapamil in a dose of 80 mg tid on nitroglycerin consumption, number of anginal attacks and exercise capacity. Verapamil significantly reduced the number of anginal attacks as well as the quantity of nitroglycerin consumed after two weeks. Additionally, a significant prolongation in the exercise time was achieved. Rossi and co-workers (1979) have noted an enhancement by verapamil of the beneficial effects of exercise rehabilitation after myocardial infarction in 40 patients in a double-blind randomized study.

Recent studies (using a single-blind placebo controlled design) demonstrate that nifedipine, too, is an effective agent in the therapy of classic effort angina (Moskowitz et al, 1979), see Figures 18 and 19. In this study nifedipine therapy was administered orally (10 or 20 mg three times daily); this dosage was able to decrease anginal episodes by 37 and 44% respectively in conjunction with a decrease in nitroglycerin consumption of 47% and 53%, respectively. Objective improvement in exercise tolerance was demonstrable by an increase in treadmill exercise time by 28% and 42% with the low and high dose of nifedipine respectively. The maximal achieved heart rate and blood pressure product did not differ between treatment and placebo therapy. Since the heart rate blood pressure product is a measure of myocardial oxygen demand, the lack of an increase with nifedipine therapy suggests that the mechanism for improvement in exercise tolerance is not a result of a primary increase in coronary blood flow or myocardial oxygen consumption. Rather, the beneficial effects of nifedipine may be a result principally of its peripheral vasodilatory properties, a mode of action similar to that of nitrates (Lichtlen, 1975). Since nifedipine administration produces little change in contractility, reduction in myocardial oxygen consump-

tion at a given work load as a result of a negative inotropic effect is also unlikely (Lichtlen, 1975). Unlike the nitrates, however, nifedipine does not appear to produce peripheral venous pooling to the same degree (Mostbeck et al, 1976).

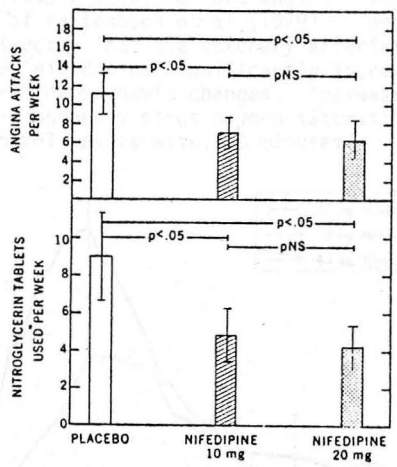

Figure 18. *Effect of nifedipine therapy (10 mg and 20 mg orally every 8 hrs) compared with that of placebo on frequency of anginal attacks and nitroglycerin used per week in 10 patients with stable angina.*

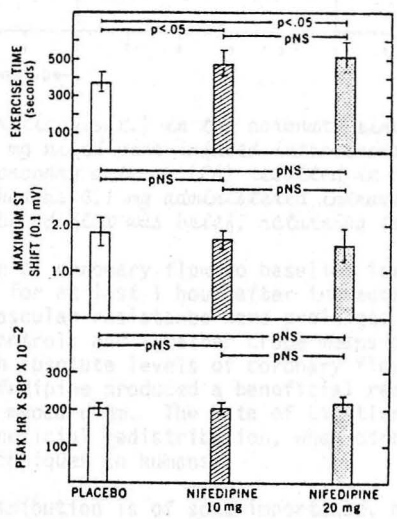

Figure 19. *Effect of nifedipine therapy (10 mg and 20 mg orally every 8 hrs) on peak treadmill exercise time, maximal S-T segment shift and product of heart rate and systolic blood pressure (HR X SBP) at peak exercise in 10 patients with stable angina.*

Thus, it appears that, although nifedipine is capable of producing a primary increase in coronary blood flow by means of coronary arteriolar relaxation, such increases do not account for a primary role in nifedipine's antianginal efficacy, at least in classic stable effort angina. This conclusion is supported by the recent data of Kaltenbach et al (1979). These investigators injected 100 µg of nifedipine directly into the coronary arteries of 10 patients. They found that intracoronary nifedipine significantly increased coronary flow in the absence of peripheral hemodynamic changes. Increased coronary flow was manifested by an increase in coronary sinus oxygen saturation; but coronary flow quickly returned to control levels within 5 minutes.

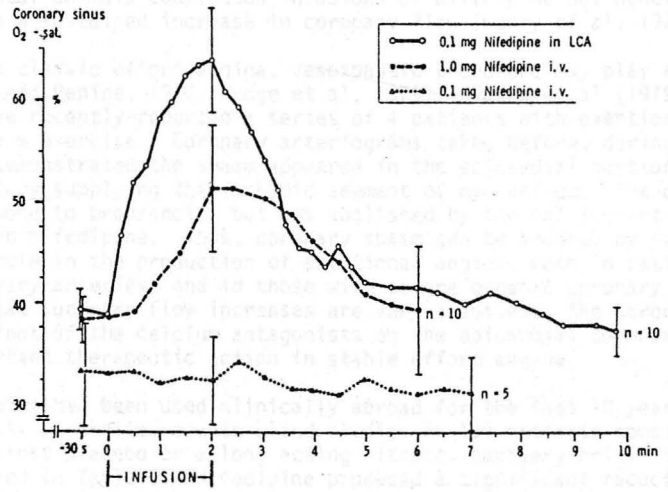

Figure 20. *Oxygen saturation (sat.) in the coronary sinus during three different interventions: 1.0 mg nifedipine infused intravenously (i.v.) and 0.1 mg infused into the left coronary artery (LCA) resulted in a significant increase in oxygen saturation, whereas 0.1 mg administered intravenously had no effect. The increased coronary blood flow was brief, returning to control by 5 minutes.*

Despite the rapid return of coronary flow to baseline levels, exercise tolerance was measurably improved for at last 1 hour after intracoronary nifedipine. Decreases in peripheral vascular resistance were prolonged. This study suffers from lack of adequate controls and a rather crude means of measuring coronary flow. Thus, even though absolute levels of coronary flow returned to normal one might postulate that nifedipine produced a beneficial redistribution of flow from normal to ischemic myocardium. The data of Lichtlen et al (1976) however, failed to reveal any beneficial redistribution, when coronary flow was assessed with Xenon clearance techniques in humans.

The issue of redistribution is of some importance, best illustrated by the effects of nitroglycerin. Total coronary blood flow has been found to increase only for 1 or 2 minutes after the administration of nitroglycerin. Drugs less efficacious clinically than nitroglycerin actually increase total coronary flow to a greater degree and for a longer period of time. An example would be dipyridamole (Persantin), a drug which causes marked and sustained increases in

coronary flow, but which has proven to be no more efficacious than placebo in the treatment of angina pectoris (Newhouse and McGregor, 1965; Sbar and Schlant, 1967). The answer to this seeming paradox probably rests upon the potent preload, or venodilating effects of nitroglycerin (Chiong et al, 1972) and upon its ability to redistribute coronary flow to the endocardium in both normal and acutely ischemic myocardium without increasing total coronary flow (Horwitz et al, 1971; Winbury et al, 1971). There is little information regarding the effects of verapamil and nifedipine in affecting a redistribution of coronary flow; our own results, as yet preliminary, suggest that the endocardial/epicardial myocardial flow ratio is not altered by a continuous infusion of nifedipine. In experimental animals continuous infusions of nifedipine do, however, appear to result in a sustained increase in coronary flow (Henry et al, 1978).

Even in classic effort angina, vasospastic phenomena may play an important role (Shang and Pepine, 1977; Mudge et al, 1979). Yasue et al (1979), for example, have recently reported a series of 4 patients with exertional angina induced by arm exercise. Coronary arteriograms taken before, during and after the attack demonstrated the spasm appeared in the epicardial portion of the coronary artery supplying the ischemic segment of myocardium. The chest pain did not respond to propranolol but was abolished by the calcium antagonist diltiazem and nifedipine. Thus, coronary spasm can be induced by exercise and may play a role in the production of exertional angina, both in patients with normal coronary arteries, and in those with severe organic coronary stenosis. Although total coronary flow increases are very transient, the coronary vasodilatory effect of the calcium antagonists on the epicardial coronary arteries may be important therapeutic action in stable effort angina.

Nifedipine has been used clinically abroad for the last 10 years. The results of six controlled double-blind studies in 199 patients comparing nifedipine against placebo or a long acting nitrate, pentaerythrityl tetranitrate are summarized in Table 3. Nifedipine produced a significant reduction in the frequency of anginal attacks, compared to placebo, in each study. The magnitude of the decrease varied between 56% and nearly 90% (Kimura et al, 1972; Camerini et al, 1974; Maggi, 1975; Maggi and Piscitello, 1975; Sakuma and Kimura, 1975; Mena et al, 1975).

TABLE 3.

Author	n	Daily Dose	Days	Reduction Freq Angina	P	Remarks
Kimura	16	30 mg	14/14	56.6%	<0.05	DB PL
Camerini	48	30 mg	14/14	68.7%	<0.01	DBCO PL
Maggi	50	30 mg	14/14	88.0%	<0.003	DB PETN
Sakuma	25	30 mg	14/14	62.0%	<0.01	DBCO PL
Maggi	30	30 mg	21/21	60.0%	<0.01	DBCO PETN
Mena	29	40 mg	56/56	66.9%	<0.01	DBCO PL

DBPL=double blind vs. placebo; DBCO PL=double blind crossover vs. placebo; PETN=pentaerythrityl tetranitrate; n=number patients.

These data illustrate that nifedipine is superior in antianginal efficacy to long-acting nitrates. Maggi (1975), for example, examined this question in a single blind randomized cross-over study. Nifedipine (10 mg tid) was compared

to pentaerythrityl tetranitrate (80 mg tid); 44 of 50 patients studied had fewer anginal attacks with nifedipine therapy. The efficacy of nifedipine and beta blockers is comparable (Sakuma and Kimura, 1975). The antianginal efficacy of nifedipine (30 mg qd) in combination with a beta blocker (oxprenolol, 60 mg daily) has been examined. The antianginal efficacy of the combination was not any greater than either drug alone. It appears that nifedipine can be used safely in patients with angina pectoris who have disorders of A-V conduction, and in those receiving beta adrenergic blocking agents (Rowland et al, 1979). Verapamil should never be given concomitantly with beta-adrenergic blocking agents.

The antianginal effects of nifedipine do not appear to be reversed by digoxin therapy (Ebner, 1975).

There are two clinical situations in which anginal syndromes may actually be exacerbated by nifedipine. First, in those patients in whom a marked hypotensive effect is produced with a resultant reflex tachycardia, angina may worsen. In April, 1979, the Committee on Safety of Medicines (in England) noted in its newsletter, Current Problems, that it has received a number of reports of increased angina and myocardial infarction in patients treated with nifedipine. No causal relationship has been established, however. Second, the substitution of nifedipine for a beta-adrenergic blocker should not be made after abrupt withdrawal of the beta-blocker. Nifedipine, used in this manner may increase the frequency of a beta-blocker withdrawal syndrome (Meinertz, 1979), presumably by enhancing sympathetic β-adrenergic cardiac stimulation (Pedersen et al, 1979).

Thus, we can draw the following conclusions:

(1) The antianginal efficacy of nifedipine and verapamil is comparable to that of propranolol but superior to that of the long-acting nitrates.

(2) The mechanism of action of the calcium antagonists in classic effort angina appears to be a result of peripheral arterial vasodilatory effects. There may, however, be a coronary vasospastic element even in classic effort angina; such dynamic changes in coronary arterial resistance would be expected to improve with calcium antagonist and to be exacerbated or unchanged by propranolol.

(3) Both nifedipine and verapamil prolong the duration of exercise, increase the maximal workload obtained, and tend to reduce the magnitude of ST segment depression.

(4) β-adrenergic blocking agents should not be abruptly discontinued with the substitution of nifedipine. Verapamil reduces the resting and peak heart rate-blood pressure product but nifedipine does not.

B. The Slow-Channel Calcium Antagonists in Unstable or Rest Angina and Prinzmetal's Angina

In the vast majority of patients with classic effort angina atherosclerotic obstructive lesions of the coronary arteries are present. The symptom of angina pectoris is probably a result, in most cases, of an imbalance between a restricted myocardial oxygen supply and a transiently increased metabolic demand.

In contrast, in patients with unstable or rest angina, a primary reduction in coronary flow may play a central pathophysiologic role. For example, in the studies of Berndt et al (1977), the heart rate blood pressure products in patients with spontaneous attacks of angina pectoris who were shown to have atherosclerotic coronary artery disease were not significantly different during an attack in comparison with pain free periods. During pacing-induced angina, on the other hand, double products were markedly elevated. Maseri et al (1978) studied a subset of 76 patients with angina at rest with invasive hemodynamic monitoring, thallium-201 myocardial scintigraphy or coronary arteriography. In this subgroup of patients, the authors were able to implicate coronary spasm in the genesis of rest angina. In the eight of the 76 patients who developed myocardial infarction, the onset of the infarction was indistinguishable from the onset of an attack of spontaneous angina. Other studies have confirmed a role of spasm in myocardial infarction (Oliva and Breckinridge, 1977). These latter authors demonstrated that in 6 of 15 patients arteriogramed within 12 hours of acute myocardial infarction, patency could be re-established in the occluded coronary arteries by the intracoronary administration of nitroglycerin.

Coronary artery spasm has also been implicated in the pathogenesis of various arrhythmias including ventricular fibrillation (Lasser and de la Paz, 1973).

Coronary artery spasm is now known to represent the pathogenic mechanism of variant or Prinzmetal's angina (Oliva et al, 1973; Meller et al, 1976). Further, at least in variant or Prinzmetal's angina, propranolol is ineffective or may actually increase the number of attacks (Yasue et al, 1974). This probably occurs because beta-adrenergic blockade increases relative coronary alpha-adrenergic tone, favoring vasoconstriction (Luchi and Chahine, 1979). Although nitrates are known to be effective in the alleviation of coronary vasospasm (Maseri et al, 1979), the duration of action of these agents is short and headache or hypotension are frequent side effects with the high doses which are often necessary. Coronary artery bypass surgery is usually ineffective (Gaasch et al, 1974).

The calcium antagonists may be ideally suited for the treatment of coronary vasospastic phenomena because:

(1) The calcium-antagonists do not block the vasodilatory coronary beta-2 receptors and thus do not increase relative alpha-adrenergic tone.

(2) These agents have a long duration of action (6-8 hours); although in some cases nifedipine must be administered every 4 hours (Previtali et al, 1980).

(3) The calcium antagonists may be effective in cases where nitrates have failed (Heupler and Proudfit, 1979).

(4) The calcium-antagonists have a beneficial effect in patients with fixed obstructive coronary artery disease.

Diltiazem, a 1,5 benzothiazipine derivative with calcium antagonistic effects, is also effective in spontaneous Prinzmetal's angina (Endo et al, 1976) and in coronary vasospasm induced by hyperventilation and Tris-buffer infusion (Yasue et al, 1978).

Goldberg et al (1979) demonstrated that the acute administration of nifedipine was effective in 11 of 12 patients with Prinzmetal's angina; 7 of the 11 had long-term relief with dosages of 40-120 mg/d in divided doses every 4 to 6 hours. Withdrawal of the nifedipine led to a recurrence of the angina in 4 patients.

Verapamil too, is effective in Prinzmetal's angina and unstable or rest angina. Parodi et al (1979) studied 12 patients with unstable angina in a randomized blind-blind cross-over study using verapamil (480 mg/d).

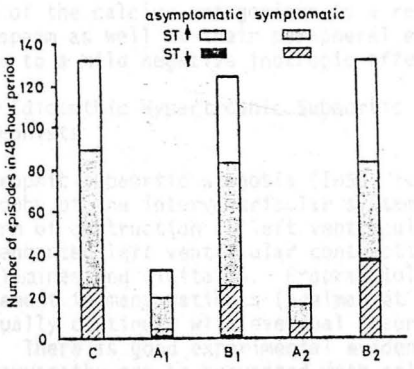

Figure 21. *The total number of episodes in 12 patients with unstable angina in a double-blind cross-over study. C indicats a run-in period; A_1, A_2 verapamil periods; B_1, B_2 placebo periods. Control and placebo periods show similar number and type of ischemic episodes, while during treatment with verapamil there is a significant reduction in frequency of all types of episodes.*

Symptomatic and asymptomatic episodes of ST segment elevation and depression were measured. During the 48 hour treatment period verapamil reduced the number of such episodes from 128 to 31 in the first trial and from 123 to 23 in the second. The drug seemed to be most efficacious in those patients with the most numerous episodes. The beneficial effects of verapamil appeared to be maintained during long term treatment. Hansen and Sandoe (1978) have contributed additional confirmatory data.

Piccolo et al (1977), in a nonrandomized open study, examined the effects of intravenous verapamil in patients with unstable angina or Prinzmetal's angina refractory to propranolol and nitrate therapy. In 2/3 of the patients verapamil was effective with complete relief of angina or conversion to angina with effort.

At present the relative efficacy of the calcium antagonists in the treatment of unstable angina, rest angina or Prinzmetal's angina is not well understood. Nifedipine has been noted in one study (Theroux et al, 1979) to be superior to perhexiline maleate in the suppression of ergonovine-induced coronary artery spasm in 10 patients with variant angina. Perhexiline is a calcium antagonist with a long half life but a relatively high incidence of side effects (Pilcher et al, 1973).

Thus, in the treatment of unstable or variant angina we can draw the following conclusions:

(1) Coronary artery spasm probably plays an important role in the genesis of the ischemia;

(2) The calcium antagonists are effective therapy even in cases refractory to nitrates with or without beta blockers;

(3) The efficacy of the calcium antagonists is a result of their ability to block coronary vasospasm as well as their peripheral effects and, at least with verapamil, perhaps to a mild negative inotropic effect.

C. Treatment of Idiopathic Hypertrophic Subaortic Stenosis with Calcium Antagonists

Idiopathic hypertrophic subaortic stenosis (IHSS) is a disease characterized by marked hypertrophy of the interventricular system resulting in many cases, in a dynamic form of obstruction to left ventricular outflow. Patients with IHSS demonstrate enhanced left ventricular contractility with an increased sensitivity to catecholamines and digitalis. Propranolol produces symtomatic and hemodynamic improvement in many patients (Adelman et al, 1972), yet progression of the disease usually continues with eventual recurrence of symptoms (Stenson et al, 1973). There is good experimental evidence demonstrating that certain forms of cardiomyopathy can be prevented with calcium antagonists. Examples include the hereditary cardiomyopathy of the Syrian hamster (Jasmin and Bajusz, 1975) and cardiomyopathy induced by adriamycin in rabbits (Daniels et al, 1976).

The hypercontractile state of the myocardium in IHSS suggests that altered calcium kinetics may play a role. Thus, it will be important to assess the ability of the calcium antagonists to reduce the progression of this disease. Kaltenbach and coworkers (1979) described their results with the use of verapamil in patients with IHSS. After 15 months of therapy they found subjective symptoms improved in 2/3 of the patients who had been symptomatic during propranolol therapy. Twelve of the 20 patients demonstrated a reduction in QRS voltage, 16 of 20 a decrease in heart size and a decrease in LV mass in 7 of 10 patients. In 5/8 patients the left ventricular outflow gradient was reduced. More recently Rosing et al (1979a) have examined the acute hemodynamic effects of verapamil in 27 patients. The highest dose of verapamil (21 μg/kg/min) increased heart rate (from 72±3 to 81±6) and reduced systolic blood pressure (from 118±8 to 99±5) with a concomitant drop in the basal left ventricular outflow gradient (from 94±14 to 49±14). Cardiac output remained unchanged indicating that the fall in gradient resulted from an actual increase in effective orifice size. Left ventricular end diastolic pressure was unchanged. Although the majority of patients respond in a favorable way to verapamil a considerable amount of caution should be exercised before initiating therapy. The reduction in systemic vascular resistance produced by verapamil can in certain circumstances, actually increase the gradient. Thus, in their latter study (Rosing et al, 1979a) one patient demonstrated an <u>increase</u> in the basal left ventricular gradient with verapamil infusion from 35 to 80 mmHg with a simultaneous fall in systolic blood pressure from 160 to 105 mmHg. Reductions in systolic blood pressure should be limited to 15 mmHg or less to avoid provocation of existing gradients, see Figure 22.

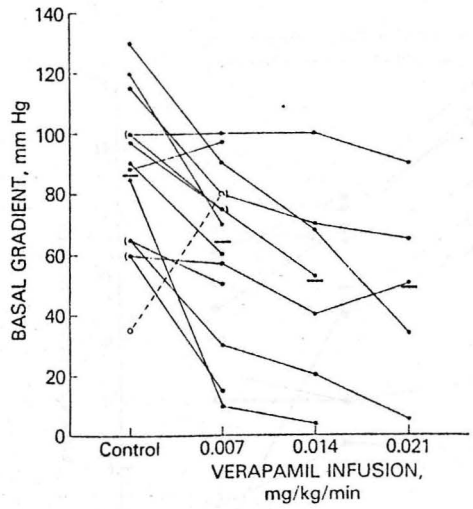

Figure 22. *Effect of increasing doses of verapamil on basal left ventricular outflow tract gradient in patients with IHSS. Broken line with open circles indicates a patient whose systolic blood pressure decreased by more than 15 mmHg during verapamil administration. Horizontal bars indicate mean values.*

In an accompanying article Rosing et al (1979b) demonstrated a 26% increase in exercise capacity (compared to 21% on propranolol). No correlation was noted however, between the degree of reduction of the left ventricular outflow gradient and demonstrable improvement in exercise tolerance. After a 3.5 to 6 month course of chronic oral verapamil therapy exercise tolerance improved even more (45%) compared to placebo (21%), see Figure 23. Thus, verapamil can improve exercise capacity and symptomatic status in some patients with IHSS.

Long term evaluation of the effects of verapamil on sudden death are needed, both in patients with ischemic heart disease and IHSS.

D. Arrhythmias

1. Treatment of Supraventricular Arrhythmias with Verapamil

Intravenously administered verapamil has been shown to be extremely effective in the treatment of supraventricular arrhythmias. The mechanism of action of verapamil in this setting is a result, at least in part, of its ability to block trans-sarcolemmal calcium flux. As we have seen, depolarization of the sinoatrial and atrioventricular nodes is mediated by slow channel mechanisms which are thought to result from calcium ion flux (Zipes et al, 1975). Further, within the atrio-ventricular (A-V) node, cells demonstrate a continuum of dependence on the slow current contribution for depolarization (Zipes et al, 1975). In addition, in certain pathological conditions such as ischemia, hypoxia or digitalis intoxication a so called "slow response" emerges in cells which normally are rapidly depolarized by rapid channel sodium fluxes (Cranefield, 1975). Fibers which demonstrate such a slow response pattern may cause re-entrant arrhythmias because of their slow conduction velocity through partially depolarized fibers. Alternatively, "automatic" foci may arise as a result of pacemaker-like characteristics of such fibers. A calcium antagonist such as verapamil may

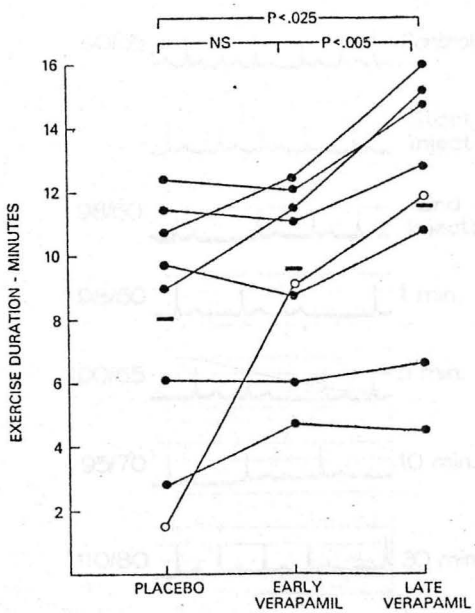

Figure 23. *Effects of verapamil on exercise capacity while administered short-term during a double-blind study in hospital (early verapamil) and after chronic administration over 3.5-6 months (late verapamil). Horizontal bars indicate mean values. Closed circles represent patients with obstructive hypertrophic cardiomyopathy; open circles, patients with nonobstructive disease.*

therefore be able to abolish both re-entrant arrhythmias as well as automatic tachyarrhythmias. Clinical evidence suggests that this may be the case.

Verapamil administered to patients in normal sinus rhythm results in p-r interval prolongation with little effect on the R-R, QRS or QTC intervals. The major action of verapamil is on the slow response fibers of the A-V node. The frequency of sinoatrial discharge is affected to a lessor degree, either because of a reflex sympathetic stimulatory effect, or because of differences in the ionic composition of the depolarizing current (Singh and Roche, 1977). His bundle electrocardiography has confirmed the predominant site of action of verapamil on the A-V node with little effect on intra-atrial or intraventricular conduction times (Angus et al, 1976).

a. atrial fibrillation

Intravenous verapamil, 3-10 mg intravenously over several minutes is usually effective in reducing the rate of ventricular response in patients in atrial fibrillation with a rapid ventricular response. Three principal types of responses have been observed to verapamil in this situation. Most commonly A-V nodal conduction is inhibited with a slowing of the ventricular response. The inhibitory effects of verapamil are relatively brief as a result of the short half-life when given as an intravenous bolus (Schomerus et al, 1976). The effect of verapamil on the A-V node is attenuated after 30 min and the ventricular response will accelerate unless an infusion of the drug is begun (usual dose is 5 µg/kg/min) (Singh et al, 1978), see Figures 24 and 25.

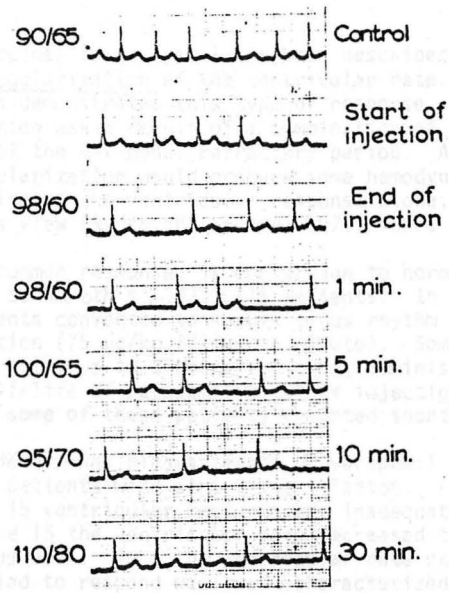

Figure 24. *Illustrates the typical response when verapamil is used in the treatment of atrial fibrillation with a rapid ventricular response. The heart rate in the control period was 116/min; at 10 minutes it was reduced to 72 and at 30 minutes to 78/min.*

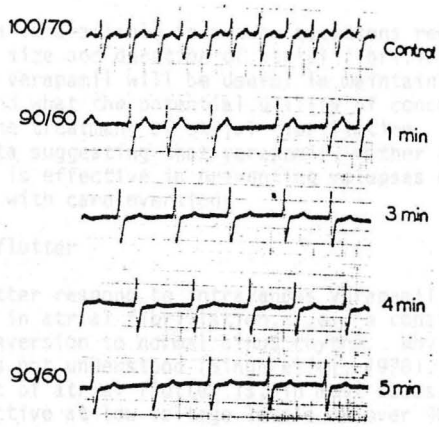

Figure 25. *Illustrates the "regularization" of the ventricular response at 5 minutes first noted by Schamroth. Such regularization is postulated to be a result of a stabilizing effect of verapamil on the A-V nodal refractory period. Note the fall in blood pressure which occurs despite adequate slowing of the ventricular response.*

The second type of response to verapamil has been described by Schamroth (1971) and consists of a regularization of the ventricular rate. Seventy-one of 115 of Schamroth's patients demonstrated this type of response. Schamroth postulated that regularization was a result of a combination of increased A-V block and a stabilization of the A-V nodal refractory period. Although one might expect that such regularization would produce some hemodynamic improvement beyond that seen with slowing of the ventricular response alone, data available to date do not support this view (Ryden and Saetre, 1971; Vohra et al, 1974a).

The third, and least common response, is conversion to normal sinus rhythm. This occurred in only 1 of Schamroth's (1971) 115 patients. In Aronow's recent report (1979) 3 of 20 patients converted to normal sinus rhythm 7 to 160 minutes after verapamil administration (75 µg/kg IV over 1 minute). Some patients converted to normal sinus rhythm up to 3 hours following administration of the drug -- given the short half-life of verapamil after IV injection this raises the question as to whether some of these patients reverted spontaneously.

Dominic et al (1979) determined plasma levels of verapamil and related it to ventricular response in patients with atrial fibrillation. Fifteen patients were studied, in 13 of the 15 ventricular response was inadequately controlled with digitalis. In 9 of the 15 the ventricular rate decreased to less than 100 after a 75 µg/kg intravenous dose. In 6 the ventricular rate remained above 100. The patients who failed to respond well were characterized by the presence of acute congestive heart failure manifested by orthopnea, rales and pulmonary congestion. The CHF group did respond to a second dose (115 µg/kg) given 30 min later. The initial failure to respond was thought to be a result of high sympathetic tone. This study illustrates that verapamil can be administered to patients who have already received digitalis. Physicians should bear in mind, however, that these drugs will have an additive effect to produce A-V block.

At present, little data is available to answer questions regarding the relationship of left atrial size and duration of atrial fibrillation to the ease of conversion; whether verapamil will be useful in maintaining sinus rhythm after d.c. cardioversion; and what the potential utility of concomitant digitalis therapy might be in the treatment of atrial fibrillation. Krikler (1974) has reported preliminary data suggesting that verapamil, either alone or in combination with quinidine, is effective in preventing relapses of atrial arrhythmias initially treated with cardioversion.

b. atrial flutter

Patients in atrial flutter respond to intravenous verapamil in a qualitatively similar way as those in atrial fibrillation, i.e., a consistent increase in A-V block with a rare conversion to normal sinus rhythm. Why some patients convert and others do not is not understood (Singh et al, 1978), see Figures 26 and 27. The usual treatment of atrial flutter is, in most cases, d.c. cardioversion -- a treatment effective at low voltage levels in over 90% of patients (Selzer et al, 1966). Thus, verapamil has little clinical utility in the treatment of atrial flutter although it may be useful in the maintenance of normal sinus rhythm following conversion. Additionally, Heng et al (1975) feel that a single dose of verapamil may be of diagnostic value in differentiating rapid atrial flutter from paroxysmal supraventricular tachycardia when difficulty exists in diagnosis. Conversion of atrial flutter to atrial fibrillation occurs in somewhat less than one-fifth of patients (Heng et al, 1975; Aronow et al, 1979).

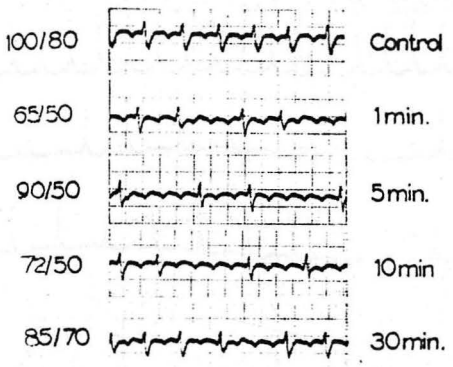

Figure 26. *The usual response of atrial flutter with 2:1 conduction to a 10 mg intravenous dose of verapamil. After verapamil there is an increase in A-V block with a consequent slowing of the ventricular rate and a fall in blood pressure. Maximum A-V block occurred between 5-10 minutes after injection of verapamil. d.c. cardioversion is the preferred mode of treatment for this arrythmia.*

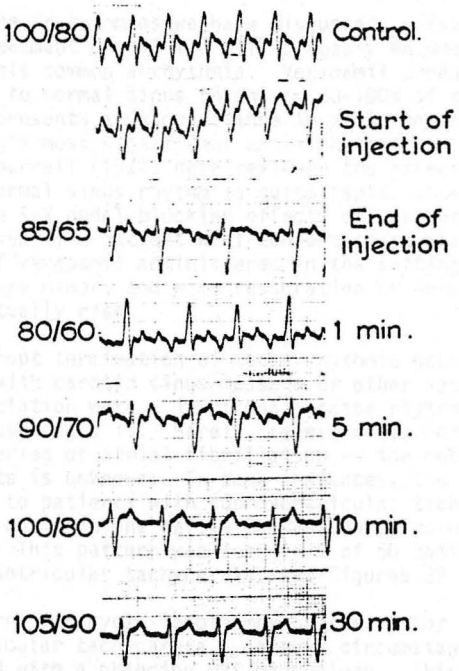

Figure 27. *An example of conversion of atrial flutter to normal sinus rhythm, an unusual response. Note the transient atrial fibrillation at 10 minutes after drug injection. Sinus rhythm was restored at 30 minutes.*

c. paroxysmal supraventricular tachycardia (PAT)

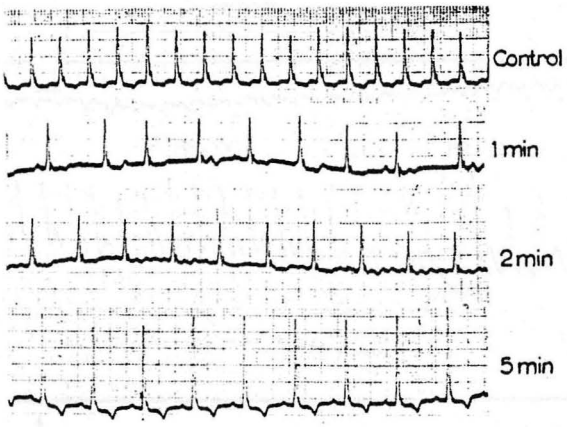

Figure 28. *Example of response supraventricular tachycardia to 10 mg of verapamil intravenously. Note the emergence of A-V dissociation at 1 minute; atrial fibrillation occurred at 2 minutes; stable normal sinus rhythm was restored at 5 minutes.*

In contrast to the arrhythmias we have discussed, verapamil is uniformly efficacious in the treatment of PAT and will probably become the drug of choice in the treatment of this common arrhythmia. Verapamil produces a rapid and predictable reversion to normal sinus rhythm in 80-100% of cases. The high degree of efficacy represents a major advance in antiarrhythmic therapy and clinically is the drug's most significant antiarrhythmic property (Singh et al, 1978). Krikler and Spurrell (1974) have reviewed the effects of verapamil on PAT. Conversion to normal sinus rhythm is quite rapid, usually within 2 to 5 min -- a time when the A-V nodal blocking effects of verapamil are maximal (Heng et al, 1975). Occasionally a patient will convert to atrial fibrillation. The hypotensive effects of verapamil administered in the setting of rapid supraventricular tachycardia are minor, and with restoration of normal sinus rhythm blood pressure may actually rise.

In most cases abrupt termination of the arrhythmia occurs, a response similar to that seen with carotid sinus massage or other vagal maneuvers. In other cases A-V dissociation with a junctional escape rhythm appears before normal sinus rhythm supercedes it. Rarely, reversion to normal sinus rhythm is preceded by a short period of atrial fibrillation -- the mechanism underlying this sequence of events is unknown. In some instances, the administration of intravenous verapamil to patients with supraventricular tachycardia may provoke premature ventricular contractions before conversion to normal sinus rhythm (Vohra et al, 1974b). This pattern was seen in 6 of 50 patients with a reciprocating form of supraventricular tachycardia, see Figures 29 and 30.

Finally, an alternating cycle length may be seen prior to conversion in paroxysmal supraventricular tachycardia. In this circumstance varying cycle lengths are associated with a changing QRS morphology. This response is also seen primarily in patients with reciprocating tachycardia, an arrythmia presumably involving dual A-V nodal pathways. Such variation in cycle length may be a result of a 2:1 block in the antegrade pathway with an unmasking of a third pathway -- antegrade conduction then occurs over 2 pathways with different rates of antigrade conduction, see Figure 31.

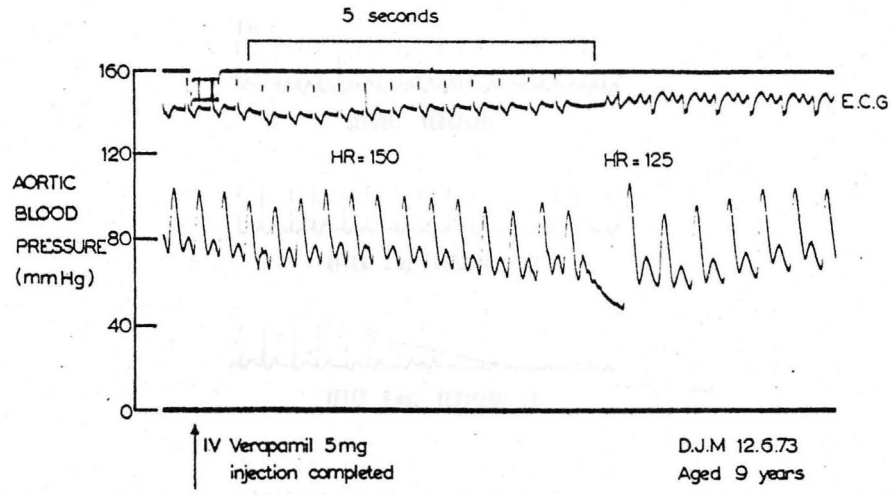

Figure 29. *Effect of intravenous verapamil in a patient who developed SVT during cardiac catheterization. Reversion to sinus rhythm occurred 5 seconds after completion of injection of verapamil; the restoration of sinus rhythm was preceded by transient asystole. Note the absence of effect on arterial pressure.*

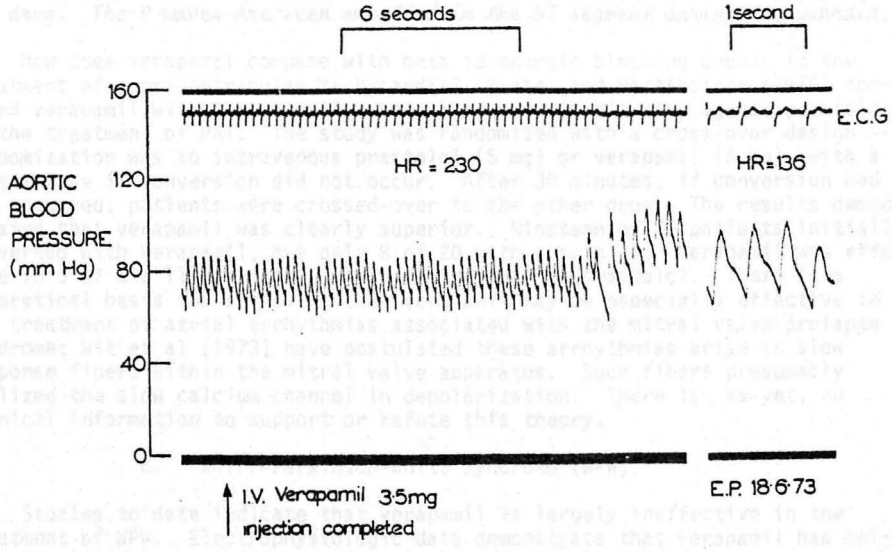

Figure 30. *Effect of verapamil on arterial pressure during conversion by the drug of rapid SVT (230/min) to sinus rhythm (136/min) during cardiac catheterization. Note the prompt response of the arrhythmia to verapamil, and the accompanying improvement in blood pressure.*

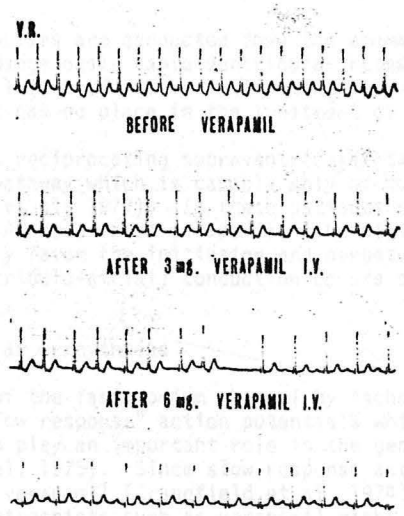

Figure 31. *The first strip shows lead II during tachycardia with a constant RR cycle length of 380 msec. After 3 mg verapamil, alternating RR cycle lengths measured 420 and 540 msec. Reversion to sinus rhythm occurred after 6 mg of the drug. The P waves are seen embedded in the ST segment during tachycardia.*

How does verapamil compare with beta adrenergic blocking agents in the treatment of supraventricular tachycardia? Hartel and Hartikainen (1976) compared verapamil with the selective beta-1 adrenergic blocking agent, practolol, in the treatment of PAT. The study was randomized with a cross-over design -- randomization was to intravenous practolol (5 mg) or verapamil (5 mg), with a repeat dose if conversion did not occur. After 30 minutes, if conversion had not occurred, patients were crossed-over to the other drug. The results demonstrated that verapamil was clearly superior. Nineteen of 20 patients initially converted with verapamil, but only 8 of 20 with practolol. Verapamil was effective in 9 of the 11 patients who did not respond to practolol. There is a theoretical basis for believing that verapamil may be especially effective in the treatment of atrial arrhythmias associated with the mitral valve prolapse syndrome; Wit et al (1973) have postulated these arrhythmias arise in slow response fibers within the mitral valve apparatus. Such fibers presumably utilized the slow calcium channel in depolarization. There is, as yet, no clinical information to support or refute this theory.

d. Wolff-Parkinson-White Syndrome (WPW)

Studies to date indicate that verapamil is largely ineffective in the treatment of WPW. Electrophysiologic data demonstrate that verapamil has only a minimal effect on antegrade or retrograde conduction in anomalous pathways or Kent bundles (Spurrell et al, 1974a; Neuss and Schlepper, 1974). The electrophysiologic studies are consistent with the clinical observation that verapamil, in contrast to quinidine or procainamide, is ineffective in controlling atrial fibrillation complicating WPW (Spurrell et al, 1974b). In WPW syndrome with

atrial fibrillation impulses are conducted down the anomalous pathway with the potential for causing dangerously rapid ventricular rates or even ventricular fibrillation. Verapamil is ineffective in limiting the ventricular response in this situation and thus has no place in the treatment of WPW syndrome.

Some patients with reciprocating supraventricular tachycardia may have a "concealed" A-V nodal pathway which is capable only of conducting in a retrograde fashion (Wellens et al, 1977). In these patients selective slowing of conduction through the AV node makes verapamil, like digitalis and propranolol, a drug that may actually favor the initiation and perpetuation of the tachycardia if retrograde (ventriculo-atrial) conduction occurs over an accessory pathway (Denes et al, 1973).

2. Ventricular Arrhythmias

The inactivation of the fast sodium channel by ischemia or hypoxia results in the emergence of "slow response" action potentials which are thought by many electrophysiologists to play an important role in the genesis of ventricular arrhythmias (Zipes et al, 1975). Since slow response action potentials are selectively blocked by verapamil (Cranefield et al, 1974) it seems reasonable to suppose that calcium antagonists such as verapamil might be effective in the treatment of ventricular arrhythmias. A review of 31 uncontrolled studies (Investigators Brochure, 1977) in which 239 episodes of ventricular tachyarrhythmias were treated with verapamil revealed that verapamil restored normal sinus rhythm in two-thirds of the episodes. However, in a recent study (Wellens et al, 1977) verapamil was ineffective in four patients with sustained ventricular tachycardia. Ventricular arrhythmias are often most severe in patients with a significant compromise in left ventricular function -- a situation in which the negative inotropic effects of verapamil would limit its usefulness.

The antiarrhythmic efficacy of verapamil with chronic oral administration is not well known. Methods have recently been developed to reliably measure serum levels however, (McAllister and Howell, 1976) enabling a better understanding of its therapeutic efficacy. Verapamil (0.2 mg/kg) given intravenously to dogs before left anterior descending coronary artery occlusion reduces the incidence of ventricular fibrillation (Elharrar et al, 1977). No data is available regarding any effects verapamil may have on sudden death in patients with coronary artery disease. Although more work needs to be done it is the opinion of most authors that verapamil is not particularly effective in the treatment of ventricular arrythmias (Singh et al, 1978; Heng et al, 1975; Gotsman et al, 1972; Wellens et al, 1977).

In summary we can say:

(1) Verapamil is clearly effective and probably the drug of choice in the treatment of supraventricular tachycardia, except those associated with a concealed A-V nodal bypass tract.

(2) Verapamil is effective in slowing the ventricular response to atrial fibrillation but not in converting atrial fibrillation to normal sinus rhythm.

(3) Verapamil is also effective in limiting the ventricular response to atrial flutter but d.c. cardioversion is the preferred node of therapy in most cases.

(4) Verapamil is ineffective in controlling the ventricular response to atrial fibrillation in the WPW syndrome and should not be used.

(5) Verapamil has a modest antiarrhythmic effect on ventricular ectopy but other, more efficacious agents are available.

Table 4 provides a summary of antiarrhythmic effects of verapamil.

TABLE 4.

Type of arrhythmia		Elective (intravenous)	Prophylactic (oral)
I	Paroxysmal supraventricular	Sinus rhythm restored in 75-100% of cases (especially effective in reciprocating tachycardias including those complicating WPW syndrome). Mode of conversion characterised by: a) Abrupt cessation of the arrhythmia b) Restoration of sinus rhythm preceded by alternating cycle length, or c) Restoration of sinus rhythm preceded by the occurrence of premature ventricular extrasystoles d) Conversion preceded by atrial fibrillation	May be of value but experience limited
IIa	Atrial fibrillation	1) Increase in AV block 2) Slowing of ventricular rate 3) Ventricular rate sometimes 'regularised' 4) Sinus rhythm rarely restored 5) Blood pressure usually reduced	Effect on relapse rate from sinus rhythm to atrial fibrillation after DC cardioversion unknown (when used alone or in combination with other agents)
IIb	Atrial fibrillation with WPW syndrome	No effect	No effect
III	Atrial flutter	1) Increase in AV block 2) Slowing of ventricular rate 3) No effect on flutter rate but fibrillation sometimes precipitated 4) Sinus rhythm occasionally restored 5) Blood pressure usually reduced	Effect on sustained atrial flutter unknown
I	Ventricular premature contractions	Frequency reduced	Effect not known
II	Ventricular tachycardia	Sinus rhythm rarely restored (hypotension common)	Effect on recurrent ventricular arrhythmias unknown

E. Hypertension

Hydralazine, diazoxide, and minoxidil act as direct arterial vasodilators and have been used with a variable degree of success in the acute and chronic treatment of hypertension. Several of these agents promote a reflex tachycardia, renin release and plasma volume expansion necessitating the concomitant use of a beta blocker and a diuretic in most cases. Recently (Olivari et al, 1979) nifedipine has been found to be an effective antihypertensive in both acute and chronic settings. After a 10 mg oral dose in 27 patients with primary hypertension, nifedipine reduced mean arterial pressure by 21% at 30 minutes and 16% at 2 hours. The antihypertensive effect was reported to last 8-12 hours; heart rate increased at 30 minutes but not thereafter. Unfortunately the study was not placebo contolled. Peripheral vascular resistance fell and cardiac output

increased as a combined result of increases in stroke volume and, to a lessor degree, heart rate. Although renin was elevated at 4 hours after nifedipine it returned to control levels after 30 days of treatment, prompting the authors to speculate that nifedipine may block distal tubular calcium delivery, a mechanism thought to represent an important functional part of the macula densa-glomerular feedback loop (Gutsche et al, 1975).

Another uncontrolled study used the calcium antagonist diltiazem in patients with congestive heart failure and documented a significant increase in sodium excretion without a concomitant detectable alteration in renal hemodynamics (Kinoshita et al, 1979).

Thus, the calcium antagonists, especially nifedipine, are able to: (1) reduce arterial blood pressure in hypertensive patients by reducing peripheral vascular resistance, (2) leave plasma renin levels unaltered with chronic therapy, and (3) the drug provides a beneficial antianginal effect at the same time arterial pressure is reduced.

F. Potential Advantages of the Calcium Antagonists

In patients with chronic obstructive pulmonary disease the available data indicate that the calcium antagonists do not effect pulmonary function (Ringquist, 1974; Kentera et al, 1979). Further McMurty et al (1976) have established that bronchoconstriction occurring in response to hypoxia is mediated by a transmembrane calcium flux. The calcium antagonists may limit this response. No change in airways resistance occurs in asthmatics given verapamil (Hills, 1970).

In patients with symptomatic peripheral vascular disease propranolol may exacerbate claudication. In contrast, because calcium plays an important role in the maintenance of peripheral arterial vascular tone (Bevan et al, 1976), the calcium antagonists verapamil and nifedipine produce increases in skin, and to a lesser extent renal flow. Thus, in contrast to propranolol, the calcium antagonists are unlikely to worsen peripheral ischemic symptoms. Effects on cerebral blood flow are negligible (Lydtin et al, 1975).

Propranolol, and to a lessor extent metoprolol, are hazardous in diabetics prone to hypoglycemia (Lager et al, 1979). Propranolol does not potentiate the hypoglycemic action of insulin, but does retard the recovery from hypoglycemia and causes severe bradycardia and elevated diastolic pressure during hypoglycemia. Although pancreatic beta cells are highly dependent on calcium for insulin secretion the administration of verapamil to normals fasted for 12 hours has been shown not to effect basal serum levels of glucose or insulin (Röjdmark, 1979). Thus, the calcium antagonists are probably superior to beta adrenergic blocking agents in the treatment of ischemic heart disease in insulin dependent diabetics.

G. Contraindications to the Use of Calcium Antagonists

The principal contraindications for the use of the calcium antagonists are (1) presence of advanced heart failure (especially verapamil); (2) greater than first-degree atrioventricular block (especially verapamil); (3) sick sinus syndrome (especially verapamil); (4) cardiogenic shock or other hypotensive states; (5) concomitant therapy with beta adrenergic blocking agents or disopyramide phosphate (Norpace); (6) pregnancy.

Verapamil has a variable influence on sinus node function in the sick sinus syndrome (Husaini et al, 1973; Singh et al, 1978). Until more clinical experience is gained, it would be wise to use verapamil with caution in patients with sick sinus syndrome. Because nifedipine has a less depressant effect on A-V nodal conduction and ventricular function than verapamil and is probably preferable in patients with A-V nodal block (Amlie and Landmark, 1978; Rowland et al, 1979; Podeletti et al, 1979) or impaired left ventricular function. Nifedipine has been used safely with selective β_1 blockers but the intravenous administration of verapamil to patients receiving propranolol has been reported to result in asystole (Johansson, 1978). In the absence of impaired A-V nodal conduction prior digitalization is not a contraindication to the use of verapamil (Schamroth, 1971). Digoxin can, at least in part, reverse the negative inotropic effects of verapamil (Singh and Vaughn Williams, 1972).

Predictably, verapamil poisoning can be successfully treated with intravenous calcium gluconate (Perkins, 1978).

V. METABOLISM AND SIDE EFFECTS

Although verapamil is nearly completely absorbed from the gastrointestinal tract the overall bioavailability is only 10-22% because of an extensive first pass hepatic metabolism. Verapamil is 90% protein bound. To achieve comparable serum levels the oral dose must be 8-10 times that of an intravenous dose. Plasma levels of the N-dimethylated form are twice as high as those of verapamil (Schomerus et al, 1976) but little information is available regarding the pharmacological effects of the metabolites. Seventy per cent of an oral or intravenous dose was recovered in the urine and 16% in the feces.

Nifedipine is rapidly absorbable through the oral mucosa (5 min) or after being taken orally (20 min). Peak serum levels are reached in 30 to 120 minutes. Nifedipine is greater than 90% protein bound. Half-life is 4 to 5 hours and elimination is primarily renal.

Side Effects

Side effects are infrequent with either nifedipine or verapamil. In 8,072 patients side effects severe enough to discontinue verapamil therapy occurred in 1% -- the principal types of side effects included are:

(1) Cardiovascular (34%) -- bradycardia, hypotension, A-V block

(2) Gastrointestinal (33%) -- constipation, nausea and vomiting, gastric intolerance

(3) Central nervous system (35%) -- dizziness, headache, weakness

Nifedipine had a comparable rate of side effects: headache 5-9%, vomiting 3.6%, dizziness 2.7% (mild); constipation is relatively frequent but easily treatable.

VI. SUMMARY

Verapamil and nifedipine are calcium ion antagonists which are effective in the treatment of stable angina pectoris, unstable angina pectoris, and variant, or Prinzmetal's angina. The primary action of these drugs is to limit transsarcolemmal calcium flux during the plateau phase of the action potential in cardiac and smooth muscle. Nifedipine appears to act exclusively on vascular smooth muscle with little in vivo effect on cardiac contractility or atrioventricular nodal conduction. Verapamil, in contrast, is capable of producing A-V block and depressing cardiac contractility. Verapamil, is therefore, effective in the treatment of supraventricular arrythmias, especially PAT. It is marginally effective in the treatment of ventricular arrythmias and should not be used in the treatment of the Wolff-Parkinson-White Syndrome. Considerable caution should be exercised in using verapamil in patients with sick sinus syndrome or high grade A-V block, with severely depressed left ventricular function or patients receiving disopyramide (Norpace) or propranolol (Inderal).

REFERENCES

Adelman AG, Wigle ED, Ranganathan N, et al: The clinical course in muscular subaortic stenosis: A retrospective and prospective study of 60 hemodynamically proved cases. Ann Intern Med 77:515-525, 1972.

Adelstein RS, Hathaway DR: Role of calcium and cyclic adenosine 3':5' monophosphate in regulating smooth muscle contraction. Am J Cardiol 44:783-787, 1979.

Amlie JP, Landmark K: The effect of nifedipine on the sinus and atrioventricular node of the dog heart after β-adrenergic receptor blockade. Acta Pharm Tox 42:287-291, 1978.

Andersson K-E: Effects of calcium and calcium antagonists on the excitation-contraction coupling in striated and smooth muscle. Acta Pharm Tox 43 (Suppl I): 5-14, 1978.

Andreasen F, Boye E, Christoffersen D, et al: Assessment of verapamil in the treatment of angina pectoris. Europ J Pharm 2:443-452, 1975.

Angus JA, Dhumma-Upahorn P, Cobbin LB, et al: Cardiovascular action of verapamil in the dog with particular reference to myocardial contractility and atrioventricular conduction. Cardiovasc Res 10:623-632, 1976.

Aronow WS, Landa D, Plosencia G, et al: Verapamil in atrial fibrillation and atrial flutter. Clin Pharmacol Ther 26:578-583, 1979.

Atterhög JH, Ekelund LG: Hemodynamic effects of intravenous verapamil at rest and during exercise in subjectively healthy middle-aged men. Europ J Clin Pharm 8:317-322, 1975.

Berndt TB, Fitzgerald J, Harrison DC, et al: Hemodynamic changes at the onset of spontaneous versus pacing-induced angina. Am J Cardiol 39:784-788, 1977.

Bevan JA: Second International Symposium on Vascular Neuroeffector Mechanisms. Ed by JA Bevan, G Burnstock, B Johansson, et al. Basel: S Karger AG, 1976.

Burton KB: Lanthanum probe studies of cellular pathophysiology induced by hypoxia in isolated cardiac muscle. J Clin Invest 60:1289-1302, 1977.

Camerini F, Angelino PF, Bobba P, et al: Nifedipine in angina pectoris. Comparison with placebo and trinitroglycerine. G Ital Cardiol 4:565-574, 1974.

Chiong MA, West RD, Parker JO: Influence of nitroglycerin on myocardial metabolism and hemodynamics during angina produced by atrial pacing. Circulation 45:1044-1056, 1972.

Clark RE, Christlieb IY, Henry PD, et al: Nifedipine: A myocardial protective agent. Am J Cardiol 44:825-831, 1979.

Cranefield PF: The Conduction of the Cardiac Impulse. New York: Futura, 1975.

Cranefield PF, Wit AL, Hoffman BF: Conduction of the cardiac impulse. III. Characteristics of very slow conduction. J Gen Physiol 59:227-246, 1972.

Cranefield PF, Aronson RS, Wit AL: Effect of verapamil on the normal action potential and on a calcium-dependent slow response of canine cardiac purkinje fibers. Circ Res 34:204-213, 1974.

daLuz PL, deBarros LF, Leite JJ, et al: Effect of verapamil on regional coronary and myocardial perfusion during acute coronary occlusion. Am J Cardiol 45:269-275, 1980.

Daniels JR, Billingham ME, Gelhart A, et al: Effect of verapamil and propranolol on adriamycin-induced cardiomyopathy in rabbits. Circulation 53,54:20, 1976 (abstract).

Denes P, Wu D, Dhingra RC, et al: Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardia. Circulation 48:549-555, 1973.

Dominic J, McAllister RG, Kuo CS, et al: Verapamil plasma levels and ventricular rate response in patients with atrial fibrillation and flutter. Clin Pharm Ther 26:710-714, 1979.

Ebner F: Survey and Summary of Results Obtained during the World-Wide Clinical Investigations of Adalat (Nifedipine). Second International Adalat Symposium, pp 348-360, 1975.

Ekelund L-G: Ca-blockers and peripheral circulation--physiological viewpoints. Acta Pharm Tox 43(Suppl I):33-43, 1978.

Elharrar V, Gaum WE, Zipes DP: Effect of drugs on conduction delay and incidence of ventricular arrhythmias induced by acute coronary occlusion in dogs. Am J Cardiol 39:544-549, 1977.

Endo M, Hirosawa K, Kaneko N, et al: Prinzmetal's variant angina. Coronary arteriogram and left ventriculogram during attack induced by methacholine. NEJM 294:252-255, 1976.

Endo M, Yanagisawa T, Taira N: Effects of calcium antagonistic coronary vasodilators, nifedipine and verapamil, on ventricular automaticity of the dog. Arch Pharm 302:235-238, 1978.

Fagher B: Double-blind comparison of verapamil and practolol in the treatment of angina pectoris. Postgrad Med J 53:61-65, 1977.

Ferlinz J, Easthope JL, Aranow WS: Effects of verapamil on myocardial performance in coronary disease. Circulation 59:313-319, 1979.

Fleckenstein A: Adalat, a powerful Ca-antagonistic drug. Second International Adalat Symposium, ed by W Lochner, W Braasch, G Kroneberg. Berlin: Springer-Verlag, pp 56-65, 1975.

Fleckenstein A: On the basic pharmacological mechanism of nifedipine and its relation to therapeutic efficacy. Third International Adalat Symposium, ed by AD Jatene, PR Lichtlen. Amsterdam: Excerpta Medica, pp 1-13, 1976.

Fleckenstein A, Janke J, Doering HJ, et al: Key role of Ca in the production of noncoronarogenic myocardial necroses. Recent Adv Med Cardiol Struct Metabol 6:21-32, 1975.

Gaasch WH, Lufshanowski R, Leachman RD, et al: Surgical management of Prinzmetal's variant angina. Chest 66:614-621, 1974.

Gergely J: Excitation-contraction coupling--cardiac muscle events in the myofilaments. Fed Proc 35:1283-1287, 1976.

Goldberg S, Reichek N, Wilson J: Nifedipine in the treatment of Prinzmetal's (variant) angina. Am J Cardiol 44:804-810, 1979.

Gotsman M, Lewis B, Bakst A, et al: Verapamil in life-threatening tachyarrhythmias. South African Med J 46:2017-2019, 1972.

Gutsche HU, Muller-Suur R, Schurek HJ: Ca^{++}-antagonist prevents feedback induced SN-GFR decrease in rat kidney. Kidney Int 8:477, 1975 (abstract).

Hansen JF, Sandoe E: Treatment of Prinzmetal's angina due to coronary artery spasm using verapamil: a report of three cases. Europ J Cardiol 7/4: 327-335, 1978.

Hariman RJ, Mangiardi LM, McAllister RG, et al: Reversal of the cardiovascular effects of verapamil by calcium and sodium: differences between electrophysiologic and hemodynamic responses. Circulation 59:797-804, 1979.

Hartel G, Hartikainen M: Comparison of verapamil and practolol in paroxysmal supraventricular tachycardia. Europ J Cardiol 4:87-90, 1976.

Hearse DJ, Garlick PB, Humphrey SM: Ischemic contracture of the myocardium: mechanisms and prevention. Am J Cardiol 39:986-993, 1977.

Heng MK, Singh BN, Roche AHG, et al: Effects of intravenous verapamil on cardiac arrhythmias and on the electrocardiogram. Am Heart J 90:487-498, 1975.

Henry PD, Shuchleib R, Davis J, et al: Myocardial contracture and accumulation of mitochondrial calcium in ischemic rabbit heart. Am J Physiol 233:H677-H684, 1977.

Henry PD, Shuchleib R, Bordas LJ, et al: Effects of nifedipine on myocardial perfusion and ischemic injury in dogs. Circ Res 43:372-380, 1978.

Henry PD, Scuchleib R, Clark RE, et al: Effect of nifedipine on myocardial ischemia: analysis of collateral flow, pulsatile heat and regional muscle shortening. Am J Cardiol 44:817-824, 1979.

Heupler FA, Proudfit WL: Nifedipine therapy for refractory coronary arterial spasm. Am J Cardiol 44:798-803, 1979.

Hills EA: Iproveratril [verapamil] and bronchial asthma. Brit J Clin Pract 24:116-117, 1970.

Horwitz LD, Gorlin R, Taylor WJ, et al: Effects of nitroglycerine on regional myocardial blood flow in coronary artery disease. J Clin Invest 50:1578-1584, 1971.

Husaini MH, Kurasnicka J, Ryden L, et al: Action of verapamil on sinus node, atrioventricular and intraventricular conduction. Brit Heart J 35:734-737, 1973.

Jasmin G, Bajusz E: Prevention of myocardial degeneration in hamsters with hereditary cardiomyopathy. Ed by A Fleckenstein, G Rona, Baltimore: University Park Press. Recent Adv in Stud Cardiol Str and Metab 6:219-217, 1975.

Jennings RB: Relationship of acute ischemia to functional defects and irreversibility. Circulation 53(Suppl I):I-26--I-29, 1976.

Johansson BW: Clinical aspects of Ca-blocking agents. Acta Pharm Tox (Scand) 43:45-56, 1978.

Kaltenbach M, Hopf R, Bussman WD, et al: Treatment of hypertrophic obstructive cardiomyopathy with verapamil. Brit Heart J 42:35-42, 1979.

Kaltenbach M, Schulz W, Kober G: Effects of nifedipine after intravenous and intracoronary administration. Am J Cardiol 44:832-837, 1979.

Karlsberg RP, Henry PD, Ahmed SA, et al: Lack of protection of ischemic myocardium by verapamil in conscious dogs. Europ J Pharm 42:339-346, 1977.

Kass RS, Tsien RW: Multiple effects of calcium antagonists on plateau current in cardiac purkinje fibres. J Gen Physiol 66:169-192, 1975.

Katz AM: Physiology of the Heart. New York: Raven Press, 1977.

Katz AM, Reuter H: Cellular calcium and cardiac cell death. Am J Cardiol 44:188-190, 1979.

Kentera D, Susic D, Zdravkovi M: Effects of verapamil and aspirin on experimental chronic hypoxic pulmonary hypertension and right ventricular hypertrophy in rats. Respiration 37:192-196, 1979.

Kimura E, Mabuchi G, Kikuchi H: The clinical effect of [nifedipine] (Bay a 1040) on angina pectoris evaluated by sequential analysis. Arzneim Forsch 22:365-367, 1972.

Kinoshita M, Kusukawa R, Shimono Y, et al: The effect of diltiazem hydrochloride upon sodium diuresis and renal function in chronic conjestive heart failure. Arznium-Forsch/Drug Res 29:676-681, 1979.

Krikler DM, Spurrel RAJ: Verapamil in the treatment of paroxysmal supraventricular tachycardia. Postgrad Med J 50:447-453, 1974.

Kurita A, Ogawa T, Kanazawa M, et al: Effects of Adalat (nifedipine) on left ventricular hemodynamics in angina pectoris: Comparative study with propranolol. Cath Cardiovasc Diag 2:361-367, 1976.

Lager I, Blohme' G, Smith U: Effect of cardio selective and non-selective β-blockade on the hypoglycemic response in insulin-dependent diabetics. Lancet 1:458-462, 1979.

Lasser RP, DeLaPaz NS: Repetitive transient myocardial ischemia, Prinzmetal type, without angina pectoris, presenting with Stokes-Adams attacks. Chest 64:350-352, 1973.

Lehninger AL: Ca^{2+} transport by mitochondria and its possible role in the cardiac contraction-relaxation cycle. Circ Res 35:83-88, 1974.

Lichtlen P: Coronary and left ventricular dynamics under nifedipine in comparison to nitrates, beta-blocking agents and dipyridamole. Second International Adalat Symposium, ed by W Locher, W Braasch, G Kroneberg. Berlin: Springer-Verlag, pp 212-224, 1975.

Livesley B, Cathy PF, Campbell RC, et al: Double blind evaluation of verapamil, propranolol and isosorbide dinitrate against placebo in the treatment of angina pectoris. Brit Med J 1:375-378, 1973.

Luchi RJ, Chahine RA: Coronary artery spasm. Ann Intern Med 91:441-449, 1979.

Lydtin H, Lohmöller G, Lohmöller R, et al: Hemodynamic studies on Adalat [nifedipine] in healthy volunteers and in patients. Second International Adalat Symposium, ed by W Lochner, W Braasch, G Kroneberg. New York: Springer-Verlag, pp 112-122, 1975.

Magee PG, Flatterty JT, Bixler TJ, et al: Comparison of myocardial protection with nifedipine and potassium. Circulation 60(Suppl I):I-151--I-157, 1979.

Maggi GC: Clinical observations on the efficacy of nifedipine versus timed disintegration capsules of pentaerythrityl tetranitrate. First International Adalat Symposium. Tokyo: Tokyo University Press, pp 160-162, 1975.

Maggi GC, Piscitello F: Clinical observations on the efficacy of adalat compared with a pentaerythrityl tetranitrate preparation. Second International Adalat Symposium, pp 281-284, 1975.

Magnussen I, Kudsk FN: Effects of verapamil and propranolol on contractility, frequency, coronary flow and oxygen consumption in the isolated rabbit heart. Acta Pharm Tox 34:141-151, 1974.

Mahler F, Ross J Jr, O'Rourke RA, et al: Effects of changes in preload, afterload and inotropic state on ejection and isovolumic phase indices. Am J Cardiol 35:626-634, 1975.

Mangiardi LM, Hariman RJ, McAllister RG Jr, et al: Electrophysiologic and hemodynamic effects of verapamil. Correlation with plasma drug concentrations. Circulation 57:366-372, 1978.

Maseri A, L'Abbate A, Baraldi G, et al: Coronary vasospasm as a possible cause of myocardial infarction. NEJM 299:1271-1277, 1978.

Maseri A, L'Abbate A, Chierchia S, et al: Significance of spasm in the pathogenesis of ischemic heart disease. Am J Cardiol 44:788-792, 1979.

Massingham RA: Study of compounds which inhibit vascular smooth muscle contraction. Europ J Pharm 22:75-82, 1973.

Mayer SE: Effect of catecholamines on cardiac metabolism. Circ Res 35:129-135, 1974.

McAllister RG, Howell SM: Fluorometric assay of verapamil in biological fluids and tissues. J Pharm Sci 65:431-432, 1976.

McMurty JF, Davidson AB, Reeves JT, et al: Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circ Res 38:99-104, 1976.

Meinertz T, Just H, Kasper W, et al: Beta-blocker withdrawal syndrome? Lancet 1:270, 3 Feb, 1979.

Meller J, Pichard A, Dack S: Coronary arterial spasm in Prinzmetal's angina: a proved hypothesis. Am J Cardiol 34:938-940, 1976.

Mena J, Traina M, Cassera JC, et al: Results of a double-blind study with adalat under short- and long-term treatment. Second International Adalat Symposium, pp 333-340, 1975.

Moskowitz RM, Piccini PA, Nacarelli GV, et al: Nifedipine therapy for stable angina pectoris: preliminary results of effects on angina frequency and treadmill exercise response. Am J Cardiol 44:811-816, 1979.

Mostbeck A, Partsch H, Pesche L: Investigations of peripheral blood distribution. Third International Adalat Symposium, pp 91-97, 1976.

Mudge GH, Goldberg S, Gunther S, et al: Comparison of metabolic and vasoconstrictor stimulis on coronary vascular resistance in man. Circulation 59:544-550, 1979.

Naylor WG, Szeto J: Effect of verapamil on contractility, oxygen utilization, and calcium exchangeability in mammalian heart muscle. Cardiovasc Res 6:120-128, 1972.

Naylor WG, Garu A, Slade A: A protective effect of verapamil on hypoxic heart muscle. Cardiovasc Res 10:650-662, 1976.

Naylor WG, McInnes I, Swann JB, et al: Some effects of iproveratril on the cardiovascular system. J Pharm Exp Ther 161:247-261, 1968.

Neuss H, Schlepper M: Influence of various antiarrythmic drugs (aprindine, ajmaline, verapamil, oxprenolol, orciprenaline) on functional properties of accessory AV pathways. Acta Cardiologica 18(Suppl):279-288, 1974.

Newhouse MT, McGregor M: Long term dipyridamole therapy of angina pectoris. Am J Cardiol 16:234-237, 1965.

Oliva PB, Potts DE, Pluss RG: Coronary arterial spasm in Prinzmetal angina: documentation by coronary arteriography. NEJM 288:745-751, 1973.

Oliva PB, Breckinridge JC: Arteriographic evidence of coronary arterial spasm in acute myocardial infarction. Circulation 56:366-374, 1977.

Olivari MT, Bartorelli C, Polese A, et al: Treatment of hypertension with nifedipine, a calcium antagonistic agent. Circulation 59:1056-1062, 1979.

d'Oliveira J, Calderon NR, Garcilazo E, et al: Haemodynamic changes after a single dose of nifedipine (Adalat). Third International Adalat Symposium, ed by AD Jatene, PR Lichtlen. Amsterdam: Excerpta Medica, pp 50-54, 1976.

Parodi O, Maseri A, Simonetti I: Management of unstable angina at rest by verapamil. A double-blind cross-over study in coronary care unit. Brit Heart J 41:167-174, 1979.

Pedersen OL, Mikkelsen E, Christensen NJ, et al: Effect of nifedipine on plasma renin, aldosterone and catecholamines in arterial hypertension. Europ J Pharm 15:235-240, 1979.

Perkins CM: Serious verapamil poisoning: treatment with intravenous calcium gluconate. Brit Med J 2:1127, 1978.

Piccolo E: Verapamil in the therapy of acute coronary insufficiency. Ahi Giornata Cardiologica 2-10, 1977.

Pilcher J, Chandrasekhar KP, Rees JR, et al: Long-term assessment of perhexiline maleate in angina pectoris. Postgrad Med J 49(Suppl III):115-118, 1973.

Podeletti L, Franchi F, Brat A, et al: The cardiac electrophysiological effects of nifedipine. Int J Clin Pharm Biopharm 17:290-293, 1979.

Polese A, Fiorentini C, Olivari M, et al: Clinical use of a calcium antagonistic agent (nifedipine) in acute pulmonary edema. Am J Med 66:825-830, 1979.

Previtali M, Salerno JA, Tavazzi L, et al: Treatment of angina at rest with nifedipine: a short-term controlled study. Am J Cardiol 45:825-830, 1980.

Reimer KA, Lowe JE, Jennings RB: Effect of the calcium antagonist verapamil on necrosis following temporary coronary artery occlusion in dogs. Circulation 55:581-587, 1977.

Reuter H: The dependence of slow inward current in Purkinje fibers on the extracellular calcium concentration. J Physiol (London) 192:479-792, 1967.

Reuter H: Exchange of calcium ions in the mammalian myocardium. Circ Res 34:599-605, 1974.

Ringquist T: Effect of verapamil in obstructive airways diseases. Europ J Clin Pharm 7:61-64, 1974.

Robert EW, Guthaner DF, Wexler L, et al: Six year clinical and angiographic followup of patients with previously documented complete re-vascularization. Circulation 58(Suppl I):I-194--I-199, 1978.

Röjdmark S: Effect of verapamil on insulin response to alchohol hypoglycemia in patients with primary hyperparathyroidism. Diabetes 28:20-25, 1979.

Rosen MR, Wit AL, Hoffman BF: Electrophysiology and pharmacology of cardiac arrythmias. I. Cellular electrophysiology of the mammalian heart. Am Heart J 88:380-385, 1974.

Rosenberger L, Triggle DJ: Calcium, calcium translocation and specific calcium antagonists. In: Calcium in Drug Action, ed by GB Weiss, New York: Pleneum Press, pp 3-31, 1978.

Rosing DR, Kent KM, Borer JS, et al: Verapamil therapy: a new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. I. Hemodynamic effects. Circulation 60:1201-1207, 1979a.

Rosing DR, Kent KM, Maron BJ, et al: Verapamil therapy: A new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. II. Effects on exercise capacity and symptomatic status. Circulation 60:1208-1213, 1979b.

Rossi P, Giordano A, Tamiz A, et al: Effects of training and of verapamil on exercise capacity in patients recovering from myocardial infarction. Cardiology 64:372-385, 1979.

Rowland E, Evans T, Krikler D: Effect of nifedipine on atrioventricular conduction as compared with verapamil. Brit Heart J 42:124-127, 1979.

Roy PR, Spurrell RAJ, Sowton E: The effect of verapamil on the cardiac conduction system in man. Postgrad Med J 50:270-275, 1974.

Ryden L, Saetre H: The haemodynamic effect of verapamil. Europ J Clin Pharm 3:153-157, 1971.

Sakuma A, Kimura E: Interim report on a cooperative double-blind clinical trial with nifedipine. Second International Adalat Symposium, pp 329-332, 1975.

Sandler G: Investigation of verapamil in the treatment of angina pectoris. Bruxelles-Medical 9:669-673, 1970.

Sandler G, Clayton GA, Thornicroft S: Clinical evaluation of verapamil in angina pectoris. Brit Med J 3:224-227, 1968.

Sbar S, Schlant RC: Dipyridamole in the treatment of angina pectoris. JAMA 201:865-867, 1967.

Schamroth L: Immediate effects of intravenous verapamil on atrial fibrillation. Cardiovasc Res 5:419-424, 1971.

Schneider JA, Sperelakis N: Slow Ca^{2+} and Na^{+} responses induced by isoproterenol and methylxanthines in isolated perfused guinea pig hearts exposed to elevated K+. J Mol Cell Cardiol 7:249-273, 1975.

Schomerus M, Spiegelhalder B, Stieren B, et al: Physiological disposition of verapamil in man. Cardiovasc Res 10:605-612, 1976.

Selzer A, Kelly JJ, Johnson RB, et al: Immediate and long-term results of electrical conversion of arrythmias. Prog Cardiovasc Dis 9:90-104, 1966.

Shang SJ, Pepine CJ: Transient asymptomatic S-T segment depression during daily activity. Am J Cardiol 39:396-402, 1977.

Shigenobu K, Schneider JA, Sperelakis N: Verapamil blockade of slow Na^{+} and Ca^{++} responses in myocardial cells. J Pharm Exp Ther 190:280-288, 1974.

Singh BN, Roche AH: Effects of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 94:593-599, 1977.

Singh B, Ellrodt G, Peter CT: Verapamil: A review. Drugs 15:169-248, 1978.

Singh BN, Vaughan Williams EM: A fourth class of anti-dysrhythmic action? Effect of verapamil on ouabain toxicity on atrial and ventricular intracellular potentials and other features of cardiac function. Cardiovasc Res 6:109-119, 1972.

Smith HJ, Goldstein RA, Griffith SM, et al: Regional contractility--selective depression of ischemic myocardium by verapamil. Circulation 54: 629-634, 1976.

Smith HJ, Singh BN, Nisbet HD, et al: Effects of verapamil on infarct size following experimental coronary occlusion. Cardiovasc Res 9:569-578, 1975.

Spurrell RAJ, Krikler DM, Sowton GE: The effect of verapamil on the electrophysiological properties of the anomalous atrioventricular connections in Wolff-Parkinson-White Syndrome. Brit Heart J 36:256-257, 1974a.

Spurrell RAJ, Krikler DM, Sowton GE: Concealed bypasses of the atrioventricular node in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. Am J Cardiol 33:590-595, 1974b.

Stenson RE, Flamm MD, Harrison DC, et al: Hypertrophic subaortic stenosis. Clinical and hemodynamic effects of long-term propranolol therapy. Am J Cardiol 31:763-773, 1973.

Stoney WS, Alford WC, Burrus GR, et al: The cost of coronary bypass procedures. JAMA 240:2278-2280, 1978.

Taira N, Motomura S, Narimatsu A, et al: Experimental pharmacological investigations of effects of nifedipine on atrioventricular conduction in comparison with those of other coronary vasodilators. Second International Adalat Symposium, pp 40-48, 1975.

Tecklenberg PL, Alderman EL, Miller DC, et al: Changes in survival and symptom relief in a longitudinal study of patients after bypass surgery. Circulation 51,52(Suppl I):I-98--I-104, 1975.

Theroux P, Waters DD, Affaki GS, et al: Provocative testing with ergonovine to evaluate the efficacy of treatment with calcium antagonists in variant angina. Circulation 60:504-510, 1979.

Vohra J, Sloman G, Hunt D: Antiarrythmic and hemodynamic properties of verapamil. Austr N Zeal J Med 4:102, 1974a (abstract).

Vohra J, Peter CT, Hunt D, et al: Verapamil induced premature beats before reversion of supraventricular tachycardia. Brit Heart J 36:1186-1193, 1974b.

Wellens HJJ, Tan SL, Bär FWH, et al: Effect of verapamil studied by programmed electrical stimulation of the heart in patients with paroxysmal re-entrant supraventricular tachycardia. Brit Heart J 39:1058-1066, 1977.

White SW, Porges WL, McRitchie RJ: Coronary haemodynamic effects of nifedipine (Bay a 1040) and glyceryl trinitrate in unanesthetized dogs. Clin Exp Pharm Physiol 1:77-86, 1974.

Winbury MM, Howe BB, Weiss HR: Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension--further evidence for redistribution of myocardial flow. J Pharm Exp Ther 176:184-199, 1971.

Wit AL, Fenoglio JJ, Wagner BM, et al: Electrophysiologic properties of cardiac muscles in the anterior mitral valve leaflet and adjacent atrium of the dog: Possible implications for the genesis of atrial arrythmias. Circ Res 32:731-738, 1973.

Wit AL, Cranefield PF: Effect of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanism by which it arrests reentrant atrioventricular nodal tachycardia. Circ Res 35:413-425, 1974.

Wrogemenn K, Pena SDJ: Mitochondrial calcium overlaod: a general mechanism for cell necrosis in muscle diseases. Lancet 1:672-673, 1976.

Yasue H, Ornote S, Takizawa A, et al: Exertional angina pectoris caused by coronary arterial spasm: effects of various drugs. Am J Cardiol 43: 647-652, 1979.

Yasue H, Nagao M, Omote S, et al: Coronary arterial spasm and Prinzmetal's variant form of angina induced by hyperventilation and tris-buffer infusion. Circulation 58:56-62, 1978.

Yasue H, Touyama M, Shimamoto M, et al: Role of autonomic nervous system in the pathogenesis of Prinzmetals variant form of angina. Circulation 50:534-539, 1974.

Zipes DP, Fischer JC: Effects of agents which inhibit the slow channel on sinus node automaticity and atrioventricular conduction in the dog. Circ Res 34:184-192, 1974.

Zipes DP, Besch HR, Watanabe AM: Role of the slow current in cardiac electrophysiology. Circulation 51:761-766, 1975.

Zipes DP, Troup PJ: New antiarrythmic agents. Am J Cardiol 41:1005-1024, 1978.