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Influence of Calcium Administration on the Short-Term Hemodynamic And Anti-Ischemic Effects of Nifedipine

DAVID H. W. WOHNS, MD, J. HERBERT PATTERSON, PharmD, SUSAN CLARKE, BSN, STEPHANIE DUNLAP, DO, MARY BETH BLAUWET, MS, GARY KOCH, PhD, KIRKWOOD F. ADAMS, Jr., MD

Chapel Hill, North Carolina

This prospective study investigated whether pretreatment with intravenously administered calcium would influence the effect of nifedipine on rest hemodynamics and treadmill performance in patients with ischemic heart disease. Seventeen patients were studied after undergoing a qualifying treadmill exercise test that revealed ST segment depression indicative of ischemic heart disease. Study subjects performed three additional treadmill tests as part of the protocol. One treadmill test was obtained from each patient to provide baseline measurements without a preceding intravenous infusion and in the absence of all antianginal drugs including nifedipine; two additional exercise tests were preceded by an infusion and 10 mg of bite-and-swallow nifedipine. The infusions, administered in a randomized, double-blind, crossover fashion, consisted of either 10 ml of 10% calcium chloride (13.6 mEq) in 50 ml of 5% dextrose in water or 5% dextrose in water alone.

Rest systolic blood pressure (134 ± 4.6 mm Hg) was unchanged after placebo infusion (135 ± 4.6 mm Hg) but decreased to 124 ± 4.1 mm Hg ($p < 0.01$) 25 min after nifedipine administration. Rest systolic blood pressure increased after calcium infusion (from 139 ± 4.3 to 148 ± 4.8 mm Hg, $p < 0.01$) and then decreased significantly 25 min after nifedipine administration to 135 ± 4.2 mm Hg ($p < 0.01$). Despite a decrease at the time of peak nifedipine effect after either infusion, systolic blood pressure was significantly lower after administration of nifedipine alone than after administration of calcium and nifedipine (124 ± 4.1 vs. 135 ± 4.2 mm Hg, $p < 0.01$). Peak exercise systolic blood pressure was reduced after placebo and nifedipine (170 ± 7.5 mm Hg, $p < 0.05$), but not after calcium and nifedipine, in comparison with the value of 178 ± 8.2 mm Hg on the baseline treadmill test.

Exercise duration was longer ($p < 0.05$) than baseline duration (365 ± 27 s) after placebo and nifedipine (405 ± 32 s) but was not significantly changed after calcium and nifedipine (391 ± 34 s). Maximal ST segment depression on baseline testing (1.35 ± 0.1 mm) was significantly reduced ($p < 0.05$) after administration of either nifedipine alone (0.79 ± 0.1 mm) or calcium and nifedipine (0.85 ± 0.2 mm). All 17 patients had ST segment depression on baseline exercise testing compared with only 12 of 17 subjects after nifedipine alone and only 10 after calcium and nifedipine.

Conclusions: Calcium administration was associated with a significant increase in systolic blood pressure in patients with ischemic heart disease. Nifedipine reversed the increase in blood pressure induced by calcium but systolic pressure did not decrease below baseline values. By electrocardiographic criteria, treadmill performance was still improved compared with baseline values when administration of nifedipine was preceded by calcium.

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Calcium channel antagonists, through their influence on the membrane transport of calcium, have a salutary effect in patients with a wide variety of cardiovascular diseases (1). Drugs in this class may lessen symptoms of ischemic heart disease by inducing coronary vasodilation and reducing myocardial oxygen demand and also may lessen symptoms of supraventricular arrhythmia (2) by an inhibitory effect on sinus and atrioventricular node conduction. Despite these beneficial effects, calcium channel antagonists induce significant peripheral vasodilation, which may produce serious hypotension in patients with arrhythmia or myocardial ischemia (3–5). Several investigators (4–10) have found that administration of intravenous calcium may reverse or prevent the unwanted reduction in blood pressure induced in patients during antiarrhythmic treatment with the calcium channel antagonist verapamil. It is not clear whether calcium would exert a similar effect on the action of nifedipine, a calcium channel antagonist that has more potent vasodilator effects. Although calcium administration does not appear to lessen the antiarrhythmic effectiveness of verapamil, the influence of this ion on the anti-ischemic action of calcium antagonists has not been determined.

From the Departments of Medicine and Radiology, School of Medicine, School of Pharmacy and the Department of Biostatistics, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. This study was supported in part by a grant-in-aid from the Chapel Hill, North Carolina Affiliate of the American Heart Association and a Public Health Service research Grant, MO1 RR00046 from the General Clinical Research Centers, University of North Carolina, Chapel Hill and the Division of Research Resources, Washington, D.C.

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Address for reprints: Kirkwood F. Adams, Jr., MD, Division of Cardiology, University of North Carolina at Chapel Hill, CB# 7075, Burnett-Womack Building, Chapel Hill, North Carolina 27599-7075.

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The present prospective study was designed to extend previous work by assessing the potential of intravenous calcium to lessen the hypotensive and anti-ischemic effects of the calcium channel antagonist nifedipine. Hemodynamic variables were monitored in patients at rest during a study protocol that called first for an infusion of calcium or placebo, administered in a randomized, double-blind crossover fashion, followed by administration of bite-and-swallow nifedipine. The influence of calcium on exercise performance was investigated by comparing results of baseline treadmill testing without infusion or nifedipine with results of treadmill tests performed after infusion of either placebo or calcium and administration of nifedipine.

Methods

Study patients. Subjects for the study were recruited from patients undergoing treadmill performance evaluation in the clinical exercise laboratory at the University of North Carolina Hospitals. The protocol was approved by the Institutional Review Board of the University of North Carolina on April 8, 1987. Written informed consent was obtained from all subjects before participation in the study.

Patients were considered for inclusion in the protocol if they were determined to have ischemic heart disease by a positive result on an exercise treadmill test conducted in this laboratory while they were receiving no antianginal medications. Results of this qualifying test were interpreted as positive based on electrocardiographic (ECG) criteria, including 1) ≥1 mm of horizontal or downsloping ST segment depression from an isoelectric baseline, and 2) ≥1 mm additional ST segment depression in leads with baseline ST segment depression. These ST segment changes had to occur in the absence of left bundle branch block, digoxin therapy or left ventricular hypertrophy, any of which would have made accurate interpretation of ischemic changes on the ECG impossible.

A total of 18 patients who met these criteria participated in the study. Patients who enrolled in the study had no evidence of these exclusion criteria: acute myocardial infarction ≤2 weeks after the baseline exercise test, allergy or intolerance to nifedipine or inability to discontinue antianginal drugs before undergoing the treadmill tests called for in the protocol. The symptoms of all subjects remained stable and no subject underwent nonmedical therapy for angina before enrollment and subsequent termination of the study. Most subjects were given antianginal therapy after the baseline exercise test. Antianginal treatment included beta-adrenergic blocking agents in 11 patients, long-acting nitrates in 9 and calcium channel blocking agents in 10. Administration of antianginal agents was discontinued in the manner necessary to eliminate drug effects before performance of the protocol. Administration of long-acting nitrates was stopped ≥24 h before exercise testing. No subject was receiving a sustained release calcium channel antagonist and all but two patients discontinued these drugs >24 h before treadmill testing. In these two patients, nifedipine was last taken 14 and 18 h, respectively, before exercise, so the residual effects of the drug should have been negligible. The subjects had their beta-adrenergic blocking agents discontinued 24 to 48 h before performance of the protocol.

All 18 subjects completed the study without incident. One patient was subsequently excluded from analysis after coronary angiography failed to demonstrate obstructive coronary artery disease. Evidence of coronary artery disease in the subjects included significant obstruction (≥70% stenosis) of at least one major epicardial vessel on coronary angiography in 11 patients. Four subjects had an abnormal stress radionuclide ventriculogram with an exercise-induced wall motion abnormality consistent with ischemia. Two patients were believed to have coronary disease on the basis of chronic stable angina and multiple treadmill tests that were positive by ECG criteria.

The study group had a mean age of 62 years and 14 of the 17 subjects were male. Evidence of symptomatic ischemic heart disease was present in all 17 patients, with prior myocardial infarction in 7 and typical exertional angina in 14.

Exercise treadmill testing. Symptom-limited exercise tests were performed on a motorized treadmill system (Sensormedics) using the standard Bruce protocol (11). Leads II, V_4 and V_5 were monitored continuously throughout exercise and after exercise for 6 min or until the ECG returned to baseline levels. A 12-lead ECG was recorded every minute during and for at least 6 min after exercise or until it returned to baseline levels. Additional 12-lead ECG recordings were made when ST segment changes were noted. Once the patient began to exercise, blood pressure and heart rate were measured after the 1st 2 min of each stage of the protocol and every 2 min after exercise for at least 6 min. A timer was used to initiate the protocol and the duration of treadmill exercise was recorded for each patient to the nearest second. Chest pain intensity was graded on a scale of 1 to 10, with 10 defined as the most severe pain the subject had previously experienced. Patients were instructed to immediately inform the investigators of the onset and resolution of chest pain. If chest pain occurred, the time to the nearest second was noted. Heart rate and blood pressure were measured at the time significant ST segment depression was noted.

Study design. Patients were studied in our exercise laboratory in the General Clinic Research Center. In addition to the clinically indicated qualifying exercise test, the subjects underwent three additional treadmill tests as part of the study protocol. These tests were conducted while patients were receiving only protocol medications. Two exercise tests during treatment were preceded by an infusion of calcium or placebo administered in a randomized, crossover fashion and followed in each case by bite-and-swallow nifedipine (Fig. 1). These two tests were performed in a consecutive fashion separated by 1 to 6 days (mean 2.2 [15 of 17 tests were performed within 2 days]). To establish baseline values for exercise performance, a third test was performed without a preceding intravenous infusion and in the

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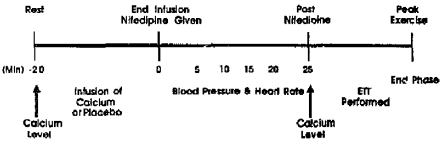

Figure 1. The details of infusions, nifedipine administration and exercise phases of the study are shown. ETT = exercise treadmill test.

absence of antianginal medications including nifedipine. In 14 of the subjects, this test was obtained at the start of the protocol and the randomized part of the study proceeded 48 h later. In three subjects, this baseline exercise test was conducted after the randomized tests. Criteria for ECG interpretation of the study treadmill exercise tests were the same as those for the qualification test.

On the days of infusion, rest blood pressure and heart rate were determined and a heparin well was placed in a large arm vein for the administration of calcium or placebo to the patient. A blood sample was taken from the patient's contralateral arm for the measurement of serum calcium by standard clinical chemistry techniques. The subjects were then given an infusion either of a solution of 10 ml of 10% calcium chloride (13.6 mEq) in 50 ml of 5% dextrose in water or of a solution of 5% dextrose in water only over approximately 20 min and heart rate and blood pressure were measured again. Each subject then received 10 mg of nifedipine that was chewed and swallowed. This method of nifedipine administration was chosen as it allows more rapid absorption of the drug by the patient, with peak levels reached earlier than by the sublingual route (12). Blood pressure and heart rate were measured in each patient every 5 min for 25 min after the administration of nifedipine. A second blood sample was taken for determination of serum calcium 25 min after nifedipine administration. The subjects then immediately performed symptom-limited exercise treadmill tests as described earlier.

The order of infusion of calcium and 5% dextrose in water (the placebo for calcium) was randomized so that nine subjects received calcium before nifedipine and eight received placebo before nifedipine. Care was taken to ensure that the research staff who monitored the hemodynamic variables and the cardiologist who supervised the exercise testing had no knowledge of which patients received calcium and which received placebo. All medications and randomization codes for the study were prepared by the Investigational Drug Service of the University of North Carolina Hospitals Department of Pharmacy. A study pharmacist or nurse administered the protocol medications and conducted blood pressure and heart rate monitoring before the exercise test. The cardiologist conducting the protocol exercise tests was available for the patients' safety and knew that patients would be receiving nifedipine. However, the cardiologist was unaware of which tests were preceded by calcium or placebo infusion and the changes in values of the hemodynamic variables during the infusions. No adverse effects warranting disclosure of protocol medication occurred.

Statistical analysis. Differences between rest hemodynamics and exercise performance during the various stages of the protocol in the same subject were analyzed. Hemodynamic data obtained on the day of the protocol infusions were used to determine the effect on blood pressure and heart rate of the administration of calcium or placebo followed by nifedipine. Data from the baseline treadmill test were compared with exercise tests performed on the days of infusion of calcium or placebo followed by administration of nifedipine. The significance of any difference detected was evaluated with use of the Wilcoxon signed rank test and results were confirmed with use of the paired *t* test. Data are presented as mean values ± SEM; a p value < 0.05 was considered significant.

The following variables from the treadmill test were analyzed: exercise duration; maximal degree of ST segment depression; time to onset of chest pain; time to onset of ST segment depression; rate-pressure product (heart rate × systolic blood pressure) at ST segment depression or chest pain, or both; blood pressure response and time for reversal of ST changes. The study variables of greatest interest were 1) systolic blood pressure at rest, after protocol infusions, after nifedipine and at peak exercise; 2) exercise duration; and 3) magnitude and time to onset of ST segment depression during treadmill exercise testing.

Results

Effects of infusion (Table 1). Serum calcium levels in the patients were similar before the infusion of placebo or calcium chloride. The serum level of calcium was significantly higher than baseline values after the 20 min infusion of calcium chloride (9.3 ± 0.1 vs. 10.8 ± 0.2 mEq/liter, $p < 0.01$) and was unchanged after the 20 min infusion of placebo (9.2 ± 0.1 vs. 9.1 ± 0.1 mEq/liter, p = NS). There was no significant change in heart rate during either of the infusions or after nifedipine administration. An increase in systolic blood pressure was noted after infusion of calcium but not placebo. From this point on, a significant reduction was noted in systolic blood pressure when nifedipine was administered after either calcium or placebo infusion. However, a significant net decrease in blood pressure from rest values before infusion to those after nifedipine was noted only after placebo (from 134 ± 4.6 to 124 ± 4.1 mm Hg, $p < 0.01$), and

Table 1. Effect of Calcium on the Hemodynamic Actions of Nifedipine in 17 Patients

	Calcium plus Nifedipine	Placebo plus Nifedipine
Rest, before infusion		
Systolic BP (mm Hg)	139 ± 4.3	134 ± 4.6
Diastolic BP (mm Hg)	83 ± 2.6	83 ± 2.3
Heart rate (beats/min)	64 ± 2.5	64 ± 2.9
End infusion, before nifedipine		
Systolic BP (mm Hg)	148 ± 4.8*	135 ± 4.6
Diastolic BP (mm Hg)	86 ± 2.6	80 ± 2.1
Heart rate (beats/min)	59 ± 2.1	61 ± 2.3
25 min after nifedipine		
Systolic BP (mm Hg)	135 ± 4.2*	124 ± 4.1
Diastolic BP (mm Hg)	78 ± 2.7	74 ± 2.2
Heart rate (beats/min)	66 ± 2.4	69 ± 2.6

*$p < 0.01$ versus the placebo group. Values are mean values ± SEM.
BP = blood pressure.

not after calcium (from 139 ± 4.3 to 135 ± 4.2 mm Hg, p = NS). Furthermore, systolic blood pressure was significantly lower 25 min after nifedipine alone than after nifedipine and calcium (124 ± 4.1 vs. 135 ± 4.2 mm Hg, $p < 0.01$).

Calcium and treadmill response (Table 2). During the baseline treadmill test, significant ST segment depression occurred in all 17 patients and chest pain typical of angina developed in 9. The subjects reached a peak rate-pressure product (peak heart rate × peak systolic blood pressure) of 23,821 ± 1,553 on this exercise test. Systolic blood pressure immediately before exercise was similar for the baseline and for the calcium plus nifedipine tests. Systolic pressure before exercise in these tests tended to be higher than that of the placebo plus nifedipine test (p = NS). The peak systolic blood pressure during exercise after administration of placebo plus nifedipine was significantly less than that seen on the baseline treadmill test. However, when nifedipine was administered after calcium infusion, peak exercise blood pressure did not differ significantly from that achieved on the baseline test. Heart rate before exercise was significantly lower after calcium plus nifedipine than that on the baseline test (66 ± 2.4 vs. 74 ± 3.9 beats/min, $p < 0.05$) but not lower than that on the test conducted after placebo plus nifedipine treatment. Peak exercise heart rate was similar for all three treadmill tests. Exercise duration was significantly longer after administration of placebo plus nifedipine compared with that on the baseline treadmill test (409 ± 32 vs. 365 ± 27 s, $p < 0.05$). In contrast, after administration of calcium plus nifedipine (391 ± 345) exercise duration was not significantly longer than the baseline value. Exercise duration did not differ significantly with placebo plus nifedipine versus calcium plus nifedipine.

All 17 subjects developed ST segment depression diagnostic of ischemic heart disease on the baseline exercise test compared with only 10 subjects after administration of nifedipine plus calcium and 12 after administration of nifed

Table 2. Influence of Calcium on Nifedipine-Induced Changes in Exercise Hemodynamics and Treadmill Performance

		Study Treadmill Tests	
	Baseline	Calcium plus Nifedipine	Placebo plus Nifedipine
Pre-Ex SBP (mm Hg)	133 ± 3.8	135 ± 4.2	124 ± 4.1
PSBP (mm Hg)	178 ± 8.2 (n = 16)	174 ± 8.1	170 ± 7.5*
Pre-Ex HR (beats/min)	74 ± 3.9 (n = 16)	66 ± 2.4*	69 ± 2.6
PHR (beats/min)	133 ± 4.4 (n = 16)	135 ± 4.6	135 ± 4.4
Peak PROD (PHR × PSBP)	23,821 ± 1,553 (n = 16)	23,971 ± 1,759	23,160 ± 1,473
ETT Dur (s)	365 ± 27	391 ± 34	409 ± 32*
Max ST Dep (mm)	1.35 ± 0.1	0.85 ± 0.2*	0.79 ± 0.1*
Time to chest pain (s)	236 ± 28 (n = 9)	275 ± 38 (n = 7)	296 ± 44 (n = 7)
Time to ECG changes (s)	251 ± 16	320 ± 31 (n = 10)	343 ± 48 (n = 12)
PROD (HR × SBP) at ST Dep or chest pain	19,880 ± 1,260 (n = 16)	21,230 ± 1,798 (n = 11)	21,222 ± 1,485 (n = 13)
Time for reversal of ST Dep (s)	363 ± 63	504 ± 111 (n = 10)	467 ± 77 (n = 11)

Unless otherwise indicated, n = 17. *p < 0.05 versus baseline. ECG = electrocardiogram; ETT Dur = duration of treadmill exercise; HR = heart rate; Max ST Dep = maximal ST segment depression; PHR = peak heart rate; Pre-Ex = pre-exercise; PROD = rate-pressure product; PSBP = peak systolic blood pressure; SBP = systolic blood pressure at ST segment depression; ST Dep = ST segment depression.

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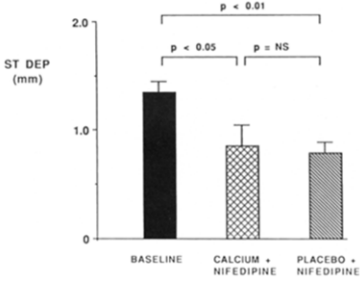

Figure 2. The influence of calcium or placebo infusion on maximal ST segment depression observed during treadmill exercise testing after ingestion of nifedipine. The p values compare maximal ST segment depression during exercise testing after administration of calcium or placebo and nifedipine with that seen on the baseline exercise test conducted in the absence of antianginal agents. Electrocardiographic evidence of ischemia is reduced under both protocol conditions. ST DEP = ST segment depression.

ipine plus placebo. After nifedipine, the maximal degree of ST segment depression during exercise testing was significantly lower than the baseline value whether or not calcium was administered (Fig. 2). Examination of other indexes of treadmill performance (Table 2) revealed that the results of the exercise test conducted after calcium and nifedipine administration tended to be between those seen after nifedipine alone and on the baseline test. Because of the small number of subjects, conclusions concerning the effect of study infusions on time to onset of chest pain are unclear.

Discussion

Study findings. This study represents the first investigation of the effects of calcium administration on the hypotensive and anti-ischemic actions of nifedipine in patients with ischemic heart disease. Pretreatment with calcium was associated with a significant increase in systolic blood pressure but no change occurred in this variable after placebo infusion. Subsequent administration of nifedipine was associated with a significant decrease in systolic blood pressure in the presence or absence of calcium, but rest systolic blood pressure decreased to values below baseline only when nifedipine was administered after placebo infusion. Likewise, peak exercise blood pressure was reduced compared with that on the baseline exercise test after administration of nifedipine alone but was unchanged after calcium and nifedipine.

Analysis of the study results permits preliminary assessment of the effect of calcium administration on the anti-ischemic action of nifedipine. As expected, nifedipine alone produced a significant increase in exercise duration and a decrease in ST segment depression compared with levels seen on the baseline treadmill test performed in the absence of antianginal therapy. Analysis of treadmill responses suggested that some anti-ischemic effect of nifedipine was present after calcium infusion as well. Reduction in the degree of exercise-induced ST segment depression was similar whether intravenous calcium or placebo was administered before nifedipine. Although exercise duration was significantly longer than that on the baseline treadmill test only after administration of nifedipine alone, treadmill time was not significantly different on tests conducted when nifedipine was given after calcium or placebo infusion. Other indexes suggested a trend for exercise performance after calcium and nifedipine to be between that achieved on treadmill tests performed at baseline and after nifedipine alone. The limited number of subjects in the present study may have obscured these differences. Study of a larger patient group will be required to resolve this issue.

Previous work: influence of calcium on hypotensive effect of verapamil. Several investigators (4–10) have documented the potential of calcium to reverse the hypotension that may follow the administration of the calcium antagonist verapamil in the treatment of atrial tachyarrhythmia. Lipman et al. (4) first reported this phenomenon in a patient who developed atrial fibrillation 3 days after a myocardial infarction. Verapamil administration resulted in severe hypotension but the patient's blood pressure returned to baseline values after 2 ampules of calcium chloride were given over 15 min. A similar case was reported by Morris and Goldschlager (5). Weiss et al. (6) noted that administration of verapamil in a patient with atrial tachyarrhythmia resulted in a predictable decrease in systolic pressure, a hemodynamic effect that was reversed by administration of calcium. In addition, they found that calcium pretreatment prevented a decrease in blood pressure after verapamil administration. The interaction of verapamil and calcium in the treatment of multifocal atrial tachycardia was reported by Salerno et al. (7), who studied 16 consecutive patients, 5 of whom were pretreated with calcium gluconate. Although systolic blood pressure decreased in both groups after verapamil, the reduction was greater in the patients who did not receive calcium. More recently, Barnett and Touchon (8) reported no significant change in mean arterial pressure after administration of calcium and verapamil in 19 patients with atrial arrhythmias.

In a nonrandomized sequential study, Haft and Habbab (9) examined the hypotensive and antiarrhythmic efficacy of the administration of verapamil preceded by calcium in two groups of patients with atrial fibrillation and flutter. One group received verapamil alone; the other received calcium chloride before the administration of verapamil. Mean systolic blood pressure decreased significantly in patients treated with verapamil alone but did not change in patients pretreated with calcium chloride. Heart rate decreased to the

same degree in all patients after verapamil administration irrespective of calcium pretreatment. Systolic blood pressure decreased to <100 mm Hg in 29% of patients treated without calcium but in none pretreated with calcium. Hariman et al. (10) studied the reversibility of verapamil-induced hemodynamic and electrophysiologic changes in a dog model. They noted that an increase of 1 to 2 mEq/liter in serum calcium abolished the depressive effect of verapamil on cardiac function and diminished drug-related hypotension. These actions of calcium occurred without an effect on the electrophysiologic actions of verapamil. These studies indicate that calcium can diminish or prevent the hypotensive effect of verapamil without interfering with the antiarrhythmic action of the drug.

Mechanism of calcium's hypertensive effect. Although our work cannot define the mechanism, the increase in systolic blood pressure we observed after calcium administration has been reported by other investigators. The work of Suzuki and Aoki (13) offers one potential explanation for the hypertensive effect of calcium seen in the present study. These workers studied the hemodynamic responses of 32 normotensive and hypertensive subjects during a 1-h infusion of calcium gluconate. Serum calcium levels increased in both groups, as did systolic blood pressure. In a subset of 16 patients who were monitored hemodynamically during calcium infusion, total peripheral resistance increased but cardiac output did not change, thus suggesting that the hypertensive effect of calcium resulted from an increase in peripheral vascular tone as opposed to a positive inotropic effect on the myocardium. These investigators (13) also found in a subgroup of 12 patients that simultaneous administration of verapamil inhibited increases in both systolic blood pressure and total peripheral resistance during calcium infusion.

In the present randomized and placebo-controlled study, calcium had an effect on the hypotensive action of nifedipine similar to that seen with verapamil. This similarity was noted despite evidence that suggests that nifedipine is a more potent vasodilator than verapamil and may differ somewhat in mechanism of action (14). Previous work specifically investigating the influence of calcium on the actions of nifedipine is scant but the results of the present study are supported by the work of Morris et al. (15), who studied potentiation by nifedipine and diltiazem of the hypotensive response commonly induced by contrast angiography. They showed that the decrease in blood pressure after bolus injection of ionic contrast medium at angiography was more profound and prolonged in patients who were receiving nifedipine or diltiazem. In contrast, patients who received an injection of a nonionic agent, which does not lower serum calcium levels, did not have an exaggerated hypotensive response during concomitant therapy with nifedipine. These data suggest a relation between the level of serum calcium and the hypotensive effect of nifedipine treatment similar to that described in our work.

Study implications. Our results may have practical application related to the use of nifedipine in patients with acute ischemic heart disease. This drug reduces calcium ion movement into myocardial and vascular smooth muscle cells (16,17) to promote coronary vasodilation and decrease systemic vascular resistance. These hemodynamic effects usually act simultaneously to reduce myocardial work load and to improve myocardial perfusion. Many placebo-controlled, randomized studies (1,18) have demonstrated that administration of these agents improves treadmill performance and reduces systolic and diastolic arterial blood pressure in patients with coronary artery disease. Despite these salutary effects, nifedipine may increase myocardial ischemia by producing sufficient systemic vasodilation to reduce coronary perfusion pressure or to induce reflex tachycardia. In a large retrospective study in which investigators were aware of patient data, Stone et al. (19) found that 14% of 716 patients reported an increase in anginal symptoms during treatment with nifedipine. Boden et al. (3) described the hazard of nifedipine-induced hypotension even when reflex tachycardia was prevented by administration of a beta-adrenergic blocking agent. They studied a group of patients who regularly reported angina pectoris within 10 to 20 min after oral ingestion of nifedipine; this change was associated with a decrease in mean systolic blood pressure from 109 to 94 mm Hg and no change in heart rate. The authors (3) hypothesized that although the rate-pressure product decreased during symptomatic episodes, myocardial ischemia developed because of a reduction in coronary artery perfusion. Although such adverse consequences of nifedipine may be lessened by the use of one of the newer sustained release formulations that slows the onset of hemodynamic effects, rapid induction of nifedipine action by the bite-and-swallow approach is still often sought in the setting of acute ischemia.

The present study results indicate that pretreatment with intravenous calcium in doses similar to those used to reverse the hypotension associated with verapamil prevented the hypotensive effect of nifedipine. In the clinical setting, treatment with calcium would be especially attractive if the hypotensive but not the anti-ischemic effects of nifedipine were reversed. Analysis of the treadmill test results from our study suggest a continued beneficial effect of nifedipine on exercise performance despite calcium pretreatment, which suggests that calcium might offer a useful way to ameliorate symptomatic hypotension induced by nifedipine in patients with angina.

Limitations. The potential limitations of the present study must be addressed. Some caution must be applied to the interpretation of the treadmill test data. The baseline exercise test, although performed in the absence of nifedipine, was not conducted with a true placebo test because neither an intravenous dextrose infusion nor a bite-and-swallow placebo was given before exercise. However, the tests on the infusion days do provide direct assessment of the influence of calcium on nifedipine-mediated changes in exercise performance. More subtle differences in treadmill

testing between the two infusion protocols might have been detected had a larger number of subjects been tested. The dose of calcium chloride used in this protocol was arbitrary because the effect on the blood pressure response to administration of 10 mg of bite-and-swallow nifedipine had not been studied. We chose the standard dose used to reverse or prevent a hypotensive response to administration of intravenous verapamil given its apparent safety and efficacy in published reports. The present study does not provide data on the possible effects of higher doses of intravenous calcium on the hypotensive and anti-ischemic effect of nifedipine, nor can we speculate as to what the results might have been if calcium had been administered after nifedipine. Additional studies in patients suffering from more severe myocardial ischemia will be necessary to establish the safety and utility of calcium treatment in alleviating hypotensive complications associated with nifedipine therapy.

Conclusion. The study results indicate that calcium given in a dose reported to abolish the hypotensive effect of verapamil reduces the hypotensive action of nifedipine at rest and at peak exercise in patients with ischemic heart disease. Some improvement in treadmill exercise performance was noted after nifedipine administration despite the hemodynamic effects of calcium.

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