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Acute Nifedipine Withdrawal: Consequences of Preoperative and Late Cessation of Therapy in Patients With Prior Unstable Angina

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Reports of acute ischemic events after withdrawal of calcium antagonist therapy in outpatients and during bypass surgery in patients with prior angina at rest prompted the examination of the effect of nifedipine withdrawal in 81 patients who had completed a prospective, double-blind randomized trial of nifedipine versus placebo for rest angina. Thirty-nine patients underwent bypass surgery for uncontrolled angina or left main coronary artery disease. No significant difference between patients withdrawn from nifedipine or placebo was seen in the incidence of perioperative myocardial infarction, hypotension requiring intraaortic balloon counterpulsation, vasopressor or vasodilator requirements or incidence of significant arrhythmias.

An additional 42 patients had completed 2 years on a protocol consisting of nitrates and propranolol in addition to nifedipine or placebo. During a mean of 66 hours of continuous monitoring after withdrawal of nifedipine or placebo, heart rate and blood pressure were unchanged. A worsening of previously present angina at rest occurred in five patients who had continued to experience rest angina before drug withdrawal, four of whom were withdrawn from nifedipine. No patient with class I to III angina experienced new onset of rest angina during drug withdrawal. No patient experienced myocardial infarction. There was no significant difference between patients withdrawn from nifedipine or placebo in the duration or frequency of ischemic ST changes on continuous electrocardiographic monitoring, or in duration or positive results of serial exercise treadmill testing.

Thus, no early adverse effects of acute nifedipine withdrawal were found in patients with prior rest angina at the time of bypass surgery or in stable patients receiving long-term medical therapy. Patients with continued symptoms of rest angina, however, may experience adverse ischemic events with nifedipine withdrawal.

Abruptly stopping treatment with vasoactive drugs may be hazardous. Early reports (1–4) of myocardial infarction and sudden death among munitions workers without coronary artery disease suggested that rebound vasospasm occurs after acute withdrawal from long-term nitrate exposure. Rapid withdrawal of sodium nitroprusside is associated with hemodynamic deterioration in patients with congestive heart failure, and there have been reports that clonidine withdrawal causes a profound rebound hypertensive state (5,6).

A similar phenomenon has been reported after acute withdrawal of calcium antagonist therapy in patients who have coronary spasm with persistent rest angina and in patients undergoing coronary artery bypass surgery (7–13). In clinical practice, questions regarding the safety of calcium antagonist drug withdrawal usually occur in two settings. The first is in patients who are no longer experiencing symptoms of rest angina after an extended period of medical therapy. Prior prospective studies (14,15) of unstable angina have demonstrated that most unfavorable outcomes occur within 8 to 12 weeks after the onset of rest angina. The necessity for extended, long-term medical therapy in patients who have passed the high risk period and who are no longer experiencing symptoms of rest angina is uncertain. In addition, the expense, inconvenience and side effects of a complex anti-ischemic regimen often prompt the patient whose condition is stable and the physician to ask if life-

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long therapy is necessary. Also, the value of continued calcium antagonist therapy is an important question in patients with persistent symptoms. If patients are continuing to experience rest angina, the concern may be that the drug was or has become ineffective and the question of the benefit and need for continuing therapy arises.

Finally, it is expected that patients undergoing coronary artery bypass surgery will not require further calcium antagonist therapy and continued treatment is not usually recommended. However, reports (8,16) of severe coronary vasospasm and sudden cardiovascular collapse during the perioperative period have prompted concern about the potential risk of withdrawing calcium antagonist drugs in the setting of coronary artery bypass surgery. In addition, there have been reports (17) of an antiplatelet effect of these drugs which may potentiate postoperative bleeding.

There have been no controlled studies describing the effect of acute nifedipine withdrawal in these groups of patients The short-term results of a randomized trial of nifedipine in patients with unstable angina have previously been reported (14). The termination of that study in a group of patients after 2 years of medical treatment and in another group of patients at the time of coronary artery bypass surgery afforded us a unique opportunity to compare the effects of withdrawal of nifedipine and placebo in a large group of patients with prior unstable angina. Our study examines the question of the existence of an acute nifedipine rebound withdrawal phenomenon in these patient groups.

Methods

Study patients. Our study group consists of 81 patients who had been enrolled in a double-blind, randomized, placebo-controlled trial of nifedipine in addition to conventional medical therapy, including propranolol and long-acting nitrate preparations in those with unstable rest angina (14). One group of 39 patients taking the blinded study drug (nifedipine, 80 mg daily, or placebo) underwent coronary artery bypass surgery for control of persistent angina or left main coronary disease. Eight additional patients underwent surgery at other institutions and were unavailable for study. The study drug was discontinued 1 to 14 hours (mean 5.4) before surgery and the patients were followed up during the postoperative period for evidence of the following: coronary artery spasm, myocardial infarction defined by the appearance of new pathologic Q waves greater than 0.04 second in duration and serum creatine kinase increase to greater than twice normal with at least 10% MB fraction, hypotension requiring intraaortic balloon counterpulsation, postoperative hypertension defined by systolic pressure greater than 170 mm Hg, bleeding requiring reoperation or transfusion, vasodilator and vasopressor medication requirements, and significant arrhythmias consisting of paroxysmal atrial tachycardia, atrial fibrillation or flutter and ventricular tachycardia defined by three or more consecutive ventricular beats at a rate greater than 100 beats/min. Data are presented as mean ± standard error.

Thirty-six additional patients successfully completed 2 years of therapy on the randomized double-blind protocol consisting of nifedipine or placebo in addition to long-acting nitrates and beta-adrenergic blocking agents. Thirty-two patients were in stable condition and experiencing no rest angina, with occasional pain only at more than usual activity. Four patients were continuing to have rest angina but were not surgical candidates. In addition, six patients who had been enrolled in the trial and who were taking open label nifedipine (one patient after bypass surgery and five patients who were not operative candidates) also agreed to be hospitalized for the withdrawal protocol. Four of these six patients were continuing to experience occasional episodes of rest angina while taking nifedipine. At 2 years of therapy, these patients agreed to be admitted to the Clinical Research Center of the Johns Hopkins Hospital and were monitored during withdrawal of the study drug. The withdrawal protocol was approved by the Joint Committee on Clinical Investigation.

Study protocol. Patients were admitted to the Clinical Research Center after giving informed written consent and with the permission of each patient's physician. Initial studies included history and physical examination, 12 lead electrocardiogram at rest, chest X-ray examination and a graded symptom-limited exercise treadmill test using a modified Bruce protocol. Continuous two channel electrocardiographic recording for number and total duration of ischemic episodes defined by ST segment depression or elevation of 1 mm or greater was performed throughout the hospital stay (18). After completion of the initial studies, the study drug was reduced from 20 to 10 mg for one dose and subsequently discontinued. The patients were monitored for a mean (± SD) of 66 ± 15 hours after the withdrawal of the study drug. Twelve lead electrocardiograms were obtained in all patients who experienced chest discomfort. If there was electrocardiographic evidence of ischemia, patients were treated with sublingual nitrates and then started on open label nifedipine. Those patients who completed the withdrawal period without recurrent angina underwent repeat exercise treadmill testing.

Data analysis. The treadmill results and long-term electrocardiographic data were randomized and reviewed by two independent observers. The incidence, number and duration of overt and clinically silent ischemic episodes as detected by continuous electrocardiographic monitoring and serial exercise treadmill positivity and duration were compared in those patients who were withdrawn from nifedipine and placebo therapy. Data are presented as mean ± standard

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error. Noncontinuous data were examined by contingency table analysis using chi-square tests of significance. Continuous function variables were analyzed using paired and nonpaired *t* tests of significance where appropriate.

Results

Surgical Group

Thirty-nine patients taking the study drug underwent coronary artery bypass surgery at the Johns Hopkins Hospital for persistent ischemia (31 patients) or for left main coronary stenosis (8 patients). At the time of surgery, 17 patients were withdrawn from nifedipine and 22 were withdrawn from placebo (Table 1). There was no significant difference between the groups with respect to age, sex, left ventricular ejection fraction, incidence of significant left main coronary disease, other anti-ischemic medications, the number of bypass grafts placed or time on cardiopulmonary bypass. The mean time between the last dose of study drug and initiation of anesthesia was 5.4 ± 1.8 hours.

Effect of study drug withdrawal (Table 2). The intraaortic balloon pump was required for hypotension in one patient who was withdrawn from nifedipine and three who were withdrawn from placebo. One nifedipine- and two placebo-treated patients sustained a perioperative myocardial infarction, and two in each group had perioperative hypertension. There was no significant difference between the groups with respect to the number of patients who received vasopressors (9 nifedipine- and 9 placebo-treated patients), vasodilators (15 nifedipine- and 20 placebo-treated patients) or the maximal dose or duration of either therapy. No patient had postoperative bleeding that required reoperation. The mean number of red cell units transfused postoperatively (3.0 ± 0.6 for nifedipine- and 3.4 ± 0.4 placebo-treated patients) and the mean number of days of intensive care unit stay (2.8 ± 0.4 nifedipine- and 3.1 ± 0.3 placebo-treated patients) were also not significantly different between the two groups. The incidence of supraventricular (four nifedipine- and three placebo-treated patients) and ventricular (four nifedipine- and three placebo-treated patients) arrhythmias was also the same.

Table 1. Clinical Characteristics of Patients Withdrawn From Nifedipine and Placebo at Coronary Bypass Surgery*

	Nifedipine (n = 17)	Placebo (n = 22)
Age (yr)	58 ± 3	57 ± 2
Sex (M/F)	12/5	18/4
Ejection fraction (%)	61 ± 3	63 ± 4
Left main coronary artery stenosis > 50% (no. of patients)	4	4
Medications		
Propranolol (mg/day)	277 ± 43	278 ± 45
Nitrates, topical (inches/day)	14 ± 2	15.7 ± 2
Number of grafts	2.9 ± 0.2	3.0 ± 0.2
Cardiopulmonary bypass time (min)	117 ± 13	103 ± 8

*There is no statistically significant difference between the groups for any characteristic listed. F = female; M = male.

Table 2. Clinical Outcome of Patients Withdrawn from Nifedipine and Placebo at Coronary Bypass Surgery*

	Nifedipine (n = 17)	Placebo (n = 22)
Hypotension requiring intraaortic balloon	1	3
Perioperative hypertension (systolic > 170 mm Hg)	2	2
Perioperative myocardial infarction (new Q waves, CK-MB increase)	1	2
Vasopressor therapy	9	9
Duration (hr)	23.3 ± 7.3	34.4 ± 10.3
Vasodilator therapy	15	20
Duration (hr)	23.5 ± 4.1	27.6 ± 3.6
Maximal dose (μg/kg per min)	11.7 ± 3.3	13.9 ± 2.5
Red cell transfusions (units)	3.0 ± 0.6	3.4 ± 0.4
Intensive care unit stay (days)	2.8 ± 0.4	3.1 ± 0.3
Arrhythmias		
PAT, Afib or flutter	4	3
VT (three or more beats)	4	3

*There is no statistically significant difference between the groups for any characteristic listed. Afib = Atrial fibrillation; CK = creatine kinase; PAT = paroxysmal atrial tachycardia; VT = ventricular tachycardia.

Medical Group

Clinical profiles of the 42 patients who were withdrawn from nifedipine and placebo after 2 years of therapy are presented in Table 3. Twenty-five patients were withdrawn from nifedipine and 17 were withdrawn from placebo. The groups were similar with respect to age, sex, history of myocardial infarction and extent of coronary artery disease

Table 3. Clinical Characteristics of Patients Withdrawn From Nifedipine and Placebo at 2 Years

	Nifedipine (n = 25)	Placebo (n = 17)
Age (yr)	63 ± 2	65 ± 2
Sex (M/F)	17/8	10/7
Prior myocardial infarction	16	11
Coronary lesion > 70% (no. of patients)	16/18	8/10
Medications		
Propranolol (mg/day)*	177 ± 13	282 ± 41
Nitrates (mg/day)	109 ± 11	92 ± 17

*p = 0.053. There is no statistically significant difference between the groups for any other characteristic listed. F = female; M = male.

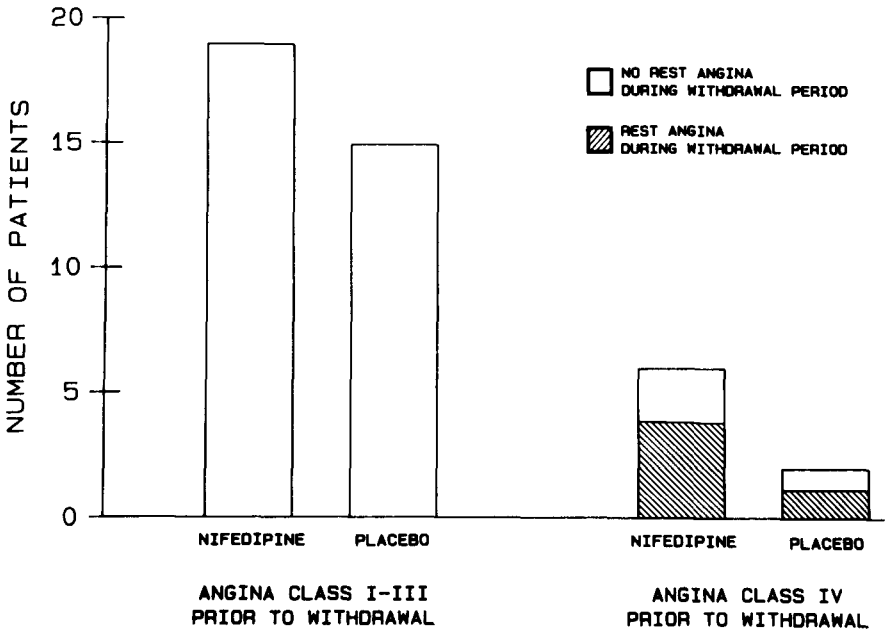

Figure 1. The number of patients who did and did not experience rest angina during the period of withdrawal of nifedipine and placebo. Note the absence of recurrent rest angina in the 34 patients in stable condition with class I to III angina before withdrawal.

as determined by angiography. Although nitrate doses were similar, the mean dose of propranolol was lower in the group that was withdrawn from nifedipine.

Angina during the withdrawal period. During the observation period after the withdrawal of nifedipine or placebo, five of eight patients in the group with persistent rest angina before drug withdrawal had a significant worsening of their angina as evidenced by severe rest angina associated with ischemic electrocardiographic changes. Of these five patients, four were withdrawn from nifedipine (two blinded and two open label) and one was withdrawn from placebo. However, none of the 34 patients who were no longer experiencing rest angina before drug withdrawal had a worsening of their anginal pattern or the new development of rest angina (Fig. 1). Nifedipine therapy was initiated in the five patients who subsequently had no recurrent episodes of rest angina. No patient experienced myocardial infarction after drug withdrawal.

Exercise performance (Fig. 2, Table 4). There was no evidence in either group of a significant change in heart rate at rest or blood pressure during the withdrawal period. There was no significant difference between the groups in the number of patients with a positive test, total exercise duration, work load expressed as heart rate-systolic pressure

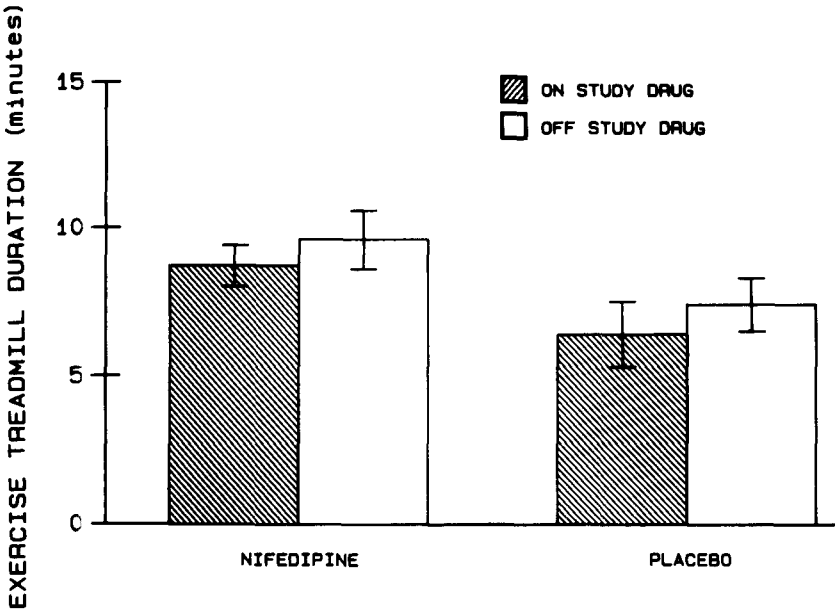

Figure 2. The total duration of treadmill exercise before and after withdrawal of nifedipine and placebo. There is no significant difference between the two groups.

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Table 4. Results of Exercise Treadmill Testing During and 48 Hours After Withdrawal of Nifedipine or Placebo Therapy*

	Nifedipine (n = 25)	Placebo (n = 17)
Total duration (min)		
During therapy	8.2 ± 0.8	6.4 ± 0.9
After withdrawal†	9.5 ± 0.9	7.4 ± 0.8
Positivity (ST shift > 1 mm)		
During therapy	11	8
After withdrawal	9	10
Time of onset of ST shift (min)		
During therapy	6.2 ± 0.6	5.3 ± 0.6
After withdrawal	6.1 ± 0.7	6.6 ± 0.7
HR × BP (beats/min × mm Hg)		
During therapy	18,048 ± 1,136	16,673 ± 1,475
After withdrawal	17,672 ± 1,132	14,741 ± 1,409

*There is no statistically significant difference between the two groups for any variable listed. †Treadmill testing performed in 22 nifedipine- and 16 placebo-treated patients. BP = blood pressure; HR = heart rate.

product, or time to the onset of ST shift in those patients with a positive test.

Long-term electrocardiographic monitoring. The results of continuous electrocardiographic monitoring for a mean of 66 hours during the study drug withdrawal period are shown in Figure 3. There was no significant difference between the groups with regard to the total number of episodes of ischemic ST segment shift per 24 hours (nifedipine 0.78 ± 0.07 and placebo 0.73 ± 0.11) or total duration of ST segment shift per 24 hours (nifedipine 24.5 ± 3.3 minutes and placebo 22.6 ± 5.0 minutes) during the withdrawal period. The data were also examined separately for each 12 hour period for evidence of any time-dependent increase in silent ischemia, but none was found in either treatment group.

Discussion

Reports of uncontrolled studies have suggested an acute ischemic rebound phenomenon after nifedipine withdrawal in some patients. In one study (7), five of seven patients in a nonrandomized trial of nifedipine for unstable angina had recurrent rest angina and one had a fatal infarction within 48 hours of withdrawal or tapering of nifedipine. Another report (8) suggested that severe postoperative coronary spasm in one patient may have been due to nifedipine withdrawal at the time of bypass surgery. A recent controlled study (9) of the effect of nifedipine withdrawal in patients with continuing rest angina demonstrated a worsening of anginal symptoms in 7 of 19 patients in whom nifedipine was withdrawn as compared with only 1 of 19 who continued to take nifedipine. Two of the patients who demonstrated a significant increase in anginal symptoms had been concomitantly withdrawn from both nitrates and beta-adrenergic blocking agents. These prior reports refer to patients studied soon after starting nifedipine or in whom significant rest symptoms persisted despite calcium antagonist therapy.

Our report describes a controlled trial of nifedipine withdrawal in patients who had extensive coronary disease at the time of coronary artery bypass surgery or after 2 years of medical therapy. Other medications were continued so that our observations can be attributed exclusively to withdrawal of nifedipine or placebo.

Nifedipine withdrawal at bypass surgery. In patients undergoing coronary artery bypass surgery, it is expected that further anti-ischemic drug treatment is not required and it is not routinely recommended. However, the recognition of the syndrome of severe coronary spasm in the perioperative period has focused attention on the potential hazard of abrupt withdrawal of calcium channel blocker therapy. For some of these drugs (nifedipine, for example) acute withdrawal is routine since light inactivation may occur

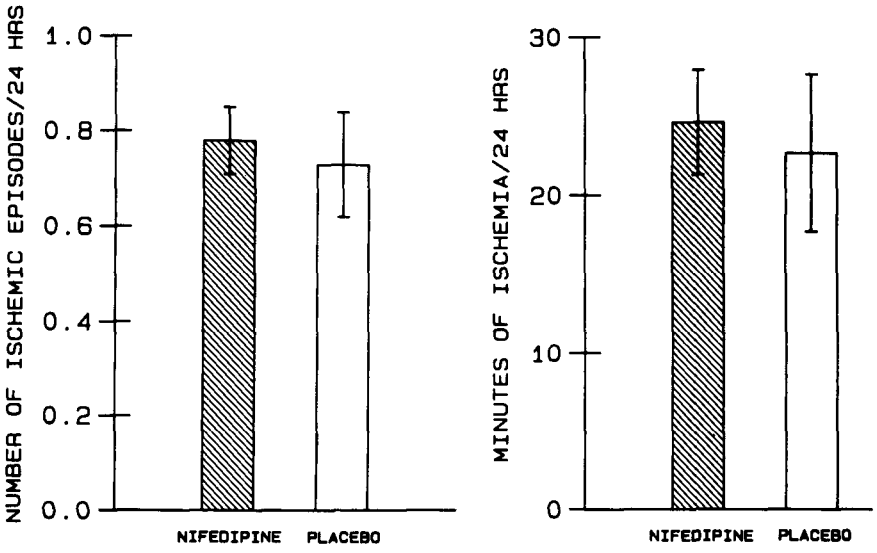

Figure 3. The number of episodes and total duration of ischemic ST segment shift as recorded by continuous electrocardiographic monitoring in patients withdrawn from nifedipine and placebo. There is no significant difference between the two groups.

despite parenteral administration (19), and hemodynamic instability in the perioperative period may preclude the use of potent vasodilators. Although perioperative coronary artery spasm has been well documented (16), we found no evidence to suggest that this phenomenon is either induced or exacerbated by perioperative nifedipine withdrawal. Furthermore, there was no evidence of an association between perioperative hemodynamic instability, bleeding or significant arrhythmias and nifedipine withdrawal in these patients.

Nifedipine withdrawal after long-term therapy. Consequences of drug withdrawal are also of concern in patients whose anginal pattern has stabilized for an extended period of time on medical therapy. The long-term expense, inconvenience and potential side effects of these medications are appreciable. If the drug was initially utilized for a vasospastic state such as unstable angina, remission may occur making long-term therapy unnecessary. In our patients with prior rest angina whose condition had stabilized on a medical regimen consisting of nitrates, beta-adrenergic blocking agents and either nifedipine or placebo and who were no longer experiencing rest angina, there was no evidence of clinically significant acute ischemic events after nifedipine withdrawal. Therefore, the early risk of nifedipine withdrawal in these patients appears to be minimal. In contrast, of the eight patients who continued to experience occasional episodes of rest angina, five had an acute worsening of their anginal pattern after withdrawal of the study medication (four nifedipine and one placebo-treated patient). Thus, our findings support previous studies (7,9) suggesting that nifedipine withdrawal in patients with persistent rest angina may be associated with a significant risk of adverse ischemic events.

Limitations of study. First, these results apply only to patients in whom nifedipine has been withdrawn and who have been maintained on propranolol and long-acting nitrate therapy. It is not known whether these results apply if patients are receiving nifedipine as their only antianginal agent. Second, the length of in-hospital observation, a mean period of 66 hours after drug withdrawal, was relatively short and allowed for observation of only acute effects. Although this withdrawal period was longer than that in prior reports describing significant rebound effects, we do not know if further adverse effects would have occurred over an extended withdrawal period. In addition, the patients available for study at 2 years were those who had responded to medical therapy and not those who had bypass surgery and, thus, were not representative of the total group. Because nifedipine was effective in decreasing the need for surgery (14), those patients receiving placebo may have had less severe disease, thus creating a potential bias in favor of the placebo group. However, no significant adverse effects were noted in either patient group at the time of bypass surgery or at 2 years in the patients whose condition had stabilized on medical therapy.

Implications. Those patients with rest angina who undergo coronary artery bypass surgery or whose condition has stabilized on medical therapy demonstrated no acute adverse effects from nifedipine withdrawal. This suggests that lifetime therapy with calcium channel blocker medications may not be necessary after the high risk period has passed. Prior studies (14,15,20,21) suggest that the period of highest risk after the development of angina is variable and may last for only 8 to 12 weeks. Acute endothelial injury and subsequent healing is a recognized sequence of events accompanying the development of atherosclerosis (22), and it is possible that endothelial injury may be both caused by spasm and result in an increased susceptibility for further coronary spasm until healing occurs. Alternatively, the high incidence of early adverse events may be related to a hypercoagulable state after plaque disruption. The uneventful acute withdrawal from effective calcium antagonist therapy in these patients with prior rest angina whose condition has stabilized on treatment supports the concept that the development of unstable angina with its attendant short-term risk of death, myocardial infarction and continued angina requiring surgery may represent only a transient period of instability.

In contrast, there may be some risk associated with nifedipine withdrawal in patients who continue to experience symptoms of rest angina, suggesting a continued benefit of therapy in those patients with a continuing predisposition to vasospasm. Thus, these patients would appear to benefit from long-term calcium antagonist therapy.

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