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# Effect of Beta-Blockade on Low Heart Rate-Related Ischemia During Mental Stress

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**To explore the effect of beta-adrenergic blockade on low heart rate-related (mental stress) ischemia, 19 patients with coronary artery disease were randomized into a double-blind crossover trial of metoprolol, 100 mg twice daily, and underwent serial mental stress/bicycle exercise studies. Mental stress-induced wall motion abnormalities occurred at a lower heart rate than exercise-induced wall motion abnormalities during placebo administration (81 ± 16 vs. 123 ± 20 beats/min, $p < 0.05$). Metoprolol reduced the mean magnitude of exercise-induced wall motion abnormalities (2.8 ± 2.0 vs. 1.6 ± 2.4, $p = 0.003$); improvement was related to the magnitude of hemodynamic beta-blockade effect. Metoprolol did not significantly reduce the mean magnitude of mental stress-induced wall motion abnormalities (3.0 ± 2.2 vs. 2.6 ± 2.2), although individual responses predominantly either improved (50%) or worsened (29%).**

**Unlike exercise, the magnitude of hemodynamic beta-blockade did not predict mental stress response and metoprolol did not block mental stress-induced blood pressure elevations. Patients with abolition of exercise-induced ischemia were more likely to have reduction of mental stress-induced ischemia. Patients whose ischemia worsened with metoprolol during mental stress had more easily inducible ischemia, as assessed by exercise-induced placebo wall motion abnormality, chest pain and prior myocardial infarction. Beta-blockade was associated with a lowering of ischemia-related hemodynamic thresholds compared with placebo.**

**These results suggest that beta-blockade has a variable effect on low heart rate-related ischemia that may be due to a lack of effect on mental stress-induced blood pressure elevation in patients with easily induced ischemia or to effects on coronary vasomotor tone, or both.**

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Modeled mental stress in the laboratory is a potent stimulus of transient myocardial ischemia in patients with coronary artery disease (1). Mental tasks designed to promote frustration or specific emotions frequently induce ischemic ventricular dysfunction, often of a magnitude similar to that induced by strenuous exercise. Because most ischemic episodes induced by mental stress occur at relatively low heart rate elevations compared with those induced by exercise, mental stress and exercise-induced ischemia may have different pathophysiologic mechanisms. Although ischemia occurring at relatively low heart rate elevations has typically been attributed to a decrease in myocardial oxygen supply, our prior work demonstrates that increased demand also plays an important role in the genesis of low heart rate-related ischemia. Specifically, we (1,2) and others (3) have found substantial blood pressure elevations during mental stress-induced ischemia.

Beta-adrenergic blockade is an effective anti-ischemic therapy, predominantly working by decreasing myocardial oxygen demand through reductions in heart rate and blood pressure (4). Thus, an intervention designed to decrease cardiac demand may modify the ischemic response to mental stress. Additionally, studies of pharmacologic agents that alter cardiac demand could enhance our understanding of the contributory pathophysiologic mechanisms in the genesis of low heart rate-related ischemia. Thus, we undertook a study to evaluate the comparative effects of a cardioselective beta-adrenergic blocker (metoprolol) on mental stress-induced and exercise-induced ischemia.

## Methods

**Selection of patients.** Thirty patients who fulfilled the following criteria were initially recruited for participation into our study: a history of cardiac chest pain; and a positive treadmill exercise electrocardiographic stress test, defined as ≥1.0 mm horizontal or downsloping or ≥1.5 mm upsloping ST segment depression, measured at 0.08 ms after the J

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point. Patients with mild to moderate hypertension were preferentially selected for this study, according to a concomitant protocol (5). Nineteen of the 30 patients had clinical coronary artery disease and formed the study population. They included patients with either documented coronary disease (10 patients) or a high (≥90%) Bayesian probability of coronary disease (9 patients) based on clinical and radionuclide exercise test variables (6). The rationale for the use of serial Bayesian analysis as an alternative referent standard has been described (7).

After an initial visit and maximal or symptom-limited treadmill exercise testing, patients were randomized into a double-blind crossover trial involving 3 weeks each of placebo or metoprolol, 100 mg twice daily. Patients underwent the mental stress/bicycle exercise radionuclide ventriculographic laboratory stress studies, described later, at the end of each 3 week period. Each subject signed an informed consent form approved by our Human Subjects Committee on March 1, 1986.

**Laboratory study protocol.** Patients were studied in a fasting state at approximately the same time of the day (early afternoon) for each testing period. Each subject received an injection of technetium-99m in vitro labeled red blood cells. Mental stress testing always preceded the exercise testing; the two test protocols were separated by a 15 to 30 min relaxation period. After an initial relaxation period of 10 min, the patients performed the mental tasks sequentially, with each task lasting 3 to 5 min, separated by 7 min rest periods. A 2 min radionuclide ventriculogram was obtained before and after the initial 10 min rest period, during each mental task and during the final 2 min of each 7 min rest period. Task order was counterbalanced between the first and second testing dates, using two order sequences: 1) arithmetic, Stroop word and public speaking; and 2) Stroop word, public speaking and arithmetic. Patients with an odd study identification number were assigned task order sequence 1. To minimize habituation to the mental stressors, an alternate mental stress protocol of similar but different tasks was used during the second study period. These alternate tasks were always performed for the second mental stress period.

**Mental tasks.** A series of three paired mental tasks were used. The three tasks, which we used in a previous study (1), lasted 3 to 5 min each and are described briefly:

*1. Mental arithmetic.* Patients were instructed to subtract serial 7s from a 4 digit number as quickly and as accurately as possible during the first study. The "alternate" task was to sum the figures of a 4 digit number, subtract that sum from the original number and serially repeat the process.

*2. Stroop color word task.* Patients were shown a series of slides in rapid series, displaying the names of colors (e.g., blue) written in a different color (e.g., red). Patients were to pick the color of the ink, not the color word. The "alternate" task used colored slides different from the first set. Additionally, a tape recording of rapidly spoken, random color names was played during the second testing period to distract the patient.

*3. Simulated public speaking.* Patients were asked to give a 5 min speech in front of two observers regarding personal faults or undesirable habits. The "alternate" task was to describe a stressful or embarrassing event in detail, in front of a videorecorder camera.

**Exercise protocol.** Exercise testing was performed using an upright bicycle ergometer, with graded work load increases of 200 kilopond-meters (2,000 J)/min every 3 min. Patients exercised to the point of exhaustion, marked chest pain, marked hypertension or significant arrhythmia. Radionuclide images were obtained in the upright exercise position immediately before the onset of exercise, during the last 2 min of each 3 min stage and immediately after exercise.

**Data acquisition.** During mental stress testing, subjects were positioned with the upper torso semi-erect, at approximately a 45° angle; during bicycle exercise, the subjects were upright. R wave-synchronized, multigated equilibrium radionuclide ventriculography was performed at 20 frames/cardiac cycle with use of a mobile gamma camera equipped with a 0.25 in. (0.64 cm) sodium iodide crystal and an all-purpose collimator (8). Imaging was performed with the camera positioned in the left anterior oblique angle that best separated the left and right ventricles. Two-minute imaging resulted in approximately 100,000 counts/frame. Cardiac rhythm, 12 lead ST segments and heart rate were continuously monitored. During mental tasks, blood pressure was monitored at 2 min intervals with use of an automated cuff; during exercise, it was monitored at 3 min intervals with use of a standard mercury sphygmomanometer.

**Data interpretation.** Left ventricular ejection fraction and segmental wall motion were determined for each rest condition and intervention. A computer operator who did not know the clinical data determined ejection fraction values, using light-pen assignment of end-diastolic, end-systolic and background regions of interest (8). Segmental wall motion was assessed visually with use of a continuous loop video display of the images after spatial and temporal smoothing of the data. The video format involved an eight-image display in which the first two images were initial rest images. The subsequent six images were three pairs of alternating pre-task and during-task images, with the control images preceding each task image. Control images were also placed randomly in the during-task image positions for quality control evaluation. Wall motion was scored independently by two experienced observers. Discrepant studies were scored a third time, without knowledge of previous findings, by the same two observers who read concurrently and scored according to consensus. The mental task studies were interpreted before the exercise studies.

*For wall motion scoring*, the left ventricle was separated into five segments (two septal, one apical and two posterolateral), each graded on a 5 point scale: 3 (normal wall motion), 2 (mild hypokinesia), 1 (moderate to severe hypokinesia), 0 (akinesia), and −1 (dyskinesia) (8). Segmental

**Table 1.** Clinical Characteristics of 19 Patients

| Pt. No. | Age (yr)/ Gender | Prior MI | Prior Coronary Angio | Prior CABG | CAD Prob (%) | Chest Pain Frequency | HTN | ECG LVH |
|---|---|---|---|---|---|---|---|---|
| 1 | 59/M | | | | 93 | ≤1/wk | + | |
| 2 | 50/M | | | | 92 | ≤1/wk | | |
| 3 | 51/M | | + | | — | >1/wk | + | |
| 4 | 59/M | | | | 98 | >1/wk | + | |
| 5 | 77/M | + | + | | — | >1/wk | + | |
| 6 | 66/F | + | + | | — | ≥1/day | + | |
| 7 | 57/M | | | | 99 | >1/day | | |
| 8 | 55/M | | + | | — | >1/day | | |
| 9 | 58/M | | | | 96 | >1/wk | + | |
| 10 | 67/M | + | + | | — | >1/wk | | |
| 11 | 61/M | + | + | | — | ≥1/day | + | + |
| 12 | 68/M | | | | 99 | ≤1/wk | + | |
| 13 | 65/M | | | | 99 | >1/wk | + | |
| 14 | 56/F | | + | | — | >1/wk | + | + |
| 15 | 52/M | | + | + | — | ≤1/wk | + | |
| 16 | 60/M | | | | 95 | >1/wk | + | |
| 17 | 63/M | | + | | — | ≥1/day | | |
| 18 | 61/M | | | | 99 | ≥1/day | + | |
| 19 | 61/M | + | | | — | >1/wk | + | |

Angio = angiography; CABG = coronary artery bypass grafting; CAD Prob = posttest probability of coronary artery disease; ECG LVH = electrocardiographic left ventricular hypertrophy; F = female; HTN = history of hypertension; M = male; MI = myocardial infarction; + = present.

wall motion was considered to have worsened when the peak score decreased 1 from both the initial baseline score and the immediately preceding rest score. The reliability of wall motion scoring in our laboratory is excellent (1). Among 84 randomly selected images (420 segments) read twice by our observers from 33 patient studies in a prior analysis, agreement was 88% (weighted kappa, mean [± SE], 0.86 ± 0.02). We have also demonstrated (1) that the presence and location of these wall motion abnormalities during mental stress correspond to significant angiographic coronary stenoses and reversible stress thallium defects. A summative wall motion worsening score was calculated by adding the measures of extent (number of wall motion segments worsening) and severity (number of scores an individual wall motion segment worsened). Evidence of inducible wall motion abnormality was defined as a worsened score ≥1 during an exercise stage or mental task. When comparing the wall motion responses between metoprolol and placebo therapy, a net change in summative wall motion score ≥2 in either direction was defined as a significant change (i.e., improvement or worsening) between the testing periods. A net change ≤1 was defined as no change.

*Peak heart rate and blood pressure during each task and exercise stage* were used for hemodynamic calculations. ST segments were measured at 0.08 ms after the J point. A net change of ≥1.0 mm horizontal/downsloping or ≥1.5 mm upsloping ST segment depression was considered significant. For appropriate comparisons, metoprolol exercise stage work loads were matched to the highest stage work load achieved during placebo exercise.

**Statistical analysis.** Data were expressed as either mean values ± SD or as proportions. Comparisons of mean data for patients on placebo and metoprolol were performed using the paired *t* test. Comparisons of proportions were performed using McNemar's test of symmetry and Fisher's exact test. To examine the effect of task ordering and study order analysis, analysis of variance with repeated measures was performed. In all tests a p value ≤ 0.05 was considered significant.

## Results

**Study patients.** The demographic and clinical characteristics of the 19 patients are summarized in Table 1. They had an overall mean age of 60 ± 7 years and included 17 men (89%). All patients had a rest ejection fraction >50%. During placebo treatment, 15 (79%) of the 19 patients had evidence of an inducible wall motion abnormality at maximal bicycle exercise and 14 (74%) had worsening of wall motion during mental stress testing.

**Group effects of metoprolol on ischemic markers.** A mental stress wall motion abnormality occurred only among the patients with an exercise-induced wall motion abnormality, during both placebo and metoprolol treatment. Metoprolol did not significantly reduce the overall frequency of positive wall motion abnormality results during exercise (from 79% to 58%) or mental stress (from 74% to 64%).

The comparative frequencies of chest pain and ST segment depression and the magnitudes of wall motion abnormality and ejection fraction change with exercise and mental stress testing during placebo and metoprolol therapy are shown in Figure 1. For matched work loads, metoprolol decreased the frequency and magnitude of all ischemic markers during exercise ($p < 0.05$ for wall motion abnormal-

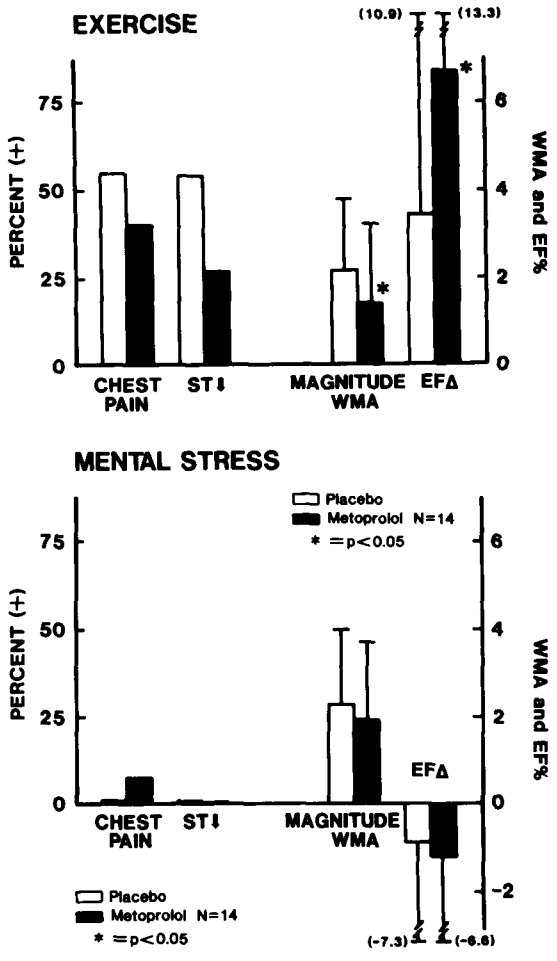



**Figure 1.** Frequency and magnitude of ischemic markers with exercise and mental stress during placebo (**open bars**) and metoprolol (**closed bars**) administration in 14 patients. Chest pain and ST segment depression (ST ↓) responses are plotted as percent positive (+) on the **left**; the magnitude of induced wall motion abnormality (WMA) and left ventricular ejection fraction change (EF %) on the **right**. * = $p < 0.05$, comparing metoprolol and placebo.

ity and ejection fraction change). Of the 15 patients with exercise-induced ischemia on placebo, 9 had improvement in wall motion abnormality during metoprolol therapy, 5 had no change and 1 patient could not be matched because of missing metoprolol exercise stage radionuclide data. No patient had worsening of wall motion during metoprolol therapy. During placebo treatment, the mean magnitude of wall motion abnormality during mental stress was comparable to that during exercise (Fig. 1). This mean score was not significantly decreased by metoprolol, but individual subject responses varied substantially. Of the 14 patients with abnormal placebo mental stress test results, 7 had improvement in wall motion abnormality, 3 had no change and 4 had worsening with metoprolol. The subgroup without improvement (the seven patients with either no change or worsening) tended to be functionally sicker, as evidenced by a significantly greater magnitude of exercise-induced wall motion abnormality during placebo administration (3.9 ± 2.3 vs. 1.7 ± 0.8, $p < 0.05$), a higher frequency of prior myocardial infarction (71% vs. 0%, $p < 0.05$) and a trend toward more frequent chest pain (43% vs. 0%, $p = 0.19$) compared with findings in the subgroup of seven patients who had improved wall motion abnormality.

We further evaluated the mental stress test response among the 14 patients with both mental stress- and exercise-induced ischemia as it related to the success of metoprolol in abolishing exercise-induced wall motion abnormality. Complete abolition of exercise wall motion abnormalities occurred in 5 (38%) of the 14 patients. Of the nine patients with residual wall motion abnormality on exercise during metoprolol therapy, only two (25%) had improvement in mental stress wall motion scores with metoprolol. In contrast, four (80%) of the five patients with abolition of exercise-induced wall motion abnormality during metoprolol treatment had improvement in mental stress-induced wall motion abnormality ($p = 0.10$).

**Hemodynamic effects.** The group effects of metoprolol treatment on hemodynamic responses during exercise and mental stress are shown in Figure 2. Beta-blockade significantly reduced the mean values for rest and peak heart rate and rate-pressure product and peak arterial blood pressure during exercise. Metoprolol also reduced the mean rest and peak heart rate and the response of rate-pressure product to mental stress. However, there was no significant reduction in the peak systolic or diastolic blood pressure response to mental stress during metoprolol.

*We further evaluated the hemodynamic thresholds for the onset of the ischemic markers during exercise and mental stress.* Mental stress-induced wall motion abnormalities occurred at a lower heart rate than did exercise-induced wall motion abnormalities during placebo (81 ± 16 vs. 123 ± 20 beats/min, $p < 0.05$). Metoprolol reduced the mean heart rate threshold at which exercise-induced ST segment depression first occurred from 113 ± 15 to 97 ± 15 beats/min ($p < 0.05$). The comparative hemodynamic thresholds associated with the onset of wall motion abnormalities during exercise and mental stress are shown in Table 2. The threshold for wall motion abnormality-related heart rate ($p < 0.05$ for exercise and mental stress) and rate-pressure product ($p < 0.05$ for exercise) was lower with metoprolol than with placebo.

*Hemodynamic analyses of the subgroups with improved and unimproved wall motion abnormalities* during exercise and mental stress are shown in Figure 3. Compared with the nine patients whose condition during exercise improved on metoprolol therapy, the patients without such improvement tended to demonstrate less beta-blockade effect, as indicated by smaller metoprolol-associated reductions in heart rate, systolic blood pressure and rate-pressure product responses during exercise. In contrast, during mental stress testing there was no apparent difference between the improved and unimproved groups in any of the calculated hemodynamic responses.

**Task and study order analysis.** With placebo and with metoprolol administration, wall motion abnormalities were

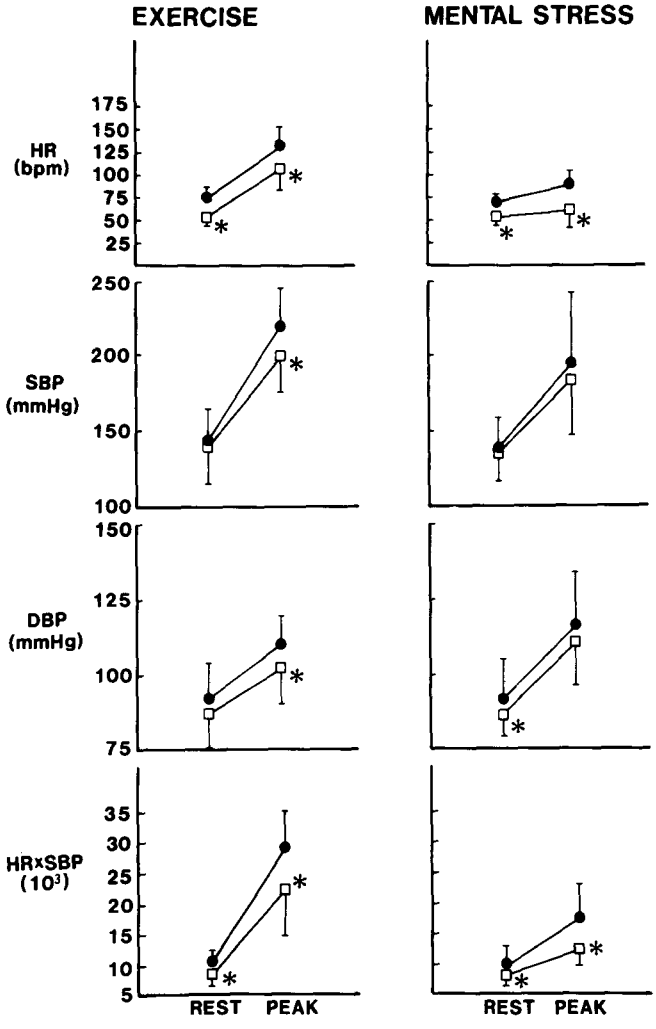



**Figure 2.** Effect of metoprolol on group hemodynamic variables during exercise and mental stress at rest and at peak response in 19 patients. Mean measurements and SD for heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) and rate-pressure product (HR × SBP) are shown. The measurements obtained during placebo are shown as **closed circles** and those during metoprolol as **open squares**. * = $p < 0.05$, comparing metoprolol and placebo.

most common during the speech task (Fig. 4). The frequency of wall motion abnormalities for the speaking task did not change when the task orders changed (i.e., with the speaking task as the last or as the middle task) (Fig. 5). The mathematics task more often caused an abnormality when it was performed last than when it was performed first, although this difference was not significant ($p = 0.14$).

*We also tested our results for a study order effect* to assess whether habituation to the mental stressors could mask or confound our mental stress results. Specifically, we assessed whether the frequency of mental stress-induced wall motion abnormalities during the placebo and metoprolol phases varied according to the first study versus the second study period. The frequency and magnitude of mental stress-induced wall motion abnormality was not different among the first study versus the second study subgroup during placebo (40% vs. 48% and 2.8 ± 2.0 vs. 2.3 ± 1.6, respectively, both p = NS) and metoprolol (48% vs. 30% and 2.8 ± 1.5 vs. 2.6 ± 1.8, respectively, both p = NS). Also, comparative analysis of variance of mental task hemodynamic reactivity on placebo between the first and second study period groups revealed no significant differences in heart rate, blood pressure and rate-pressure product responses (main group effects × trial interactions for task ordering and study ordering = NS).

**Table 2.** Effect of Metoprolol on Ischemia-Related Hemodynamic Variables During Exercise and Mental Stress

| | HR (beats/min) | SBP (mm Hg) | DBP (mm Hg) | HR × SBP (×10³) |
|---|---|---|---|---|
| Exercise | | | | |
| Placebo ischemia | 123 ± 20 | 197 ± 27 | 103 ± 16 | 24 ± 6 |
| Metoprolol ischemia (n = 15) | 105 ± 19* | 185 ± 31 | 96 ± 12 | 19 ± 7* |
| Mental stress | | | | |
| Placebo ischemia | 81 ± 16 | 180 ± 48 | 109 ± 19 | 15 ± 5 |
| Metoprolol ischemia (n = 11) | 64 ± 13* | 185 ± 38 | 114 ± 13 | 12 ± 4 |

*$p < 0.05$ versus placebo. DBP = diastolic blood pressure; HR = heart rate; HR × SBP = rate-pressure product; SBP = systolic blood pressure.

## Discussion

Our findings parallel other recent observations regarding the frequency and characteristics of mental stress-induced ischemia in patients with coronary artery disease. A high frequency of mental stress-induced left ventricular dysfunction in patients with coronary artery disease has been demonstrated with a variety of techniques, including radionuclide ventriculography (1), echocardiography (3) and stationary (2) and ambulatory (9) left ventricular radionuclide monitoring probes. These studies and our current results demonstrate that mental stress-induced ischemia, compared with exercise-induced ischemia, occurs at relatively lower heart rate elevations, is more likely to be clinically and electrocardiographically silent and is seen primarily in patients with exercise-induced ischemia. Thus, simulated mental stress in the laboratory appears to be a potent and reproducible causal agent for low heart rate-related myocardial ischemia in patients with coronary artery disease.

**Effects of metoprolol on ischemic indexes during mental stress testing and exercise.** Beta-adrenergic blockade had a beneficial effect on the magnitude of high heart rate-related (exercise) ischemia. Left ventricular ejection fraction was elevated to a greater magnitude during exercise during the metoprolol phase. These results are consistent with prior studies (10–12) showing a reduction in ischemic markers and enhancement of ventricular performance during exercise among patients with coronary disease treated with beta-blockers.

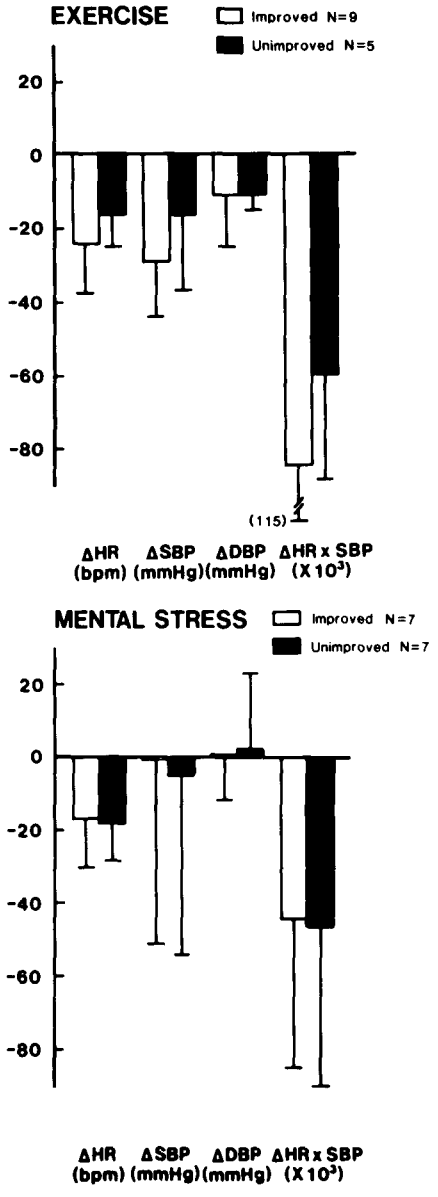



**Figure 3.** Hemodynamic changes during exercise and mental stress in 14 patients receiving metoprolol. "Improved" and "unimproved" indicate wall motion abnormality response to metoprolol. Patients with improvement during exercise and mental stress (n = 9 and 7, respectively) are shown by **open bars** and those without improvement (n = 5 and 7, respectively) by **closed bars**. Values are expressed as mean values ± SD. Changes (Δ) in heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) and rate-pressure product (HR × SBP) are shown.

*In contrast, metoprolol demonstrated a variable effect on low heart rate-related (mental stress) ischemia in this study.* Although metoprolol elicited no significant change in the mean wall motion abnormality value, this result is misleading because the individual responses predominantly followed two directions. Half of the patients had an improved score with metoprolol and one third had a worsened score. Patients whose wall motion abnormality improved usually showed abolition of exercise-induced wall motion abnormalities with metoprolol. These results imply that titration of drug to abolition of exercise-induced ischemia may be important in the treatment of low heart rate-related ischemia, although this hypothesis could not be tested because patients were given a fixed dose of the drug. Although the hemodynamic results during mental stress did not support a correlation between the magnitude of beta-blockade effect and the

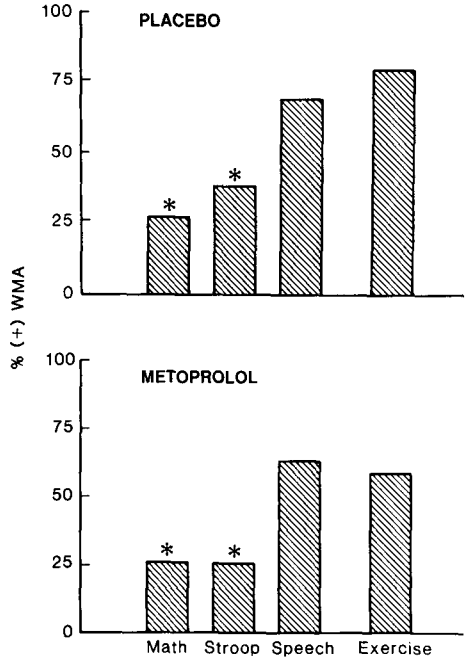
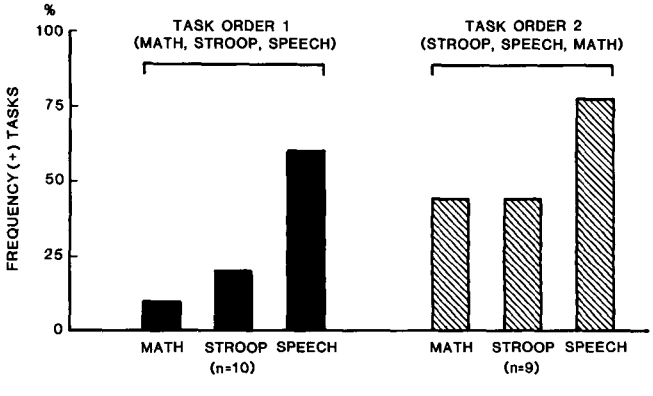



**Figure 4.** Frequency of wall motion abnormality (WMA) (**vertical axis**) during the different mental tasks and during exercise with placebo, and with metoprolol in 19 patients. Wall motion abnormality was induced more commonly with speech than with the other mental tasks.

**Figure 5.** Frequency of wall motion abnormality (+) with mental stress according to task order sequence during placebo administration. Task order 1 is shown by **closed bars**, and task order 2 by **hatched bars**. For both sequences, wall motion abnormality was most frequently induced by the speaking task. There was no statistically significant difference between the frequency of abnormality induced by each task during study order 1 and that induced during study order 2.



direction of mental stress response, only further testing using titrated doses of metoprolol can resolve this question.

**Pathophysiologic considerations.** Multiple lines of evidence now demonstrate that myocardial ischemia is a complex phenomenon that involves both increases in the determinants of myocardial oxygen demand (1–3) and a decrease in coronary blood supply (13,14). Beta-blockers are believed to predominantly affect myocardial oxygen demand, reducing it by lowering heart rate and blood pressure (4). The importance of these alterations in demand on high heart rate-related ischemia is readily supported by the results of this study: reduction in ischemia with exercise during the metoprolol phase was associated with reductions in heart rate, systolic blood pressure, diastolic blood pressure and rate-pressure product. In contrast, the pathophysiology of low heart rate-related ischemia is not well understood. Blood pressure may increase rapidly and often markedly during mental stress (1–3), and a blood pressure increase accompanied ischemic responses in this study. However, metoprolol had a minimal hemodynamic effect on mental stress-induced blood pressure elevation, as has been reported with other beta-blockers (15,16). This may explain why metoprolol was not as effective in reducing mental stress-induced ischemia compared with exercise-induced ischemia. Because patients without improvement during mental stress were functionally sicker, as evidenced by both clinical variables and the magnitude of exercise-induced ischemia during placebo administration, the threshold for induction of ischemia by mental stress may be lower in these patients. Therefore, the unaffected blood pressure elevations may be proportionately more important in ischemia induction in this subgroup than in patients with less functional disease.

Our demonstration of beta-blocker–associated reductions in ischemia-related hemodynamic thresholds compared with placebo was previously reported. McLenachan et al. (17) observed a propranolol-associated reduction in ischemia-related heart rate using ambulatory Holter ST segment monitoring. Steele et al. (18) demonstrated worsened thallium scintigraphic perfusion defects at matched heart rate and blood pressure values in patients who exercised twice, during propranolol and during placebo treatment. This evidence raises the possibility of a beta-blockade–mediated limitation to coronary blood supply. Beta-receptor stimulation is a mediator of coronary vasodilation (19), and systemic beta-blockade has been shown to decrease coronary artery caliber (20) and coronary blood flow (21) in both normal and atherosclerotic segments. Increased coronary artery vasomotor tone does not necessarily result in greater ischemia, however, and may, in some patients, be beneficial by maintaining an even distribution of transmural blood flow (22). This paradox may explain our variable ischemia response to metoprolol during mental stress. Further work directly evaluating beta-blockade effects on coronary luminal caliber, blood flow and ischemia induction simultaneously must be performed to explore this hypothesis.

**Task potency and study order effect.** We found previously (1) that the personally relevant public speaking task, designed to be emotionally arousing, was more potent than other mental tasks in inducing wall motion abnormalities in the laboratory. A potential limitation of this prior study design was the performance of this task after the other mental tasks were completed. Thus, we could not exclude the possibility that a task-ordering effect was responsible for our observations, perhaps related to an increasingly activated neuroendocrine axis. In the current study, therefore, we compared two task orders, one in which the mental arithmetic task was performed as the first task, and one in which it was performed as the last task, after public speaking. In both orders, public speaking was the most potent task, confirming its independent potency as a mental stressor. The frequency of abnormality during the mental arithmetic task, however, was higher when it was performed last, suggesting a potential task-ordering effect.

Because our study was designed to assess the effects of mental stress tasks during two separate periods, we were concerned about habituation to the mental tasks resulting in a study order effect that would mask or confound drug effects. For this reason, the tasks were adapted between the first and second testing periods. We evaluated the relative results when mental stress testing during placebo and metoprolol therapy was performed as the first or second test: with habituation, a lesser frequency of abnormality would be expected when the respective testing was performed as the second test. We found no significant differences in responses to placebo or metoprolol between study periods for any of the mental stress-induced changes, suggesting that habituation was not a significant factor in our study. In support of this observation, McKinney et al. (23) also found that hemodynamic reactivity to serial mental stress testing is reproducible and stable over time.

**Limitations.** Because our patient population was relatively small, our subgroup analyses were limited. Moreover, our subgroup findings may represent random variation rather than true pathophysiologic differences due to our post priori subgroup analyses. Prospective evaluation of additional patients is needed to confirm these findings. The use of a fixed dose of metoprolol, rather than a titrated, optimal dose regimen designed to maximize ischemia reduction, may have contributed to an underestimation of metoprolol's efficacy, especially in light of the favorable effect noted among patients with abolition of exercise-induced ischemia. The preferential selection of hypertensive patients may limit generalization of these findings to normotensive patients with coronary artery disease (25). Previous work questioned the specificity of radionuclide ventriculographic wall motion abnormalities for detection of coronary artery disease (ischemia) in hypertensive patients. More recent evidence (26,27), however, suggests that false positive radionuclide ventriculographic results appear to correlate with left ventricular hypertrophy, which was evident in only 2 (11%) of our patients, one of whom had coronary artery disease docu-

mented by arteriography. The other patient had a negative exercise test for wall motion abnormality.

**Clinical implications.** Our results both confirm and extend previous observations regarding myocardial ischemia and beta-blockade therapy. A beta-blocker is an effective anti-ischemic medication for ischemia associated with high myocardial oxygen demand, as demonstrated by these and other exercise study results (10–12). Our mental stress results suggest that beta-blockade may have less effect on low heart rate-related ischemia, a finding recently described in a study using ambulatory Holter monitoring (17). Patients with beta-blockade worsening of low heart rate-related ischemia had a higher frequency of prior myocardial infarction, a finding analogous to that of Rainwater et al. (24), who demonstrated worsened exercise thallium scintigraphic findings during propranolol therapy in patients with prior myocardial infarction. Our results suggest that abolition of exercise-induced ischemia by beta-blockade may be a predictor of improvement of mental stress-induced ischemia.

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