

Usefulness of Laboratory Mental Stress Test in Patients with Stable Coronary Artery Disease

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Summary

Background and hypothesis: Many episodes of ischemia in daily life are silent occurring during sedentary activities and may be related to mental stress. In 35 patients with stable angina and positive exercise test awaiting bypass surgery, we investigated whether laboratory mental stress tests would trigger ischemia of a comparable severity to that occurring in daily life and attempted to elucidate some of the underlying mechanisms.

Methods: All patients underwent exercise testing, personality assessment, 2-day Holter monitoring, and laboratory mental stress tests while on their usual medications.

Results: Only four patients (12%) had positive mental stress test (ST depression ≥ 0.1 mV). All episodes were silent and usually associated with fast heart rate (>90 beats/min). In contrast, ambulatory ischemia was common (average duration of 51 min per 24 h), and at least one episode was recorded in 27 patients (77%) including the 4 with positive test. Patients with positive mental stress test had a higher heart rate during testing (124 ± 24 vs. 86 ± 16 beats/min, $p < 0.01$), and a shorter exercise time and time to 1 mm ST depression on cycle ergometry than those with negative mental stress test. None of the four patients were on beta blockers. There was no difference in personality inventory between the two groups. Comparisons between patients with and without positive mental

stress test revealed no difference in the duration and frequency of ambulatory ischemia, or in the occurrence of silent ischemia. However, the heart rate at onset of ambulatory ischemia tended to be higher in the patients with positive mental stress test (96 ± 9 vs. 62 ± 43 , $p = 0.07$). Further subgroup analysis in patients without beta blockers (4 mental stress test positive and 18 negative) showed similar results.

Conclusions: Laboratory mental stress test is a weak inducer of ischemia detected by electrocardiographic monitoring in patients with frequent ambulatory ischemia. Wall motion evaluation during mental stress test may improve sensitivity. While larger scale studies may determine its clinical role, the present study illustrated that patients with heightened heart rate response to mental stress were identified in whom beta blockers could be the drug of choice.

Introduction

Myocardial ischemia is readily induced with exercise testing, but most episodes of ischemia in daily life occur during sedentary activities,¹⁻⁵ and many of these episodes are silent. Ischemia can be triggered by nonexercise stimuli such as mental stress,⁶⁻⁸ smoking,^{9,10} and cold immersion,¹¹ although the myocardial ischemia is generally milder with less ST changes and symptomatic angina^{2,6,7,12} and may require more sophisticated methods for diagnosis based on wall motion or perfusion abnormalities.^{6,7,12} Few studies had attempted to document the clinical significance and prognostic importance of laboratory mental stress-induced myocardial ischemia. Recently, studies on silent ambulatory ischemia (the ASIST trial¹³ and the ACIP project¹⁴) have supported the use of medical therapy and/or revascularization in these patients. The role of laboratory mental stress test in patients with coronary disease is unclear and it would be useful if the test could help direct clinical management.

In this study of patients with stable coronary artery disease, we investigated whether laboratory mental stress tests will trigger myocardial ischemia of a comparable severity to that occurring in their daily life, and whether those patients with positive mental stress test have special pathophysiologic and therapeutic considerations.

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Methods

Patients

We prospectively studied 35 patients (28 men and 7 women, mean age 61 ± 9 years) with stable angina and positive exercise stress test awaiting coronary artery bypass surgery. Of these patients, 13 had triple-vessel disease, 16 had double-vessel disease, and 6 had single-vessel disease. All were on stable medications prescribed by their own cardiologists, including 13 on beta blocker, 23 on calcium antagonist, and 24 on regular long-acting nitrate therapy. Five patients had prior coronary angioplasties and two had prior bypass surgery. All patients completed four self-administered personality inventories including the FRAM 10 question type A behavior survey,¹⁵ two questionnaires on type A behavior and self-induced stress¹⁶ and the Spielberger anger inventory,¹⁷ and an angina questionnaire. Patients were stable on their usual medications throughout the study period, and the study protocol was approved by the institute ethics review board.

Exercise test

All patients underwent symptom-limited cycle-ergometry¹⁸ monitored by the Marquette Case II recorder with standard 12-lead plus 3 bipolar lead electrocardiogram (ECG). The two leads that showed the maximum ST depression were used for the subsequent Holter monitoring. All patients had isoelectric ST segments on their initial resting ECGs. For all ST segment analyses, an ischemic episode was defined as ≥ 0.1 mV (1 mm) ST depression measured 60 ms after the J point (ST₆₀).

Holter Monitoring

Holter recording was performed for 2 days using the two-channel recorder (QMED-TC30) on the two leads identified from the exercise test. For each episode of ST-segment depression detected, the time of onset, duration, magnitude, and heart rate at onset of ischemia were recorded. The patients were asked to keep an angina diary during monitoring to identify the symptomatic episodes.

Mental Stress Test

On the day that Holter recording was completed, patients underwent the laboratory mental stress test with the same 15-lead monitor by the Marquette Case II recorder. The mental stress tests included four tests previously used by Rozanski⁶ and another test using a competitive computer game. Systolic blood pressure was monitored by standard sphygmomanometer immediately before and after each test.

Mental arithmetic: This involved subtraction of serial 7s from a 4-digit number for 5 min, with speed prompted from the investigators. Failure feedback was used to increase stress if no ST change was documented in 3 min.

Stroop color word task: This involved showing a series of rapidly changing slides, containing the name of a color written in letters of a nonmatching color (e.g., the word "blue" written in green color), and requiring the patients to identify the color of the letter. The difficulty was increased by stimulus overload with a simultaneous auditory task.

Public reading: The patient was asked to read out loud a prose passage on a neutral subject in front of three observers.

Emotionally-charged public speaking: The patient was asked to speak for 5 min about personal faults or undesirable habits, with which he or she was dissatisfied, in front of three observers. This task was considered more personally relevant and natural.

Competitive computer game: The patient was instructed to play a video game similar to "space invaders" with elements of threat, uncertainty, and avoidance. This game had been shown to produce quite marked cardiovascular responses.¹⁹

Statistics

Differences in means between groups were compared with the Wilcoxon rank sum test where appropriate. Differences in proportions were compared using the exact binomial conditional test. P values of < 0.05 (2-tailed) were considered to be significant.

Results

Exercise Performance

Only 22 patients experienced angina despite the fact that all had ≥ 0.1 mV (1 mm) ST-segment depression. The maximum workload was 60 ± 16 W with total exercise duration of 4.4 ± 2.0 min. The time to 1 mm ST-segment depression was 3.7 ± 2.1 min.

Mental Stress Test (Table I)

Only four patients (12%) had significant ST depression ≥ 0.1 mV during mental stress test, but none had angina. Of these (ages 63, 69, 40, and 60), one had single-vessel, one had double-vessel, and two had triple-vessel coronary disease.

TABLE I Hemodynamic and ST responses during mental stress tests in the four patients with positive tests

	Maximum heart rate	ST depression (≥ 0.1 mV)
Mental arithmetic	114,117,80,98	-, +, -, -
Stroop word color recognition	117,118,84,89	+, +, -, -
Public reading	110,146,96,89	+, +, +, -
Public speaking	143,130,87,112	+, +, -, +
Competitive computer game	124,115,83,84	+, -, +, -

Results in each of the four patients were reported consecutively.

None had prior coronary angioplasty or bypass surgery. For antianginal medications, one was on calcium antagonist only, one on nitrate only, one on a combination of the two drugs, while the remaining patient was not on regular antianginal medications. None of the four patients was on beta blockers. ST-depression appeared to accompany fast heart rate (>90 beats/min) during the tests, and two of the four patients had a particularly marked tachycardiac response to most components of the tests with ST-segment depression (Table I). Systolic blood pressure, however, remained unchanged (120 ± 5 pre-test and 120 ± 5 post-test).

Holter Recording

In contrast to the rarity of ST depression during mental stress tests, ambulatory ischemia was found in 27 patients (77%), including the four with positive mental stress tests. For the whole group of 35 patients, the average number of episodes of ischemia (i.e., ST depression ≥ 0.1 mV) was 5.5 and the total duration was 51 min per 24 h of recording. Silent ischemia was noted in 25 of the 27 patients.

Comparison between Patients with and without ST Depression during Mental Stress Test (Table II)

Patients with mental stress test-induced ST depression (i.e., positive test) had a higher heart rate during mental stress (124 ± 24 vs. 86 ± 16 beats/min, $p < 0.01$), and a shorter exercise time and time to 1 mm ST depression on cycle ergometry. None was on beta blockers, while 13 of the 31 patients with negative tests were on beta blockers. There was no difference in personality inventory between the two groups. There was also no difference in the total duration (48 ± 25 vs. 52 ± 108 min per 24 h, $p = \text{NS}$) and the number of episodes (7.9 ± 5.5 vs. 5.2 ± 7.5 , $p = \text{NS}$) of ambulatory ischemia, and in the oc-

currence of silent ischemia. However, the heart rate at onset of ambulatory ischemia tended to be higher in the four patients with positive mental stress test (96 ± 9 vs. 62 ± 43 , $p = 0.07$).

Mental Stress Test in Patients Not on Beta Blockers: Comparison of the 4 Patients with Positive Mental Stress Test with the Other 18 Patients (Table III)

Patients with mental stress test-induced ST depression had a higher heart rate during mental stress test (124 ± 24 vs. 93 ± 14 beats/min, $p < 0.01$), and a shorter exercise time and time to 1 mm ST depression on cycle ergometry. There was no difference in the total duration and the number of episodes of ambulatory ischemia, and in the occurrence of silent ischemia. The heart rate at onset of ambulatory ischemia tended to be higher in the four patients with positive mental stress test, although this was not statistically significant.

Discussion

The clinical interpretation of a positive mental stress test in contrast to a positive exercise stress test is less well defined. As myocardial ischemia induced by nonexercise stimuli is generally milder with a lesser degree of ST depression while detectable by more sophisticated analysis of wall motion^{6,12} or reduction in cation uptake on positron tomography,⁷ studies on mental stress-induced ischemia had used variable definitions of ischemia and variable patient inclusion criteria. Few studies attempted to document the clinical significance of a positive response to mental stress. In this study, we used a uniform criterion of ischemia as ≥ 0.1 mV (1 mm) ST₆₀ segment depression for the exercise stress test, mental stress test, and ambulatory recording in a homogeneous group of patients with coronary disease awaiting bypass surgery. We showed that labo-

TABLE II Comparison between patients with and without ischemia during mental stress test

Patients	MS+ve (n=4)	MS-ve (n=31)	p Value
Use of beta blocker	0/4	13/31	NS
Personality inventory and questionnaire	No difference between the two groups		
Maximum heart rate during mental stress test	124 ± 24	86 ± 16	<0.01
Exercise test			
Exercise time (min)	2.4 ± 1.1	4.6 ± 2.0	<0.05
Workload (W)	47 ± 8	62 ± 17	NS
Time to 1 mm ST depression (min)	1.5 ± 0.8	3.8 ± 1.9	<0.05
Heart rate at 1 mm ST depression	118 ± 19	106 ± 15	NS
Maximum heart rate achieved	122 ± 3	108 ± 14	NS
Holter recording			
Ambulatory ischemia	4/4	23/31	NS
Silent ischemia	4/4	21/23	NS
Total duration of ischemia (min/24 h)	48 ± 25	52 ± 108	NS
No. of episodes /24 h	7.9 ± 5.5	5.2 ± 7.5	NS
No. of symptomatic episodes /24 h	1.1 ± 1.6	1.3 ± 2.7	NS
Heart rate at onset of ischemia	96 ± 9	62 ± 43	0.07

Abbreviations: MS = mental stress, +ve = positive, -ve = negative, NS = not significant.

TABLE III In patients without beta blockade, comparison between patients with and without ischemia during mental stress test

Patients	MS+ve (n=4)	MS-ve (n=18)	p Value
Max heart rate during mental stress test	124 ± 24	93 ± 14	<0.01
Exercise test			
Exercise time (min)	2.4 ± 1.1	4.3 ± 1.6	<0.05
Workload (W)	47 ± 8	60 ± 13	NS
Time to 1 mm ST depression (min)	1.5 ± 0.8	3.5 ± 1.5	<0.05
Heart rate at 1 mm ST depression	118 ± 19	108 ± 15	NS
Maximum heart rate achieved	122 ± 3	113 ± 13	NS
Holter recording			
Ambulatory ischemia	4/4	14/18	NS
Silent ischemia	4/4	14/18	NS
Total duration of ischemia (min/24h)	48 ± 25	60 ± 120	NS
No. of episodes /24h	7.9 ± 5.5	5.3 ± 7.5	NS
No. of symptomatic episodes /24h	1.1 ± 1.6	1.0 ± 1.4	NS
Heart rate at onset of ischemia	96 ± 9	72 ± 46	NS

Abbreviations as in Table II.

ratory mental stress test was a much weaker inducer of myocardial ischemia than physical stress with exercise testing in this group of patients with severe disease and relatively frequent ambulatory ischemia.

In this study, patients with positive mental stress test had a shorter exercise time and time to 1 mm ST depression on cycle ergometry. A recent study by Gottdiener *et al.*¹² showed that patients with mental stress-induced ischemia detected on two-dimensional echocardiography had a greater risk of sedentary ischemia in daily life than when detected by ambulatory ST-segment recording. Notably, patients with positive mental stress test in that study¹² had more regional wall motion abnormalities induced by exercise, suggesting more myocardial ischemia. Taken together, this may suggest that patients with positive mental stress test have more extensive coronary artery disease, although there are no definitive data on this aspect. Apart from anatomic stenoses, the link between mental stress-induced ischemia and coronary disease may also involve abnormalities of vasomotion. Yeung *et al.*²⁰ examined coronary vasomotor responses to mental stress with mental arithmetics in 26 patients undergoing catheterization and found dilatation of normal arteries but constriction of atherosclerotic arteries. This dilatation and constriction pattern paralleled the response of the arteries to acetylcholine²¹ and reflects an impairment of endothelium-mediated vasodilatation in diseased arteries with atherosclerosis.^{20, 21}

The hemodynamic and neurohumoral response during mental stress recently has been receiving more attention. From the Psychophysiological Investigation of Myocardial Ischemia study database,^{22, 23} Becker *et al.* reported that laboratory mental stress provoked a substantial sympathetic response with heart rate and blood pressure increase even in normal middle aged persons.²² Stone *et al.* reported that during supervised stressful speech, patients with ischemia (i.e., new regional wall motion abnormalities) exhibited more tachycardia and blood pressure increase than patients without

ischemia.²³ In the present study, patients with positive mental stress test also had a higher heart rate than patients with negative test, but maximum heart rate attained during exercise tests was similar between the two groups. In fact, tachycardia during the various components of mental stress test tended to be accompanied by ST depression in these patients (Table I). The different heart rate responses during mental stress could not be explained by difference in personality traits, but it was noteworthy that none of the positive patients was on beta blockers. We therefore compared them with the other 18 patients who were also not on beta blockers but had negative mental stress test. The difference in the heart rate response during laboratory mental stress test persisted between the two groups. Thus, mental stress could induce myocardial ischemia causing significant ST depression through a heightened heart rate response in predisposed patients. In keeping with this contention, there was also a trend toward a higher heart rate during ambulatory ischemic episodes in these patients. Unlike heart rate changes which were continuously monitored, blood pressure was recorded only after the mental stress tests in this study and we were unable to find a difference between the two groups. Patients in this study were on their usual antianginal medications, which conceivably would influence their cardiologic response to mental stress. Further studies to discern the relative merits of different categories of antianginal treatment during mental stress are warranted. Indeed, recent studies have demonstrated the usefulness of beta blockers in treating silent ambulatory ischemia.^{14, 24, 25} It is possible that this subgroup with tachycardiac response to mental stress may benefit more from their use.

In this study, all episodes of ischemia induced by laboratory mental stress were silent, while angina was much more common on exercise testing despite a similar degree of ST depression. This finding may be in keeping with a recent study²⁶ showing that mental stress (with public speaking) caused an increase in plasma beta-endorphin levels which correlated

with pain thresholds, explaining the predominance of silent ischemia during mental stress. Both findings are in keeping with the frequency of silent ischemia during sedentary daily life.

Conclusion

Laboratory mental stress test is a weak inducer of ischemia detected by electrocardiographic monitoring in patients with frequent ambulatory ischemia. Wall motion evaluation during mental stress test may improve sensitivity. While larger-scale studies may determine its clinical role, the present study illustrated that patients with heightened heart rate response to mental stress were identified in whom beta blockers could be the drug of choice.

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