Clinical Investigation

Effect of Diltiazem on Symptomatic and Asymptomatic Episodes of ST Segment Depression Occurring During Daily Life and During Exercise

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Background. Silent myocardial ischemia is an adverse prognostic marker in patients with coronary disease; however, controlled data on the effect of treatment are sparse and contradictory, and the relations among the occurrence of ST segment depression, drug efficacy, and heart rate are unclear.

Methods and Results. Sixty patients with stable coronary artery disease, a positive treadmill exercise test and asymptomatic ST segment depression on ambulatory electrocardiographic recording were assessed in a multicenter, double-blind, placebo-controlled, cross-over trial. Treadmill exercise tests and 72-hour electrocardiographic recordings were obtained at the end of two 2-week treatment periods with sustained-release diltiazem 180 mg b.i.d. or equivalent placebo. Episodes of asymptomatic ST depression decreased by 50% or more in 70% of the patients from a median number of 4.5 (range, 0–19) to 1.5 (range, 0–13) (p=0.0001); their cumulative duration also decreased from 78.5 (range, 0–60) to 24.5 (range, 0–411) minutes (p=0.001). No circadian variation was found in the efficacy of diltiazem. The occurrence of ischemic type ST segment depression was modulated by changes in heart rate rather than by absolute heart rate. Diltiazem also improved exercise test end points but to a lesser extent. Time to ST segment depression increased to 341±148 from 296±154 seconds (p=0.005). Although less frequent with diltiazem administration (45 versus 54 patients, p<0.03), exercise-induced ST depression was more often asymptomatic (98% versus 72% of patients, p=0.0001).

Conclusions. Diltiazem reduces the frequency and severity of ischemic type ST depression in patients with stable coronary artery disease. (Circulation 1991;84:15–22)

Silent myocardial ischemia has emerged as a controversial problem in modern cardiology. Although both its pathophysiological basis and its importance in routine practice remain to be more fully explored, the concept could potentially modify our clinical approach to patients with coronary artery disease. Clearly, silent ischemia occurs frequently,1–3 can be diagnosed accurately,3–8 and carries prognostic implications in patients with unstable9,10 and stable11–13 coronary artery disease. These considerations justify a more in-depth investigation of the pathophysiology, clinical features, and management of silent ischemia. Ambulatory electrocardiographic (ECG) monitoring provides an easy and accessible method to study silent ischemia and the effect of various interventions on it.6–8 Small or uncontrolled studies have suggested that silent ischemia can be partly prevented by antianginal drugs14–25 or revascularization procedures.26 However, larger and controlled studies have contradicted some of these results.27

This placebo-controlled, randomized, double-blind study was designed to determine the effect on silent ischemia of one antianginal drug, sustained-release diltiazem. In addition to this primary goal, the trial was expected to provide useful data to define the features of symptomatic and asymptomatic ST segment depression in a population of patients with stable coronary artery disease, to provide an insight...
into the pathophysiology of silent ischemia both during daily life and during exercise, and to yield clues to the mechanism of its suppression by diltiazem. For this purpose, the relation between heart rate and episodes of ST segment depression was closely monitored, and the effects of the drug on ST depression during ambulatory ECG monitoring and during exercise testing were compared.

**Methods**

**Patient Selection**

Sixty patients who meet all of the following criteria were included in the study: 1) documented coronary artery disease, 2) stable symptoms in Canadian Cardiovascular Society classes 1–3 without rest, nocturnal, progressive, or unstable angina and without a recent (≤3 months) myocardial infarction, 3) a positive treadmill exercise test according to the Bruce protocol, with 1.0 mm or more horizontal or downsloping ST depression measured 0.08 msec after the J point, with or without angina, and 4) the presence of 10 minutes or more of silent ST depression 1 mm or more in amplitude or four or more asymptomatic episodes, each lasting for at least 1 minute during 24 hours of a continuous 72-hour screening ambulatory ECG. The criteria used for the diagnosis of coronary artery disease were 1) presence of at least one coronary artery stenosis greater than 50% lumen diameter reduction, 2) a well-documented previous myocardial infarction, or 3) a positive thallium exercise test manifested by a significant exercise-induced reversible defect. Holter ECG eligibility could be determined at the clinical center, but confirmation within 72 hours by the central ECG laboratory was required or the patient would be dropped from the study.

Exclusion criteria included 1) cardiac surgery within the previous 3 months, 2) stroke within the previous 6 months; 3) congestive heart failure, 4) known valvular heart disease, 5) the presence of atrial arrhythmias, sinus bradycardia of 50 beats/min or less, ventricular preexcitation, pacemaker, conduction abnormalities, left ventricular hypertrophy, or ST depression on the resting 12-lead ECG; 6) hypertension of 160 mm Hg or more systolic or 90 mm Hg or more diastolic and hypotension of 100 mm Hg or less systolic. The study was approved by the respective Hospital Ethics Committees, and all patients gave written, informed consent for participation in the study.

One hundred ninety-six patients were screened in the five clinical centers, and 118 were excluded before study entry; the most-common exclusion factor was failure to exhibit ST depression during the 72 hours of ambulatory ECG monitoring. Eighteen patients began the trial and could not be included in the analysis because they had no ambulatory ECG recording or treadmill exercise test during the double-blind phase of the study: 10 were ineligible based on the central laboratory Holter ECG reading, two refused further participation, and six experienced adverse reactions.

At least 7 days before the screening visit, patients discontinued all β-blocking agents, digoxin, vasodilators including long-acting nitrates and calcium channel blockers, and any other drug that can interfere with interpretation of ST segment changes. Use of these medications was not permitted during the study. Sublingual nitroglycerin was allowed to treat angina episodes.

**Study Design**

The study was randomized, double-blind, and placebo-controlled. After a 7-day single-blind placebo run-in screening phase, patients received sustained-release diltiazem capsules 180 mg b.i.d., a total daily dose of 360 mg, or matching placebo capsules for two consecutive 14-day double-blind treatment phases. Each patient received each of the two treatments in a random sequence according to a 2×2 Latin square design. Compliance as evaluated by pill counts was 98±4% during diltiazem and 97±5% during placebo administration.

**Ambulatory ECG Monitoring**

ECGs were recorded on 24-hour cassette tapes with a calibrated Marquette Series 8500 recorder (Marquette Electronics Inc., Milwaukee, Wis.). A 72-hour continuous ambulatory ECG was obtained at the start of the placebo run-in phase to identify qualified patients for the study and at the end of each treatment phase, with diltiazem and with placebo. Bipolar electrodes were attached with the exploring electrodes applied to record modified V2 and V5 leads. Patients were instructed to maintain their normal daily activities and to record their activities, symptoms, and medications in a diary.

All tapes were analyzed by the Ambulatory ECG Analysis Central Laboratory at the Montreal Heart Institute using the CardioData MK4 Playback System (Cardiodata, Northborough, Mass.). Tapes were independently read by a technician and one physician; both were unaware of patient identity and treatment assignment. An ischemic episode was defined by the standard criteria of transient ST depression of 1 mm or more lasting for at least 1 minute. In the present study, the duration of the ischemic episode was calculated from the onset of ST depression to return to baseline. An isoelectric segment lasting for at least 1 minute was required between episodes. All episodes of ST depression that were identified on the trend analysis were validated by visual inspection of the ECG tracings, recorded at a paper speed of 25 mm/sec before, at the beginning, peak, and end of the ST depression. Artifacts, apparently positional changes, and upsloping ST depression of 1 mm or less at 0.06 msec after the J point were disregarded. Borderline ST depression was also not counted unless the configuration was clearly ischemic and similar to other episodes of ST depression of 1 mm or more in the same patient. The total number of
ischemic episodes and the cumulative duration were used as study end points. Heart rate was calculated 5 minutes before and at the peak of ST segment shift and as the mean per hour for the 72-hour recordings.

Intraobserver variability was studied by rereading in a blind fashion 50 tapes selected at random among the 941 study tapes. The coefficient of correlation between the two readings from the same patient was 0.93 for the number of episodes and 0.91 for the total duration. The interobserver reliability was studied by having 50 randomly selected tapes interpreted by an independent laboratory that also used the Cardiologia data Playback System. The coefficients of correlation between the two independent readings of the same patient were 0.87 for number of episodes and 0.90 for total duration of ischemic episodes.

Exercise Tolerance Testing

A maximal symptom-limited treadmill exercise test was performed at the baseline screening visit to identify eligible patients. The test was repeated at the end of each double-blind treatment phase, just before the end of the 72-hour continuous ECG recording period. All tests were performed in the morning, at the same time of day for each patient, and 2–3 hours after ingestion of a dose of the study drug. The Bruce protocol was used, and the following were recorded: blood pressure and heart rate at each stage and at each end point, reasons for stopping the test, time of onset of angina and of 1-mm ST depression, peak ST depression, maximum ST segment shift, and total exercise duration. The exercise tests were interpreted by the principal investigator at each clinical center.

Statistical Analysis

Data were analyzed using the SAS (Statistical Analysis System, Cary, N.C.), version 5.18 with Virtual Memory System. Because of the nonnormal distribution of angina frequency, nitroglycerin consumption, and frequency and duration of ischemia on Holter monitoring, statistical tests were performed by use of a parametric procedure (ANOVA) with the ranked data (Iman-Connover method28). Results for these data are presented as medians and ranges to comply with the nonnormal distribution and as means±SD as justified by the rank transformation of the data. Data on clinical characteristics and on the exercise test parameters followed a normal distribution and were analyzed by χ² and t statistics. They are presented as mean±SD.

Comparisons between the two treatments during the double-blind phase of the study were performed following the Grizzle model for a two-period Latin square design for repeated measures. Any possible residual (carry-over) effect and period effect can also be determined by this model. A center-by-treatment interaction was ruled out using a two-way analysis of variance for repeated measures. Interobserver and intraobserver variability in ambulatory ECG interpretation and the relation between episodes of ST segment depression and changes in heart rate were studied with regression correlation coefficients.

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Study Population at Entry Into Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Sex (n)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Previous myocardial infarction (n)</td>
</tr>
<tr>
<td>Previous hypertension (n)</td>
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<tr>
<td>Diabetes mellitus (n)</td>
</tr>
<tr>
<td>Previous smokers (n)</td>
</tr>
<tr>
<td>Nonsmokers (n)</td>
</tr>
<tr>
<td>Angina episodes (Number per wk)</td>
</tr>
<tr>
<td><strong>Functional class (n)</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td><strong>Electrocardiographic (n)</strong></td>
</tr>
<tr>
<td>Q wave present</td>
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<tr>
<td>1st degree AV block</td>
</tr>
<tr>
<td>Significant arrhythmias</td>
</tr>
<tr>
<td><strong>Angiographic</strong></td>
</tr>
<tr>
<td>With coronary angiography (n)</td>
</tr>
<tr>
<td>One-vessel disease</td>
</tr>
<tr>
<td>Two-vessel disease</td>
</tr>
<tr>
<td>Three-vessel disease</td>
</tr>
</tbody>
</table>

Values are mean±SD where applicable. Values in parentheses are percentages.

AV, atrioventricular.

The significance level for inferential procedures was fixed at 5%.

Results

Study Population

All 60 patients in this study had documented coronary artery disease and reversible ischemia, expressed as transient ST depression, both during daily life and during a treadmill exercise test. Coronary artery disease was documented by coronary angiography in 44 patients (73%), by a previous myocardial infarction in 18 (32%), and by a thallium exercise test showing a reversible perfusion defect in 29 (48%). Five patients had all three diagnostic criteria; 25 had two, and 30 had one criterion. Among the 30 patients with one diagnostic criterion, the disease was documented by angiography in 20 and by exercise thallium scintigraphy in 10. Angina during the treadmill test was present in 17 patients (28%); exercise was terminated during Bruce stage 2 in 21, during stage 3 in 32, during stage 4 in six, and during stage 5 in one. The clinical, ECG, and angiographic features of the patients at the time of entry into the study are listed in Table 1. The median number of chest pain episodes per week was 0 (range, 0–7) with a mean of 1.49±2.6 per patient. By entry criteria, no patient had chest pain at rest or during the night or had a clinical history suggestive of variable
Ambulatory ECG study. In 31 patients, maintained around 68.5 ± 12.9 minutes, or 10% of the total ischemic episodes (range, 0-5) with a mean of 0.34 ± 0.84 per patient, a median of 78.5 ± 175 ± 162 minutes during this period. The cumulative duration of ST depression exhibited a similar pattern.

The median number of episodes was 4.5 (range, 0–19) with placebo and 1.5 (range, 0–13) with diltiazem administration. Means were, respectively, 5.59 ± 3.78 and 2.83 ± 2.45, for a 50% reduction (p = 0.0001) (Figure 1). The cumulative duration of ST depression was similarly reduced by 44%, from a median of 78.5 (range, 0–60) minutes to 24.5 (range, 0–411) minutes, with a mean of 119 ± 107 to 67 ± 92 minutes (p = 0.001). The beneficial effect of diltiazem was maintained throughout the circadian cycle: the percent reduction in episodes was 54% from midnight to 6:00 AM, 48% from 6:00 AM to noon, 57% from noon to 6:00 PM, and 47% from 6:00 PM to midnight.

Average heart rate during the 72-hour placebo monitoring period was 74.3 ± 14.3 beats/min compared with 68.5 ± 12.9 during the diltiazem treatment period (p < 0.001). This reduction in heart rate was maintained around the clock, being only slightly less during the night compared with that during the day. The distribution of episodes of ST depression during both placebo and diltiazem treatment phases did not parallel the absolute heart rate distribution but was related to heart rate variation (Figure 2). Thus, the heart rate acceleration observed between 6:00 and 9:00 AM was accompanied by an increasing incidence of ischemic episodes and the slowing between 8:00 PM and midnight by a decreased incidence. With the more constant heart rate observed at other times, episodes of ST segment depression were stable, being slightly less with slower heart rates.

Episodes of ST depression occurred at a slower heart rate with diltiazem than with placebo treatment, 66.1 ± 9.8 beats/min versus 74.3 ± 9.8 (p = 0.001). Heart rate was, however, similar at the point of maximal ST depression, 114.1 ± 17.6 and 116.9 ± 16.4 beats/min. Blood pressure was recorded at the beginning and end of the monitoring period; systolic blood pressure was similar with placebo and diltiazem treatment, 129 ± 15 and 128 ± 15 mm Hg, but diastolic blood pressure was slightly lower with diltiazem, 77 ± 9 versus 81 ± 9 (p < 0.002).

The mean number of ventricular premature beats per hour was 26.4 ± 97.7 during screening, 31.3 ± 111 during placebo treatment, and 33.4 ± 135 during diltiazem treatment. Ventricular tachycardia was observed in 14 patients during the screening phase, in 12 patients during the placebo phase, and in only four patients during the diltiazem phase (p < 0.05).

Exercise Treadmill Test

Table 2 lists the hemodynamic, clinical, and ECG results of the exercise tests performed during screening and at the end of each treatment period. Heart rate and rate-pressure product both at rest and at peak exercise were significantly lower with diltiazem than with placebo treatment. ST depression occurred in 54 patients during the placebo test and in 45 during the diltiazem test (p = 0.03). Exercise was stopped because of angina or ST depres-
sion in 35% of the placebo tests and in 20% of the diltiazem tests ($p=0.05$). Time to 1-mm ST depression improved by 15% with diltiazem treatment, from 296±154 to 341±148 seconds ($p=0.005$). Total exercise duration improved by 6% with diltiazem treatment, from 467±156 to 494±143 seconds ($p=0.0004$), and furthermore, the amount of ST segment depression was reduced during the diltiazem tests, from 2.25±1.03 to 1.78±1.09 mm ($p=0.0002$). No correlations existed between the improvement in exercise tolerance and either mean heart rate reduction on the ambulatory ECG or reduction in the number of episodes of asymptomatic ST depression.
TABLE 2. Hemodynamic, Clinical, and Electrocardiographic Results of Exercise Testing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Screening</th>
<th>Placebo</th>
<th>Diltiazem</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74.5±11.2</td>
<td>77.0±12.2</td>
<td>68.8±12.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>134.3±13.7</td>
<td>128.7±14.6</td>
<td>128.4±15.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>10,032±1,981</td>
<td>9,945±2,157</td>
<td>8,910±2,218</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Peak exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>140.6±18.6</td>
<td>143.7±17.3</td>
<td>134.7±17.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>175.3±24.3</td>
<td>172.3±21.3</td>
<td>174.7±24.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>24,861±5,849</td>
<td>24,894±4,998</td>
<td>23,733±5,401</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression</td>
<td>60 (100)</td>
<td>54 (90)</td>
<td>45 (79)</td>
<td>0.03</td>
</tr>
<tr>
<td>With angina</td>
<td>17 (28)</td>
<td>15 (28)</td>
<td>1 (2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Without angina</td>
<td>43 (72)</td>
<td>39 (72)</td>
<td>44 (98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reason for stopping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain or ST depression</td>
<td>28 (46)</td>
<td>21 (35)</td>
<td>12 (20)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fatigue or dyspnea</td>
<td>31 (51)</td>
<td>39 (64)</td>
<td>48 (80)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total exercise duration (sec)</td>
<td>420±121</td>
<td>467±156</td>
<td>494±143</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Electrocardiographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to 1 mm ST depression (sec)</td>
<td>257±132</td>
<td>296±154</td>
<td>341±148</td>
<td>0.005</td>
</tr>
<tr>
<td>Time to maximum ST depression</td>
<td>403±113</td>
<td>447±156</td>
<td>479±141</td>
<td>0.005</td>
</tr>
<tr>
<td>Maximum ST depression (mm)</td>
<td>2.38±0.83</td>
<td>2.25±1.03</td>
<td>1.78±1.09</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Values are mean±SD. Values in parentheses are percentages.
BP, blood pressure.
p values compare placebo and diltiazem tests.

Clinical Observations

Anginal pain and nitroglycerin use were infrequent during the study. The median number of reported chest pain episodes was 0 (range, 0–45) during placebo treatment with 0 (range, 0–26) nitroglycerin tablets consumed. Respective means were 2.8±7.2 and 1.66±5.2. Patients reported 50% fewer episodes with a median of 0 (range, 0–21) and a mean of 1.43±3.3 during diltiazem treatment, and they reported 58% less nitroglycerin consumption with a median of 0 (range, 0–10) tablets and a mean of 0.69±1.87 tablets. These small numbers preclude any powerful statistical analysis.

During the diltiazem exercise test, angina occurred in only one of the 45 patients with ST depression compared with 15 of 54 patients during the placebo test (2% versus 28%, p<0.0001).

Of the 78 patients evaluated for adverse effects, including the 18 omitted from the efficacy analysis, one or more symptoms were reported during the diltiazem phase in 25 (32%) and during the placebo phase in 18 (23%). Most of these symptoms were minor and not necessarily drug related. The most frequently encountered in the diltiazem and placebo phases, respectively, were headache (13 and eight), fatigue (five and two), edema (four and three), nausea (four and three), and dizziness (three and two). During diltiazem therapy, intermittent periods of atrioventricular dissociation were observed in two patients and of Mobitz type I second-degree atrioventricular block in two others; these were asymptomatic.

In six patients, serious adverse events required termination of the study. During the placebo periods, two patients experienced a myocardial infarction and another died suddenly. During diltiazem therapy, one patient developed urticaria, one developed heart failure, and another reported worsening angina.

Discussion

In this study, diltiazem used as single therapy reduced by one half the frequency of silent ischemic episodes occurring during daily life. Exercise test parameters were also significantly improved, although the magnitude of the improvement was less than that observed during ambulatory ECG monitoring. Diltiazem also reduced angina attacks by one half, but this difference was not significant because angina was uncommon in these patients. Thus, the benefit of diltiazem on silent episodes could not be readily inferred from the symptomatic response of patients.

Characteristics of Silent Ischemia

As shown in previous studies, most episodes of ST depression occurring during daily life are not associated with symptoms. The 95% proportion of silent episodes in our study was somewhat higher than the 75–85% rates usually reported. The total number of episodes, as well as the frequency of angina, during placebo treatment was also in the low range of previously reported values. Our study population was selected to
include a relatively homogeneous group of patients with stable coronary artery disease, effort angina, a positive exercise test, and silent ST depression on ambulatory ECG monitoring to minimize the possibility of detecting a differential effect of diltiazem because of different population subsets. Most of the patients were nonsmoking men with multivessel disease.

The methodology and diagnostic criteria were similar to that used in most previous studies. Defining the beginning and the end of an episode as the point of change from baseline, rather than at 0.5 or 1 mm, affects the duration of an episode but not the number of episodes. A 72-hour monitoring period was selected because of the variability in the frequency and duration of episodes of ST depression. Previous studies have estimated sample size requirements for various degrees of therapeutic efficacy at different levels of power.

Longer monitoring periods with shorter intervals between them reduce sample size requirements. The large number of patients enrolled in our study and the long monitoring periods thus allow high statistical power to detect a beneficial effect.

Effect of Diltiazem

Previous studies indicate that long-acting nitrates, β-blockers, and calcium antagonists may be useful to control silent ischemia.

Sustained-release diltiazem was selected for this study because of its favorable effect on heart rate and because of our previous finding of a sustained protective effect against spontaneous angina and of increased exercise performance 12 hours after dose administration. The improvement in exercise test parameters in this study, with a reduction in heart rate and rate-pressure product at peak exercise, is similar to what we reported previously.

The 50% reduction in episodes of ST depression is consistent with the results of the retrospective study by Frishman and Teicher and with studies comparing diltiazem with propranolol and with atenolol. Different results were noted in a preliminary report of a recent double-blind randomized trial using propranolol, diltiazem, and nifedipine. In that report, the number of episodes of ST depression was reduced by 10% with diltiazem, a difference that was not significant, and by 52% with propranolol. Also, nifedipine had no detectable effect, and only diltiazem significantly prolonged total exercise duration. Why diltiazem was less effective in preventing silent ischemic episodes, compared with our study, is uncertain.

Mechanism of Action

The pathophysiological mechanisms involved in asymptomatic ST segment depression occurring during daily life, and the respective roles of increased myocardial oxygen demand or of decreased supply are as yet incompletely defined. The study does not allow an accurate characterization of myocardial oxygen demand because blood pressure and the inotropic state of the left ventricle were not continuously monitored. Some of the findings, however, may be relevant to the understanding of the mechanisms of silent ischemia.

First, ST segment depression occurred at a slower heart rate with diltiazem than with placebo treatment, and no circadian variation in the efficacy of diltiazem was found; the drug reduced both heart rate and ischemic episodes in a parallel and sustained fashion throughout the day. Second, the ischemic-type ST depression on ambulatory ECG monitoring was much more responsive to the drug than were any of the parameters measured during exercise testing. Third, the frequency of ST depression appeared to be modulated more by changes in heart rate than by the absolute heart rate. An accelerating heart rate was associated with a higher frequency of ischemic episodes, and the reverse was also true. When heart rate was relatively constant, episodes were less frequent. These observations suggest that one of the mechanisms involved in the pathogenesis of silent ischemia is a rapid rate of change in myocardial oxygen demand and that diltiazem has a beneficial effect by attenuating rapid increases in demand. Similar observations were recently made with ST depression occurring during treadmill exercise testing; with lower intensity exercise protocols, the onset of ST segment depression was delayed and occurred at a lower heart rate, documenting the importance of work load.

The relation between heart rate reduction and efficacy is, however, not clear. In the study by Khurmi et al using propranolol and in the study by Bonetti et al using atenolol, both diltiazem and the β-blocker were equally effective in preventing ischemia even though their effect on heart rate was markedly different. These results may reflect the importance of myocardial oxygen supply and also indicate the complexity of the interaction between supply and demand in response to various stimuli. It can be hypothesized that a common pathophysiological mechanism could lead to both an increase in demand and a reduced supply and that diltiazem could interact with this mechanism at different levels.

Exercise-induced ST depression was less frequent and, as judged by the maximum depth of ST depression, less severe during diltiazem compared with placebo exercise tests. Furthermore, during diltiazem exercise tests, ST depression was almost always silent (44 of 45 patients). There are two potential explanations for this finding. First, Margonato et al suggested in a preliminary report that diltiazem may have analgesic properties because it increased the pain threshold to three different types of stimuli. A second more likely explanation is that when diltiazem does not completely eliminate exercise-induced ischemia, it at least decreases its extent and severity and that the severity of ischemia is an important determinant of whether an episode is silent or painful.

Implications of the Study

This study demonstrates that sustained-release diltiazem can greatly reduce the frequency of silent ischemic episodes, thus extending the previously
well-documented antianginal activity of the drug. Whether medical treatment of silent ischemia improves prognosis has not been established but is currently being investigated in clinical trials. Whether the goal of therapy should be the elimination of all episodes, or whether a reduction in the number of episodes is helpful, is also unknown. These issues remain to be elucidated before recommending routine treatment of silent ischemia.

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References


Key Words • diltiazem • silent myocardial ischemia • ambulatory electrocardiographic monitoring
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