Beneficial effects of high-dose diltiazem in patients with persistent effort angina on β-blockers and nitrates: a randomized, double-blind, placebo-controlled cross-over study

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ABSTRACT The effects of orally administered diltiazem combined with maximally tolerated doses of β-blockers and nitrates were assessed in 12 patients, who during stress testing exhibited persistent effort angina and continued objective evidence for inducible myocardial ischemia. Patients performed multistage semisupine exercise on a bicycle ergometer during equilibrium-gated radionuclide angiography after consecutive 2 week treatment periods of placebo or diltiazem 90 mg qid (mean dose 340 mg/day) combined with maximally tolerated propranolol (mean dose 178 mg/day) and isosorbide dinitrate (mean dose 137 mg/day). All medications (including diltiazem or placebo) were administered four times daily for the duration of the study. Diltiazem or placebo was administered according to a double-blind design, with randomized cross-over at the end of each 2 week treatment period. The average number of angina attacks decreased during the double-blind cross-over phase of the trial (7 ± 7 episodes/week at baseline vs 4 ± 3 on placebo vs 2 ± 2 on diltiazem; p = .08). Angina pectoris was abolished during peak exercise in eight of 12 patients on diltiazem (p < .05 vs placebo). Diltiazem increased total exercise duration from 276 ± 92 to 310 ± 78 sec (p < .005 vs baseline). Diltiazem likewise increased the time to onset of angina from 231 ± 84 sec at baseline to 305 ± 77 sec (p < .005), as well as the time to the onset of 1 mm ischemic ST segment depression (p = .01). Diltiazem decreased heart rate at rest, during submaximal workload, and at peak exercise (p < .05), and decreased systolic blood pressure at peak exercise only (p < .05). A significant decline in rate-pressure product at submaximal and peak exercise was noted (p < .05). At any given workload there was significantly less ST segment depression during submaximal (p = .05) and peak exercise (p < .025). No difference was noted in mean left ventricular ejection fraction during placebo or diltiazem therapy at rest and during peak exercise. The effect of adding high-dose diltiazem to maximally tolerated doses of isosorbide and propranolol in improving exercise tolerance and reducing maximal ST segment depression suggests an attenuation of myocardial ischemia. A reduction in rate-pressure product at submaximal and peak workload indicates that patients can perform a higher degree of external work before the onset of ischemia. Thus the principal mechanism for the observed improvement in myocardial ischemia with diltiazem in patients with persistent effort angina in spite of maximally tolerated doses of β-blockers and nitrates appears to be a further incremental decrease in myocardial oxygen demand, although the decrease in heart rate may have facilitated an improvement in myocardial oxygen supply.

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CALCIUM-CHANNEL BLOCKERS are being advocated increasingly in the pharmacologic management of patients with chronic ischemic heart disease and stable effort angina, either alone or in combination with nitrates and β-blockers. Unlike β-blockers, which exert their principal antianginal effects by reducing myocardial oxygen demand, calcium-channel blockers can reduce myocardial oxygen consumption by decreasing systemic vascular resistance, while at the same time producing an increase in coronary blood flow through dilatation of larger coronary conductance vessels. Thus calcium-channel blockers may reduce myocardial ischemia in patients with exertional angina and fixed coronary artery disease as the net result of

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combined favorable effects on myocardial oxygen supply and demand.

The precise role of calcium-channel blockers in the pharmacologic management of patients with chronic stable effort angina remains controversial; traditionally, the use of long-acting nitrates, alone or in combination with β-adrenergic blocking agents, have been the mainstay of medical therapy. However, some patients with exertional angina remain symptomatic in spite of maximally tolerated doses of β-blockers and nitrates. Others cannot tolerate effective doses because of side effects or other concomitant medical problems (bronchospasm, congestive heart failure, peripheral vascular disease, insulin-dependent diabetes mellitus). Clearly, these clinical situations warrant the use of alternative forms of antianginal treatment.

Calcium-channel blockers possess important differences with respect to drug effects on myocardial contractile state, as well as on vascular smooth muscle of the coronary and peripheral arteries.6-10 Because these agents have divergent inotropic, chronotropic, and dromotropic effects, they may differ not only in their respective primary antianginal mechanisms but also in their interactions with β-adrenergic blocking agents. For example, verapamil has been shown to produce significant negative inotropic and chronotropic effects in patients treated with β-blockers.11-13 Additional clinical reports of hypotension and ventricular asystole — when verapamil was administered to patients receiving propranolol and other β-adrenergic antagonists — have raised serious concerns about the adverse hemodynamic consequences of this drug combination.14 Although nifedipine does not usually provoke cardiac failure when administered alone15,16 or with β-blockers,1,4 there have been published reports of congestive heart failure occurring with monotherapy17 and with concomitant β-blocker therapy.18,19 In contrast, diltiazem has been shown to be safe and effective when administered with propranolol in the management of patients with angina pectoris.20,21 Although each of the available calcium-channel blockers has been shown to possess negative inotropic effects during experimental acute myocardial ischemia,22 the resultant peripheral vasodilatation and associated reflex sympathetic stimulation of the heart tend to offset the negative inotropic effects observed clinically.22 Nevertheless, it would appear that in clinically relevant doses, diltiazem possesses the least negative inotropic effects — even in patients with severe heart failure.23

To date there have been few systematic studies on the safety and efficacy of therapy with calcium-chan-

nel blockers when combined with maximally tolerated doses of β-blockers and nitrates in patients with persistent effort angina. The primary objective of this study was to assess the effectiveness of high-dose diltiazem vs placebo (when each was added to a stable regimen of β-blockers and nitrates) in patients with refractory chronic stable effort angina and continued objective evidence for inducible myocardial ischemia by stress testing. Evaluation end points included serial measurements of exercise performance, rest and exercise left ventricular function, and changes in anginal frequency during each treatment period. The secondary objectives were to assess the short-term safety of high-dose diltiazem in combination with propranolol and nitrates, particularly on resting electrocardiographic parameters.

Methods

Patient selection. Patients with a history of persistent effort angina in spite of maximally tolerated protocol-defined doses of propranolol and nitrates were considered for inclusion in the study. All patients were receiving individually optimized therapy with propranolol and nitrates, the doses of which could not be further advanced because of the development of side effects. Inclusion was dependent on demonstrating reproducible, classic exertional angina pectoris, as well as at least 1 mm or greater horizontal or downsloping ST segment depression during a prestudy multistage treadmill exercise test (Bruce protocol), while on a stable regimen of propranolol and nitrates. The minimal protocol-defined doses were 20 mg qid propranolol and 10 mg qid isosorbide dinitrate. Patients who had clinical congestive heart failure, unstable angina (rest/nocturnal angina), significant hypertension, arrhythmias, valvular heart disease, or cardiomyopathy were excluded from the study. Likewise, patients with resting electrocardiographic changes (left bundle branch block, left ventricular hypertrophy) that precluded ST segment interpretation during stress testing, those receiving concomitant calcium-channel blocker and antiarrhythmic therapy (including digoxin), patients with sick sinus syndrome or resting atrioventricular block greater than first-degree, and individuals who had sustained a myocardial infarction less than 3 months before study were excluded from participation.

Twelve male patients gave informed written consent to participate in the study. All patients were maintained on a stable regimen of their preexisting doses of oral nitrates and propranolol for a minimum of 4 weeks before study, and no other adjustments in propranolol or nitrates could be made during this period. The only additional cardiac medication permitted was sublingual nitroglycerin, as needed, for relief of angina. Prophylactic sublingual nitroglycerin was not permitted. Three patients had a prior myocardial infarction longer than 3 months before study. Seven patients underwent previous cardiac catheterization in which 70% or greater luminal diameter coronary narrowing was found in one artery (two patients), two arteries (three patients), and three arteries (two patients). Three patients had neither evidence for prior myocardial infarction nor angiographically proven coronary artery disease but gave a history of reproducible effort angina in the setting of previously positive treadmill exercise tests.

Before study, all patients underwent a training multistage bicycle exercise test to familiarize themselves with the prospective exercise protocol.
Experimental protocol (figure 1). Before randomization, all patients received placebo (three tablets qid) for 1 week, while baseline anginal frequency and sublingual nitroglycerin consumption were assessed (placebo run-in). At the conclusion of this week, a second multistage bicycle exercise test was performed (baseline), against which subsequent exercise tests during diltiazem vs placebo treatment were compared. Thus each patient had two consecutive positive (>1 mm ST segment depression) exercise tests on isosorbide and propranolol before randomization to diltiazem or placebo. Each patient next underwent a 1 week dose-finding trial, in which diltiazem was increased from 120 to 360 mg/day, as tolerated. All but two patients were able to tolerate maximum (360 mg/day) orally administered diltiazem for the duration of the study, and these two individuals took 240 mg/day. At the end of the 1 week dose-finding trial, patients were randomly assigned to receive diltiazem or placebo at their optimally tolerated dose. At the end of the 2 week treatment period, each patient crossed over to the alternative drug therapy for the remaining 2 weeks. On each day of dose titration and during the drug treatment periods, patients transmitted a resting electrocardiographic rhythm strip (MCL5) transtelephonically (Cardiobeeper, Survival Technology, Inc.) 3 h after ingestion of drug. Thus patients transmitted strips daily for the first 3 days (120, 240, 360 mg/day, respectively) during the dose-finding trial and during each of the 2 week treatment periods. As noted, diltiazem doses were reduced in two patients (from 360 to 240 mg/day) because of sinus bradycardia (less than 45 beats/min) in one and nausea in the other. Exercise testing was routinely performed on the morning of day 13 or 14 of each 2 week treatment period, 2 h after the last dose of study medication. The use of identical study medication (diltiazem or placebo) ensured that treatments appeared identical to all patients at all times. All drugs were dispensed by the Pharmaceutical Division of Marion Laboratories, Inc. (Kansas City, MO), which also kept all treatment codes. These codes were not known by the patients or investigators until completion of the entire protocol.

All stress tests and gated blood pool scans were reviewed by two investigators, each of whom was blinded to the specific nature (e.g., diltiazem or placebo) of treatment at the time of data analysis.

Exercise testing protocol. Multistage semisupine (30 to 40 degrees) exercise on a bicycle ergometer was performed with equilibrium-gated radionuclide angiography at baseline and at the end of each of the 2 week treatment periods. Exercise testing was performed with the patient in a fasting state, at the same time of morning of each treatment period. Semisupine bicycle exercise was initiated at a workload of 50 W for 2 min. Thereafter the workload was increased every 2 min by 25 W until an end point of angina, dyspnea, fatigue, or ischemic electrocardiographic changes occurred.

The following exercise end points were measured: time to onset of angina or limiting symptoms in the absence of angina, time to onset of 1 mm ST segment depression, time to onset of 2 mm ST segment depression (if present), and total exercise duration. Changes in heart rate, resting electrocardiographic PR and QT segment duration, blood pressure, and rate-pressure product (maximum heart rate × maximum systolic blood pressure + 100) were assessed at baseline and at the end of each 2 week treatment period. Data were analyzed at rest, at submaximal exercise (defined as the next-to-last workload the patient was capable of performing), and at peak exercise during each of the exercise testing sessions.

Radionuclide imaging protocol. The patient's red blood cells were labeled in vivo by injecting stannous pyrophosphate, followed in 10 minutes by injecting 20 mCi of 99mTc pertechnetate. Imaging was performed with an Elscint Apex 215-M gamma camera interfaced to a dedicated computer system (DEC PDP 11/34 with an 80 megabyte on-line disk). Cardiac imaging was performed in the left anterior oblique projection providing optimal ventricular separation with a 30 degree caudally angled slant-hole collimator. A resting gated study was collected in the normal framed format at 24 frames per cardiac cycle. During exercise, list-mode imaging was begun 6 min before the previously determined end point and continued for 1 min after the termination of exercise. The shortest RR intervals of the list-mode collection, representing 3 min of exercise at maximum heart rate, were formatted into a framed study at 24 frames per cycle and analyzed in an identical fashion to the resting study. Such a protocol guaranteed that only cardiac cycles during peak exercise were analyzed, regardless of the exact duration of exercise. Left and right ventricular ejection fractions and regional left ventricular wall motion were analyzed for the rest and exercise studies by standard computer programs.24, 25

Statistical analysis. A nonparametric two-period cross-over analysis was performed with data at the end of each 2 week treatment period (weeks 4 and 6).26 According to the randomization schedule, patients were assigned to two sequences of test medication during the cross-over phase: (1) diltiazem followed by placebo or (2) placebo followed by diltiazem. Test procedures for hypotheses concerning residual effects of treatment, direct effects of treatment, and period effects were formulated in terms of Wilcoxon rank sum statistics calculated on appropriate intrapatient linear functions of the observations. Residual effects were tested by applying the Wilcoxon rank sum test to the sums of the two intrapatient observations. If residual effects were not significant, direct effects, i.e., diltiazem vs placebo, were tested by applying the Wilcoxon rank sum test to the
differences between the two intrapatient observations. If the residual effects were not significant, period effects were tested by applying the Wilcoxon rank sum test to the cross-over differences. The cross-over differences were the diltiazem value minus the placebo value for each patient. The responses analyzed were the changes at weeks 4 and 6 compared with baseline (end week 1). For all parameters, both residual and period effects were analyzed with two-tailed tests of significance, whereas direct effects were analyzed with a one-tailed test.

Data are expressed as mean ± SD, and p values less than .05 were considered statistically significant.

Results

All 12 male patients (mean age 55 years, range 39 to 68) completed the 4 week double-blind protocol without complications or adverse effects. All but two patients tolerated high-dose (360 mg/day) diltiazem throughout the course of the study, and the mean dose for the entire group was 340 mg/day. There were no changes in diltiazem or placebo dosage during the double-blind cross-over phase of the trial. The average doses of isosorbide and propranolol at baseline for the study group were 137 mg/day (range 40 to 160) and 178 mg/day (range 80 to 320), respectively.

The average number of anginal attacks during the double-blind cross-over phase of the trial decreased from 7 ± 7 episodes/week at baseline to 4 ± 3 with placebo (p = NS) and 2 ± 2 with diltiazem (p = .08 compared with baseline). There were no significant differences in average weekly consumption of sublingual nitroglycerin during the different treatment periods.

Exercise tolerance and ischemic electrocardiographic responses. Statistical analyses revealed no significant test-order effect. Exercise-induced angina occurred in all 12 patients on placebo and was associated with ischemic ST segment depression (≥ 1 mm) in 11. One patient who had twice previously (before study and at baseline) displayed exercise-induced ST segment depression on propranolol/nitrates did not exhibit these objective changes during the 2 week double-blind placebo phase of the protocol. Angina pectoris was abolished during exercise in eight of 12 patients on diltiazem (p < .05 vs placebo).

Figure 2 demonstrates the total exercise duration, time to the onset of angina pectoris, and time to the onset of ischemic ST segment depression during placebo and diltiazem treatment. Diltiazem increased total exercise duration (and hence peak workload) from 276 ± 92 to 310 ± 78 sec (p < .005 compared with baseline) as well as the time to onset of angina pectoris from 231 ± 84 to 305 ± 77 sec (p < .005). Similarly, diltiazem increased the time to onset of 1 mm ischemic ST segment depression (n = 12 patients) from 206 ± 117 to 260 ± 79 sec (p = .01) compared with baseline. In four patients diltiazem increased the time to onset of 2 mm ST segment depression or greater at peak exercise from 247 ± 108 to 303 ± 79 sec (p < .05 compared with baseline). In all of the above comparisons between placebo and baseline, the changes were nonsignificant.

Figure 3 illustrates the improvement in exercise-induced ST segment depression during diltiazem treatment at submaximal and maximal workload compared with placebo, when each treatment period was compared with baseline. During both submaximal and peak exercise the addition of high-dose diltiazem to maximally tolerated doses of isosorbide and propranolol was associated with a statistically significant reduction in maximal ST segment depression (electrocardio-
graphic lead $V_5$, implying a favorable effect on the improvement in myocardial ischemia.

**Effect on rest and exercise hemodynamics.** Changes in heart rate, systolic blood pressure, rate-pressure product, and ST segment depression (at rest, during submaximal, and peak exercise) are listed in Table 1 for baseline, placebo, and diltiazem treatment periods. Compared with baseline (isosorbide dinitrate plus propranolol), diltiazem decreased heart rate at rest, during submaximal workload, and at peak exercise ($p < .05$), but differences between diltiazem and placebo were nonsignificant. Systolic blood pressure at rest and during submaximal exercise was not reduced by the addition of maximum-dose diltiazem, but at peak exercise there was an average 11 mm Hg decline in systolic blood pressure ($p = .05$) during diltiazem treatment. Primarily because of the reduction in heart rate, diltiazem caused a significant ($p < .05$ compared with baseline) decline in rate-pressure product at submaximal exercise and at peak exercise. Diltiazem, in a mean dose of 340 mg/day, was not associated with a significant prolongation of resting PR or QT intervals, although there was a trend toward lengthening of the PR interval (168 ± 26 to 176 ± 26 msec) during combined diltiazem/propranolol/nitrate therapy ($p = .07$). The QT interval at baseline (403 ± 29 msec) did not change significantly during placebo (419 ± 30 msec) or diltiazem (428 ± 32 msec) therapy.

**Effect on electrocardiographic evidence of myocardial ischemia.** The relationship between the magnitude of

![Graph](image-url)
peak ST segment depression and rate-pressure product at submaximal and maximal exercise is shown in figure 4. There was significantly less ST segment depression at any given workload during submaximal (p = 0.05) and peak exercise (p < 0.025) during diltiazem treatment compared with placebo. Thus patients who displayed electrocardiographic evidence of myocardial ischemia on maximally tolerated nitrates and propranolol exhibited an attenuation in the magnitude of exercise-induced ST segment depression during additional diltiazem treatment. This reduction in rate-pressure product, an indirect index of myocardial oxygen demand, indicates that patients treated with diltiazem could perform a higher degree of external work before the onset of ischemia, implying a favorable net effect on the imbalance in myocardial oxygen supply and demand.

Effect on rest and exercise left ventricular function (figure 5). The mean left ventricular ejection fraction at rest and during peak exercise at baseline for the entire study group was 55 ± 8% and 59 ± 8%, respectively. During diltiazem treatment, the mean resting left ventricular ejection fraction was 57 ± 6% compared with 56 ± 7% during placebo therapy; neither value was significantly different from baseline.

There was a trend toward improved left ventricular function with diltiazem treatment during peak exercise. The mean left ventricular ejection fraction during diltiazem treatment (62 ± 7%) was higher than that during placebo therapy (59 ± 8%), although these values were not significantly different from baseline.

The addition of high-dose (340 mg/day) diltiazem to a stable regimen of maximally tolerated β-blockers and nitrates was not associated with any further depression of resting or exercise left ventricular ejection fraction in any of the 12 patients.

Discussion

This study demonstrates the efficacy of adding high-dose diltiazem (mean dose 340 mg/day) to a maximally tolerated regimen of β-blockers and nitrates in the management of refractory chronic exertional angina pectoris. We showed that diltiazem, but not placebo,
significantly improved exercise-induced ST segment depression at submaximal and maximal exercise, as well as the time to the onset of 1 mm ST segment depression, the time to the onset of 2 mm ST segment depression, and the total duration of exercise compared with baseline.

The use of high-dose diltiazem in this group of patients improved the frequency of angina pectoris during sequential stress testing and completely abolished exercise-induced angina in eight of 12 patients at peak workload. Moreover, in spite of the beneficial effects of adding high-dose diltiazem to a stable regimen of propranolol and isosorbide dinitrate, we encountered no adverse clinical effects, electrocardiographic abnormalities, or depression of left ventricular function during the 4 week double-blind, cross-over period. Thus short-term, high-dose diltiazem, when combined with nitrates and β-blockers in the management of patients with persistent effort angina, was both safe and effective.

Pathophysiology of effort angina. Why diltiazem should significantly improve angina pectoris and multiple objective indexes of myocardial ischemia in a population of patients with chronic exertional angina is not precisely clear. Angina pectoris results from the development of myocardial ischemia, which may be the result of either a decrease in coronary blood flow or an increase in myocardial oxygen need that is not met by an appropriate augmentation of coronary blood flow.27 In the classic setting of Heberden’s effort angina, sympathetic tone is enhanced during exercise, which leads to an increase in heart rate, contractility, and blood pressure. All of these factors facilitate an increase in myocardial oxygen requirements. At the same time, an increase in heart rate leads to a reduction in the diastolic time during which nutritive coronary blood flow can occur, thereby resulting in a further attenuation of coronary blood flow. Thus exercise-induced tachycardia results in both a decrease in coronary flow and an increase in oxygen demand.

There is emerging evidence that many patients with exertional angina pectoris have both coronary atherosclerosis and increased coronary vasomotor tone.27-29 Coronary vasoconstriction may occur at the site of an atherosclerotic plaque or in other areas of the coronary circulation, providing a “dynamic obstruction” to blood flow. Such coronary spasm superimposed on a given degree of fixed atherosclerotic coronary artery disease may result in significant variability in anginal threshold during exertion and may be a major contributing factor to the pathogenesis of myocardial ischemia in a variety of patients with angina pectoris.30 The true incidence of this type of “mixed” or “variable threshold” angina is unclear and is currently an area of active clinical investigation.

Diltiazem combination with nitrates and β-blockers. Specific treatment for exertional angina pectoris with pharmacologic agents has been logically directed toward reversing the physiologic perturbations noted above. Since a variety of therapeutic modalities aimed at decreasing myocardial oxygen requirements and augmenting oxygen supply is now available to clinicians, a stepwise use of drug therapy has been advocated in the management of patients with angina pectoris.31,32 Such a “step-care” approach to therapy entails the initial use of nitrates, followed by the addition of β-adrenergic blocking agents. In cases of angina pectoris refractory to nitrates and β-blockers, the addition of a calcium-channel blocker is warranted.29,31

Combination therapy comprising the use of nitrates and β-blockers, as well as β-blockers and calcium-channel blockers, is becoming increasingly more widespread in the management of patients with ischemic heart disease.3,4,18-21 The combination of β-blockers and nitrates is particularly salutary, since the beneficial effects of each drug tend to counterbalance the adverse effects of the other (i.e., changes in heart rate and ventricular cavity dimensions). Because the actions of these drugs occur at different sites, their therapeutic effectiveness appears to be complementary in nature.33 When effort angina is moderate-to-severe, combination therapy with nitrates and β-blockers is a proven therapeutic regimen of clinical efficacy.34,35 Alternatively, therapy with diltiazem1-2 or other calcium-channel blockers alone may be equally effective in these patients.

Recently, several reports have been published regarding the combination of β-blockers and calcium-channel blockers.11-14,18-21 It would appear that a combination of a β-blocker and diltiazem20,21 is safer than a β-blocker and verapamil13-14 or nifedipine,18,19 especially in the setting of significant left ventricular dysfunction or overt congestive heart failure. However, strictly controlled studies addressing this issue do not exist.

There are no published studies to guide our decision-making in the use of calcium-channel blockers with nitrates and β-blockers. Clearly, use of multiple pharmacologic agents requires an empiric approach that embodies an evaluation of the severity of the underlying disease, followed by a rational plan of medical therapy for each patient that is highly individualized. Such a “step-care” approach — starting with nitrates
and $\beta$-blockers, followed by the addition of calcium channel-blockers if symptoms of angina and signs of myocardial ischemia do not abate — appears justifiable.29-31

Antianginal mechanisms of combination pharmacologic therapy. In our study, high-dose diltiazem in combination with isosorbide and propranolol produced a significant reduction in heart rate and rate-pressure product at rest as well as during submaximal and peak exercise. Such a reduction in rate-pressure product, an indirect index of myocardial oxygen demand,36 permitted patients to work to a higher work level before the onset of ischemia. A reduction in myocardial oxygen demand appears to be the principal antianginal mechanism for propranolol. Although much evidence indicates that the systemic venous and arterial dilating effects of nitrates are responsible for the relief of myocardial ischemia, the central or direct actions on the coronary circulation are probably important in some patients.

However, in spite of maximally tolerated doses of nitrates and $\beta$-blockers, our group of patients exhibited persistent angina pectoris as well as reproducibly positive exercise tests consistent with inducible myocardial ischemia. Diltiazem clearly improved both subjective and objective indexes of myocardial ischemia. Moreover, examination of the relationship between ST segment depression and rate-pressure product, illustrated in figure 4, indicated that for any given rate-pressure product, diltiazem produced less electrocardiographic ischemia than placebo. This observation is consonant with previously published reports of diminished exercise-induced ST segment depression with low-dose (120 mg/day)37 and high-dose (360 mg/day)30, 21 diltiazem.

The explanation for the observed reduction of electrocardiographic ischemia when diltiazem is added to nitrates and $\beta$-blockers is presently unclear. Diltiazem has been shown to augment resting coronary blood flow in man38-41 and to increase coronary collateral blood flow, although this is controversial.42 Since diltiazem decreases sinoatrial and atrioventricular nodal automaticity,43 an additive reduction in resting and exercise heart rate (over and above that induced by combined isosorbide and propranolol) could increase the diastolic time for coronary perfusion. Diltiazem has been shown to attenuate ischemic injury potentials in the presence of ischemia, presumably by improving intracellular calcium homeostasis.44 Finally, diltiazem produces a reduction in ventricular volume and cardiac inotropic state.45

However, we believe that the beneficial action of diltiazem in stable effort angina most likely is the result of decreased myocardial oxygen demand, since diltiazem consistently decreased both submaximal and peak rate-pressure product without diminishing the level of external work, presumably by lowering afterload. Yet, an alteration in ventricular loading conditions may not be the sole explanation for the observed improvement in the imbalance between myocardial oxygen supply and demand, since systolic blood pressure declined significantly only during peak exercise.

In our study group, diltiazem elicited a uniform decrease in heart rate, both at rest and during submaximal and peak exercise. The finding is consistent with the published observations noted above,20, 37, 38, 43 and supports the hypothesis that diltiazem increases the diastolic time during which coronary blood flow can occur. Thus calcium-channel blockers may increase myocardial oxygen supply, but it is unclear whether this represents a major mechanism responsible for the diminution in electrocardiographic ischemia that we observed.

Effect on left ventricular function. High-dose diltiazem (340 mg/day) was associated with increased levels of left ventricular ejection fraction at rest and during peak exercise, compared with placebo, but these positive directional changes did not attain statistical significance. These data are similar to those reported by Hung et al.,20 who used a dose of diltiazem of 360 mg/day. Since calcium-channel blockers have negative inotropic effects in vitro45 and in vivo,41-43 it is clear that their interaction with $\beta$-blockers may be hazardous, particularly in patients with a history of congestive heart failure13, 17-19 or with a low (less than 40%) ejection fraction.29

In the patients we studied, high-dose diltiazem, when combined with isosorbide and propranolol, did not produce any significant left ventricular dysfunction. However, patients with congestive heart failure were specifically excluded from this study, and all but four of the 12 patients had normal resting left ventricular ejection fractions.

Therapeutic implications. In summary, diltiazem in an average daily dose of 340 mg appeared to be a safe and effective addition to maximally tolerated doses of isosorbide dinitrate and propranolol in patients with persistent chronic stable effort angina. Diltiazem increased exercise tolerance (submaximal and maximal workload), as well as the time to the onset of electrocardiographic ischemia in all patients. Exercise-induced angina pectoris was totally abolished in eight of 12 patients. Rest and exercise left ventricular ejection fraction was augmented by diltiazem, and there was no
evidence of adverse inotropic, chronotropic, or dromotropic effects in the study group.

It is still unclear whether or not all patients with compromised left ventricular function can safely receive calcium-channel blockers, although nifedipine and particularly diltiazem appear to be safer than verapamil. Recommendations for the use of combined therapy with calcium-channel blockers, nitrates, and β-blockers in patients with depressed left ventricular function must await further study.

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