Anti-Ischemic Effects of Atenolol Versus Nifedipine in Patients With Coronary Artery Disease and Ambulatory Silent Ischemia

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The anti-ischemic effects of atenolol and nifedipine were compared in a randomized double-blind crossover manner in 24 patients with stable exertional angina and transient silent ischemia during ambulatory electrocardiographic monitoring. Both atenolol and nifedipine were effective (p < 0.005) in reducing the average number and duration of transient ischemic events, but therapy with atenolol was associated with a significantly greater reduction in the mean number (p < 0.05) and duration (p < 0.01) of silent ischemic events.

Analyses of the silent ischemic activity during the morning hours revealed that only therapy with atenolol produced a significant reduction in the average duration per patient (139 ± 54 vs. 1,699 ± 468 s, p < 0.01) and in the average duration of silent ischemia per event between 6 AM and 12 noon (62 ± 21 vs. 206 ± 24 s, p < 0.005). There were fewer adverse experiences during therapy with atenolol.

These results show that although both atenolol and nifedipine are effective in reducing silent ischemic events, treatment with atenolol is associated with significantly greater efficacy, particularly on the morning surge of silent myocardial ischemia.

Methods

Patient selection. Men with chronic exertional angina (≥6 months' duration) and documented coronary artery disease were enrolled from the cardiology clinics of the Fresno Veterans Affairs Medical Center between February 1, 1988 and December 31, 1988. The protocol and informed consent were approved by the center's human study and research committee in November 1987. All patients gave written informed consent for participation before enrollment in the study.

Coronary artery disease was documented by one or more of the following: coronary artery stenosis defined as ≥70% luminal diameter narrowing of one or more major coronary arteries; reversible perfusion defects on exercise thallium-201 scintigraphy; or presence of Q waves diagnostic of myocardial infarction on the 12 lead ECG. All patients had evidence of exercise-induced ischemia before entry into the study. Patients were excluded if they had conditions that precluded the use of a beta-blocker or a calcium channel blocker. These included significant bronchospasm or emphysema, greater than first degree atrioventricular (AV) block, congestive heart failure or sinus bradycardia <50 beats/min (without medication), and those with past hypersensitivity to nitrates (14) and calcium channel antagonists (15) in patients with silent myocardial ischemia. Direct comparison among the various classes of anti-ischemic drugs is lacking. This study was designed to assess and compare the anti-ischemic effects of titrated doses of atenolol and nifedipine on transient ischemic events detected during ambulatory electrocardiographic (ECG) monitoring in patients with stable angina.

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Silent myocardial ischemia occurs far more frequently than do anginal symptoms in patients with known coronary artery disease (1–3). In patients with stable exertional angina, silent ischemic events occur despite control of symptoms with conventional antianginal drugs (4). Because silent myocardial ischemia is not associated with any patient discomfort, treatment is generally not considered necessary. However, silent ischemia during daily life is associated with an increased risk of coronary events and cardiac death (5–7). Antianginal therapy should possibly be directed toward control of total ischemic burden, i.e., symptomatic and silent ischemia (8).

Several studies (9–12) have evaluated the effects of various drugs on the number, magnitude and duration of episodes of ST segment depression in patients with angina pectoris. However, most of these studies provide only indirect evaluation of therapy for silent ischemia since they were primarily conducted for testing the efficacy of antianginal drugs on angina frequency and ischemic threshold during exercise testing. Although some recent studies have specifically evaluated the role of beta-adrenergic blockers (13),
betablockers or calcium channel antagonists. Also excluded were patients with conditions (left bundle branch block, severe left ventricular hypertrophy, Wolff-Parkinson-White syndrome, pacemaker rhythms, uncorrected hypokalemia) or drugs (digitalis, tricyclic antidepressants) affecting the ST segment.

Study design (Fig. 1). Therapy with nitrates, calcium channel blockers and beta-adrenergic blockers was stopped for a minimum of 48 h or 3 half-lives of the prescribed drugs before enrollment in the study, but sublingual nitroglycerin was provided for relief of anginal symptoms. The study protocol (Fig. 1) consisted of a placebo run-in single blind study qualification phase lasting 7 to 10 days, during which time matching placebo drugs were administered and patients were asked to keep angina diaries. Patients underwent ambulatory ECG monitoring for 48 h at the end of the placebo phase. For study qualification all patients were required to have evidence of ambulatory ischemia during daily life with a minimum of five ischemic episodes or a total duration of ischemia ≥5 min/48 h. Patients who fulfilled these criteria were randomly assigned in a double blind manner to receive atenolol, 50 mg once daily (9:00 AM), or nifedipine, 20 mg three times daily (9:00 AM, 4:00 PM and 11:00 PM), for 1 week, when 48 h ambulatory ECG monitoring was repeated. If ischemia during ambulatory ECG monitoring was abolished, the treatment was continued at the same dosage for 2 more weeks. However, if ambulatory ECG monitoring at the end of 1 week revealed the presence of transient ischemia, the doses of study medications were increased: atenolol to 100 mg once daily or nifedipine to 30 mg three times daily and continued for 2 more weeks. Ambulatory ECG monitoring was repeated at the end of the 3 week treatment period (Fig. 1).

After the first active treatment phase all patients entered a second 1 week placebo period followed by crossover to the alternate treatment for 3 more weeks. The doses of study medications were titrated in similar fashion as described earlier. Ambulatory ECG monitoring was performed at 1 week and at the end of this phase.

Ambulatory ECG monitoring. Continuous 48 h two channel ambulatory ECG recordings were obtained at the end of placebo, withdrawal and active treatment phases with validated and calibrated amplitude modulated (AM) tape-recorders (series 8500 Holter recorder, Marquette Electronics) with a frequency-response between 0.05 and 100 Hz, which meets the American Heart Association standards for evaluation of the ST segment (16). A left precordial and an inferior or anterior ECG lead were selected and corresponded to the location of maximal ST segment depression during the exercise treadmill test. The ECG leads with Q waves or baseline ST segment depression were avoided. Baseline ECG recordings were made on each patient before and after hyperventilation, and in the supine, prone, sitting and standing positions to ensure that the ST segment was not affected by these changes in position. Patients were instructed to press an event button on the recorder if they experienced an episode of angina and to record the number and duration of episodes in a diary. The ambulatory ECG monitoring tapes were scanned at 60 to 120 times real time on a playback analyzer unit (8000 Holter analysis system, Marquette electronics) by an experienced technician for the presence, frequency and duration of ischemic episodes.

An ischemic episode was defined as ≥1 mm horizontal or downsloping ST depression measured 80 ms from the J point and lasting ≥1 min. The onset of the ischemic episode was defined as the time when the ST segment became depressed ≥1 mm and the offset time was defined after ST depression became <1 mm. An interval of at least 2 min during which the ST segment returned to the baseline was required before another episode was counted. The technician scanning the Holter tapes identified all potential ischemic episodes meeting these criteria and recorded the time of onset, peak ST depression and termination of ischemic events. Electrocardiographic tracings of these episodes were obtained at 25 mm/s speed for review. In addition, hourly examples of baseline ST segment without changes were recorded on paper. For each patient, the total number and duration of episodes were determined every 24 h. All episodes of ST segment depression were identified as symptomatic or silent on the basis of details obtained from the patient's diary.

Real-time printouts showing ST segment abnormalities were blindly and independently reviewed by at least two experienced investigators. In case of a discrepancy between the two observers, the tapes were reanalyzed. Only those recordings with interpretable signals for ≥40 h during the 48 h monitoring period were included in the analysis.

Statistical analysis. Continuous measures were assessed using two-sample t test; analyses of categorical variables were conducted using Fisher's exact test. In the double-
blind phase, analysis of the patients on each treatment (atenolol or nifedipine) who had abolition of ischemic events by the end of the respective active treatment period was accomplished using Fisher's exact test. The ischemic event-derived variables were evaluated using a repeated-measures crossover analysis of covariance, with the baseline measure of interest serving as the covariate. After preliminary tests showed no evidence of statistically significant carryover effects from baseline to the end of the intervening placebo washout period. Mean changes (±SE) within each active treatment from baseline to the end of the respective active treatment period were assessed using paired t tests. All statistical testing was performed at a two-sided significance level of ≥0.05.

**Results**

**Study patients (Table 1).** Of the 24 men enrolled, 5 were excluded during the placebo run-in period because they did not meet the qualification criteria for randomization. Three additional patients were excluded from the efficacy analysis because there were no ambulatory ECG monitoring data during one of the active treatment phases. The anti-ischemic efficacy of atenolol and nifedipine was compared in the remaining 16 patients with analyzable data during both active treatment periods. The baseline clinical characteristics of these patients are shown in Table 1. The mean age of the group was 63 ± 8 years, and the majority (95%) were Caucasian. All patients had an established history (average duration 7.4 ± 5.4 years) of coronary artery disease with chronic exertional angina and eight patients had a history of previous (>6 months) myocardial infarction. All patients had

<table>
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<th>Table 1. Baseline Clinical Characteristics of 16 Patients</th>
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<td><strong>Mean age ± SD (yr)</strong></td>
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<tr>
<td><strong>Mean duration of CAD ± SD (yr)</strong></td>
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<tr>
<td><strong>Diagnosis of coronary artery disease</strong></td>
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<tr>
<td>Previous MI (n)</td>
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<tr>
<td>Angiographic findings (n)</td>
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<tr>
<td>&lt;70% luminal obstruction</td>
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<tr>
<td>1 vessel (%)</td>
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<tr>
<td>Thallium-201 scintigraphy (n)</td>
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<td>Exercise test findings</td>
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<td>Total exercise time (min)</td>
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<td>DP (HR × SBP/100) at ischemia</td>
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<td>Ambulatory ECG findings</td>
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<td>Mean number of ischemic events ± SE</td>
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<td>Silent events (%)</td>
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<td>Mean duration of ischemic event (sec)</td>
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<td>Average duration/ischemic event ± SE (s)</td>
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CAD = coronary artery disease; DP = double (rate-pressure) product; ECG = electrocardiographic; HR = heart rate; MI = myocardial infarction; n = number of patients; SBP = systolic blood pressure; ST 1 = ST segment depression.

**Figure 2.** Comparison of anti-ischemic effects on the frequency (upper) and duration (lower) of ischemic episodes between the treatment groups. Compared with placebo, both atenolol (screened bar) and nifedipine (hatched bar) significantly (p ≤0.005) decreased the number of ischemic events during the monitoring period. However, atenolol was significantly better than nifedipine in reducing the frequency (p < 0.05) and duration (p < 0.01) of ischemic episodes.

**Hemodynamic effects of study medications.** The heart rate response and blood pressure were evaluated with the patient seated. The heart rate during the placebo phase was 80 ± 2 beats/min and was reduced significantly to 67 ± 2 beats/min during therapy with atenolol. In contrast, treatment with exercise-induced ischemia as well as evidence of transient myocardial ischemia (five or more episodes or ≥5 min duration/48 h) during ambulatory ECG monitoring.
Figure 3. Comparison of atenolol and nifedipine in totally suppressing ischemic activity. Treatment with atenolol abolished ischemic activity in more patients, particularly during the morning hours between 6:00 AM and 12:00 noon.

Nifedipine produced a slight increase in heart rate to 82 ± 1 beats/min. The systolic blood pressure was 145 ± 4 mm Hg during placebo and was reduced to 139 ± 3 and 138 ± 2 during therapy with atenolol and nifedipine, respectively. During placebo, the diastolic blood pressure was 86 ± 2 mm Hg and was reduced to 78 ± 1 and 79 ± 2 mm Hg, respectively, during therapy.

Ambulatory electrocardiographic monitoring results. (Fig. 2 and 3). During the placebo phase there was an average of 16.4 ± 3.7 episodes of transient myocardial ischemia, of which 97% were asymptomatic. The average duration of transient myocardial ischemia per patient was 4,103 ± 1,071 s during the 48 h ambulatory ECG monitoring period. Double blind therapy with atenolol or nifedipine produced a significant reduction in the number (p < 0.005 for both drugs) and duration (p < 0.005 for both drugs) of episodes compared with placebo (Fig. 2). Comparison between the anti-ischemic effects of the two drugs revealed that atenolol produced a significantly (p < 0.05) greater reduction in the average number of silent ischemic episodes (3.2 ± 0.7 vs. 6.2 ± 1.3) as well as in the total duration of silent ischemia (634 ± 155 vs. 1,296 ± 276 s, p < 0.01) (Fig. 2).

The evaluation of study medications in abolishing transient ischemia during the monitoring period revealed atenolol to be more effective than nifedipine. Treatment with atenolol was associated with a total suppression of ischemic activity in 50% of patients compared with only a 25% suppression rate with nifedipine (Fig. 3).

Effects of therapy on the morning surge of ambulatory ischemic activity (Fig. 4 to 6). Because it is known that there is a surge in silent ischemic events between 6:00 AM and noon, we evaluated the effects of study medications during this time period. During the placebo phase the hourly total number (Fig. 4) and duration (Fig. 5) of ischemic episodes showed a marked increase between 7:00 AM and 11:00 AM. Fifty percent of the ischemic episodes occurred between 6:00 AM and noon, and accounted for 39% (1,609 ± 468 s) of the total ischemic time per patient. Although both atenolol and nifedipine produced significant reductions in the number of ischemic episodes during these hours, treatment with atenolol was significantly (p < 0.05) more effective than treatment with nifedipine (Fig. 6). Only atenolol produced a significant reduction (p < 0.01) in the average duration of silent ischemia per patient (139 ± 54 vs. 1,609 ± 468 s, p < 0.01) during this period. The average duration per silent ischemic episode was also significantly (p < 0.005) reduced only with atenolol (62 ± 21 vs. 208 ± 24 s). Although the difference was not statistically significant, atenolol abolished the morning surge of ischemic activity in 64% of the patients compared with the suppression rate of 27% during therapy with nifedipine (Fig. 3).

Adverse effects. Fewer adverse experiences were reported during atenolol therapy than were reported during treatment with nifedipine. During treatment with nifedipine dizziness was noted in five patients, peripheral edema in four, asthenia in four and paresthesia in two. In contrast, only two patients reported asthenia during therapy with atenolol.

Figure 4. Hourly distribution of the total number of ischemic episodes between 6:00 AM and 12 noon during placebo and active treatment periods.
Discussion

Pathogenesis of silent ischemia in patients with angina

Appropriate selection of a therapeutic regimen should be based on the underlying pathophysiologic process. Although the precise mechanism of silent myocardial ischemia has not been established, on the basis of data showing minimal or no increase in heart rate during the 5 to 15 min preceding silent ischemic events, it has been postulated that silent ischemia during daily life occurs predominantly as a result of decrease in coronary blood supply (17,18). This concept has been further supported by findings that show that heart rate is significantly lower at the onset of silent ischemic events during daily life than during exercise testing in the same patients (17). However, findings from recent studies in patients with chronic exertional angina demonstrate that most episodes of ambulatory silent ischemia are preceded by a significant increase in heart rate and blood pressure (19,20). Furthermore, silent ischemic events have been shown to increase in frequency as well as duration during the morning hours when both heart rate and blood pressure have the greatest increases during the 24 h period (21).

These data, along with the results of recent reports (10–13) showing beneficial effects of beta-blocking agents in the treatment of silent ischemic episodes, have clearly established a role of increased myocardial oxygen demand in the pathogenesis of ambulatory silent ischemia. Nevertheless, some episodes of silent ischemia occur without any evidence for increased myocardial oxygen demand and clearly must occur secondary to alterations in coronary blood supply (20).

Previous studies in therapy of silent ischemia. The anti-ischemic therapy for control of silent ischemic events will vary depending on the clinical subsets of patients being treated and the predominant mechanism responsible for the ischemic episodes. All antianginal agents, including nitrates, adrenergic blockers (both alpha- and beta-blocking drugs) and calcium channel blockers, are effective in the management of patients with angina pectoris and have been shown to reduce the number and duration of ST segment depression during ambulatory ECG monitoring (9–12). However, most of these studies were primarily designed to demonstrate the antianginal efficacy of these drugs and did not specifically evaluate the effects on ambulatory silent ischemia.

Several studies (13–15) have specifically evaluated the anti-ischemic effects of nitrates, beta-blockers and calcium channel blockers in patients with demonstrable silent myocardial ischemia. Although the results of these studies show that all antianginal drugs are effective in reducing the frequency and duration of silent ischemic events, careful evaluation reveals considerable variation in their efficacy. It has been suggested (13,15) that drugs that lower heart rate are more effective in controlling silent ischemic events during daily life. However, little information is available regarding direct comparison of anti-ischemic agents with different hemodynamic effects in the treatment of patients with transient myocardial ischemia during routine daily activities.

Anti-ischemic efficacy of atenolol and nifedipine during ambulatory ECG monitoring. This study shows that both atenolol and nifedipine are effective in reducing the frequency and duration of silent ischemic events during daily life. Atenolol was significantly (p < 0.05) more effective than nifedipine in reducing the average number and average duration of silent ischemic events during the monitoring period. Also more patients (50% vs. 25%) were free of silent ischemia during therapy with atenolol.

Although we cannot provide a specific reason for the difference in the anti-ischemic efficacy of atenolol and nifedipine in this study, there are several possible explanations. Beta-blockers exert their beneficial effects in patients with angina pectoris primarily by reducing the heart rate, systolic blood pressure and cardiac contractility (22,23). Because all of our patients had evidence of exertional myocardial ischemia, it is likely that an increase in myocardial oxygen demand played a significant role in the genesis of ambulatory silent ischemia in these patients. Because atenolol produced a significant reduction in the heart rate response it is likely that this effect is partially responsible for its greater antiischemic efficacy. Our results are similar to those reported...
Figure 6. Comparison of effects of atenolol and nifedipine on the frequency (upper) and duration (lower) of silent ischemic episodes during the morning hours of 6:00 AM to 12:00 noon. Both treatments produced a significant reduction in the frequency of ischemic episodes, but the treatment with atenolol produced a greater (p < 0.05) reduction in the number of ischemic episodes. During the morning hours, only atenolol produced a significant (p < 0.01) reduction in the average duration of ambulatory silent ischemia.

Previously with metoprolol in a smaller group of patients with silent myocardial ischemia (13).

Treatment with nifedipine also produced a significant reduction in the number and duration of silent ischemic events; however, its anti-ischemic effects were less remarkable than those of atenolol. Although nifedipine was associated with a smaller degree of reduction in blood pressure, it failed to lower the heart rate response, which may partly account for its lesser anti-ischemic efficacy in our patients.

Role of atenolol in reducing silent ischemia during the early morning hours. The atenolol was significantly more effective (p < 0.05) than nifedipine in suppressing the ischemic activity during the morning hours between 6:00 AM and noon (Fig. 6). This suggests significant residual anti-ischemic effect of atenolol 24 h after dosing and is consistent with previous data (24) showing sustained beta-blocking efficacy of atenolol during a similar dosing schedule. Because nifedipine has a relatively shorter half-life (6 to 8 h) and was given at 11:00 PM and 9:00 AM, it is possible that a therapeutic gap existed between 6:00 AM and 10:00 AM (Fig. 4 and 5).

Although this hypothesis is not established, the morning surge in transient ischemic events may act as a trigger for acute myocardial infarction and sudden cardiac death, which occur with increased frequency during this time period. The anti-ischemic effects of atenolol in suppressing the morning surge of ischemic activity may prove beneficial in reducing the risk of myocardial infarction and sudden cardiac death (25).

Conclusions. Atenolol and nifedipine are effective anti-ischemic drugs in the treatment of ambulatory silent ischemia. In most patients, atenolol effectively reduced the morning surge of ischemic activity and abolished silent ischemia between 6:00 AM and noon. Treatment with atenolol may reduce the risk of acute myocardial infarction and sudden cardiac death by suppressing silent ischemic events, particularly during the morning hours when the risk of these events is significantly increased. Large controlled studies are needed, however, to document the beneficial effects of anti-ischemic therapy in patients with ambulatory silent ischemia.

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References