MEDICAL GRAND ROUNDS

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THE CLINICAL EFFICACY OF THE CALCIUM ANTAGONISTS

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OUTLINE

I. INTRODUCTION

Over the past 2 years, 3 pharmacologic agents known as "calcium antagonists" or "slow channel calcium blockers" have become available in this country. Prior to their approval by the Food and Drug Administration, numerous studies both here and abroad demonstrated a wide range of disease entities for which they were beneficial, and more recent investigations have continued to expand the horizons of their clinical applicability. This review is intended to provide a detailed update of the clinical utility of the 3 calcium blockers now available in this country-- verapamil (marketed by Knoll Pharmaceutical Company as "Isoptin" and by Searle Laboratories as "Calan"), nifedipine (marketed by Pfizer Pharmaceutical Company as "Procardia"), and diltiazem (marketed by Marion Laboratories as "Cardizem").

II. THERAPY OF TACHYARRHYTHMIAS

A. Supraventricular Tachyarrhythmias Verapamil prolongs atrioventricular (AV) conduction by exerting a depressant effect on the portion of the conducting system immediately proximal to the bundle of His (1). In the individual with normal sinus rhythm, intravenous verapamil, 0.15 mg/kg, increases the atrial-His (A-H) interval by an average of 28 milliseconds and the PR interval by 19 milliseconds (from 186 to 205)(2). Because of verapamil's depressant effect on AV conduction, it is efficacious in converting paroxysmal supraventricular tachycardia to sinus rhythm as well as in slowing the ventricular response during atrial flutter or fibrillation.

1. Paroxysmal Supraventricular Tachycardia *A.B. is a 37 year old white woman with a 30 year history of well-documented paroxysmal supraventricular tachycardia (PSVT). During the 1970s, her PSVT was well controlled on propranolol and digoxin. In 1979, however, despite both medications, she began to have more frequent episodes of PSVT, usually accompanied by weakness and dizziness. Because of these worsening symptoms, she was referred for a trial of oral verapamil.*

Physical examination revealed a small white female in no distress. BP was 100/78, pulse 88 and regular. The general examination was normal. Her 12 lead ECG was normal, as were her chest xray and routine laboratory studies.

In December, 1980, an invasive electrophysiologic study was performed to determine the mechanism of her PSVT, which revealed a concealed bypass tract between her left atrium and ventricle for

ventriculoatrial reciprocation. Subsequently, she was enrolled in a randomized, double-blind comparison of placebo and oral verapamil. During 2 months of placebo therapy, she averaged 4.8 episodes of PSVT/week by diary and 9.4 episodes/week by Holter monitor. These episodes lasted a total of 7½ hours/week. During these 2 months, she required 7 emergency room visits for sustained PSVT, each of which was reverted to sinus rhythm with intravenous verapamil. During 2 months of oral verapamil (480 mg/day), she averaged only 0.25 episodes of PSVT/week by diary and 5.4 episodes/week by Holter monitor. However, most of these were extremely short-lived, since their total duration was only 6 minutes. During these 2 months, the patient did not require conversion with intravenous verapamil.

Since completion of this study, A.B. has been continued on oral verapamil, with a sustained beneficial effect.

PSVT has one of 3 electrophysiologic mechanisms. First, it is most commonly an atrioventricular nodal reentrant tachycardia usually associated with dual AV nodal pathway conduction. Second, it may occur in patients with an accessory atrioventricular bypass tract, such as those with the Wolff-Parkinson-White syndrome. Third, on rare occasions, PSVT occurs as a sinus nodal reentrant tachycardia (3-5). Since this rhythm disturbance is often due to AV nodal reentry, intravenous verapamil has proven highly effective in inducing a reversion to sinus rhythm (Figure 1). Schamroth et al (6) treated 20 consecutive episodes of PSVT with intravenous verapamil, 10 mg administered over 15-30 seconds; all reverted to sinus rhythm, usually within 2 minutes of drug administration. Similarly, Heng et al (2) successfully reverted 13 of 17 PSVT episodes (76%) to sinus rhythm with intravenous verapamil. As noted by Schamroth et al, when verapamil was effective in causing a reversion, it usually occurred within 2-3 minutes of intravenous administration. Other studies (7,8) have reported reversion rates of 60-100% following an intravenous bolus of verapamil, with an overall average of 87% (Table 1, page 6).

Some studies have suggested that the success with which intravenous verapamil reverts PSVT to sinus rhythm depends on the electrophysiologic mechanism of the tachycardia. In individuals with AV nodal reentrant tachycardia, verapamil prolongs antegrade (but does not affect retrograde) conduction. In those with an accessory pathway, verapamil does not affect the electrophysiologic properties of the pathway but does slow AV nodal antegrade conduction. In the study of Rinkenberger et al (9), 5-10 mg of intravenous verapamil was highly efficacious in those individuals whose PSVT was an AV nodal reentrant tachycardia (6 of 6), whereas it was less effective in those in whom an accessory pathway was utilized for retrograde conduction (4 of 6). In contrast, other studies have demonstrated that intravenous verapamil is of similar

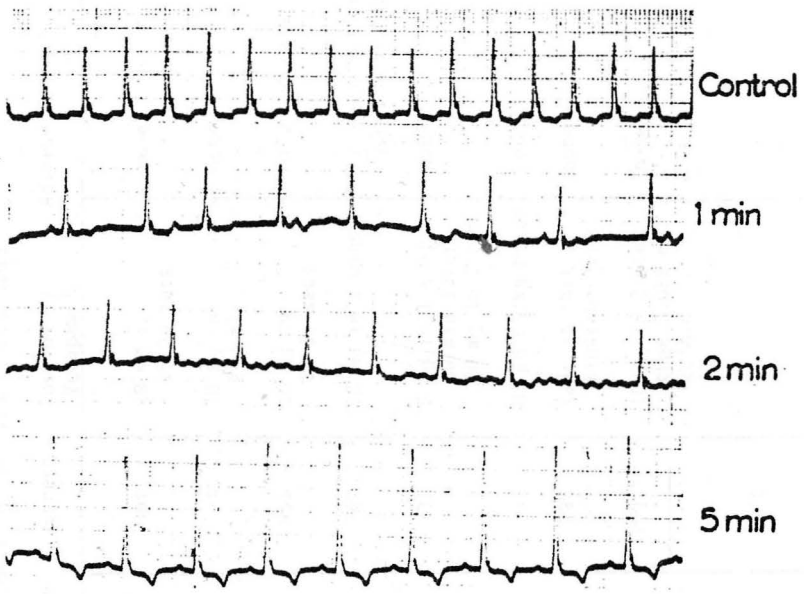


Figure 1: Serial electrocardiographic recordings from a patient with PSVT in the control setting (top panel) as well as 1, 2, and 5 minutes after intravenous verapamil, 10 mg. At 1 minute, the patient developed AV dissociation with slowing of the ventricular rate. At 2 minutes, he briefly developed atrial fibrillation, after which he reverted to sinus rhythm (bottom panel). From reference # 2.

efficacy in reverting PSVT regardless of its electrophysiologic mechanism: Sung et al (5) successfully reverted 6 of 9 individuals with AV nodal reentrant tachycardia and 7 of 9 with a reciprocating tachycardia utilizing a bypass tract (Table 1, page 6).

In short, *intravenous* verapamil is extremely effective in inducing a reversion of PSVT to sinus rhythm, and its use in patients with this tachyarrhythmia has largely supplanted that of pressors, edrophonium (Tensilon), digoxin, and beta-adrenergic blocking agents. The overall success with which it causes a reversion may be slightly higher in those with AV nodal reentrant tachycardia than in those in whom an accessory pathway is utilized for retrograde conduction. Even in the latter group, however, verapamil is often efficacious in accomplishing such a reversion.

TABLE 1

REVERSION OF PSVT EPISODES TO SINUS RHYTHM WITH INTRAVENOUS VERAPAMIL

AUTHORS	# Pts with PSVT	# Reverted to SR with IV Verapamil	% Success	Dose of IV Verapamil	Adverse Effects
Schamroth et al (6)	20	20	100%	10 mg in 15-30 secs	none
Gotsman et al (7)	8	5	63%	10 mg in 2-3 mins	none
Krikler et al (8)	60	57	95%	10 mg in 15-30 secs	mild hypotension in 4
Heng et al (2)	17	13	76%	10 mg in 2 mins	AV dissociation with junctional escape in 4
Rinkenberger et al (9)	12	10	83%	5 mg in 1 min; 30 min later, 10 mg in 1 min	none
Sung et al (5)	19	15	79%	0.075 mg/kg bolus	none
Waxman et al (10)	29	23	79%	same as that of Rinkenberger	none
Klein et al (11)	7	7	100%	10 mg in 2 min, then 0.005 mg/kg/min	none
TOTALS	172	150	87%		

Abbreviations: Pts = patients; SR = sinus rhythm.

Although *intravenous* verapamil is highly effective in reverting most episodes of PSVT to sinus rhythm, there are conflicting data on whether long-term, *oral* verapamil is effective in preventing recurrent episodes. In an uncontrolled and unblinded evaluation, Rinkenberger et al (9) treated 10 patients with PSVT with oral verapamil; it was generally not effective as a single agent in preventing recurrent episodes of tachycardia, even though intravenous verapamil was highly effective in ending tachycardia in these same patients. In contrast, Tonkin and associates (12) gave open-label oral verapamil to 13 patients with refractory PSVT due to AV nodal reentry; 11 had symptomatic improvement. Finally, in a recently published randomized and double-blind assessment, Mauritson et al from this institution (13) demonstrated that orally

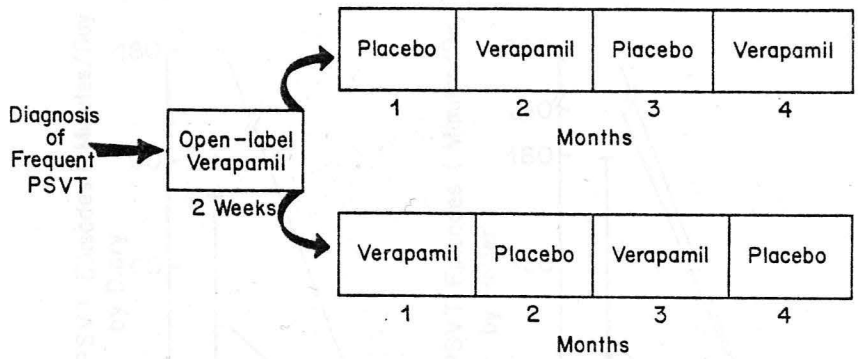
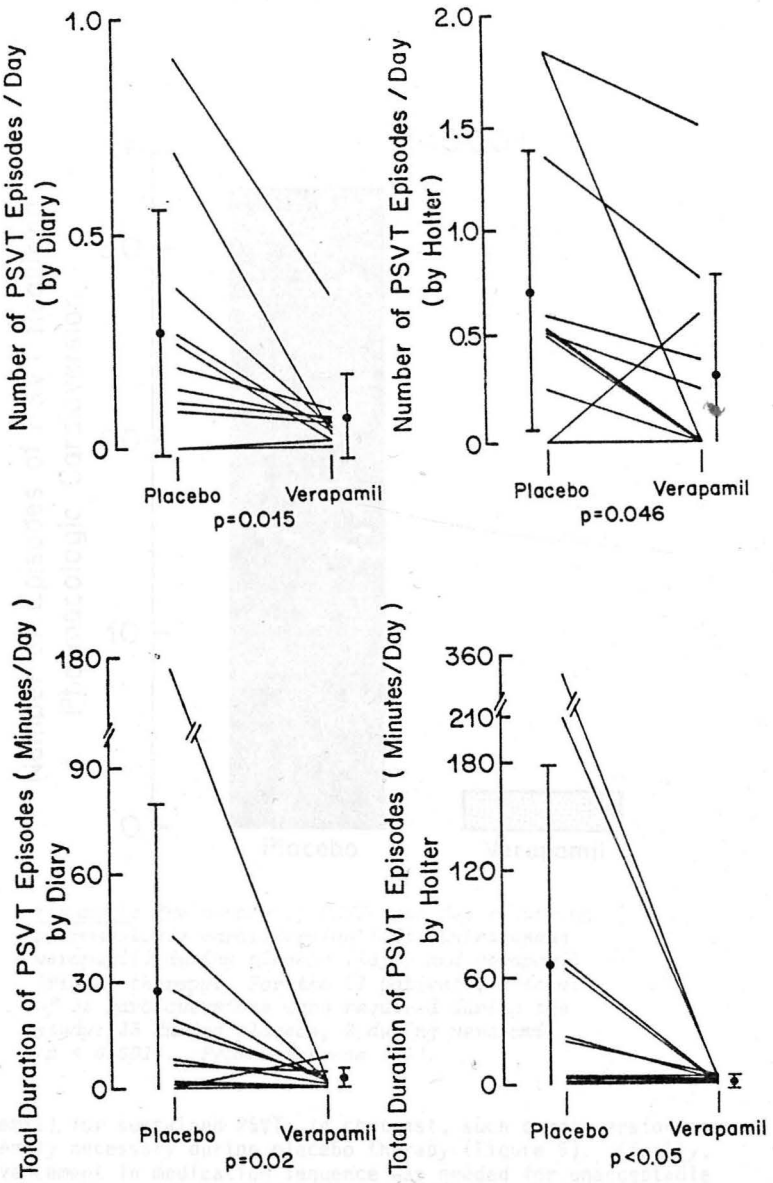


Figure 2: A schematic outline of the study design of Mauritson et al (reference # 13). Each patient was treated with open-label verapamil for 2 weeks, after which they were randomly placed in alternating 1-month periods of placebo and verapamil for 4 months.

administered verapamil (average dose, 458 mg/day given 3 times daily) is highly effective in the long-term treatment of patients with PSVT (Figures 2-5). In comparison to placebo, verapamil reduced the number of episodes of tachycardia (Figure 3) as well as the duration of tachycardia (Figure 4), as assessed by patient diaries and weekly ambulatory electrocardiographic (Holter) monitoring. During blinded verapamil administration, the patients rarely required pharmacologic cardioversion (with intravenous



Figures 3 & 4: The number of PSVT episodes/day (top panel) and the total duration of PSVT episodes (in minutes/day)(bottom panel), as assessed by patient diary (left) and by Holter monitoring (right) during the 2 months of placebo and the 2 months of verapamil therapy. Each line represents the data from 1 patient, and the mean ± SD is shown on either side of each set of lines. In comparison to placebo, verapamil reduced both the frequency and the duration of tachycardia. From reference # 13.

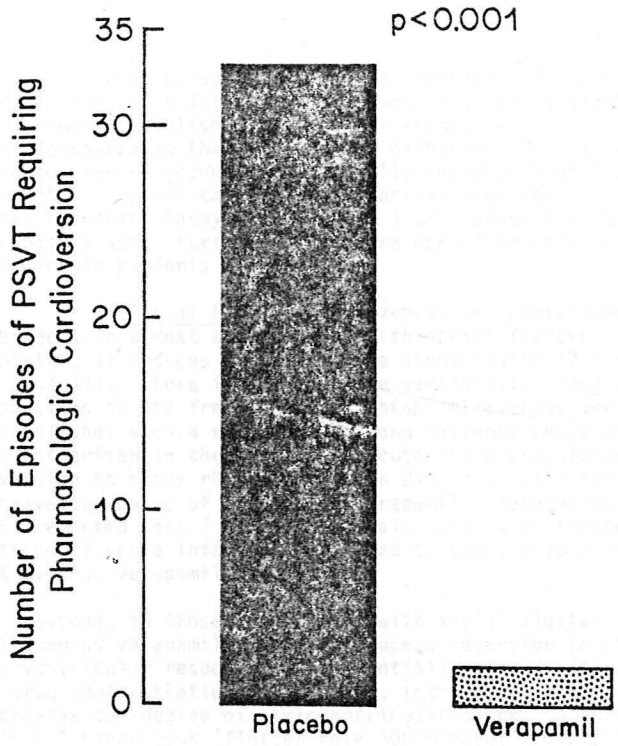


Figure 5: The number of PSVT episodes requiring pharmacologic cardioversion (with intravenous verapamil) during placebo (left) and verapamil (right) therapy. For the 11 patients, a total of 35 cardioversions were required during the study: 33 during placebo, 2 during verapamil ($p < 0.001$). From reference # 13.

verapamil) for sustained PSVT; in contrast, such cardioversion was frequently necessary during placebo therapy (Figure 5). Finally, an advancement in medication sequence was needed for unacceptable tachycardia during 5 of 22 placebo treatment periods; no patient required advancement from verapamil to placebo because of recurrent tachycardia. Thus, in most individuals with frequent episodes of PSVT, *oral* verapamil is effective in reducing the frequency and duration of such episodes.

Similar to verapamil, diltiazem depresses AV nodal conduction, but its use as an antiarrhythmic agent has been extremely limited. In a recently published preliminary report, Rozanski and associates (14) demonstrated that intravenous diltiazem, 0.25 mg/kg administered over 60 seconds, successfully reverted 5 of 7 patients with PSVT. Specifically, such reversion occurred in 4 of 5 with AV nodal reentrant tachycardia and in 1 of 2 whose tachycardia utilized a bypass tract. Further studies are needed to determine diltiazem's efficacy in patients with PSVT.

2. Atrial Flutter Intravenous verapamil exerts one of 2 effects in almost all patients with atrial flutter. First, in a minority, it induces a reversion to sinus rhythm (2,6,9,15,16)(Table 2, page 11). There is considerable variability among different reports as to the frequency with which intravenous verapamil accomplishes such a reversion. Among patients whose atrial flutter has not arisen in the setting of acute myocardial infarction, reversion to sinus rhythm occurs in 21% (2,6,9,16) following an intravenous bolus of 5-10 mg of verapamil. Interestingly, Hagemeijer (15) reported that 7 of 8 individuals (87%) with flutter in the setting of acute infarction reverted to sinus rhythm following intravenous verapamil.

Second, in those individuals with atrial flutter in whom intravenous verapamil does not induce a reversion to sinus rhythm, the ventricular response is substantially slowed within minutes of drug administration. Typically, intravenous verapamil acutely increases the degree of atrioventricular block, so that the patient with 2:1 conduction (flutter rate 300/minute, ventricular response 150/minute) develops 3:1, 4:1, and 5:1 conduction (flutter rate 300/minute, ventricular response 80-110/minute). Thus, in the patient with atrial flutter and a rapid ventricular response, intravenous verapamil accomplishes the same slowing of the ventricular response within minutes that would be induced with intravenous digoxin only after several hours.

3. Atrial Fibrillation As in the patient with atrial flutter, intravenous verapamil exerts one of 2 effects in almost all patients with atrial fibrillation. Although it induces a reversion to sinus rhythm in an occasional individual, the overall incidence of such reversion is only about 2-3% (Table 3, page 12), distinctly lower than that for patients with atrial flutter. In most individuals with atrial fibrillation, intravenous verapamil slows the ventricular response (Figure 6). An initial injection of 5-10 mg over 1-2 minutes usually causes the ventricular rate to fall to 80-110/minute. Subsequently, the ventricular response is maintained at that level with a continuous intravenous infusion of roughly 0.005 mg/kg/minute (11), the exact infusion rate adjusted to achieve the desired

TABLE 2

EFFECT OF INTRAVENOUS VERAPAMIL IN PATIENTS WITH ATRIAL FLUTTER

AUTHORS	# Pts with A Flutter	# Reverted to SR	% Reverted to SR	# with Slowed Vent Response	% with Slowed Vent Response	Dose	Adverse Effects
Schamroth et al (6)	15	4	27%	11	73%	10 mg in 15-30 sec	none
Heng et al (2)	11	2	18%	9	82%	10 mg in 2 min	mild-moderate fall in BP
Hagemeijer (15)	8	7	87%	1	13%	1 mg/min to 20 mg	slight fall in BP in 2
Aronow et al (16)	7	1	14%	6	86%	5-10 mg in 10 min	none
Rinkenberger et al (9)	1	0	0%	1	100%	5 mg in 1 min; 30 min later, 10 mg in 1 min	none
TOTALS	42	14	33%	28	67%		

Abbreviations: Pts = patients; SR = sinus rhythm; Vent = ventricular.

TABLE 3

EFFECT OF INTRAVENOUS VERAPAMIL IN PATIENTS WITH ATRIAL FIBRILLATION

AUTHORS	# Pts with A Fib	# Reverted to SR	% Reverted to SR	# with Slowed Vent Response	% with Slowed Vent Response	Dose	Adverse Effects
Schamroth (17)	20	0	0%	19	95%	10 mg in 15-60 sec	none
Schamroth et al (6)	115	1	1%	111	97%	10 mg in 15-30 sec	none
Heng et al (2)	12	1	8%	11	92%	10 mg in 2 mins	mild-moderate fall in blood pressure
Hagemeijer (15)	8	1	13%	7	87%	1 mg/min to 20 mg	none
Aronow et al (16)	20	3	15%	17	85%	5-10 mg in 10 mins	none
Dominic et al (18)	15	0	0%	15	100%	5-15 mg in 30 mins	none
Rinkenberger et al (9)	13	0	0%	12	92%	5 mg in 1 min; 30 min later, 10 mg in 1 min	none
TOTALS	203	6	3%	192	95%		

Abbreviations: Pts = patients; SR = sinus rhythm; Vent = ventricular.

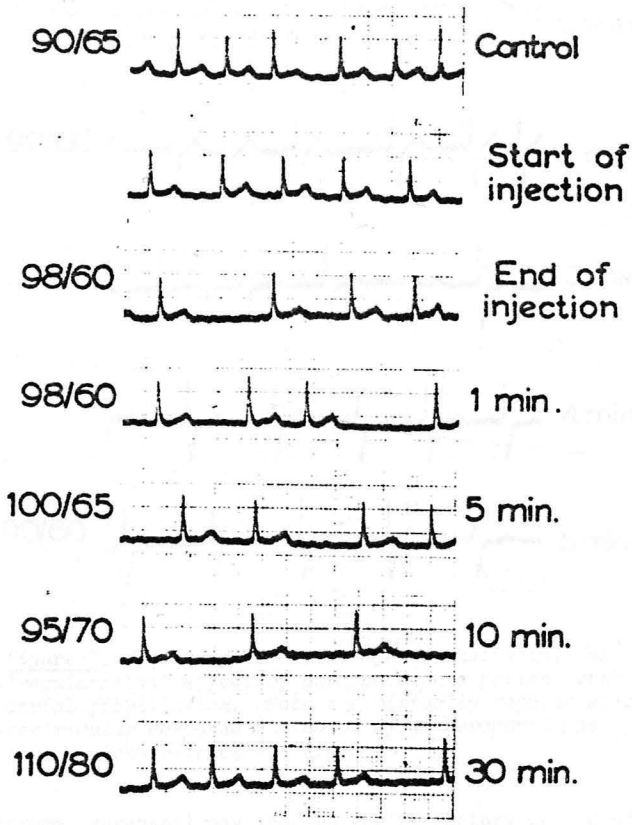


Figure 6: Serial electrocardiographic recordings illustrating the typical effect of verapamil in a patient with atrial fibrillation and a rapid ventricular response (top panel). Ten minutes after verapamil was administered, the ventricular rate was reduced to 72/minute, and at 30 minutes it was 78/minute. From reference # 2.

ventricular response.

In most patients with atrial fibrillation, intravenous verapamil both slows and regularizes the ventricular response (Figure 7). Such regularization appears to be less frequent and less marked in the elderly (6). The exact electrophysiologic mechanism by which verapamil induces such regularization is uncertain.

In the patient with atrial fibrillation and the Wolff-Parkinson-

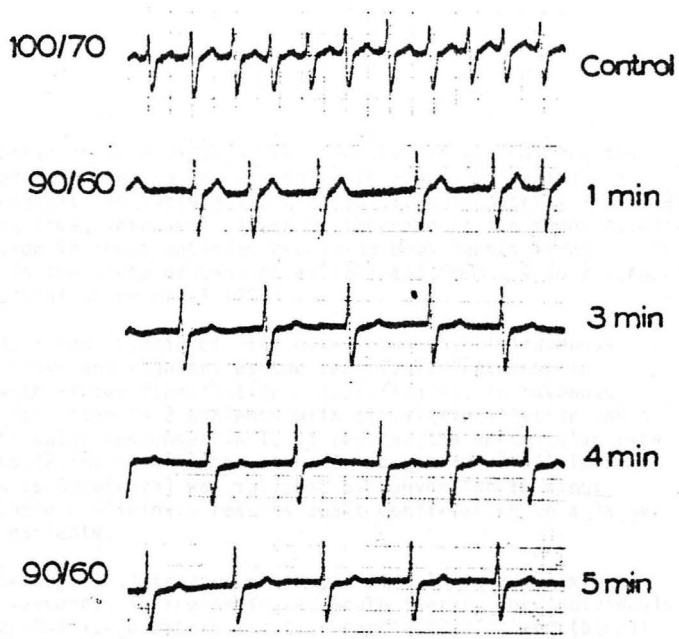


Figure 7: Sequential ECG tracings demonstrating the "regularizing" effect of verapamil in a patient with atrial fibrillation. Note the virtually regular slower ventricular response 5 minutes after verapamil was given. From reference # 2.

White syndrome, verapamil may shorten the refractory period of the accessory pathway, resulting in an acceleration of the ventricular response (19), a phenomenon known to occur in some patients following digitalis administration. Gulamhusein et al (19) have hypothesized that verapamil shortens the accessory pathway's refractory period because of a reflex increase in adrenergic tone brought about by its peripheral vasodilating effect. Thus, verapamil should not be administered to slow the ventricular response during atrial fibrillation when most QRS complexes are preexcited. The safety of verapamil in individuals with the Wolff-Parkinson-White syndrome should be established by electrophysiologic testing prior to its use.

Although *intravenous* verapamil is effective in controlling the ventricular response in patients with atrial fibrillation, *oral* verapamil has yet to be studied in a large number of patients with this atrial tachyarrhythmia. However, 3 recent studies (20-22) have shown that maintenance oral verapamil (240-480 mg/day), alone

or in combination with digoxin, is effective in controlling the ventricular response and, as a result, in improving maximal exercise capacity in individuals with longstanding atrial fibrillation. At the same time, verapamil causes an increase in the serum digoxin concentration in those patients receiving both agents (from 0.7 to 1.2 ng/ml in the study of Lang et al {20} and from 1.4 to 2.1 ng/ml in the study of Stern et al {22}).

Rozanski and associates (14) have shown that intravenous diltiazem slows and regularizes the ventricular response in patients with atrial fibrillation. Specifically, intravenous diltiazem was given to 2 patients with atrial fibrillation and a rapid ventricular response: in 1, it reduced the ventricular rate from 160 to 120/minute; in the other, a more marked fall in rate (to as low as 60/minute) was followed by conversion to sinus rhythm. These preliminary results await confirmation in a larger number of patients.

In summary: (a)Intravenous verapamil, 5-10 mg administered over 30-60 seconds, is the preferred acute therapy for individuals with paroxysmal supraventricular tachycardia (PSVT), and (b)oral verapamil, 320-480 mg/day given 3 times daily, is an effective prophylactic agent in patients with frequent episodes of such tachycardia. (c)Intravenous verapamil (administered at the same dosage as above) slows the ventricular response in those with atrial flutter or fibrillation, and in a minority it induces a reversion to sinus rhythm. (d)Oral verapamil is usually effective in achieving rate control in patients with atrial flutter or fibrillation in whom digitalis alone is inadequate. Finally, (e)preliminary evidence suggests that intravenous diltiazem exerts the same effects as those of verapamil, that is, a reversion of PSVT to sinus rhythm and an immediate reduction of the ventricular response in those with atrial flutter or fibrillation.

B. Ventricular Tachyarrhythmias The success with which the calcium antagonists abolish ventricular ectopic activity is dependent on the pathophysiology of such ectopy. First, some patients with Prinzmetal's variant angina develop high-grade ventricular ectopy--including short runs of ventricular tachycardia-- during the several minutes after an episode of ischemia (23). These short bursts of ectopy are presumably causally linked to myocardial reperfusion. Any therapeutic agent, therefore, which prevents episodes of variant angina will also abolish the ventricular ectopy that follows. In this regard, we have shown that long-term oral verapamil diminishes the severity of ventricular ectopic activity in patients with frequent episodes of variant angina (24). In all probability, nifedipine and diltiazem exert the same beneficial effect, though their influence in this regard has not been studied.

Second, myocardial ischemic injury inactivates the fast

sodium channel and allows the emergence of "slow response" action potentials, which are believed important in the genesis of ventricular arrhythmias (25). Since slow response action potentials are selectively blocked by the calcium antagonists, these pharmacologic agents may be effective in those ventricular arrhythmias occurring in temporal proximity to ischemic injury. In experimental animals with coronary artery occlusion, verapamil, nifedipine, and diltiazem reduce the frequency and severity of ventricular ectopy (26-30), and similar observations (in the case of verapamil) have been made in patients with acute myocardial infarction (31). In short, the triggered activity that leads to ventricular ectopy during the days after infarction is dependent on calcium ion activity, which can be blocked by verapamil, nifedipine, and diltiazem.

Although the calcium antagonists diminish ventricular ectopic activity in the setting of myocardial ischemic injury, the mechanism by which they do so remains unclear, since it is unknown if the ischemic myocardium is depolarized to a level at which slow-channel dependent electrical activity participates in the formation or conduction of impulses. During both acute and chronic ischemia, the drugs that depress the rapid inward current are more effective in treating ventricular arrhythmias than are the slow-channel blocking drugs. For these reasons, some authors (32) have hypothesized that the calcium antagonists improve conduction in the ischemic myocardium by favorably influencing myocardial perfusion and metabolism.

Third, the beneficial effect of the calcium antagonists in patients with longstanding ventricular ectopy (including sustained ventricular tachycardia) remote from an acute myocardial infarction is uncertain. On the one hand, Wellens et al (33) have shown that verapamil is not effective in 4 patients with sustained ventricular tachycardia. On the other hand, Mason (34) has reported recently that intravenous and oral verapamil may be effective in some patients with recurrent ventricular tachycardia. Of 18 individuals with recurrent and inducible tachycardia, verapamil exerted a salutary effect in 6 (33%). This agent was especially likely to be effective in younger patients without structural heart disease.

In short, the efficacy of the calcium antagonists in the therapy of ventricular ectopy depends on the underlying mechanism of such ectopy. On the one extreme, these agents diminish or even abolish the ectopic activity associated with variant angina. On the other extreme, their utility in patients with longstanding recurrent or sustained ventricular tachycardia is probably limited. However, further studies are required to establish precisely the place of the calcium antagonists-- particularly verapamil-- in this clinical setting.

III. THERAPY OF HYPERTENSION

A. Systemic Arterial Hypertension Since the calcium antagonists are peripheral arterial dilators, it is not surprising that they diminish systemic arterial pressure both in normal and in hypertensive individuals. For many years, intravenous verapamil has been known to reduce systemic arterial pressure, and more recently, several studies have demonstrated that chronic oral verapamil is efficacious in patients with mild or moderate hypertension. In a randomized and double-blind assessment of 23 individuals with essential hypertension, Lewis et al (35) showed that verapamil, 360 mg/day (administered 3 times daily), reduced systolic arterial pressure from 188 to 161 mm Hg and diastolic pressure from 106 to 84 mm Hg (Table 4). Subsequently, several open-label (36-38) or single-blind (39,40) assessments have confirmed verapamil's antihypertensive effects in patients whose hypertension is of similar magnitude to that of the patients described by Lewis et al (Tables 5 and 6, pages 18 and 19). In addition, Leary and Asmal (39) have shown that verapamil (240 mg/day given 3 times daily) in combination with reserpine (0.1 mg/day) reduces systemic arterial pressure in patients with mild or moderate hypertension. In short, oral verapamil is beneficial as an antihypertensive agent in patients whose blood pressure is modestly elevated. Its use in combination with more well-established antihypertensive agents is

	Placebo	80mg t.d.s.	120mg t.d.s.
Lying B.P.	187.9 ± 24	172.7 ± 22	160.6 ± 21
	106.3 ± 10	92.8 ± 11	84.2 ± 11
Standing B.P.	183.2 ± 24	163.9 ± 20	152.3 ± 19
	109 ± 9	95.7 ± 11	87.1 ± 12
Heart rate	80.7 ± 8	81.4 ± 9	77.4 ± 8

Mean values ± standard deviation

Table 4: Effect of verapamil, 240 mg/day and 360 mg/day, on supine and standing blood pressures and heart rate in 23 individuals with essential hypertension. From reference # 35.

Table 5: Ambulatory and intraarterial blood pressures in 20 patients with essential hypertension before and after therapy with verapamil, 360-480 mg/day. From reference # 37.

	Before therapy	After therapy
Clinic BP, supine	182/105 ± 19/10	149/82 ± 20/10
Clinic BP, standing	183/110 ± 25/12	145/86 ± 18/12
Intraarterial BP, mean daytime (noon to 6 pm)	180/95 ± 22/13	158/79 ± 26/11
Supine rest (minutes)		
1	173/88 ± 25/12	146/71 ± 20/9
2	174/88 ± 24/12	146/72 ± 20/9
3	174/88 ± 26/13	146/71 ± 21/9
4	174/90 ± 28/14	148/73 ± 21/9
5	174/90 ± 25/13	147/73 ± 20/10

$p < 0.001$ before vs after treatment for all measurements, systolic and diastolic.

Abbreviation: BP = blood pressure.

largely unexplored.

As with verapamil, the acute administration of either sublingual or oral nifedipine has been shown to lower systemic arterial pressure. Guazzi and associates (41) gave 10 mg of oral nifedipine to 17 individuals with diastolic blood pressures above 120 mm Hg; 30 minutes later, mean systemic arterial pressure had fallen by 36 mm Hg. A similar decline of arterial pressure was observed after 10 mg of sublingual nifedipine. Aoki et al (42) demonstrated a fall in systolic pressure from 173 to 130 mm Hg and in diastolic pressure from 113 to 87 mmHg (25 and 23 percent reductions, respectively) following 10 mg of oral nifedipine.

In addition to its well-documented *acute* antihypertensive effects, nifedipine, either alone or in combination with methyldopa or propranolol, has proven effective in the *chronic* management of patients with essential hypertension. Specifically, Olivari and colleagues (43) showed that 40 mg/day of oral nifedipine (administered 4 times daily) reduced systemic arterial pressure

TABLE 6

CHRONIC TREATMENT OF ESSENTIAL HYPERTENSION WITH THE CALCIUM ANTAGONISTS

AUTHORS	Study Design	# Pts	Medication Dose	Average Fall in BP	Adverse Effects
A. VERAPAMIL					
Lewis et al (35)	Randomized, Double-blind	23	240, 360 mg/day (given tid)	188/106 placebo; 173/93 on 240 mg/day; 161/84 on 360 mg/day	Dizziness (2); constipation (6)
Pedersen (36)	Open-label	5	320-640 mg/day (given tid)	174/120 before Rx; 160/108 at peak dose	Flushing (2)
Leary & Asmal (39)	Single-blind	40	320 mg/day (bid)	178/110 on placebo; 157/102 verapamil	none
Leonetti et al (40)	Single-blind	12	240-480 mg/day (given tid)	177/111 on placebo; 150/96 verapamil	Flushing (2); Wenckebach (1)
Gould et al (37)	Open-label	20	360-480 mg/day (given tid)	182/105 on placebo; 149/82 verapamil	Constipation (4); epigastric pain (1); flushing (1)
Agabiti-Rosei et al (38)	Open-label	12	240 mg/day (tid)	161/105 on placebo; 143/95 verapamil	none
B. NIFEDIPINE					
Olivari et al (43)	Open-label	13	40 mg/day (qid)	202/120 on placebo; 165/98 nifedipine	Headache, flushing, palpitations

Abbreviations: Pts = patients

from 202/120 to 165/98 (Table 6). Guazzi et al (44) demonstrated the potent antihypertensive effects of nifedipine and methyldopa administered together (Table 7), and a similar beneficial effect

TABLE 7. *Hemodynamic Data (mean ± SEM) in Groups 1 and 2 Before and After Treatment with Nifedipine and Methyldopa Combination* *From reference # 44*

	Control	Treatment
HR (beats/min)	79 ± 3.8	71 ± 2†
MSAP (mm Hg)	158.6 ± 3.2	113.9 ± 3.4†
CI (ml/min/m²)	3023 ± 167	3826 ± 261†
SI (ml/m²)	38.2 ± 2.9	53.7 ± 3†
MPAP (mm Hg)	19.4 ± 1.6	15.1 ± 1*
PWP (mm Hg)	10 ± 1.31	6.5 ± 0.87*
SVR (dyn-sec-cm⁻⁵)	2209 ± 168.2	1352 ± 102.4†
PAR (dyn-sec-cm⁻⁵)	136 ± 10.2	103.8 ± 8.7*
PV (ml)	3205 ± 77	3148 ± 75.7

has been documented for the combination of nifedipine and propranolol (42). Thus, nifedipine, either alone or with another antihypertensive agent, is efficacious in individuals with mild or moderate hypertension, and limited studies (41) have suggested that it may be salutary in patients with more severe hypertension, including hypertensive encephalopathy.

B. Pulmonary Hypertension *D.M. is a 40 year old white woman referred to Dr. Lewis Rubin for therapy of primary pulmonary hypertension. In September, 1980, she complained of fatigue and dyspnea, and cardiac catheterization revealed moderate pulmonary hypertension. After a trial of oral hydralazine, she was referred here in September, 1981. At that time, her blood pressure was 95/60, pulse 90 and regular, and she was afebrile. Her cardiac exam revealed a loud pulmonic component of the second heart sound. There were no murmurs or gallops. She had trace pretibial edema.*

Cardiac catheterization (off all medications) revealed the

following: heart rate, 103 beats/minute; cardiac index, 0.96 liters/minute/m^2; pulmonary artery pressure, 55/31 (mean, 43) mm Hg; femoral artery pressure, 125/90 mm Hg; pulmonary vascular resistance, 1591 dynes-sec-cm^{-5} (normal, 20-120); and systemic vascular resistance, 3977 dynes-sec-cm^{-5} (normal, 770-1500).

The patient was begun on oral nifedipine, 20 mg four times daily. Two days later, repeat catheterization revealed: heart rate, 81 beats/minute; cardiac index, 1.9 liters/minute/m^2; pulmonary artery pressure, 48/24 (mean, 33) mm Hg; femoral artery pressure, 118/80; pulmonary vascular resistance, 626 dynes-sec-cm^{-5}; and systemic vascular resistance, 1826 dynes-sec-cm^{-5}.

D.M. was discharged on this dose of nifedipine. She gradually increased her activities, and 3 months later she returned to work. Six months after her initial evaluation, she was completely asymptomatic and working full-time. A repeat catheterization revealed: heart rate, 72 beats/minute; cardiac index, 2.5 liters/minute/m^2; pulmonary artery pressure, 70/27 (mean, 43) mm Hg; femoral artery pressure, 125/75; pulmonary vascular resistance, 610 dynes-sec-cm^{-5}; and systemic vascular resistance, 1603 dynes-sec-cm^{-5}.

Presently the patient continues to feel well and work full-time on 80 mg/day of oral nifedipine.

All 3 calcium antagonists have been administered to limited numbers of patients with primary pulmonary hypertension, with generally encouraging results, especially in the case of nifedipine. Of the 3 pharmacologic agents, verapamil appears to exert the least beneficial effect, probably because of its powerful negative inotropic influence on the right ventricle. Landmark and associates (45) administered an intravenous bolus of verapamil (6.9-12 mg) to 9 individuals with primary pulmonary hypertension; pulmonary arterial pressure declined minimally (mean, 56 to 50 mm Hg), mainly because of a verapamil-induced fall in cardiac index (3.5 to 3.0 liters/minute/m^2). In fact, pulmonary vascular resistance fell only slightly with intravenous verapamil (749 to 716 dynes-sec-cm^{-5}) (Table 8). Similarly, although the number of patients studied thusfar is small, diltiazem appears to exert a salutary effect of only modest proportion in patients with primary pulmonary hypertension. In the resting state, intravenous diltiazem causes a slight decline of pulmonary arterial pressure without inducing a change in cardiac output or pulmonary vascular resistance (46). Oral diltiazem has been evaluated in only one patient with primary pulmonary hypertension; in this individual, it caused an impressive fall in pulmonary arterial pressure and resistance as well as a rise in cardiac output (47). This beneficial effect was sustained

TABLE 8

TREATMENT OF PRIMARY PULMONARY HYPERTENSION WITH CALCIUM ANTAGONISTS

AUTHORS	# Pts	Dose of Drug	Effects	Adverse Effects	Notes
A VERAPAMIL					
Landmark et al (45)	9	6.9-12 mg IV	PA mean fell from 56 to 50 mm Hg; CI fell from 3.5 to 3.0 L/min/m^2; PVR fell from 749 to 715 d-s-c.	none	acute study only
B NIFEDIPINE					
Camerini et al (48)	1	100 mg qd for 3 months	PA mean fell from 63 to 46 mm Hg; CO rose from 2.23 to 6.44 L/min; PVR fell from 2255 to 620 d-s-c.	none	
McLeod et al (49)	4	20 mg SL	PA fell from 95/63 to 72/30; CO rose from 2.9 to 3.9 L/min; PVR fell from 1370 to 771 d-s-c.	none	Repeat study in 2 pts after 4 months of oral Rx showed sustained benefit
C. DILTIAZEM					
Kambara et al (47)	1	10 mg IV	PA mean fell from 63 to 40; CI rose from 1.7 to 2.1	none	After 11 months of oral diltiazem, pt was completely asymptomatic
Crevey et al (46)	4	0.25 mg/kg IV in 1 min; infusion of 1.4 micrograms/min	PA mean fell from 49 to 44 mm Hg; CO and PVR did not change	none	Acute study only

Abbreviations: PA = pulmonary artery; CI = cardiac index; CO = cardiac output; PVR = pulmonary vascular resistance; SL = sublingually.

for 11 months on maintenance oral diltiazem (30 mg 3 times daily).

In contradistinction to the inconsistent results obtained with verapamil and diltiazem in patients with primary pulmonary hypertension, nifedipine appears promising in these individuals. Both Camerini et al (48) and McLeod et al (49) have demonstrated that either acute sublingual or chronic oral nifedipine induces a substantial fall in pulmonary arterial pressure and resistance and a rise in cardiac output (Table 8, page 22). At Parkland Memorial Hospital, Drs. Brian Firth, Lewis Rubin, and associates have studied 7 patients with primary pulmonary hypertension before and after acute and chronic nifedipine administration (Table 9, page 24). In general, nifedipine therapy has induced a fall in pulmonary arterial pressure and resistance, a rise in cardiac output, and an improvement in symptoms.

In addition to its apparent beneficial effect in patients with primary pulmonary hypertension, nifedipine has been shown to inhibit hypoxia-induced pulmonary arterial vasoconstriction (50) without exerting a deleterious effect on arterial oxygenation in patients with chronic airflow obstruction and acute respiratory failure. However, the potential benefit of long-term nifedipine in the treatment of these patients is conjectural.

IV. THERAPY OF CONGESTIVE HEART FAILURE

Several isolated reports have demonstrated that nifedipine is an effective "unloading" agent in patients with congestive heart failure. Matsumoto and associates (51) administered 20 mg of sublingual nifedipine to 8 patients with mild or moderate congestive heart failure of various etiologies (valvular in 5, hypertensive in 1, arteriosclerotic in 1, and cardiomyopathic in 1). In response to nifedipine, these individuals had a rise in cardiac index (3.5 to 4.1 liters/minute/m^2), a fall in mean systemic arterial pressure (85 to 76 mm Hg) and systemic vascular resistance, but no change in left ventricular filling pressure (11 to 12 mm Hg)(Figure 8). Polese et al (52) gave 10 mg of sublingual nifedipine to 24 patients with acute pulmonary edema (hypertensive in origin in 7, cardiomyopathic in 7, and valvular in 10). Nifedipine consistently lowered systolic and diastolic arterial pressure as well as systemic vascular resistance, and cardiac output uniformily increased (from 2.4 to 3.2 liters/

TABLE 9

PMH EXPERIENCE USING NIFEDIPINE IN PATIENTS WITH PRIMARY PULMONARY HYPERTENSION

atient	Age/Sex	BASELINE PA mean	CI	TPR	AFTER 10-20 MG SL NIFEDIPINE PA mean	CI	TPR	AFTER 40-80 MG/DAY NIFEDIPINE X 48 HOURS PA mean	CI	TPR	AFTER 40-80 MG/DAY NIFEDIPINE X 6 MONTHS PA mean	CI	TPR
E.B.	61 M	45	1.6	1246	45	2.8	714	39	1.9	734	40	2.0	914
D.M.	39 F	43	1.0	2012	30	1.6	842	33	1.9	793	43	2.5	749
B.H.	26 F	54	2.3	1091	38	3.0	581	46	3.0	722			
K.B.	16 M	63	2.6	1026	57	2.7	865	NOT PERFORMED			NOT PERFORMED		
B.W.	45 F	74	1.0	3503	72	1.4	2515	NOT PERFORMED			NOT PERFORMED		
P.T.	22 F	59	1.2	2524	54	1.8	1577	45	1.8	1286			
R.L.S.	25 M	50	2.6	871	66	3.8	800	NOT PERFORMED			NOT PERFORMED		
TOTALS		55	1.8	1753	52	2.4	1128						

Abbreviations: SL = sublingual; PA = pulmonary artery; CI = cardiac index (in liters/minute/m^2); TPR = total pulmonary resistance.

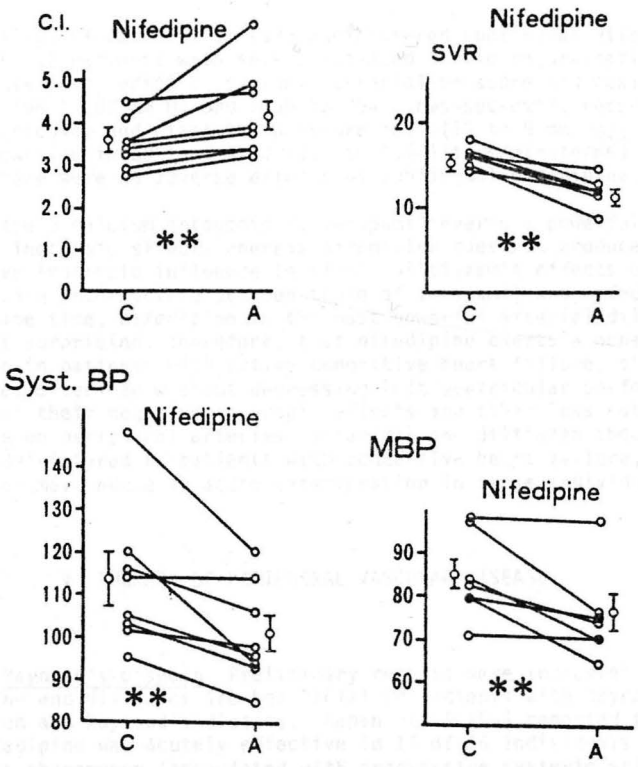


*Figure 8: Effects of sublingual nifedipine on cardiac index (CI, in liters/minute/m^2), systemic vascular resistance (SVR), systolic blood pressure (Syst. BP, in mm Hg), and mean blood pressure (MBP, in mm Hg) in 8 patients in the control setting (C) and after nifedipine administration (A). Each line represents the data from one patient, and the means ± SEM are shown on either side of each set of lines. Nifedipine induced a fall in SVR and blood pressure and a rise in cardiac index. ** $p < 0.01$. From reference # 51.*

minute/m^2). In contrast to the study of Matsumoto et al, pulmonary capillary wedge pressure fell with nifedipine (from 31 to 21 mm Hg). All patients progressively experienced less dyspnea following

nifedipine administration, and no adverse effects were observed.

Finally, Fioretti et al (53) administered sublingual nifedipine (20 mg) to 12 patients with severe isolated aortic regurgitation. In response to nifedipine, systemic arterial pressure and resistance declined (98 to 80 mm Hg and 1135 to 794 dynes-sec-cm^{-5}, respectively), left ventricular end-diastolic pressure fell (19 to 9 mm Hg), and forward cardiac index increased (3.8 to 4.4 liters/minute/m^2). Again, there were no adverse effects of sublingual nifedipine.

Of the 3 calcium antagonists, verapamil exerts a powerful negative inotropic effect, whereas nifedipine does not produce such a negative inotropic influence in vivo. Diltiazem's effects on inotropy are intermediate between those of verapamil and nifedipine. At the same time, nifedipine is the most powerful arterial dilator. It is not surprising, therefore, that nifedipine exerts a beneficial influence in patients with active congestive heart failure, since it reduces afterload without depressing left ventricular performance. Because of their negative inotropic effects and their less potent influence on peripheral arteries, verapamil and diltiazem should not be administered to patients with congestive heart failure, since they may induce an acute deterioration in these individuals (54).

V. THERAPY OF PERIPHERAL VASCULAR DISEASE

A. Raynaud's Disease. Preliminary reports have indicated that nifedipine and diltiazem are beneficial in patients with Raynaud's phenomenon and Raynaud's disease. Kahan et al (55) reported that oral nifedipine was acutely effective in 14 of 16 individuals with Raynaud's phenomenon (associated with progressive systemic sclerosis in 6 patients, systemic lupus erythematosus in 4, and idiopathic in 6). Subsequently, 10 of these patients were maintained on nifedipine, 20 mg 3 times daily, for 3 winter months. The average number of digital vasospastic episodes/week decreased from 29.5 to 4.3, and 4 of the 10 were completely free of attacks. Similarly, 26 patients with Raynaud's disease were randomly and blindly assigned to either placebo (n = 13) or diltiazem therapy (n = 13)(60 mg 3 times daily)(56). In comparison to placebo, diltiazem significantly reduced disability and the number of vasospastic episodes. Thus, nifedipine and diltiazem appear promising in the treatment of individuals with Raynaud's phenomenon or disease.

In contradistinction to these reports, verapamil does not appear effective in patients with Raynaud's phenomenon. Kinney

and associates (57) enrolled 16 individuals with severe Raynaud's phenomenon in a 12-week randomized and double-blind comparison of placebo and verapamil, 160-320 mg/day. Of the 16 patients, 10 had progressive systemic sclerosis, 2 had mixed connective tissue disease, 2 had systemic lupus erythematosus, and 2 had Raynaud's disease. Of the 14 patients who kept analyzable diaries, only one had a substantial decrease in the frequency of Raynaud's phenomenon while on verapamil.

B. Arteriosclerotic Peripheral Vascular Disease Since platelet activation is calcium dependent, the calcium antagonists may act to inhibit platelet activation in vivo. Animal studies have suggested that verapamil inhibits platelet deposition in both gortex and autologous vein grafts (58). Thusfar, there are no published studies of the calcium antagonists in patients with peripheral vascular disease and resultant claudication.

VI. THERAPY OF CARDIOMYOPATHY

A. Hypertrophic Cardiomyopathy Of the available calcium antagonists, verapamil appears to be the most effective in patients with hypertrophic cardiomyopathy. Rosing et al (59) administered intravenous verapamil to 27 patients with asymmetric septal hypertrophy to assess its acute effects on left ventricular filling pressure and the degree of left ventricular outflow tract obstruction. Following an intravenous injection of 0.1 mg/kg of verapamil (administered over 2 minutes), each patient received a continuous intravenous infusion of 0.007, 0.014, and 0.021 mg/kg/minute. During administration of the highest verapamil dosage, heart rate increased (from 72 to 81 beats/minute), systolic arterial pressure decreased (from 118 to 99 mm Hg), and left ventricular outflow tract gradient declined (from 94 to 49 mm Hg). Cardiac index increased slightly but significantly (2.5 to 2.8 liters/minute/m^2), while left ventricular filling pressure was unchanged. Thus, acutely administered verapamil causes substantial hemodynamic improvement in patients with asymmetric septal hypertrophy.

Subsequent reports by Rosing and associates have demonstrated, first, that oral verapamil improves exercise capacity and symptomatic status in some patients with obstructive hypertrophic cardiomyopathy and, second, that these improvements are sustained during long-term (i.e., 6-30 months) verapamil therapy. In 19 individuals with hypertrophic cardiomyopathy, verapamil (320-480 mg/day administered 4 times daily) improved exercise capacity by 26%, and 12 of the 19 improved their exercise duration by at least 15% in comparison to

placebo. In 8 patients who continued oral verapamil for 3½ to 6 months after completion of the acute study, exercise capacity improved an additional 21% above the values obtained during acute therapy with verapamil (60). Of 78 individuals treated with long-term (mean, 14 months) verapamil, 42 (54%) experienced sustained

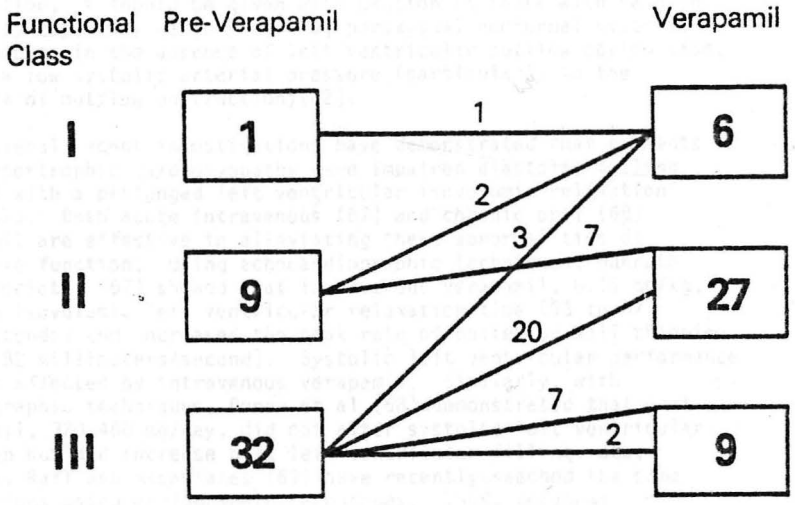


Figure 9: Change in functional class of 42 patients who described their style of living as improved and, therefore, continued taking the medication. Upsloping lines connecting the same functional class indicate persons who described a decrease in symptoms but whose functional class remained unchanged. The 2 patients who were still in functional class 3 and had no change in the severity of symptoms stated that they felt "better" with verapamil and, therefore, chose to continue the medication. The patient who was in functional class 1 began therapy with verapamil because it decreased the incidence of ventricular tachycardia. From reference # 61.

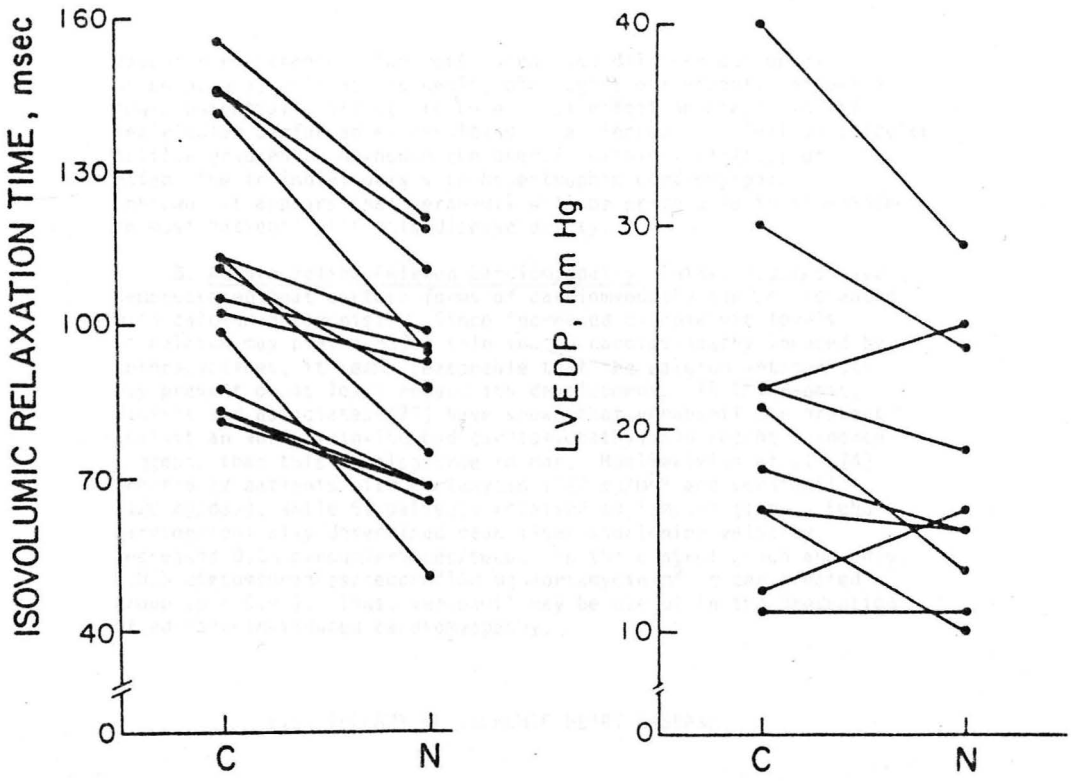
symptomatic improvement (61)(Figure 9). However, the administration of verapamil was associated with adverse hemodynamic effects in 9 patients (12%) and adverse electrophysiologic effects in 10 (13%). As a result, the use of verapamil in patients with hypertrophic

cardiomyopathy is probably contraindicated in those with: (a)high pulmonary capillary wedge pressure (greater than 25 mm Hg) in the presence of left ventricular outflow obstruction; (b)a history of paroxysmal nocturnal dyspnea or orthopnea in the presence of outflow obstruction; and (c)sick sinus syndrome or atrioventricular junctional disease without an implanted pacemaker. In addition, it should be given with caution to those with (a)high pulmonary capillary wedge pressure, paroxysmal nocturnal dyspnea, or orthopnea in the absence of left ventricular outflow obstruction; and (b)a low systolic arterial pressure (particularly in the presence of outflow obstruction)(62).

Several recent investigations have demonstrated that patients with hypertrophic cardiomyopathy have impaired diastolic filling (63-66) with a prolonged left ventricular isovolumic relaxation time (67). Both acute intravenous (67) and chronic oral (68) verapamil are effective in alleviating these abnormalities of diastolic function. Using echocardiographic techniques, Hanrath and associates (67) showed that intravenous verapamil, 0.15 mg/kg, reduced isovolumic left ventricular relaxation time (93 to 67 milliseconds) and increased the peak rate of posterior wall thinning (64 to 82 millimeters/second). Systolic left ventricular performance was not affected by intravenous verapamil. Similarly, with scintigraphic techniques, Bonow et al (68) demonstrated that oral verapamil, 320-480 mg/day, did not alter systolic left ventricular function but did increase peak left ventricular filling rate. Finally, Raff and associates (69) have recently reached the same conclusions using angiographic techniques. Thus, verapamil normalizes or improves left ventricular diastolic filling without affecting systolic function.

Nifedipine appears to exert a similar influence on left ventricular relaxation and diastolic filling in patients with hypertrophic cardiomyopathy. Lorell and associates (70,71) have demonstrated that sublingual nifedipine (10 mg) reduces left ventricular isovolumic relaxation time (Figure 10) and improves the peak rate of left ventricular diastolic filling and posterior wall thinning. As a result, left ventricular end-diastolic pressure declines (Figure 11), and there is a downward shift of the left ventricular diastolic pressure-dimension relationship, suggesting improved left ventricular distensibility. Indeed, recent investigations (72) have shown that nifedipine exerts this effect by improving relaxation rather than by reducing left ventricular loading. At the same time, systolic left ventricular performance is unaltered.

Presently it is unknown if the above-described abnormalities



Figures 10 & 11: Left ventricular isovolumic relaxation time, in milliseconds (left panel), and left ventricular end-diastolic pressure (LVEDP)(in mm Hg)(right panel) in 15 patients with hypertrophic cardiomyopathy at baseline (control, C) and 20 minutes after 10 mg of sublingual nifedipine (N). Each line represents the data from one patient. In response to nifedipine, both variables declined. From reference # 71.

of diastolic function in patients with hypertrophic cardiomyopathy are related to the dynamic obstruction to left ventricular outflow. Verapamil appears especially beneficial in these individuals, since it (a)improves left ventricular relaxation, (b)exerts a direct negative inotropic effect, and (c)only minimally alters systemic

vascular resistance. The more potent vasodilatory action of nifedipine as well as its negligible negative inotropic influence could potentially offset its beneficial effect on diastolic left ventricular performance, resulting in an increase in left ventricular outflow gradient. Although the overall clinical efficacy of nifedipine in individuals with hypertrophic cardiomyopathy is unknown, it appears that verapamil will be preferable to nifedipine in most patients with this disease entity.

B. Anthracycline-Related Cardiomyopathy Animal studies have demonstrated that certain forms of cardiomyopathy can be prevented with calcium antagonists. Since increased cytoplasmic levels of calcium may play a major role in the cardiomyopathy induced by anthracyclines, it seems reasonable that the calcium antagonists may prevent or at least retard its development. In the rabbit, Daniels and associates (73) have shown that verapamil can protect against an adriamycin-induced cardiomyopathy, and recent evidence suggests that this is also true in man. Muellerleile et al (74) treated 22 patients with adriamycin (322 mg/m^2) and verapamil (120 mg/day), while 61 patients received adriamycin alone. Echocardiographically determined peak fiber shortening velocity decreased 0.33 circumferences/second in the control group and only 0.025 circumferences/second/100 mg adriamycin/m^2 in the treated group ($p < 0.01$). Thus, verapamil may be useful in the prevention of adriamycin-induced cardiomyopathy.

VII. THERAPY OF ISCHEMIC HEART DISEASE

A. Prinzmetal's Variant Angina *L.C. is a 52 year old black man who was admitted to Parkland Hospital in October, 1979, with a 6-7 year history of retrosternal chest pain, both at rest and occasionally with exertion. He had smoked ½ pack/day for many years. His physical examination on admission was unremarkable, as were his routine laboratory data.*

During the initial days of his hospitalization, the patient had a typical episode of chest pain, during which an ECG revealed 4 mm of ST segment elevation in the inferior leads. Both the pain and the ST segment alterations resolved with sublingual nitroglycerin.

Cardiac catheterization revealed a left ventricular ejection fraction of 0.56. The patient had no atherosclerotic coronary artery disease. Following ergonovine maleate administration,

he developed his typical chest pain with ST segment elevation inferiorly, at which time his right coronary artery was totally occluded. Following nitroglycerin, his pain and ST elevation resolved, and his coronary artery appeared normal.

L.C. was enrolled in a long-term comparison of placebo and verapamil for the treatment of Prinzmetal's variant angina. During 4 months of blinded placebo therapy, he averaged 16 episodes/week of chest pain and 54 episodes/week of ST segment deviation by Holter monitor. In contrast, during 4 months of verapamil therapy (400 mg/day), he had only 1.3 episodes/week of chest pain and 6 episodes/week of ST segment deviation.

Subsequent to this 8 month comparison of placebo and verapamil, L.C. was treated with nifedipine, 90 mg/day, for an additional 2 months. During therapy with this calcium antagonist, he averaged 2.4 episodes/week of chest pain and 4 episodes/week of ST segment deviation.

At the end of this 10 month trial, L.C. was allowed to choose which agent he preferred for continued long-term therapy. Presently he is doing well on 360 mg/day of verapamil.

Since the calcium antagonists act to relax vascular smooth muscle tone, it is not surprising that they are effective in preventing episodes of coronary arterial spasm. In several uncontrolled and unblinded studies (75-78), oral verapamil, usually administered in a daily dosage of 320-480 mg, induced a complete abolition of anginal episodes, and this beneficial effect was sustained in some patients for over 2 years (Table 10, page 33). At our institution, Winniford, Johnson, Mauritson, and associates (24,79,80) have enrolled 27 individuals with variant angina in a long-term (9 month), randomized, double-blind comparison of placebo and verapamil (Figure 12, page 34). In comparison to placebo, oral verapamil (average dose, 450 mg/day; range, 240-560 mg/day, given 3-4 times daily) significantly diminished the frequency of angina (assessed by patient diaries), nitroglycerin consumption (assessed by tablet counts), and transient electrocardiographic ST segment deviations (assessed by weekly 24 hour ambulatory electrocardiographic {Holter} monitoring)(Figure 13, page 34). During blinded verapamil administration, one patient died, but none required hospitalization for clinical instability. In contrast, during placebo therapy, 7 patients had at least 1 episode of clinical instability requiring hospitalization or a blinded advancement in medication sequence ($p < 0.025$). In each case, an advancement to verapamil resulted in relief of symptoms. Adverse effects related to verapamil were minor and did not interfere with its proper administration.

TABLE 10

THE USE OF VERAPAMIL IN THE THERAPY OF PRINZMETAL'S VARIANT ANGINA

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Oral Drug	Length of Observation	Response
Hansen & Sandoe (75)	3	no	no	160-320 mg/day (given qid)	4 months	Total relief of pain in all 3 pts
Solberg et al (76)	1	no	no	320 mg/day (given qid)	6 weeks	Total relief of pain
Johnson et al (24)	16	yes	yes	415 mg/day range, 240-480 (given qid)	9 months	14 of 16 had a fall in anginal frequency
Freedman et al (77)	6	no	no	160-480 mg/day	Up to 11 months	Exercise-induced spasm prevented in all 6
Freeman et al (78)	7	no	no	320-480 mg/day	3-25 months	All pts, even though resistant to other Rx, had a complete response
Winniford et al (80)	27*	yes	yes	450 mg/day range, 240-560 (given tid or qid)	9 months	Good response in almost all pts

*These 27 patients are composed of Johnson's 16 plus 11 new entries.

Abbreviations: Pts = patients; Rx = therapy; tid = three times daily; qid = four times daily.

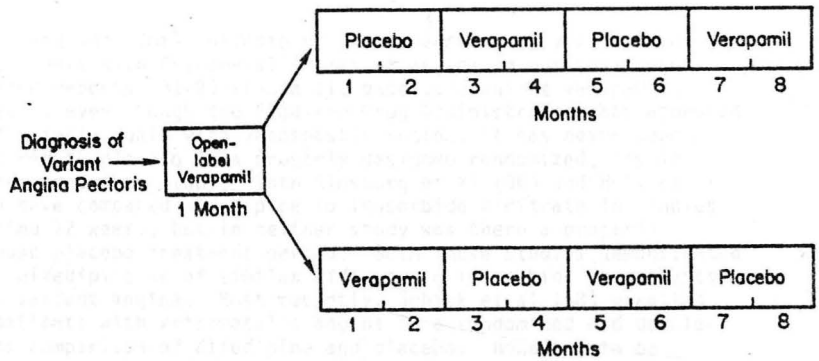


Figure 12: A schematic outline of the study design employed by Winniford et al (reference # 80). After a diagnosis of variant angina was made, each patient was treated with open-label verapamil for 1 month, after which he was randomly assigned to alternating placebo and verapamil treatment. During these 8 months, neither the physicians nor the patients knew which agent was being administered.

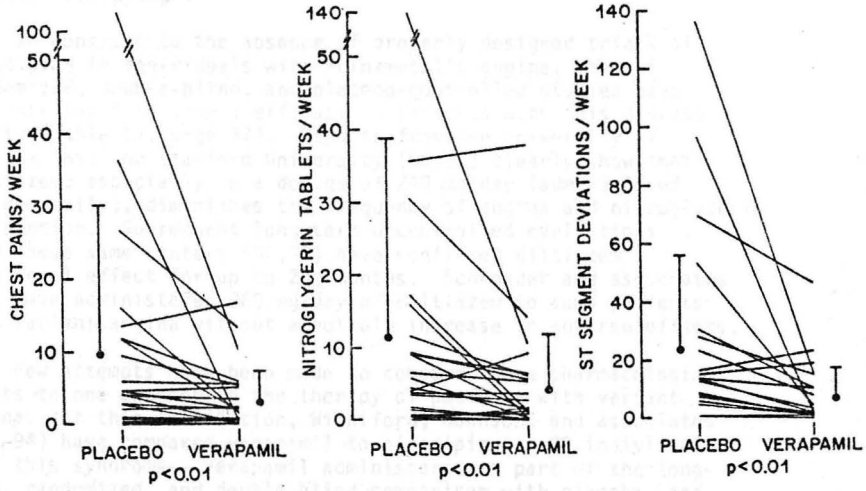


Figure 13: The number of chest pains/week (left), nitroglycerin tablets used/week (middle), and ST segment deviations/week by Holter monitor (right) during 4 months of placebo and 4 months of verapamil therapy. Each line represents the data from 1 patient, and the means ± SD are shown on either side of each set of lines. In comparison to placebo, verapamil reduced the frequency of all 3 variables. From reference # 80.

Like verapamil, nifedipine has appeared highly effective in patients with Prinzmetal's variant angina in numerous uncontrolled reports (81-85)(Table 11, page 36); unlike verapamil, however, even though the Food and Drug Administration has approved it for individuals with vasospastic angina, it has never been compared to placebo in a properly designed randomized, double-blind, crossover study. Both Ginsburg et al (86) and Hill et al (87) have compared nifedipine to isosorbide dinitrate in studies lasting 12 weeks, but in neither study was there a properly blinded placebo treatment period. Both these studies demonstrated that nifedipine is of similar efficacy to isosorbide in patients with variant angina. Most recently, Schick et al (88) enrolled 28 patients with Prinzmetal's angina in a randomized and double-blind comparison of nifedipine and placebo. However, to be eligible for enrollment, all patients were required to show clinical improvement on open-label nifedipine. During 4 weeks of blinded therapy, the 13 individuals given nifedipine had less angina than the 15 given placebo. Nifedipine was deemed "effective" in 11 of 13 patients, whereas placebo was "effective" in only 2 of 15 receiving it. Thus, even though the study of Schick et al is randomized and double-blind, it does not have a crossover design, and the enrollment criteria are slanted to give nifedipine an unfair advantage.

In contrast to the absence of properly designed trials of nifedipine in individuals with Prinzmetal's angina, several randomized, double-blind, and placebo-controlled studies have demonstrated diltiazem's efficacy in patients with this disease entity (Table 12, page 37). Reports from the University of Florida (89) and Stanford University (90,91) clearly show that diltiazem, especially in a dosage of 240 mg/day (administered 4 times daily), diminishes the frequency of angina and nitroglycerin consumption. Subsequent long-term uncontrolled evaluations from these same centers (92,93) have confirmed diltiazem's beneficial effect for up to 28½ months. Schroeder and associates (92) have administered 360 mg/day of diltiazem to some patients with variant angina without a notable increase in adverse effects.

Few attempts have been made to compare these pharmacologic agents to one another in the therapy of patients with variant angina. At this institution, Winniford, Johnson, and associates (80, 94) have compared verapamil to nifedipine in 23 individuals with this syndrome-- verapamil administered as part of the long-term, randomized, and double-blind comparison with placebo, and nifedipine given as an "open-label" medication. In comparison to placebo, both verapamil and nifedipine reduced the frequency of chest pain, nitroglycerin usage, and transient ST segment deviations by Holter monitoring. Furthermore, in all respects, the 2 calcium antagonists were similar to one another (Figure 14).

TABLE 11

THE USE OF NIFEDIPINE IN THE THERAPY OF PRINZMETAL'S VARIANT ANGINA

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Oral Drug	Length of Observation	Response
Muller & Gunther (81)	1	no	no	100 mg/day	1 month	Complete relief of pain
Heupler & Proudfit (82)	8	no	no	50 mg/day range, 40-80	2-38 months	5 pts were pain-free; 3 others had partial relief
Goldberg et al (83)	12	no	no	82 mg/day range, 60-140	2-17 months	11 of 12 had immediate relief; 7 had long-term relief
Antman et al (84)	127	no	no	64 mg/day range, 40-160	3 days-45 months	63% had total relief of pain; 87% had 50% fall in pain frequency
Bertrand et al (85)	13	no	no	32 mg/day range, 30-40	3-29 months	11 of 13 had total relief
Ginsburg et al (86)	12	yes	yes	82 mg/day	12 weeks	Nifedipine & isosorbide better than placebo; nifed better tolerated
Hill et al (87)	10	yes	yes	65 mg/day range, 40-120	12 weeks	Nifedipine & isosorbide better than placebo
Schick et al (88)	28	yes	yes	unknown	6 weeks	Nifedipine better than placebo

Abbreviations: Pts = patients.

TABLE 12

THE USE OF DILTIAZEM IN THE THERAPY OF PRINZMETAL'S VARIANT ANGINA

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Oral Drug	Length of Observation	Response
Rosenthal et al (90)	13	yes	yes	120 & 240 mg/day	10 weeks	Response especially good on 240 mg/day
Pepine et al (89)	12	yes	yes	120 & 240 mg/day	10 weeks	Diltiazem better than placebo, especially 240 mg/day
Schroeder et al (92)	36	no	no	240-360 mg/day	6-28½ months mean, 17½	Anginal frequency fell from 21½ to 1.3/week
Feldman et al (93)	12	no	no	240 mg/day	8-23 months mean, 16	5 pts totally pain-free; 2 others responded well; 2 benefited modestly
Schroeder et al (91)	48	yes	yes	120 & 240 mg/day	10 weeks	Treatment with 240/day reduced pain by 43-68%

Abbreviations: Pts = patients.

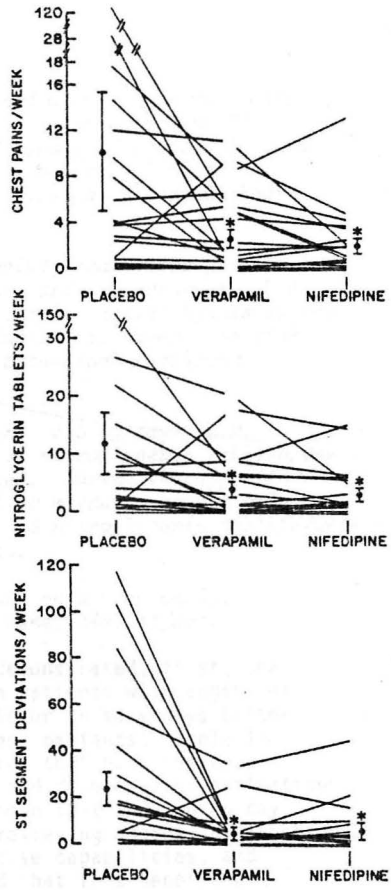


*Figure 14: Number of angina episodes per week (top panel), nitroglycerin tablets consumed per week (middle panel), and transient ST segment deviations by 2-channel ambulatory electrocardiographic monitoring (lower panel) during placebo (left), verapamil (middle), and nifedipine (right) in 23 patients with variant angina pectoris. Each line represents the data from 1 patient, and the means ± SEMs are shown for each treatment period. In comparison to placebo, both verapamil and nifedipine reduced the frequency of all 3 variables, and there was no demonstrable difference between the 2 drugs. * $p < 0.05$ in comparison to placebo. From reference # 80.*

In summary, properly designed randomized, double-blind, and crossover studies have demonstrated that oral verapamil and diltiazem are efficacious in patients with Prinzmetal's variant angina. Numerous uncontrolled observations, as well as a handful of poorly designed blinded trials, have shown that nifedipine is also an effective therapeutic agent in those with vasospastic angina. For the individual patient, the choice of a calcium antagonist will be influenced by adverse effects and personal preference.

B. Stable (Exertional) Angina *L.M. is a 55 year old white man who presented to the Veterans Administration Hospital in 1973 with severe angina of effort. Cardiac catheterization revealed severe 3-vessel coronary artery disease, and coronary artery bypass surgery was performed. Grafts were placed to the left anterior descending and right coronary arteries, but the circumflex coronary artery, even though severely diseased, was not graftable because of its size.*

In 1977, the patient began once again to have angina. From

1977 to 1981, his angina gradually worsened despite maximal medical therapy. Finally, in August, 1981, he was admitted to the VAH for repeat catheterization. Despite 320 mg/day of propranolol and 150 mg/day of isosorbide dinitrate, he was severely limited and had a clearly positive exercise tolerance test at a maximum heart rate of 100/minute.

Cardiac catheterization revealed occluded saphenous grafts to his left anterior descending and right coronary arteries. His left ventricular ejection fraction was normal. Repeat bypass surgery was recommended, but the patient was reluctant to accept its risk. Therefore, he was referred for combined beta-blocker-calcium antagonist therapy.

During therapy with propranolol alone (320 mg/day), L.M. averaged 12 episodes/week of angina and 15 nitroglycerin tablets/week. He was able to exercise for only 4 minutes. During therapy with propranolol (320 mg/day) and verapamil (480 mg/day), he had only 5 episodes/week of angina and took only 5.5 nitroglycerin tablets/week. His exercise time increased to 8½ minutes.

Subsequently, L.M. has been continued on a propranolol-verapamil combination, with a sustained beneficial effect.

Studies both here and abroad have demonstrated, first, that oral verapamil is superior to placebo in patients with angina of effort and, second, that it is comparable or in some ways better than the beta-adrenergic blockers in these patients. Table 13 (page 40) summarizes the available studies that have compared verapamil to placebo. All 4 randomized and double-blind evaluations (95-98), totalling 111 patients, have shown that 240-360 mg/day of verapamil is superior to placebo in relieving angina, diminishing nitroglycerin usage, and improving exercise capabilities, and Subramanian et al (99) have demonstrated that this beneficial response is sustained for at least 1 year. In Table 14 (page 41) are listed the 6 randomized and double-blind comparisons of verapamil and one of several beta-adrenergic blockers-- propranolol (100-103), practolol (104), or metoprolol (105). In these comparisons, totalling 119 patients, verapamil, 320-480 mg/day, was consistently similar or superior to the beta-blockers administered in reasonable antianginal dosages (Figures 15-18). Thus, numerous well-designed studies have demonstrated oral verapamil's efficacy as a single agent in patients with angina of effort.

Nifedipine, administered in a dose of 30-60 mg/day, is more effective than placebo in the alleviation of angina and the need for sublingual nitroglycerin (Figure 19). In addition, it improves exercise capacity (Figure 20) at the same time that it diminishes the magnitude of the electrocardiographic response to exertion.

TABLE 13

THE USE OF VERAPAMIL IN THE THERAPY OF ANGINA OF EFFORT: COMPARISONS WITH PLACEBO

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Oral Drug	Duration of Study	RESULTS
Andreasen et al (95)	47	yes	yes	240 mg/day (tid)	8 weeks	Anginal episodes, NTG usage fell during Rx with verapamil; exercise time rose 20%.
Subramanian et al (96)	28	yes	yes	360 mg/day (tid)	8 weeks	Exercise time 6.6 mins on placebo, 11.2 mins on verapamil. On placebo, all 28 had angina with exercise; on verapamil, only 8 had pain.
Subramanian et al (99)	28	no	no	360 mg/day	1 year	The above improvement was maintained during open-label Rx for 1 yr
Pine et al (97)	24	yes	yes	240, 360, 480 mg/day	12 weeks	On verapamil, angina & NTG usage fell, exercise time rose.
Tan et al (98)	12	yes	yes	320 mg/day	4 weeks	Verapamil increased anginal threshold & exercise capacity.

Abbreviations: Pts = patients; NTG = nitroglycerin; Rx = therapy.

TABLE 14

THE USE OF VERAPAMIL IN THE THERAPY OF ANGINA OF EFFORT: COMPARISONS WITH BETA-BLOCKERS

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Drugs	Duration of Study	Results
Sandler et al (100)	16	yes	yes	120 & 360 mg/d verapamil; 300 mg/d propranolol	5 months	Higher dose verapamil caused an improvement in angina, NTG usage, & exercise tolerance.
Livesley et al (101)	32	yes	yes	240 & 360 mg/d verapamil; 300 mg/d propranolol	4½ months	Higher dose verapamil & propranolol similar to one another, better than placebo
Fagher et al (104)	13	yes	yes	240 mg/d verapamil; 300 mg/d practolol	3½ months	Verapamil better than placebo & practolol
Johnson et al (102)	18	yes	yes	320 & 480 mg/d verapamil; 160 & 320 mg/d propranolol	8 weeks	High-dose verapamil equal to high-dose propranolol
Frishman et al (103)	20	yes	yes	240, 360, 480 mg/d verapamil; 60, 160, 320 mg/d propranolol	2½ months	High-dose verapamil better than high-dose propranolol
Arnman & Ryden (105)	20	yes	yes	360 mg/d verapamil; 200 mg/d metoprolol	14 weeks	Verapamil and metoprolol similar to one another, better than placebo

Abrreviations: Pts = patients

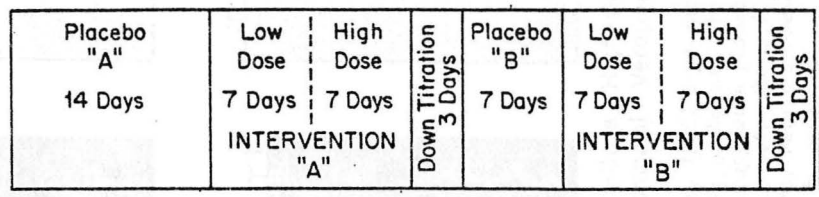


Figure 15: A schematic outline of the study by Johnson et al (reference # 102). Following a 14 day placebo period, each patient was randomly and blindly assigned to propranolol or verapamil for 14 days (7 days low dose, 7 days high dose). Then, after an intervening placebo period, the drug that was not administered during Intervention A was given for 14 days.

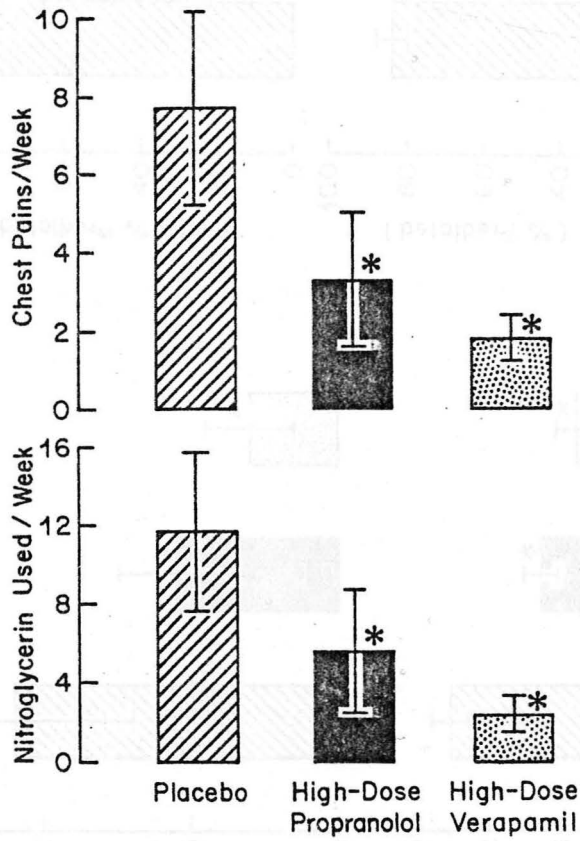


Figure 16 (left): The average number of chest pains/week (top panel) and nitroglycerin used/week (bottom panel) in 18 patients with angina of effort during placebo, high dose propranolol (320 mg/day), and high dose verapamil (480 mg/day). Means ± SD are shown. In comparison to placebo, both propranolol and verapamil reduced the frequency of both variables. From reference # 102.

$p < 0.05$ *compared to placebo*

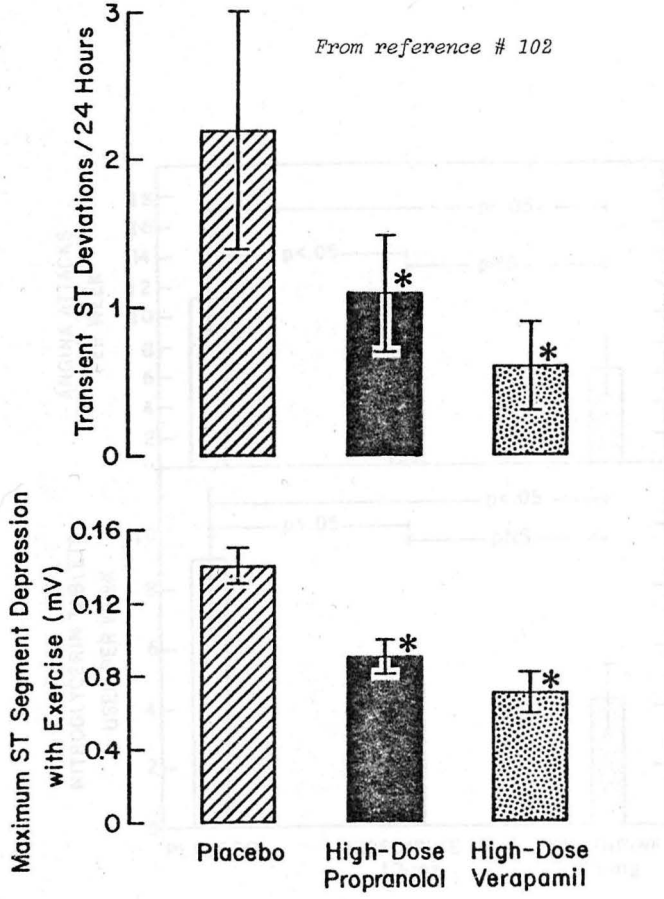


*Figure 17: The number of transient ST segment deviations/24 hours by Holter monitoring (top) and the maximum ST segment depression with exercise, in mV (bottom) during placebo, high-dose propranolol (320 mg/day), and high-dose verapamil (480 mg/day). Means ± SD are shown. Both propranolol and verapamil reduced the magnitude of both variables. * $p < 0.05$.*

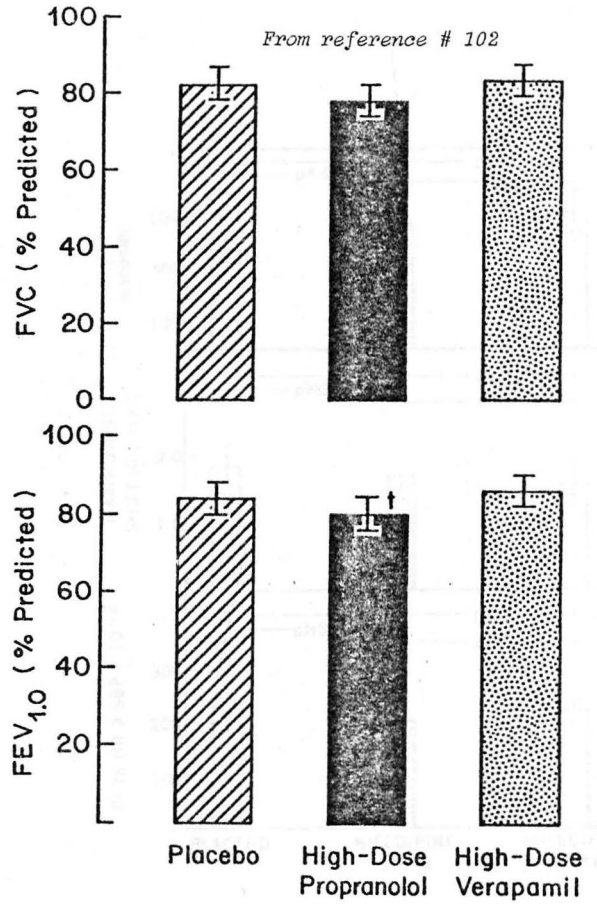


Figure 18: Forced vital capacity (FVC)(top) and forced expired volume in 1 second ($FEV_{1.0}$)(bottom), both expressed as a % of predicted, during therapy with placebo, high-dose propranolol, and high-dose verapamil. Means ± SD are shown. In comparison to placebo, $FEV_{1.0}$ worsened during propranolol but was unaffected by verapamil.

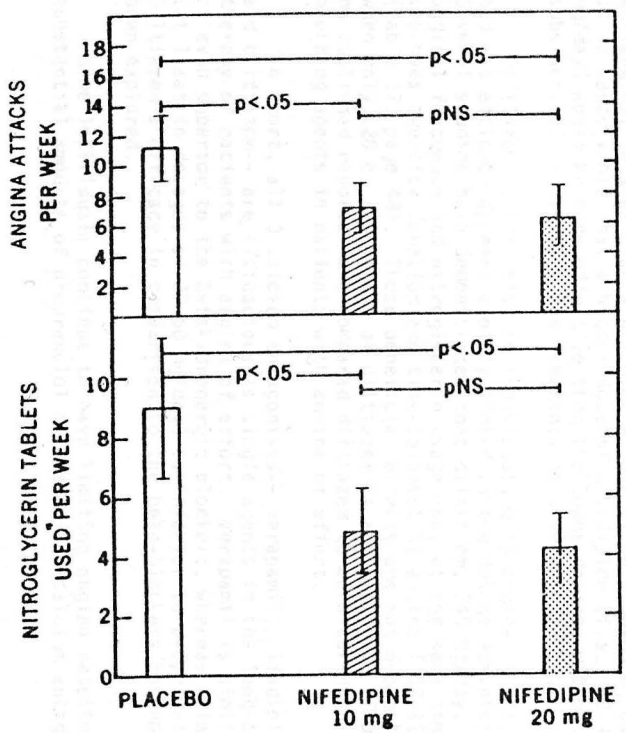


Figure 19: Anginal attacks/week (top) and nitroglycerin tablets used/week (bottom) during therapy with placebo, nifedipine (10 mg 3 times daily), and nifedipine (20 mg 3 times daily) in 10 patients with angina of effort. In comparison to placebo, both doses of nifedipine reduced both variables. From reference # 114.

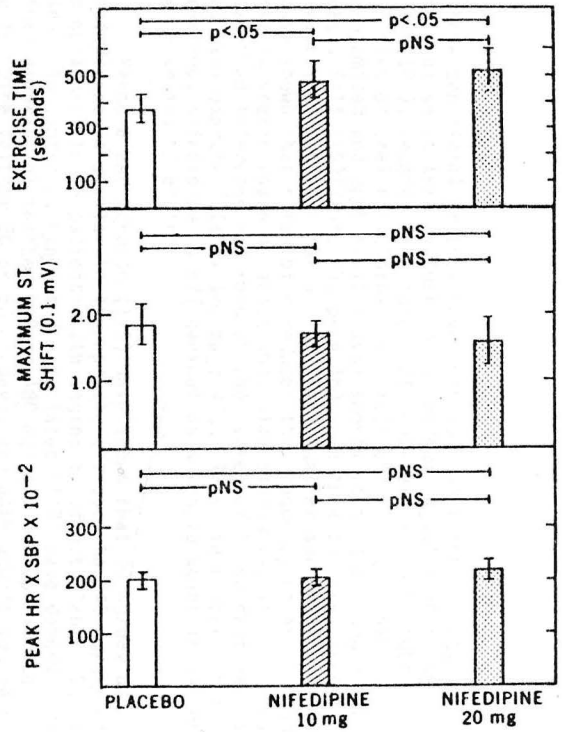


Figure 20: Exercise time (in seconds)(top), maximum ST segment shift (middle), and double product at peak exercise (bottom) during placebo, nifedipine (10 mg 3 times/day), and nifedipine (20 mg 3 times/day) in 10 patients with angina of effort. In comparison to placebo, both doses of nifedipine increased exercise time. From reference # 114.

These beneficial effects have been substantiated, first, in several short-term evaluations using sublingual nifedipine (106,107); second, in a number of long-term but unblinded studies of oral nifedipine (108-110); and third, in numerous randomized and double-blind assessments lasting as long as 20 weeks (111-115)(Table 15, page 46). In this country, recent reports by Moskowitz et al (114) and Mueller and Chahine (115) have shown that nifedipine reduces the frequency of angina and nitroglycerin usage by about 50%; simultaneously, it increases exercise tolerance and reduces the degree of ST segment depression at peak exercise (Table 16, page 47). Thus, in comparison to placebo, nifedipine is efficacious as a single agent in patients with angina of effort.

Kenmure and Scruton (116) have shown that 30 mg/day of nifedipine is similar in therapeutic efficacy to 240 mg/day of propranolol in 18 patients with angina of effort (Table 15, page 46). In contrast, Lynch and associates (117) have demonstrated that propranolol (either 240 or 480 mg/day) is superior to nifedipine (either 30 or 60 mg/day), and both agents (at both dosages) are better than placebo. In these studies, the apparent superiority of propranolol to nifedipine may be related to the dosages of each drug that were administered. A propranolol dosage of 240-480 mg/day is more in keeping with commonly employed antianginal dosages than a nifedipine dose of only 30-60 mg/day. It is conceivable that a higher dose of nifedipine (i.e., 80-90 mg/day) would be more effective than the lower dosages without substantially increasing the frequency of adverse effects.

Diltiazem is effective in individuals with angina of effort, and its efficacy appears closely linked to the dosage administered. Several studies have demonstrated that diltiazem, 240 mg/day, reduces anginal frequency and nitroglycerin usage and, at the same time, improves exercise duration and time-to-onset of angina (118-121) (Table 17, page 48). These beneficial effects are not demonstrable when only 120 or 180 mg/day of diltiazem is administered. Thusfar, no published reports have compared diltiazem to beta-adrenergic blocking agents in patients with angina of effort.

In short, all 3 calcium antagonists-- verapamil, nifedipine, and diltiazem-- are efficacious as single agents in the long-term therapy of patients with angina of effort. Verapamil is similar or even superior to the beta-adrenergic blockers, whereas nifedipine (at least in dosages of 30-60 mg/day) is inferior to propranolol. Diltiazem's efficacy in comparison to the beta-blockers has not been explored.

Some individuals continue to have limiting angina despite substantial amounts of propranolol or one of the calcium antagonists

TABLE 15

THE USE OF NIFEDIPINE IN THE THERAPY OF ANGINA OF EFFORT: COMPARISONS WITH PLACEBO AND PROPRANOLOL

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Drug	Duration of Study	Results
NIFEDIPINE-PLACEBO COMPARISONS						
Folle et al (111)	19	yes	yes	30 mg/d	18 weeks	Exercise ST depression fell with nifedipine
Gomez et al (106)	24	yes	yes	20 mg SL	3 days	SL nifedipine ↑ exercise tolerance in 67% of pts
Bidoggia & Machado (112)	28	yes	yes	40 mg/d (qid)	16 weeks	Angina, NTG usage fell markedly with nifedipine
Stein (107)	72	yes	yes	10, 20 mg SL	1 day	SL nifedipine reduced ST depression with exercise
Castilho et al (108)	12	no	no	30 mg/d	6 months	67% had "very good" or "good" response to nifedipine
Castro et al (109)	11	no	no	30 mg/d	6 months	Angina fell, exercise improved with nifedipine
Alvarado & Pineros (110)	24	no	no	30 mg/d	6 months	Angina fell with nifedipine
Menna et al (113)	33	yes	yes	40 mg/d	16 weeks	Angina fell with nifedipine
Moskowitz et al (114)	10	yes	yes	30, 60 mg/d	20 weeks	Angina fell, exercise time rose with nifedipine
Mueller & Chahine (115)	66	yes	yes	30, 60 mg/d	10-20 weeks	Angina fell, exercise time rose with nifedipine
NIFEDIPINE-PROPRANOLOL COMPARISONS						
Kenmure & Scruton (116)	18	yes	yes	30 mg/d nifedipine; 240 mg/d propr.	8 weeks	Nifedipine similar to propranolol
Lynch et al (117)	16	yes	yes	30, 60 mg/d nifedipine; 240, 480 mg/d propranolol	16 weeks	Propranolol better than nifedipine

Abbreviations: Pts = patients; SL = sublingual; NTG = nitroglycerin

and, therefore, may require additional medical therapy. Recent studies have demonstrated that a beta-adrenergic blocking agent and a calcium antagonist *in combination* are superior to either agent alone in relieving angina and improving exercise capacity. In a single blind assessment of 11 hospitalized patients with

TABLE 16

*EFFECTS OF NIFEDIPINE IN PATIENTS WITH ANGINA OF EFFORT**

VARIABLE	Nifedipine	Placebo	p
Angina/week	3.7	5.1	0.007
Nitroglycerin/week	4.8	5.5	0.08
Exercise duration (secs)	493	437	0.002
Time-to-angina (secs)	349	312	0.02
Maximal ST depression (mm)	1.40	1.58	0.03

* Modified from reference # 115. Average values are obtained from 66 patients.

severe angina of effort, Leon et al (125) showed that a propranolol-verapamil combination is more effective than either agent alone in increasing exercise time and in either delaying or ablating the occurrence of exercise-induced angina. At this institution, Winniford and associates (126) have compared propranolol alone to a propranolol-verapamil combination in 13 ambulatory outpatients with continuing severe angina despite substantial dosages of propranolol. This randomized, double blind comparison (Figure 21) has shown that a propranolol-verapamil combination (295 mg/day of propranolol, 431 mg/day of verapamil) is superior to propranolol alone (a)in the alleviation of angina and the need for sublingual nitroglycerin (Figure 22) and (b)in an improvement in exercise capacity and exercise-induced angina (Figure 23).

The combination of propranolol and verapamil may produce serious adverse effects, and anecdotal reports have described cardiovascular catastrophies when intravenous verapamil was administered to patients already receiving propranolol (127-130). Since both agents exert negative inotropic and chronotropic effects, their combined usage may induce left ventricular failure, marked

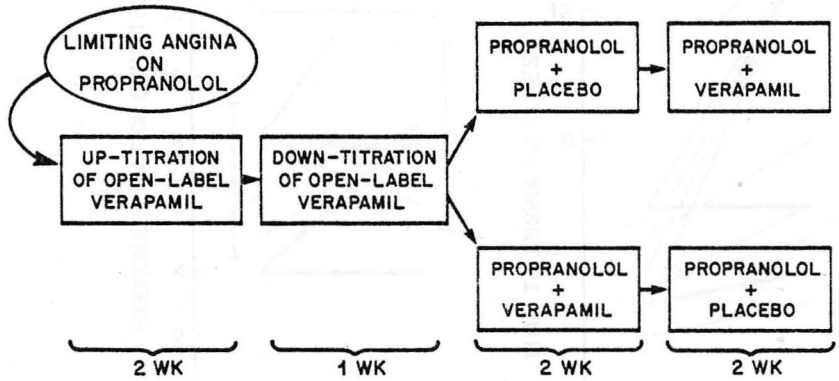
TABLE 17

THE USE OF DILTIAZEM IN THE THERAPY OF ANGINA OF EFFORT: COMPARISONS WITH PLACEBO

AUTHORS	# Pts	Randomized?	Double-Blind?	Dose of Drug	Duration of Study	Results
Pool et al (118)	15	yes	yes	120, 180, 240 mg/d	7 weeks	240 mg/d most effective in increasing exercise time
Koiwaya et al (119)	9	yes	yes	90 mg (1 dose)	3 days	Exercise tolerance ↑ by diltiazem
Hossack et al (120)	10	yes	yes	120, 180, 240 mg/d	7 weeks	240 mg/d most effective in increasing exercise time
Strauss et al (121)	63	yes	yes	120, 180, 240 mg/d	10 weeks	Diltiazem reduced angina & NTG usage
Hossack et al (122)	57	yes	yes	120, 180, 240 mg/d	7 weeks	Exercise time ↑ with diltiazem, esp at 240/day
Pool & Seagren (123)	8	no	no	240 mg/d	4 months	Time-to-angina with exercise rose with diltiazem
Wagniart et al (124)	12	yes	yes	120 mg (1 dose)	1 day	Diltiazem reduced exercise-induced ischemia

Abbreviations: Pts = patients; NTG = nitroglycerin.

Figure 21: A schematic outline of the study of Winniford et al (reference # 126). All patients had limiting angina on propranolol. After careful titration of open-label verapamil, the patient was randomly and blindly assigned to (a)propranolol + placebo or (b)propranolol + verapamil. After 2 weeks, the patient was switched to the other medication.



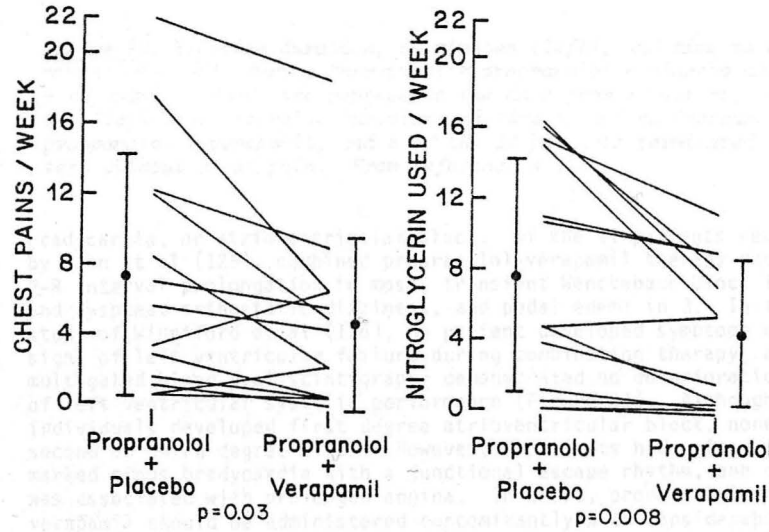


Figure 22: Chest pains/week (left) and nitroglycerin used/week (right) during propranolol + placebo and propranolol + verapamil. Each line represents the data from 1 patient, and means ± SD are displayed. In comparison to propranolol + placebo, propranolol + verapamil reduced both variables. From reference # 126.

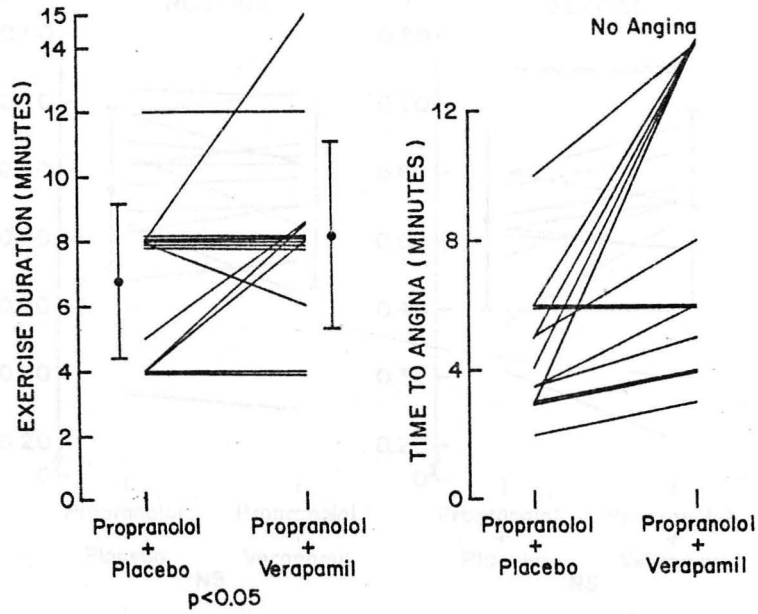


Figure 23: Exercise duration, in minutes (left), and time to angina, in minutes (right), during therapy with propranolol + placebo and propranolol + verapamil. Each line represents the data from 1 patient, and means ± SD are displayed. Exercise duration and time to angina increased during propranolol + verapamil, and 5 of the 13 patients terminated the exercise test without chest pain. From reference # 126.

bradycardia, or atrioventricular block. Of the 11 patients reported by Leon et al (125), combined propranolol-verapamil therapy caused P-R interval prolongation in most, transient Wenckebach block in 1, and dyspnea, orthostatic dizziness, and pedal edema in 3. In the study of Winniford et al (126), no patient developed symptoms or signs of left ventricular failure during combination therapy, and multigated blood pool scintigraphy demonstrated no deterioration of left ventricular systolic performance (Figure 24). Although 4 individuals developed first degree atrioventricular block, none had second or third degree block. However, 2 patients had episodes of marked sinus bradycardia with a junctional escape rhythm, one of which was associated with prolonged angina. In short, propranolol and verapamil should be administered concomitantly with considerable caution.

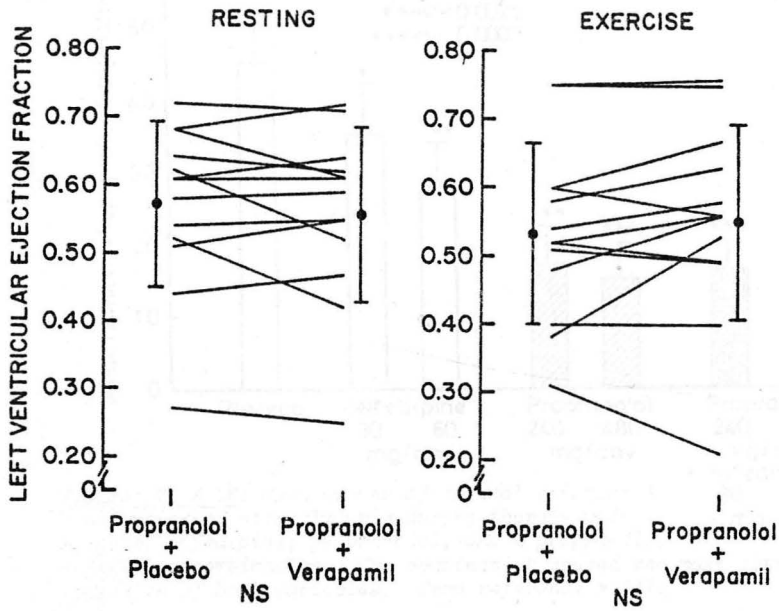
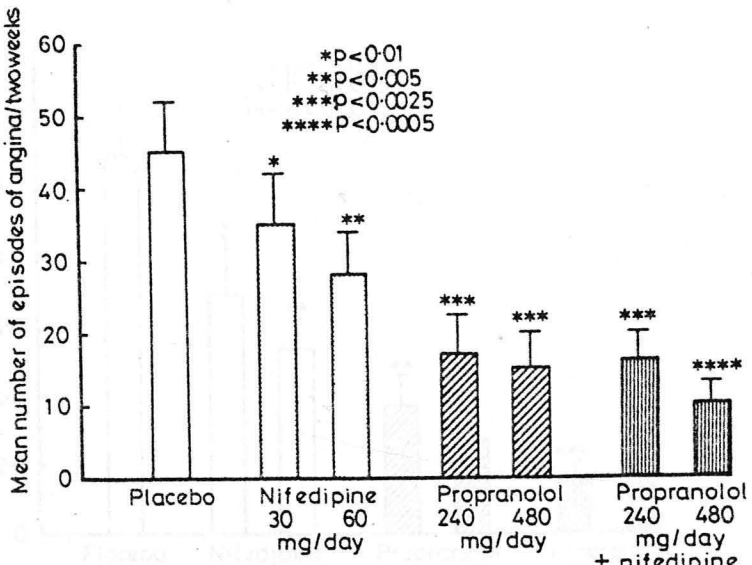
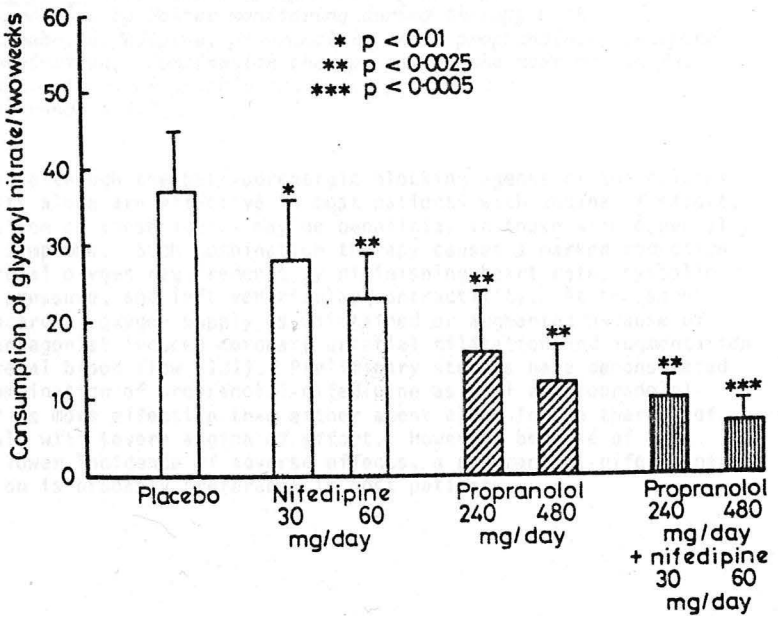


Figure 24: Left ventricular ejection fraction at rest (left) and at peak exercise (right) during therapy with propranolol + placebo and propranolol + verapamil. Each line represents the data from 1 patient, and means ± SD are displayed. A propranolol-verapamil combination caused no change in resting or peak exercise left ventricular ejection fraction. From reference # 126.

In contrast to a propranolol-verapamil combination, the administration of propranolol with nifedipine should not produce potent additive negative inotropic or chronotropic effects. Indeed, preliminary studies have indicated that this combination is efficacious and safe in patients with severe limiting angina of effort. Lynch et al (117) treated 16 patients with severe angina with propranolol (240-480 mg/day), nifedipine (30-60 mg/day), and their combination in a double-blind, placebo-controlled trial. In comparison to placebo, each agent used alone reduced anginal frequency, nitroglycerin consumption, and the amount of ST segment deviation during exercise. The combination of propranolol and nifedipine caused a significantly greater reduction in these variables than either agent alone (Figures 25-27). No serious adverse effects occurred with combination propranolol-nifedipine therapy.





Figures 25 & 26: Mean number of anginal episodes & consumption of nitroglycerin during therapy with placebo, nifedipine, propranolol, and a propranolol-nifedipine combination. The combination caused the most striking reduction of both variables. From reference # 117.

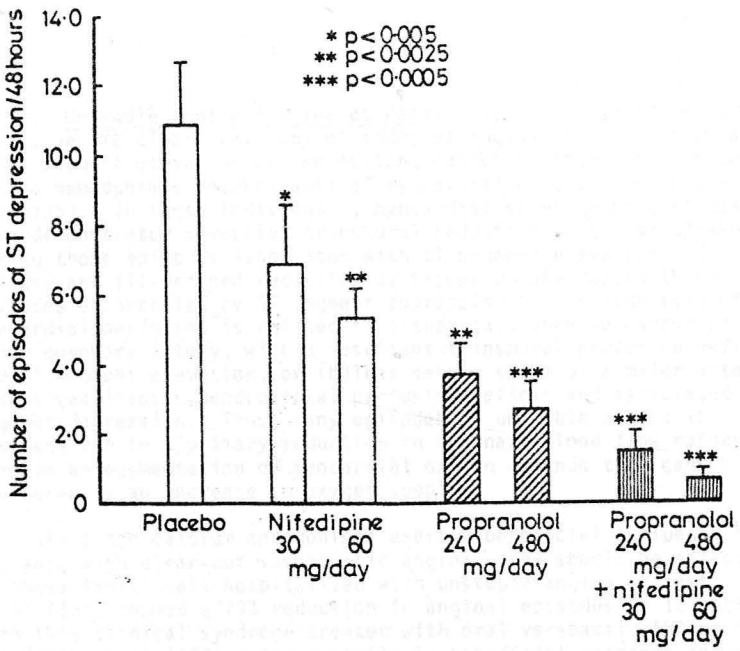


Figure 27: The number of episodes of ST segment depression by Holter monitoring during therapy with placebo, nifedipine, propranolol, and a propranolol-nifedipine combination. Combination therapy caused the most marked fall in electrocardiographic evidence of disease activity. From reference # 117.

Thus, although the beta-adrenergic blocking agents or the calcium antagonists alone are effective in most patients with angina of effort, a combination of these agents may be beneficial in those with especially limiting symptoms. Such combination therapy causes a marked reduction in myocardial oxygen requirements by diminishing heart rate, systolic arterial pressure, and left ventricular contractility. At the same time, myocardial oxygen supply is maintained or augmented because of calcium antagonist-induced coronary arterial dilatation and augmentation of collateral blood flow (131). Preliminary studies have demonstrated that a combination of propranolol-nifedipine as well as propranolol-verapamil is more effective than either agent alone in the therapy of individuals with severe angina of effort. However, because of its apparent lower incidence of adverse effects, a propranolol-nifedipine combination is probably preferable in most patients.

C. Unstable Angina (Angina at Rest) Over the past 10 years, it has become clear that many episodes of angina at rest, accompanied by ST segment elevation or depression, cannot be attributed to an increase in the hemodynamic determinants of myocardial oxygen consumption (132-135). In these individuals, myocardial scintigraphic studies have demonstrated a massive transmural reduction of tracer uptake during those episodes associated with ST segment elevation (136) or a diffuse and ill-defined reduction of tracer uptake during those episodes accompanied by ST segment depression. This reduction of myocardial perfusion is related to either (a)severe vasospasm of a major coronary artery, with a resultant transmural perfusion deficit and ST segment elevation; or (b)less severe spasm of a major artery, with a resultant subendocardial perfusion deficit and associated ST segment depression. Thus, many episodes of unstable angina at rest are due to a primary reduction in coronary blood flow rather than to an augmentation of myocardial oxygen demands that cannot be countered by an increase in oxygen supply.

Since the calcium antagonists exert a beneficial influence in patients with clear-cut vasospastic angina, they should be efficacious in those individuals hospitalized with unstable angina at rest. Parodi et al (137) showed a 79% reduction in anginal episodes in 12 patients with this clinical syndrome treated with oral verapamil, 480 mg/day, and Mehta et al (138) noted a similarly beneficial response to oral verapamil. At our institution, Mauritson and associates (139) demonstrated a reduction in anginal episodes and electrocardiographic evidence of ischemia in 11 patients with unstable angina treated with verapamil; however, 5 of the 11 failed to respond completely despite a large dose (480 mg/day) of the drug. Thus, in patients with unstable angina at rest, verapamil exerts an initial beneficial effect, but in some individuals this salutary influence is not sustained (Table 18, page 55).

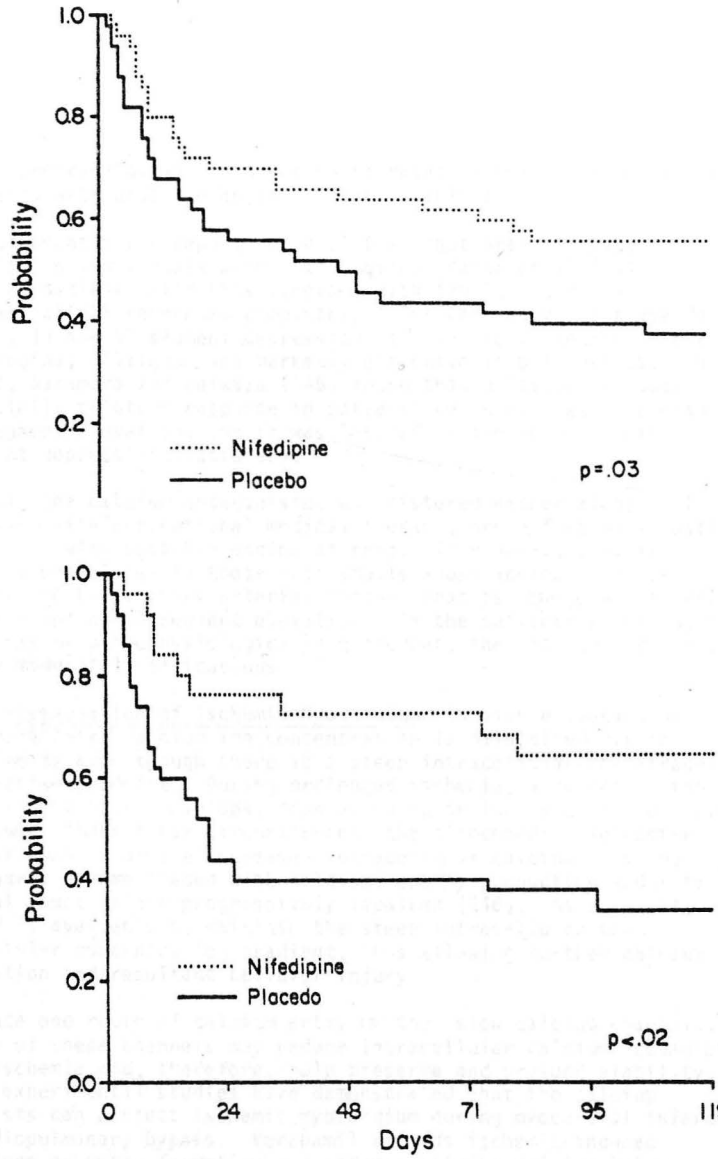
Several uncontrolled studies (140-142) have shown that nifedipine is beneficial in many patients who continue to have rest angina despite maximal tolerated dosages of beta-blockers and nitrates. Both Moses et al (141) and Hugenholtz et al (142) demonstrated that nifedipine, 30-120 mg/day, induced a substantial diminution of anginal episodes in about 85% of patients with continuing rest angina. Recently, Gerstenblith et al (143) assessed the efficacy of adding nifedipine (40-80 mg/day) to the conventional treatment of unstable angina in a prospective, randomized, double-blind, and placebo-controlled trial of 138 patients. Failure of medical treatment (defined as sudden death, myocardial infarction, or coronary artery bypass surgery within 4 months) occurred in 43 of the 70 patients given placebo and in only 30 of the 68 given nifedipine ($p = 0.03$)(Figure 28). The beneficial effects of nifedipine were particularly marked in those patients whose angina was accompanied by electrocardiographic ST segment elevation (Figure 29). Thus, the addition of nifedipine to conventional

TABLE 18

THE USE OF CALCIUM ANTAGONISTS IN THE THERAPY OF UNSTABLE ANGINA PECTORIS

AUTHORS	# Pts	Randomized?	Double-Blind?	Dosage of Drug	Results
VERAPAMIL					
Parodi et al (137)	12	yes	yes	480 mg/day	Angina decreased by 79% with verapamil
Mehta et al (138)	15	yes	yes	320-480 mg/day	12 of 13 pts receiving verapamil had a good response
Mauritson et al (139)	11	yes	yes	320-480 mg/day	5 of 11 did not achieve a complete response on verapamil
NIFEDIPINE					
Previtali et al (140)	14	no	no	50-100 mg/day	Nifedipine reduced angina from 18.7/day to 1.1/day
Moses et al (141)	19	no	no	30-120 mg/day	Nifedipine abolished angina in 14 and diminished it in 2.
Hugenholtz et al (142)	31	no	no	60 mg/day	27 responded favorably to nifedipine
Gerstenblith et al (143)	138	yes	yes	40-80 mg/day	Nifedipine superior to placebo
DILTIAZEM					
Yasue et al (144)	26	no	no	120-180 mg/day	Markedly effective in all 26 patients
Nakamura & Koiwaya (145)	8	no	no	120 mg/day	Excellent response in pts with ST elevation; less effective in those with ST depression

Abbreviations: Pts = patients.



Figures 28 and 29: The probability of failure of medical treatment over a 119 day follow-up period in patients with unstable angina treated with placebo or nifedipine. The top panel depicts the data from all patients, whereas the bottom panel shows that from only those with ST segment elevation during chest pain. Those patients given placebo had a greater probability of failing medical therapy. From reference # 143.

therapy (propranolol and long-acting nitrates) appears very effective in patients with unstable angina at rest (Table 18).

Two uncontrolled reports have claimed that oral diltiazem is beneficial in individuals with rest angina. Yasue et al (144) treated 26 patients with this syndrome with 120-180 mg/day of diltiazem; all 26 responded completely. Interestingly, of these 26 patients, 13 had ST segment depression, and 13 had ST segment elevation during angina; diltiazem was markedly effective in both groups. In contrast, Nakamura and Koiwaya (145) found that diltiazem produced an especially salutary response in patients whose pain was accompanied by ST segment elevation, and it was less effective in those with ST segment depression (Table 18).

Thus, the calcium antagonists, administered either alone or in combination with conventional medical therapy, are effective in patients hospitalized with unstable angina at rest. In general, they are especially beneficial in those individuals whose angina is almost certainly due to coronary arterial spasm-- that is, those whose chest pain is accompanied by ST segment elevation. In the patients whose angina at rest may be pathophysiologically different, the calcium antagonists are only moderately efficacious.

D. Preservation of Ischemic Myocardium In viable myocardium, the intracellular calcium ion concentration is maintained within narrow limits even though there is a steep intracellular-to-extracellular concentration gradient. During prolonged ischemia, a defect in the sarcolemmal membrane develops, thus allowing an increase in the influx of calcium. Under these circumstances, the mitochondria sequester excessive amounts of the increased intracellular calcium. As the mitochondria become loaded with calcium, energy production and mitochondrial function are progressively impaired (146). As a result, less ATP is available to maintain the steep intracellular-to-extracellular concentration gradient, thus allowing further calcium accumulation and resultant cellular injury.

Since one route of calcium entry is the "slow calcium channels," blockade of these channels may reduce intracellular calcium accumulation during ischemia and, therefore, help preserve and prolong viability. Several experimental studies have demonstrated that the calcium antagonists can protect ischemic myocardium during myocardial infarction and cardiopulmonary bypass. Verapamil retards ischemic-induced contracture or rigor formation and reduces mitochondrial calcium accumulation (146-148). In dogs, it has been reported to diminish contractility in ischemic myocardium, thus decreasing ischemic injury (149). In several different experimental settings, verapamil has been shown to reduce myocardial infarct size when it is administered before

or after coronary artery occlusion (150-152). It protects myocardial cell function and reduces structural damage when it is administered prior to the global ischemia and reperfusion associated with cardiopulmonary bypass (153-155). In preliminary studies in man, intravenous verapamil has been shown to diminish the magnitude of ST segment elevation in patients with acute myocardial infarction (156), and other studies have demonstrated that oral verapamil (360 mg/day) may reduce the incidence of reinfarction and early death (157).

In the experimental animal, nifedipine has been shown to increase collateral perfusion of ischemic myocardium, thus preserving ventricular function and reducing myocardial infarct size (158-160). Unlike verapamil, nifedipine may improve contraction in certain portions of ischemic myocardium. During cardiopulmonary bypass, it reduces postischemic myocardial stiffness and mitochondrial calcium accumulation and decreases structural damage produced by global ischemia (159-161). In cardioplegic doses, nifedipine results in preservation of myocardial structure and function similar to that obtained with potassium cardioplegia (154,159,160). Its use in patients with acute myocardial infarction has not been reported.

When administered 10 minutes after coronary artery ligation in dogs, diltiazem decreases the decline of tissue ATP, reduces the accumulation of lactic acid and free fatty acids in ischemic areas, and improves contractility (162). Furthermore, pretreatment with diltiazem preserves mitochondrial and ventricular function during subsequent reperfusion (163). Similar to nifedipine, diltiazem's effect has not been reported in patients with acute myocardial infarction.

Thus, studies in experimental animals and, to a limited extent, in man have shown that the calcium channel blockers may be useful in preserving myocardial structure and function during ischemia. Further studies are warranted to evaluate the ability of these agents to limit myocardial infarct size in man and to act as protectors of myocardial integrity during cardiopulmonary bypass.

VIII. THERAPY OF NON-CARDIOVASCULAR DISEASE ENTITIES

A. Bronchospastic Pulmonary Disease Since both the contraction of bronchial smooth muscle (164) and the secretion of mast cells (165) are calcium dependent, the calcium antagonists may be beneficial in patients with asthma. Indeed, several recent reports have demonstrated that verapamil and nifedipine are effective in preventing exercise-

induced asthma. Patel (166) studied 10 patients with this disease entity during treadmill exercise following inhaled saline, sodium cromoglycate, or verapamil (estimated dose, 3 mg). None of the 3 agents altered baseline (resting) pulmonary function. However, during exercise, $FEV_{1.0}$ fell by 45% after saline inhalation, 18% after sodium cromoglycate, and 17% after verapamil. Similar findings have been reported by Barnes et al (167) and Cerrina et al (168) following sublingual nifedipine (20 mg). Again, this calcium antagonist did not alter basal bronchial tone but did alleviate or prevent exercise-induced bronchospasm. Further studies are needed to define completely the role of calcium antagonists in patients with bronchospastic pulmonary disease.

B. Dysmenorrhea Primary dysmenorrhea occurs because of myometrial hypercontractility, which probably causes uterine ischemia and pain. The calcium antagonists inhibit both spontaneous and induced myometrial contractile activity and, therefore, may be salutary in patients with dysmenorrhea. Nifedipine, 20-40 mg orally, was administered to 10 women with severe dysmenorrhea. Within 10-30 minutes, it effectively reduced myometrial activity and relieved dysmenorrheic pain (169). Similar results recently have been reported for nifedipine (30 mg) administered concomitantly with diflunisal, a cyclooxygenase inhibitor (170).

C. Mania A recent case report in the American Journal of Psychiatry (171) describes the beneficial effect of verapamil in a manic patient. A 53 year old woman with 4 previous hospitalizations for mania over a 23 year period could not receive lithium, because it exacerbated an essential tremor. She was hospitalized 2 months after stopping all her medications. On admission, she had increased irritability, pressured speech, euphoria, hyperactivity, flight of ideas, and insomnia.

She was begun on blinded verapamil, 80 mg twice daily; by day 5, her mania had improved. During the second week of therapy, her hyperactivity and pressured speech decreased markedly. After 3 weeks of verapamil therapy, the patient was placed on placebo, and over several days her mania worsened.

Lithium, the accepted therapy of mania, exerts several actions similar to the calcium antagonists, including a decreased rate of spontaneous depolarization of the sinoatrial node and a diminished entry of calcium into neuromuscular cells. Since an excessive influx of calcium is thought to be responsible for hyperactivity of smooth muscle, cardiac, and neurosecretory cells, it is conceivable that agents that block calcium influx decrease excessive catecholamine production or release associated with an abnormal accumulation of intracellular calcium. Thus, the calcium antagonists may affect

central nervous system catecholamine turnover by inhibiting calcium movement from the extracellular to the intracellular compartment.

D. Prevention of Atherosclerosis Current evidence suggests that calcium may play a pathogenetic role in atherosclerosis. In rabbits fed a high cholesterol diet, anticalcifying and hypocalcemic agents, such as diphosphonates (172-175), thiophene compounds (176), and EDTA (177), have been shown to exert antiatherogenic effects without reducing diet-induced hypercholesterolemia. Henry and Bentley (178) have recently demonstrated a similar finding with nifedipine. In rabbits fed a high cholesterol diet, nifedipine did not alter the serum cholesterol concentration but substantially suppressed atherogenesis. This intriguing effect of a calcium antagonist is totally untested in man.

IX. ADVERSE EFFECTS AND DRUG INTERACTIONS

A. Verapamil The overall incidence of adverse effects following either intravenous or oral verapamil is reported by its manufacturers to be 9%, with severe reactions requiring discontinuation in about 1%. A review of the available literature, however, reveals that adverse effects occur more frequently, although most are mild and do not require a drastic change in the drug's administration. Following *intravenous* verapamil, a mild fall in systemic arterial pressure usually occurs (2,8,15)(Tables 1-3). On rare occasions, severe hypotension may ensue. In the patient with underlying conduction system disease or in whom a beta-adrenergic blocker has already been administered, an intravenous bolus of verapamil may cause severe bradycardia, heart block, or even asystole (127-130). Alternatively, in the patient with active congestive heart failure, intravenous verapamil may cause rapid hemodynamic deterioration (54).

Table 19 (page 61) details the adverse effects that have been reported during chronic therapy with *oral* verapamil. Although the overall incidence of adverse effects is 29%, constipation and asymptomatic first degree heart block comprise over half, and neither of these usually requires a change in verapamil administration. Of the remaining adverse effects, most are relatively mild and can be treated effectively with a slight reduction in verapamil dosage and/or the addition of another medication. For example, the pedal edema that sometimes accompanies verapamil's administration is not a manifestation of congestive heart failure and can usually be treated effectively with a mild diuretic.

During chronic therapy with oral verapamil, many patients have

TABLE 19

ADVERSE EFFECTS DURING LONG-TERM ORAL VERAPAMIL THERAPY

AUTHORS	# Pts	# Pts with Adverse Effects (%)	#(%) with Constipation	#(%) with 1° HB	Other Adverse Effects
Rinkenberger et al (9)	19	9 (47%)	3 (16%)	0	Pedal edema, ↓ BP
Mauritson et al (13)	11	6 (54%)	5 (45%)	0	Headache
Stern et al (22)	13	2 (15%)	0	0	Bradycardia, ?drug-induced hepatitis
Lewis et al (35)	23	2 (9%)	0	0	Dizziness
Pedersen (36)	5	2 (40%)	2 (40%)	0	-
Gould et al (37)	20	6 (30%)	4 (20%)	0	Burning gums, epigastric pain
Leary et al (39)	24	0	0	0	-
Leonetti et al (40)	12	1 (8%)	0	1 (8%)	-
Kinney et al (57)	16	2 (13%)	1 (6%)	0	Headache
Rosing et al (60)	19	3 (16%)	0	2 (11%)	Abdominal pain
Freeman et al (78)	7	4 (57%)	3 (43%)	0	Pedal edema
Winniford et al (80)	27	6 (22%)	4 (15%)	1 (4%)	Palpitations
Rosing et al (61)	78	35 (45%)	"frequent"	8 (10%)	See text
Tan et al (98)	12	4 (33%)	3 (25%)	1 (8%)	-
Subramanian et al (99)	28	1 (4%)	0	1 (4%)	-
Frishman et al (103)	20	2 (10%)	2 (10%)	0	-
Arnman et al (105)	20	18 (90%)	7 (35%)	0	Headache, insomnia, fatigue
Parodi et al (137)	12	4 (33%)	2 (17%)	0	Weakness, confusion
Mehta et al (138)	15	2 (13%)	0	2 (13%)	-
TOTALS	381	109 (29%)	36 (12%)	16 (4%)	

transient episodes of atrioventricular junctional rhythm, lasting seconds, minutes, or even hours (179). In the vast majority, this rhythm is asymptomatic, though it may lead to substantial hypotension and pulmonary congestion in patients with hypertrophic cardiomyopathy, a disease entity in which the atrial contribution to cardiac output (so-called "atrial kick") is especially important. This junctional rhythm is not a manifestation of verapamil toxicity and, therefore, should not force a dosage reduction or discontinuation of verapamil.

When verapamil is administered concomitantly with digoxin, it induces a distinct rise in the serum digoxin level (20,22,180). The mechanism by which this increase occurs is unclear, but Klein and associates (181) have demonstrated recently that verapamil decreases renal digoxin clearance in patients in whom the serum digoxin concentration rises. This occurs without a change in creatinine clearance. Since digoxin is eliminated in the kidney by both glomerular filtration and tubular secretion, the fact that verapamil decreases renal digoxin clearance without altering glomerular filtration (as suggested by the unchanged creatinine clearance) indicates that verapamil decreases tubular secretion of digoxin. Whatever the exact mechanism, the dose of digoxin may need readjustment in patients who are concomitantly receiving verapamil.

When verapamil and quinidine are administered concomitantly, orthostatic hypotension may occur, especially in patients with hypertrophic cardiomyopathy (182). This adverse effect probably results from a combination of quinidine's alpha-blocking influence and verapamil's peripheral vasodilating effect. In all probability, similar adverse reactions will occur when nifedipine or diltiazem are administered with quinidine.

B. Nifedipine Most of the adverse effects that occur with nifedipine administration result from its powerful dilatory influence on peripheral arteries-- headache, flushing, and orthostatic dizziness. Although the overall incidence of these side effects is about 40% (Table 20, page 63), few of them require nifedipine's discontinuation; rather, they are treated effectively by a slight reduction in the dosage administered. In our experience, only a minority of patients tolerate more than 100 mg/day of nifedipine, and the average nifedipine dosage in most studies is 65-85 mg/day (80,84,87), usually administered 4 times daily.

C. Diltiazem Investigators at the University of Florida and Stanford University have consistently stated that diltiazem's administration, even in dosages of 240-300 mg/day, is rarely associated with serious adverse effects, and a review of the available literature confirms their impression. Of the 8 studies available for review (Table 21, page 64), the overall incidence of adverse effects ranges from

TABLE 20

ADVERSE EFFECTS DURING LONG-TERM ORAL NIFEDIPINE THERAPY

AUTHORS	# Pts studied	# Pts with adverse effects	%	Nature of Adverse Effects
Guazzi et al (41)	26	22	85	Headache, palpitations, VPBs, flushing
Olivari et al (43)	13	unknown	unknown	Headache, palpitations
Winniford et al (80)	23	16	70	Headache, dizziness, pedal edema, nausea
Heupler & Proudfit (82)	8	1	13	Flushing
Goldberg et al (83)	12	1	8	Headache and flushing
Antman et al (84)	127	50	39	Dizziness, flushing, headache
Bertrand et al (85)	13	2	15	Flushing, nausea and vomiting
Ginsburg et al (86)	12	2	17	Pedal edema, dizziness
Hill et al (87)	19	18	95	Headache, dizziness, pedal edema, fatigue
Castro et al (109)	11	0	0	-
Alvarado et al (110)	24	12	50	Flushing, headache
Folle et al (111)	20	1	5	Dizziness
Moskowitz et al (114)	10	6	60	Fatigue, dizziness
Mueller & Chahine (115)	66	53	81	Dizziness, headache, flushing
Previtali et al (140)	14	4	29	Headache, dizziness, pedal edema
Moses et al (141)	19	2	11	Diarrhea, pedal edema
Gerstenblith et al (143)	68	5	7	Hypotension, diarrhea
TOTALS	472	195	41	

Abbreviations: Pts = patients

TABLE 21

ADVERSE EFFECTS DURING LONG-TERM ORAL DILTIAZEM THERAPY

AUTHORS	# Pts studied	# Pts with Adverse Effects	%	Nature of Adverse Effects
Pepine et al (89)	12	1	8	Dry mouth
Rosenthal et al (90)	13	1	8	Headache
Schroeder et al (91)	48	9	19	In only 1 patient did an adverse effect force diltiazem's discontinuation
Schroeder et al (92)	36	6	17	Pedal edema
Hossack et al (120)	10	1	10	Headache
Hossack et al (122)	57	7	12	Headache, GI upset
Pool et al (123)	8	0	0	-
Nakamura et al (145)	8	0	0	-
TOTALS	192	25	13	

Abbreviations: Pts = patients.

0 to 19%, with an average of only 13%. Similar to verapamil and nifedipine, most are relatively minor and do not require a substantial reduction in dosage or the discontinuation of diltiazem. Headache and pedal edema are the most common of diltiazem's adverse effects.

In short, each of the 3 calcium antagonists is associated with relatively minor and dose-related adverse effects in a minority of patients, but it is distinctly uncommon that any of these force a discontinuation of the pharmacologic agent being administered. In most instances, a modification in dosage or the addition of another drug is sufficient to allow the continued use of the calcium antagonist.

X. SUMMARY

Since their introduction in the United States less than 2 years ago, the calcium antagonists have already achieved an important place in the medical therapy of a number of disease entities. Table 22 (page 66) summarizes the specific diseases for which verapamil, nifedipine, and diltiazem are "very effective," "somewhat effective," "possibly effective," or "ineffective." As this Table illustrates, these pharmacologic agents differ markedly from one another in their clinical utility. A thorough understanding of each drug's hemodynamic and electrophysiologic effects will allow the practicing physician to prescribe them skillfully and safely.

TABLE 22

CLINICAL EFFICACY OF THE CALCIUM ANTAGONISTS

DRUG	VERY EFFECTIVE	SOMEWHAT EFFECTIVE	POSSIBLY EFFECTIVE	INEFFECTIVE OR DELETERIOUS
Verapamil	1. Paroxysmal supraventricular tachycardia, atrial fibrillation & flutter. 2. Hypertrophic cardiomyopathy 3. Variant angina, angina of effort, unstable angina	1. Mild-moderate systemic hypertension	1. Ventricular tachyarrhythmias	1. Pulmonary hypertension 2. Unloading agent in CHF 3. Raynaud's phenomenon or disease
Nifedipine	1. Mild-moderate systemic hypertension 2. Pulmonary hypertension 3. Variant angina, angina of effort (especially combined with a beta-blocker), unstable angina	1. Unloading agent in CHF 2. Raynaud's phenomenon or disease	1. Selected patients with hypertrophic cardiomyopathy	1. Supraventricular or ventricular tachyarrhythmias
Diltiazem	1. Variant angina, angina of effort		1. Supraventricular tachyarrhythmias 2. Pulmonary hypertension	1. Untested in systemic hypertension, Raynaud's disease, or hypertrophic cardiomyopathy

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