Suppression of Silent Ischemia by Metoprolol Without Alteration of Morning Increase of Platelet Aggregability in Patients With Stable Coronary Artery Disease

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To determine the effect of metoprolol on silent ischemia and platelet aggregability, 10 patients with coronary artery disease were studied with a randomized, double-blind, placebo-controlled, crossover trial. Patients were treated with metoprolol (200 mg b.i.d.) or placebo for 1 week and then received the alternate therapy. Two days before the end of each treatment period, platelet aggregability was studied for 24 hours, and a 48-hour ambulatory electrocardiogram was obtained. Compared with placebo, metoprolol significantly decreased the total number (from 26 to 4, \( p < 0.01 \)) and duration (from 735 to 84 minutes, \( p < 0.01 \)) of silent ischemic episodes. This decrease was accompanied by a decrease in the mean blood pressure (from 127/81 to 118/71 mm Hg, \( p < 0.01 \)) and the mean heart rate (from 70 to 54 beats/min, \( p < 0.01 \)). The incidence of silent ischemic episodes in the morning was significantly higher in untreated patients than in treated patients. The few episodes observed during metoprolol treatment occurred at the same time as the peak incidence observed during placebo treatment. During placebo treatment, platelet aggregability increased from 6:00 to 9:00 AM as reflected by a decrease in the threshold concentrations of ADP and epinephrine required to induce biphasic platelet aggregation (from 4.8±0.8 to 2.6±0.4 \( \mu \)M, \( p < 0.02 \); and from 7.3±2.3 to 1.8±0.9 \( \mu \)M, respectively, \( p < 0.02 \)). Metoprolol did not alter the basal level nor blunt the morning increase of platelet aggregability. We conclude that patients with coronary artery disease have a marked increase in platelet aggregability from 6:00 to 9:00 AM that is not affected by \( \beta \)-adrenergic blockade with metoprolol. Despite not affecting platelet aggregability, metoprolol compared with placebo decreases the number and duration of silent ischemic episodes. The decrease in the frequency of silent ischemic episodes is accompanied by a decrease in blood pressure and heart rate, suggesting that the beneficial effect of metoprolol is due, at least in part, to a reduction of myocardial oxygen demand and not to inhibition of transient platelet aggregation. The morning surge of transient ischemic events can be effectively blocked without changing platelet aggregability. (Circulation 1989;79:557–565)

The incidence of myocardial infarction, sudden cardiac death, stroke, and episodes of reversible myocardial ischemia markedly increase in the late morning.\(^1\)-\(^8\) Although the mechanisms responsible for this increase are unknown, a number of factors, such as increased coronary vasomotor tone, increased heart rate, and increased arterial pressure (possibly leading to plaque fissure) probably contribute to disease onset.\(^9\)-\(^11\) A morning increase in platelet aggregability, as has been shown in normal subjects,\(^12\) may also contribute to the increased incidence of cardiovascular events in the morning, but it has not been proven that such an increase in platelet aggregability occurs in patients with coronary artery disease.

The processes causing a morning increase in reversible ischemia may be different from those...
producing a morning increase in myocardial infarction, sudden cardiac death, or stroke because the latter are associated with formation of a fixed intraluminal thrombus. The sympathetic nervous system, which itself shows a morning increase in activity as a surge of plasma catecholamine levels, heart rate, and blood pressure, may be a principal pathophysiologic mechanism underlying the morning increase of reversible myocardial ischemia. The relation of the morning sympathetic surge to platelet aggregability and the relation of platelet aggregability to episodes of reversible ischemia are unclear.

In vitro and in vivo investigations have shown that increased concentrations of epinephrine and norepinephrine increase platelet aggregability, but the effect of \( \beta \)-adrenergic blockade on the morning surge of platelet aggregability has not been studied.

The effect of \( \beta \)-adrenergic blocking agents on platelet aggregability is also controversial. There are reports that \( \beta \)-adrenergic blockade may reduce platelet aggregability in vitro and in vivo, and clinical studies in patients after myocardial infarction suggest that some of the cardioprotective effects of \( \beta \)-blockers may, at least in part, be due to an antiplatelet effect. Other investigators, however, have reported that \( \beta \)-blockers do not reduce platelet aggregability, that the concentration required to inhibit platelet aggregability in vitro exceeds that obtained physiologically, or that these agents may even increase platelet aggregability. Although their effect on platelet aggregability is uncertain, \( \beta \)-adrenergic blocking agents have been well documented to reduce the frequency of episodes of silent ischemia in patients with effort angina. The role of a \( \beta \)-blocker–induced effect on platelet aggregability leading to a reduction in episodes of silent ischemia has not been previously studied.

The purposes of this study, therefore, were 1) to determine whether or not the morning increase in platelet aggregability observed in normal individuals also exists in patients with coronary artery disease; 2) to determine the effect of metoprolol on the morning increase in platelet aggregability; and 3) to elucidate the mechanisms suppressing silent ischemia by metoprolol by comparing its effect on transient myocardial ischemia, platelet aggregability, and determinants of myocardial oxygen demand.

**Methods**

**Study Design**

In a randomized, double-blind, placebo-controlled, crossover trial, 10 patients (two women, eight men; range, 52–77 years of age) were studied. Each patient had coronary artery disease documented by at least one of the following criteria: luminal diameter stenosis 70% or greater of one or more major coronary arteries or of their primary branches observed at coronary angiography, history of previous myocardial infarction, history of coronary artery bypass surgery, or exercise tread-

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**SCHEDULE OF STUDY EVENTS**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
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<tbody>
<tr>
<td>Metoprolol</td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>Metoprolol</td>
</tr>
</tbody>
</table>

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*Refers to 24-hour ambulatory ECG monitoring

**FIGURE 1. Protocol of the randomized, double-blind, placebo-controlled, crossover trial included two phases (metoprolol and placebo) treatment. Each was divided into an out-of-hospital period (7 days), an in-hospital period (1 day), and another out-of-hospital period (1 day). Patients were randomly assigned to start either with metoprolol therapy (Group A) or placebo (Group B), and then crossed over to the alternate therapy.*

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mill test showing horizontal or down sloping ST segment depression 1 mm or greater associated with an area of relatively decreased \( ^{203} \text{TI} \) radionuclide uptake. Eligibility criteria also included isoelectric resting ST segments that did not deviate with change in body position or hyperventilation. Exclusion criteria were a myocardial infarction within the previous 3 months, unstable angina pectoris, use of a medication that could interfere with platelet aggregation (including aspirin, nonsteroidal anti-inflammatory agents, heparin, coumadin, and calcium channel blockers), the presence of left ventricular hypertrophy or bundle branch block, and use of digitalis glycosides. The study was approved by the Human Subjects Committee of the Brigham and Women’s Hospital, Boston, Massachusetts, and all patients gave informed consent.

The patient’s standardized schedule was for 18 days and was divided into two phases (metoprolol and placebo phase, Figure 1). Each phase included an out-of-hospital period (7 days), an in-hospital period (1 day), and another out-of-hospital period (1 day). During the first out-of-hospital period, metoprolol or placebo was titrated during a 3-day period from an initial dosage of 50 mg b.i.d. to a final dosage of 200 mg b.i.d. administered at 7:00 AM and 7:00 PM. The patients were instructed to contact an investigator immediately in case of any side effects, to reduce the dosage (to 100 mg b.i.d.), or, in case of persistent side effects, to be excluded from the study. Seven and 16 days after initiation of the study, the patients were admitted for a 24-hour in-hospital period to the Clinical Research Center of Brigham and Women’s Hospital. During the 24 hours, nine venous blood samples were drawn at 3-hour intervals (separate venipuncture each time) starting and ending at noon for measuring platelet aggregability, plasma norepinephrine and epinephrine levels, and platelet and hematocrit count. Pulse
rate and systemic arterial pressure were recorded 15 minutes after each blood drawing. The patients followed a standardized schedule and diet and performed their routine daily physical activities. Patients underwent ambulatory electrocardiographic (ECG) monitoring for 48 hours: 24 hours during the hospitalization and the initial 24 hours after discharge. Patients were given a diary during the ambulatory ECG monitoring period to record the occurrence and time of anginal episodes. The diary entries were reviewed by the study nurse with the patient to ensure accuracy. After completion of the phase 1 48-hour ambulatory ECG, the patients were crossed over to receive the alternate therapy. During the 3 days, metoprolol or placebo dosage was tapered off, overlapping with titration of the alternate regimen. After completion of phase 2 48-hour ambulatory ECG, the study medication was tapered off during the following 3 days. Starting at least 10 days before the study, the patients abstained from nonstudy antianginal medication for the duration of the study except for self-administration of sublingual nitroglycerin as needed for angina.

Laboratory Methods

Ambulatory electrocardiographic analysis. Ambulatory ECG recordings were done with CardioData AM Cassette Recorders (Marlboro, Massachusetts). The recordings were analyzed with a CardioData Mk 4 playback system with modified software. Both the technician and the physician reviewer were unaware of patient identification and treatment phase. In the algorithm, an ischemic episode was defined as transient ischemic ST segment depression 1.0 mm or greater lasting at least 1 minute. The onset of the episode was defined as the time at which the ST segment became depressed 0.5 mm or greater, and the offset was defined as the time after the peak depression 1.0 mm or greater at which the ST segment returned toward the baseline and became depressed less than 0.5 mm. After an episode of ST segment depression, the baseline had to remain stable and without deviation for at least 5 minutes before new ST segment depression could qualify as a discrete additional episode. The variables evaluated included number and total and average duration of episodes of ischemic ST segment depression. Other variables noted were the maximum ST segment depression, the product of depth of ST segment depression and duration of the episode, and the ST segment depression integral, defined as the sum of the ST segment depression at each 30-second period for the duration of the episode. Episodes of ischemia identified by the ambulatory ECG were correlated with symptoms identified in the patient’s diary to determine whether the ischemic events were silent or associated with angina.

Platelet aggregability. At each time point, 20 ml venous blood were drawn with a 21 gauge butterfly needle by an experienced technician who did not know the treatment the patient was receiving nor the occurrence of ischemia identified by the ambulatory ECG. ADP- and epinephrine-induced platelet aggregability was determined in platelet-rich plasma by aggregometry. Details of the procedure and analysis have been previously described. All aggregometry tracings were analyzed by one investigator (G.H.T.) who was unaware of when the blood sample was taken and of the treatment received by the patient.

Hematologic measurements. Hematocrit and platelet counts were made in whole blood with a Coulter Counter (Coulter Electronics, Hialeah, Florida). Platelet count in platelet-rich plasma was determined with a Model R1 Coulter Counter.

Plasma catecholamines. Plasma norepinephrine and epinephrine were analyzed by a modification of the differential isotopic radioimmunoassay of Pueler and Johnson.

Relation Between Platelet Aggregability and Episodes of Ischemia

To determine the relation between platelet aggregability and the frequency of ischemic episodes, a comparison was made between the threshold concentrations of ADP and epinephrine required to produce platelet aggregation just before episodes of silent ischemia and the respective threshold concentrations at times when ischemia was not present. The analyses were performed for the placebo period, for the metoprolol period, and for both periods combined.

Statistical Analysis

The mean values of two treatment phases or two time points of platelet aggregability were compared by the two tailed paired t test for normally distributed values and the Wilcoxon’s signed rank test for values that were not normally distributed. Categorical data were compared by the \( \chi^2 \) test. Continuous variables are expressed as mean ± SE. Analysis of the threshold concentrations of ADP and epinephrine required to produce platelet aggregation and the frequency of ischemic episodes was performed with the Wilcoxon’s nonpaired rank sum total. The level of significance was considered as \( p \) less than 0.05.

Results

Effect of Metoprolol on Episodes of Silent Ischemia

None of the patients experienced angina during the 48-hour ambulatory ECG recording, although eight (80%) of the 10 study patients had episodes of silent ischemia. The frequency distribution of the episodes of silent ischemia is as follows. During the placebo phase, four patients experienced one episode of silent ischemia, and four patients had four or more episodes (one patient each manifested 4, 5, 6, or 7 episodes). During the metoprolol phase, only three patients had evidence of silent ischemia. Two
patients had one episode, and one patient had two episodes. All patients tolerated metoprolol 200 b.i.d. without major side effects. Compared with placebo therapy, metoprolol significantly reduced the total number of ischemic episodes from 26 to four \((p<0.01)\) and reduced the total duration of ischemia from 735 to 84 minutes \((p<0.01)\) (Figure 2). Average duration of the ischemic episodes, maximum ST segment depression, and integral of ST segment depression of the ischemic episodes did not differ during the two treatment phases (Table 1). The heart rate 5 and 2 minutes before the episode and at the onset of the episode and the maximum heart rate during the episode were significantly lower during metoprolol treatment compared with placebo; however, the difference in heart rate between 5 minutes before the episode and the peak heart rate during the episode was similar between the phases (Table 1). During placebo treatment, the peak incidence of ischemic episodes occurred in the morning (46% occurred between 6:00 AM and noon, \(p<0.01\) compared with other times of day [Figure 3A]). There were no ischemic episodes between midnight and 6:00 AM. Administration of metoprolol was associated with a reduction in episodes throughout the day, although the distribution of episodes still exhibited a distinct peak at the same time of day as the peak observed during the placebo phase.

**Effect of Metoprolol on Systemic Arterial Pressure and Heart Rate**

Compared with placebo, metoprolol decreased mean systolic arterial blood pressure during the in-hospital phase from 127±2 to 118±2 mm Hg \((p<0.01)\), mean diastolic pressure from 81±1 to 71±1 mm Hg \((p<0.01)\), and mean heart rate from 70±1 to 54±1 beats/min \((p<0.01)\).

**Relation Between Platelet Aggregability and Onset of Ischemic Episodes**

During the placebo treatment period, the mean threshold concentration of ADP required to produce platelet aggregation at the sampling interval immediately before episodes of ischemia was 3.7±0.6 \(\mu\text{M}\), whereas the mean threshold concentration of ADP at sampling intervals when ischemia did not occur was 3.5±0.3 \(\mu\text{M}\) \((p=NS)\). The respective values for the mean threshold concentrations of epinephrine were 4.6±1.7 versus 4.8±1.0 \(\mu\text{M}\) \((p=NS)\). During the metoprolol period, not enough episodes of ischemia occurred to allow for meaningful analysis. Combining both the placebo and metoprolol treatment periods, the respective values for the mean threshold concentration of ADP were 3.4±0.5 versus 3.1±0.2 \(\mu\text{M}\) \((p=NS)\), and the values for epinephrine were 4.1±1.4 versus 3.7±0.7 \(\mu\text{M}\) \((p=NS)\).

**Effect of Metoprolol on Platelet Aggregability**

*Morning increase of platelet aggregability.* During placebo treatment, platelet aggregability exhibited a marked increase from 6:00 to 9:00 AM as indicated by significant decreases in threshold concentrations of ADP (from 4.8±0.8 to 2.6±0.4 \(\mu\text{M}\),

**Table 1. Effect of Metoprolol in Silent Ischemia**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Placebo</th>
<th>Metoprolol</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total episodes (n)</td>
<td>26</td>
<td>4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total duration of ischemia (min)</td>
<td>735</td>
<td>84</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average duration of episodes (min)</td>
<td>28±5</td>
<td>21±8</td>
<td>NS</td>
</tr>
<tr>
<td>Average maximum ST segment depression (mm)</td>
<td>1.7±0.1</td>
<td>1.5±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Average integral of ST segment depression (mm/min)</td>
<td>24±5</td>
<td>18±10</td>
<td>NS</td>
</tr>
<tr>
<td>Average heart rate 5 min before episode (beats/min)</td>
<td>88±3</td>
<td>58±2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average heart rate 2 min before episode (beats/min)</td>
<td>91±3</td>
<td>67±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average heart rate at onset of episode (beats/min)</td>
<td>100±3</td>
<td>73±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average maximum heart rate during episode (beats/min)</td>
<td>115±3</td>
<td>89±7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Difference in heart rate from 5 min before episode to maximum during episode (beats/min)</td>
<td>27±2</td>
<td>32±5</td>
<td>NS</td>
</tr>
</tbody>
</table>
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p<0.02) and epinephrine (from 7.3±2.3 to 1.8±0.9 μM, p<0.02) required to produce biphasic platelet aggregation (Figures 3B and 3C). Platelet aggregability was not altered by metoprolol therapy. During placebo therapy, platelet and hematocrit counts in whole blood did not increase from 6:00 to 9:00 AM (238±19 vs. 236±13 counts/nl, p=NS; 39±1% vs. 40±1%, p=NS, respectively), but platelet count in platelet-rich plasma did increase during this period (from 226±26 to 268±21 counts/nl, p<0.05).

Effect of metoprolol on basal level of platelet aggregability. Metoprolol did not alter the basal level of platelet aggregability (Figures 3B and 3C). Basal level of platelet aggregability, expressed as the mean threshold concentrations of all samples for ADP during metoprolol treatment, was 3.5±0.3 versus 3.3±0.2 μM during placebo treatment (p=NS). For epinephrine, the corresponding value was 3.5±0.6 μM during metoprolol treatment versus 4.2±0.6 μM during placebo treatment (p=NS).

Compared with placebo, metoprolol did not alter the mean platelet count in whole blood (248±4 vs. 243±4 counts/nl, p=NS) and platelet-rich plasma (241±7 vs. 238±7 counts/nl, p=NS) nor the mean hematocrit count (40±0.3% vs. 39±0.3%, p=NS).

Effect of Metoprolol on Plasma Norepinephrine and Epinephrine Levels

During the placebo treatment period, the plasma norepinephrine level increased between 6:00 and 9:00 AM from 221±14 to 362±31 pg/ml (p<0.01, Figure 4A). Compared with placebo, metoprolol did not blunt the morning surge, but it increased the 24-hour average level of plasma norepinephrine from 309±23 to 392±37 pg/ml (p<0.01). During the placebo period, the plasma epinephrine level increased between 6:00 and 9:00 AM from 31±3 to 53±7 pg/ml (p<0.05, Figure 4B). Metoprolol did not suppress the morning surge of plasma epinephrine level. During metoprolol therapy, there was a trend toward an increased 24-hour average level of plasma epinephrine from 45±5 to 55±6 pg/ml (p<0.07).

Discussion

This study shows that patients with coronary artery disease exhibit a morning increase in platelet aggregability similar to that previously reported for normal subjects. This increase was not affected by β-adrenergic blockade with metoprolol, which effectively reduced the number of episodes of silent ischemia. The significant decrease in number and duration of episodes of silent ischemia during metoprolol treatment compared with placebo was accompanied by a decrease in blood pressure and heart rate but not by a decrease in platelet aggregability, suggesting that the anti-ischemic effect was caused by a reduction of myocardial oxygen demand. During either the placebo- or metoprolol-treatment period, there was no increase in platelet aggregability before episodes of ischemia compared with periods during which ischemia was not present. The observations in this study are limited by the use of the in vitro aggregometry method, which cannot be assumed to reflect in vivo changes. However, this method is the most widely used test of platelet function, and the agonists used are those suspected of promoting in vivo platelet aggregation.

Effect of Metoprolol on Silent Ischemia

Episodes of silent ischemia, as evidenced by transient ST segment depression during ambulatory ECG monitoring, are common in patients with documented coronary artery disease, although the mechanisms responsible for such episodes are
unknown. Because episodes of silent ischemia during ambulatory activities out-of-hospital occur at a lower heart rate than episodes of ischemia during a supervised exercise test, transient vasoconstriction may be responsible for some episodes, although it is unknown whether the transient vasoconstriction is due to central neurogenic phenomena, primary defects in the endothelium of the coronary artery, or to an interaction between circulating platelets and the blood vessel wall leading to release of vasoconstrictive humoral factors. The contribution of transient platelet aggregation to the mechanism of reversible ischemia in patients with stable angina is suggested by the observation that ticlopidine, a potent antiplatelet agent, is associated with a reduction in episodes of silent ischemia. Other investigators, however, have not confirmed these results. The role of platelets in episodes of reversible ischemia is further supported by the laboratory studies of Folts and coworkers, who observed episodic reductions in coronary flow in a vessel partially obstructed by a ligature. The episodes of reduced coronary perfusion were due to transient platelet aggregates obstructing the vessel lumen. Aspirin prevented the formation of platelet aggregations and the cyclic reductions in blood flow. On the other hand, other investigators consider the mechanism of asymptomatic myocardial ischemia to represent a primary increase in myocardial oxygen demand, as suggested by the observation that episodes of out-of-hospital silent ischemia are generally preceded by a significant increase in heart rate.

Our results indicate that metoprolol is effective in reducing the frequency and duration of episodes of silent ischemia and that this anti-ischemic effect is due primarily to its ability to reduce myocardial oxygen demand and not to an effect on platelet aggregability. Metoprolol may also have had a beneficial effect on episodes of myocardial ischemia by prolonging diastole and providing more time for coronary flow. The concept that metoprolol does not exert its beneficial effect by decreasing platelet aggregability is supported by the observation that there was no temporal relation between episodes of silent ischemia and increases in platelet aggregability. Imperi and coworkers recently showed that metoprolol's effect of decreasing episodes of silent ischemia was associated with a reduced heart rate both at the onset of myocardial ischemia and at the heart rate rise occurring after the onset of ischemia. Our data confirm that metoprolol lowers the heart rate before the onset of ischemia, at the onset of ischemia, and at the maximum heart rate during the episode. We found, however, unlike the results of Imperi et al, that metoprolol did not blunt the heart rate rise occurring during the episodes of ischemia.

During the placebo-treatment period, there was a marked circadian variation in the incidence of episodes of silent ischemia, with a peak incidence in the morning hours after awakening as has been reported by others. During metoprolol treatment, the few episodes that were observed also occurred at the same time as the peaks during placebo treatment. Imperi et al similarly observed that metoprolol attenuated, but did not abolish, the circadian variation in silent ischemia. In studies of hypertensive patients, metoprolol has been shown only to blunt, and not to abolish, the morning surge in heart rate and blood pressure. It is unclear whether the circadian variation of episodes of silent ischemia is due to periodic increases in myocardial oxygen demand (heart rate and blood pressure), to episodic increases in coronary vasomotor tone, or to other factors yet to be identified.

**Figure 4.** Plots of plasma norepinephrine (Panel A) and epinephrine (Panel B) levels at different times of day. From 6:00 to 9:00 AM, a significant increase occurred in plasma norepinephrine and epinephrine during the placebo phase. Compared with placebo, metoprolol increased the 24-hour average level of plasma norepinephrine (p < 0.01) and tended to increase the 24-hour average level of epinephrine (p < 0.07), but it did not alter the morning increase of plasma catecholamine levels.
Although metoprolol is an effective antianginal agent by reducing the determinants of myocardial oxygen demand, the observation that ischemia occurred at a heart rate lower during metoprolol therapy than during placebo therapy indicates that metoprolol may be exerting a minor adverse effect by reducing the ischemia threshold, perhaps by facilitating vasoconstriction. Nonselective β-blockade with propranolol potentiates the coronary vasoconstrictive response to a cold pressor stimulus in patients with chronic stable angina studied in the catheterization laboratory, but this effect of reducing myocardial oxygen supply has not been shown to occur clinically in patients with stable coronary disease. The potentiation of coronary vasoconstriction has not been shown with cardioselective β-blockers. Although metoprolol may be exerting a minor adverse effect on coronary flow, its net clinical effect is a major reduction in the manifestations of ischemia.

Effect of Metoprolol on Platelet Aggregability

Epidemiologic and clinical studies have shown a significant morning increase in the incidence of myocardial infarction, sudden cardiac death, and transient myocardial ischemia. Because platelet aggregability has been shown to have an important role in the pathophysiologic mechanism of unstable angina, sudden cardiac death, and myocardial infarction, recent evidence of an increase in platelet aggregability during the same time frame provided a possible explanation for the morning increase in the incidence of these diseases. The importance of platelets in the onset of myocardial infarction has been underscored recently by the demonstration that even apparently healthy individuals can achieve a 45% reduction in the incidence of infarction when treated with aspirin. Previous studies of the morning increase of platelet aggregability, however, were limited to healthy male volunteers, a group not at high risk for cardiovascular disease. The present study shows the presence of a morning increase in platelet aggregability in patients with coronary artery disease who have a much higher risk of developing unstable angina, myocardial infarction, and sudden cardiac death. The basal level of platelet aggregability tended to be lower in the patients enrolled in this study compared with the previous study on normal subjects, a finding at variance with previous reports that platelet aggregability is higher in patients with coronary artery disease than in normal individuals. The cardioprotective effect of β-adrenergic blockade may, in part, be due to an antiplatelet action. However, a recent study showed a marked increased incidence of left ventricular thrombi in patients treated with the nonselective β-blocker timolol after acute myocardial infarction compared with the control group, although it is unknown whether this finding is related to an effect of the β-blocker on platelets or to an effect on left ventricular wall motion. In addition, nonselective β-blockers may increase platelet aggregability. The present study shows that the relatively selective β-blocker metoprolol does not have an adverse effect on platelet aggregability.

Clinical Implications

Episodes of transient asymptomatic ischemia in patients with coronary disease are probably due to a combination of reduced myocardial oxygen supply (transient vasoconstriction) and increased myocardial oxygen demand (transient increase in heart rate and/or blood pressure), a concept supported by the observations that β-adrenergic blockers and calcium channel blockers each reduce episodes of silent ischemia out-of-hospital but that a combination of the two agents used together is more effective than either used alone. Although an increase in platelet aggregability in the morning coincides with an increase in the incidence of episodes of silent ischemia, a causal relation between the two phenomena does not seem to occur. Metoprolol effectively suppressed the episodes of silent ischemia without altering platelet aggregability. In patients with stable coronary disease, platelets do not appear to contribute to the pathogenesis of silent ischemia.

Acknowledgments

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**KEY WORDS** silent myocardial ischemia • platelet aggregability • coronary artery disease • metoprolol • Holter monitoring
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