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Effect of a Standardized Meal on the Threshold of Exercise-Induced Myocardial Ischemia in Patients With Stable Angina

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Objectives. **This study was undertaken to determine the effect of a standardized meal on the ischemic threshold and exercise capacity in a series of 20 patients with stable angina, exercise-induced ischemia and reversible exercise-induced perfusion defects.**

Background. **It is generally accepted that exercise tolerance in patients with angina is reduced after a meal. However, studies that have addressed this phenomenon have yielded results that are contradictory and inconclusive.**

Methods. **Two exercise tests using the Bruce protocol with technetium-99m (^{99m}Tc)-sestamibi were performed on consecutive days in a randomized order. One test was performed in the fasting state and the other 30 min after a 1,000-calorie meal.**

Results. **In the postprandial state, exercise time to ischemia was reduced by 20% from 248 ± 93 s to 197 ± 87 s (p = 0.0007), time to angina by 15% from 340 ± 82 s to 287 ± 94 s (p = 0.002) and exercise tolerance by 9% from 376 ± 65 s to 344 ± 86 s (p = 0.002). Rate-pressure products at these exercise test end points were not significantly different in the fasting and postprandial tests, and the quantitative ^{99m}Tc-sestamibi ischemia score was unchanged.**

Conclusions. **In patients with stable angina, a 1,000-calorie meal significantly reduced time to ischemia, time to angina and exercise tolerance because of a more rapid increase in myocardial oxygen demand with exercise. The extent and severity of exercise-induced ischemia were unchanged.**

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Since the original description of angina pectoris by Heberden, it has been well recognized that exercise tolerance in patients with angina is reduced after a meal. However, the few studies (1–4) that have investigated this phenomenon have yielded results that are contradictory and inconclusive. Goldstein et al. (2) reported that the angina threshold during upright bicycle exercise was lower after than before a meal in 11 of 12 patients. Heart rate and systolic blood pressure were higher at each level of exercise after the meal and heart rate–systolic blood pressure product at peak exercise was unchanged from the baseline test. In contrast, Hung et al. (3) found that exercise capacity was not reduced after a meal. Peak rate-pressure product was higher during the postprandial exercise test because of a higher systolic blood pressure; peak heart rate was not significantly different. Cowley et al. (4) reported that treadmill exercise time to the onset of 1-mm ST segment depression in 23 patients with angina was less after a meal. They attributed this decrease to a postprandial increase in cardiac output. Heart rate, but not systolic blood pressure, was higher during the exercise test after a meal.

In normal subjects, the effect of a meal on circulatory hemodynamics at rest and during exercise is somewhat more clearly defined. Cardiac output increases both at rest (5–7) and during exercise (5,7). The increase at rest is mediated mainly by an increase in stroke volume and end-diastolic volume, although heart rate also accelerates (6). Exercise heart rate is higher after a meal than during baseline exercise (5,7). In one study (5), but not in another (7), blood pressure was higher during the postprandial test in normal subjects.

The present study was undertaken to determine the effect of a standardized meal on ischemic threshold and exercise capacity in a series of patients with stable angina, exercise-induced ST segment depression and reversible exercise-induced perfusion defects. Patients were prospectively classified by history into two groups: 1) those who confirmed that their angina threshold was worse after meals, and 2) those who did not. The extent and severity of exercise-induced myocardial ischemia during the baseline and postprandial tests were compared by technetium-99m (^{99m}Tc)-sestamibi single-photon emission computed tomographic (SPECT) quantification; heart rate and blood pressure changes during exercise were also compared.

Methods

Patients. Patients with chronic stable angina, exercise-induced ST segment depression and reversible perfusion defects on ^{99m}Tc-sestamibi SPECT imaging during exercise were recruited into the study. Excluded were patients with

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myocardial infarction, unstable angina or coronary bypass surgery within the preceding 3 months; overt heart failure; uncontrolled hypertension; serious arrhythmias; baseline electrocardiographic (ECG) abnormalities that could interfere with the interpretation of ST segment changes during exercise, and the need for digitalis, antiarrhythmic drugs or antianginal medications other than sublingual nitroglycerin.

Twenty patients, 19 men and 1 woman, who met these criteria were included in the study. They had a mean age of 59 years (range 47 to 70) and a mean duration of angina of 79 ± 61 months (range 4 to 240). Seventeen of the 20 patients were in Canadian Cardiovascular Society angina class I and 3 were in class II. Five patients had had a myocardial infarction and three had undergone coronary bypass surgery. Coronary arteriography showed stenoses >70% of lumen diameter in all 10 patients who had undergone this study. Seven patients confirmed that they had a definitely lower angina threshold after meals; the other 13 either denied that this was so or were uncertain.

Study protocol. All antianginal medication except sublingual nitroglycerin was withdrawn ≥72 h before the study. Two treadmill tests were performed in randomized order, usually on consecutive days and always within 1 week. Patients were allowed to have a light breakfast 5 h before testing. One exercise test was performed 30 min after a standardized 1,000-calorie meal and the other in the fasting state. The meal contained 34% carbohydrates, 21% protein and 45% fat. The composition of the fats was 45% saturated fatty acids, 37% monounsaturated fatty acids and 8% polyunsaturated fatty acids. Beverages containing caffeine and theophylline were not permitted. All patients gave written informed consent, and the study protocol was approved by the Ethics Committee of our hospital.

Treadmill tests. Treadmill exercise using a Bruce protocol was performed at approximately the same hour each day. Heart rate, cuff blood pressure and perceived exertion were recorded before and at minute intervals during exercise and recovery. Electrocardiographic leads CC_5, CM_5 and CL were continuously monitored and recorded every 30 s to determine as precisely as possible the onset of ≥1-mm ST segment depression. The ST segment was measured at 0.08 s after the J point in three consecutive QRS complexes with a flat baseline. The average was compared with the baseline tracing, as previously described (8). Time to 1-mm ST segment depression, time to angina, total exercise duration, maximal ST segment depression and rate-pressure product at each of these points were recorded. End points for terminating exercise were severe angina, dyspnea or extreme fatigue.

Technetium-99m-sestamibi SPECT acquisition, reconstruction and quantification. At maximal exercise, 20 to 25 mCi of ^{99m}Tc-sestamibi was injected and exercise was continued for ≈1 min. The patient was kept fasting until the scintigraphic acquisition. For the rest of the study, which was performed on another day, the patient fasted for ≥4 h before the injection of 20 to 25 mCi of ^{99m}Tc-sestamibi, and a glass of milk was given before acquisition.

A rotating large field of view gamma camera equipped with a low energy, high resolution, parallel hole collimator was used for image acquisition. Sixty-four projections of 20 s each were obtained over a 360° variable elliptic orbit on a 64 × 64 × 16 byte matrix with a zoom of 1.44. A 20% symmetric energy window centered on the 140-keV peak was used. Total acquisition time was 25 to 30 min. Processing was done using filtered back projections with a Butterworth filter (cutoff 0.7, order 8): no attenuation correction was used. Orthogonal tomographic slices, each 1 pixel thick (6.4 mm), were reconstructed parallel to the vertical and horizontal long axes and the short axis of the left ventricle. Using the short-axis slices, a two-dimensional polar map ("bull's-eye") display was constructed (9).

Our quantitative approach has previously been described in detail (10). In summary, 25 regions of interest of equal size were automatically drawn on each polar map display, and the relative uptake in each of these regions was determined and normalized to a maximal uptake of 100. Values were compared with those on file of rest ^{99m}Tc-sestamibi SPECT studies obtained on 15 normal volunteers with a probability of coronary artery disease of <1%. Abnormal sectors were defined by normalized count values ≥2 SD below the normal mean.

Defect size was calculated as the ratio of the number of abnormal sectors to the total number of sectors. Defect intensity was defined as the ratio of the average counts in the abnormal sectors to the corresponding normal means of these sectors, subtracted from 1. Defect score was obtained by multiplying defect size times defect intensity. An ischemic score for both exercise studies was calculated by subtracting the rest from the exercise defect score.

Statistical analyses. Paired Student *t* tests were used to compare the data from the control and postprandial exercise tests. A p value < 0.05 was accepted as significant. Data are presented as mean value ± 1 SD.

The sample size calculation was based on the exercise test end points of time to 1-mm ST depression, time to angina and duration of exercise. With alpha = 0.05, beta = 0.20, an intervention effect of 0.20, a common SD of the end point between the groups of 50 s based on previous studies, a maximum of 12 patients would be required. The power of the study to detect a 20% difference in ischemia scores with alpha = 0.05 and an SD of 1.5 was 0.67.

Results

Effect of the meal at rest (Table 1). In the studies at rest, heart rate was higher after the meal by 12% (74 ± 8 vs. 66 ± 8 beats/min, p = 0.0008). Blood pressure was unchanged and rate-pressure product was 11% higher (p = 0.014).

Effect of the meal on exercise (Table 2). All patients developed angina and ≥1-mm ST depression during both exercise tests. Exercise capacity was less after the meal than

Table 1. Fasting and Postprandial Hemodynamic Measurements at Rest

	Fasting	Postprandial	Change (%)	p Value
Heart rate (beats/min)	66 ± 8	74 ± 8	+12	0.0008
Blood pressure (mm Hg)				
Systolic	135 ± 14	135 ± 14		0.7697
Diastolic	81 ± 7	81 ± 8		—
Rate-pressure product ($\times 10^{-3}$)	8.9 ± 1.6	9.8 ± 1.4	+11	0.014

Data are expressed as mean value ± SD.

during the fasting test. The time to onset of ≥1-mm ST depression was reduced by 20% from 248 ± 93 s ($p = 0.0007$), time to angina was decreased by 15% from 340 ± 82 s ($p = 0.002$) and total exercise duration decreased by 9% from 376 ± 65 s ($p = 0.002$). A decrease of ≥10% in time to ≥1-mm ST depression was seen in 15 of the 20 patients after the meal, and in 11 patients the decrease was ≥20%. The work load achieved during the postprandial test, 6.6 ± 1.4 METs, was 8% less than the work load achieved during the fasting test ($p = 0.008$).

Heart rate, systolic blood pressure and rate-pressure product at the onset of ≥1-mm ST depression, at the onset of angina and at peak exercise did not differ significantly between the fasting and postprandial tests. The mean maximal ST depression was 2.6 mm during both tests. The ischemia score, calculated by subtracting the defect score at rest from the exercise defect score, was 4.2 ± 3.2 during the fasting tests and 3.5 ± 2.6 during the postprandial tests ($p = 0.33$ [NS]) (Fig. 1).

Patients with a history of worse angina after meals. Seven patients affirmed that their angina threshold was lower after meals, and 13 noted either no difference or were unsure. The exercise data of these two groups did not differ except that angina developed at a lower heart rate during exercise in patients with a positive history (126 ± 14 vs. 142 ± 9 beats/min during the fasting test [$p = 0.005$] and 125 ± 14 vs. 140 ± 14 beats/min during the postprandial test [$p = 0.035$]). The defect score at rest was also higher in patients with a positive history (5.9 ± 5.0 vs. 1.8 ± 2.8 [$p = 0.02$]). These differences suggest that patients who reported that their angina is worse after meals may have had more left ventricular dysfunction during exercise as a result of previous

Table 2. Fasting and Postprandial Measurements During Exercise

	Fasting	Postprandial	Change (%)	p Value
At onset of 1-mm ST depression				
Duration of exercise (s)	248 ± 93	197 ± 87	−20	0.0007
Heart rate (beats/min)	122 ± 16	120 ± 12		0.41
Blood pressure (mm Hg)				
Systolic	172 ± 17	166 ± 13		0.13
Diastolic	87 ± 6	83 ± 5	−4	0.02
Rate-pressure product ($\times 10^{-3}$)	21.0 ± 3.6	20.0 ± 2.6		0.14
At onset of angina				
Duration of exercise (s)	340 ± 82	287 ± 94	−15	0.002
Heart rate (beats/min)	136 ± 14	135 ± 16		0.46
Blood pressure (mm Hg)				
Systolic	181 ± 19	182 ± 22		0.61
Diastolic	88 ± 8	86 ± 6		0.42
Rate-pressure product ($\times 10^{-3}$)	24.7 ± 4.0	24.9 ± 4.7		0.72
At peak exercise				
Duration of exercise (s)	376 ± 65	344 ± 86	−9	0.002
Heart rate (beats/min)	142 ± 12	140 ± 13		0.53
Blood pressure (mm Hg)				
Systolic	184 ± 18	184 ± 20		0.87
Diastolic	89 ± 9	86 ± 6		0.23
Rate-pressure product ($\times 10^{-3}$)	26.1 ± 3.6	25.9 ± 4.2		0.89
Work load (METs)	7.2 ± 1.1	6.6 ± 1.4	−8	0.008
Maximal ST depression (mm)	2.6 ± 1.0	2.6 ± 0.9		0.69
Defect score at rest*	3.2 ± 4.1	3.2 ± 4.1		0.33
Defect score on exercise	7.4 ± 5.5	6.7 ± 5.3		0.37
Ischemia score (exercise − rest)	4.2 ± 3.2	3.5 ± 2.6		0.33

*On technetium-99m–sestamibi single-photon emission computed tomography. Data are expressed as mean value ± SD. METs = metabolic equivalents.

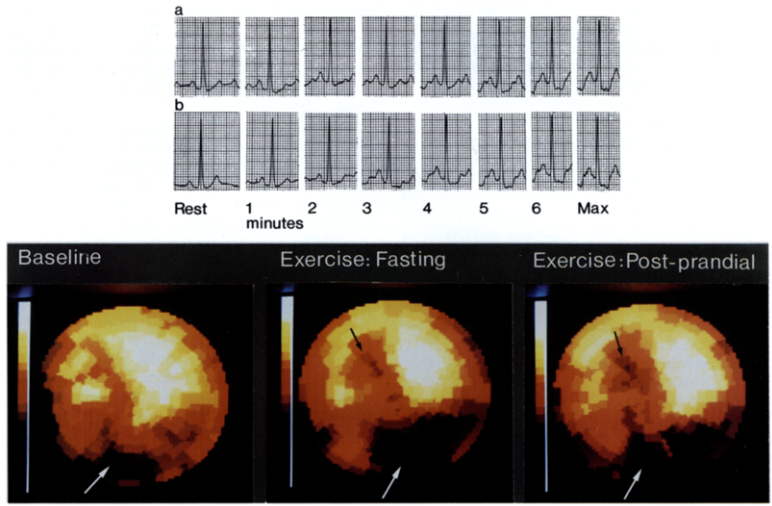

Figure 1. Results of the fasting and postprandial exercise tests in a typical patient. **Top,** Significant ST segment depression developed at 5 min during the fasting test **(a)** and after 3 min during the test after the meal **(b). Bottom,** The rest technetium-99m–sestamibi polar map **(left)** shows a posterobasal perfusion defect with posterolateral extension **(white arrow).** The fasting exercise scan **(middle)** and the postprandial exercise scan **(right)** are similar; both indicate that the posterior defect is worse and more prominent in its lateral portion. A small defect also appears in the apical area of the anteroseptal wall **(black arrow).**

infarction; however, the relation of this to their symptoms is uncertain.

Discussion

This study demonstrates that in patients with stable angina, exercise time to the onset of ischemia is reduced by 20% and time to the onset of angina by 15% after a standardized meal. This reduction was found in almost all patients, even though only a minority had recognized it. The extent and severity of ischemia, as assessed by ^{99m}Tc-sestamibi SPECT quantification, and the rate-pressure product at the onset of ischemia were similar during fasting and postprandial exercise.

Previous studies. This conclusion reaffirms the findings of older, classic studies. In 1931 Wayne and Graybiel (1) reported that exercise capacity decreased by 25% after a meal in six patients with angina and in 1971 Goldstein et al. (2) found that angina developed earlier after eating in 11 of 12 patients with angina. In these studies the exercise protocol was not standardized and exercise-induced ST depression either did not develop in most cases (2) or was not assessed (1). Hung et al. (3) reported no reduction in exercise capacity after a 1,000-calorie meal in 24 men with chronic ischemic heart disease. They also failed to demonstrate any significant difference in heart rate or rate-pressure product at rest, and rate-pressure product was higher at the onset of ischemia during the postprandial test. However, only half of the patients developed ST depression during the test, and only one third stopped exercise because of angina. The absence of exercise-induced ischemia in a large segment of their patient group probably accounts for some of the differences between the results of their study and ours.

Cowley et al. (4) reported in 1991 that exercise capacity decreased after a meal in 23 patients with angina. However, the baseline and postprandial tests were performed on the same day, and in the same patients they found that, even without a meal, exercise capacity decreased, although by much less, on the second of the two tests done the same day. Time to the onset of ST depression also decreased after a meal, but the exact values for this end point were not reported.

Mechanism. The increase in heart rate and rate-pressure product at rest in our patients after the meal were in

accordance with the results of most (1,4–7) but not all (2,3) previous studies. In our study the rate-pressure product at the onset of ST depression, at the onset of angina and at peak exercise was similar in the fasting and postprandial tests. This observation implies that the reduction in exercise capacity after a meal is due not to a decrease in coronary blood supply to the ischemic zone but to an increase in myocardial oxygen consumption. After a meal, cardiac output increases at rest and is higher at each stage of exercise than during the fasting test (4–7). Correspondingly, heart rate is higher, and the ischemic threshold is thus reached earlier during exercise.

The postprandial decrease in exercise tolerance could theoretically be attributed to noncardiac factors. If such were the case, the extent and severity of ischemia would be less during the postprandial test because of its shorter duration. However, the ischemia score, derived from the rest and exercise ^{99m}Tc-sestamibi SPECT studies, was similar during the fasting and postprandial tests. The maximal ST segment depression, a much poorer index of ischemia, was also equal during the two tests. The reduction in exercise capacity after a meal is therefore due to an increase in myocardial oxygen consumption at each level of exercise compared with values on the fasting test, so that the ischemic threshold is reached earlier.

Limitations of the study: 1) A major limitation of this study is that rate-pressure product is an inaccurate and indirect method of assessing myocardial oxygen consumption. Other factors, such as wall tension and contractility, that contribute to myocardial oxygen consumption are difficult to measure during exercise testing and are ignored. Cuff blood pressure measurements made at minute intervals during exercise lack precision.

2) The treadmill exercise test protocol does not accurately reproduce the conditions of daily life. Rate-pressure product at the onset of ischemia is fairly reproducible during serial exercise tests in patients with stable angina (11) but, during daily activities, myocardial ischemia develops over a broad range of heart rates (12). The heart rate at which ischemia develops is lower during prolonged, low level exercise test protocols (13–15), and on ambulatory ECG monitoring many ischemic episodes are preceded by slight increases in heart rate lasting from 5 to 30 min (13). Thus, the impact of meals on ischemic thresholds and patterns of angina should also be assessed with ambulatory ECG monitoring. Under nonstandardized conditions, elusive mechanisms such as modulation of coronary flow by dynamic stenoses or distal coronary vasoconstriction might contribute to reducing ischemic threshold.

3) In this study, we did not investigate the effect of meals of different size or composition, or the duration of the reduction in exercise capacity after a meal. In the study of Dagenais et al. (5), the hemodynamic changes at rest after a carbohydrate-rich meal peaked at 45 to 90 min and dissipated by 3 h; after a protein-rich meal, the changes began later and peaked at 3 h. It is likely that the reduction in exercise tolerance follows a similar pattern. The size and composition of the meal used in this study were average and corresponded roughly to the patients' usual intake. The magnitude of the reduction in exercise capacity probably varied directly with the size of the meal, but this relation was not tested.

Defect scores on the ^{99m}Tc-sestamibi SPECT studies did not differ between the two experimental conditions at rest and exercise; however, the power of our study to detect such a difference was only 0.67. Our power calculation may be inaccurate because our estimate of variance may be inaccurate. The interobserver variability in quantification of ^{99m}Tc-sestamibi defects is low for reanalysis of the same image (16,17), but reproducibility studies with repeat exercise and reacquisition of the images have not been reported for ^{99m}Tc-sestamibi. Despite this limitation, the sestamibi SPECT technique is the best method available to quantify exercise-induced ischemia. Because our study is somewhat underpowered for this end point, we cannot exclude the possibility that the severity of ischemia differed between the two test conditions. Although both the magnitude of ST segment depression and the rate-pressure product were similar (Table 2) in the fasting and postprandial tests, we cannot be certain that the postprandial tests were not associated with less ischemia.

Clinical implications. Although only 7 of the 20 patients in this study recognized that their angina threshold was lower after a meal, time to the onset of ischemia during exercise was reduced in 18 patients, and the reduction was ≥20% in 11. The absence of angina at the onset of ischemia is a partial explanation for this discrepancy. All patients with coronary disease, even those who do not complain of a lower angina threshold after eating, should therefore probably be cautioned to avoid vigorous exercise after meals.

We have previously reported that exposure to cold also reduces exercise time to ischemia in patients with angina (18). However, this reduction was limited to the one third of patients who claimed to be sensitive to cold. In contrast, nearly all patients with angina are affected by a meal. Because the decrease in exercise capacity after a meal is due to a more rapid increase in myocardial oxygen consumption, an antianginal drug that reduces myocardial oxygen consumption might be more effective in improving postprandial exercise capacity than one that increases coronary blood flow. This hypothesis should be tested.

Exercise testing is commonly used to measure the efficacy of antianginal drugs or coronary revascularization. This study demonstrates that the ischemic threshold during exercise can be shifted by 20% by a recent meal. It is therefore crucial that, for the results to be comparable, all exercise tests should be performed under fasting conditions. A food-free interval of at least 5 h should be sufficient, but the duration of the effects of a meal on exercise test end points has not been investigated.

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