Exercise above the ischemic threshold and serum markers of myocardial injury

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BACKGROUND: Current guidelines for exercise training in coronary patients state that in the presence of exercise-induced ischemia, the heart rate during exercise should be at least 10 beats/min below the heart rate associated with an ST segment depression of 1 mm or greater. For patients with a relatively low ischemic threshold, this recommendation does not allow for a sufficient training stimulus.
OBJECTIVE: To document the effects of a single session of exercise above the ischemic threshold on biochemical markers of myocardial injury in stable coronary patients with exercise-induced ischemia. Because creatine kinase (CK) and its MB isoenzyme (CK-MB) can both increase after exercise because of skeletal muscle injury, troponin T was also measured.
METHODS: Twenty-one patients with documented coronary artery disease underwent two 20 min exercise sessions. The intensity of the first exercise training session was fixed at a heart rate below the ischemic threshold (ie, approximately 10 beats/min lower than the heart rate associated with the appearance of an ST segment depression of 1 mm or greater). The intensity of the second exercise session was fixed at a heart rate above the ischemic threshold.
RESULTS: Blood test measurements at baseline, 6 h after and 24 h after the exercise sessions did not show any increase in total CK, CK-MB or troponin. The value of all measurements remained well below the lower limits associated with myocardial damage.
CONCLUSION: A 20 min period of exercise above the ischemic threshold did not result in myocardial necrosis.

Key Words: *Biochemical markers; Coronary artery disease; Exercise physiology; Preventive cardiology; Rehabilitation*

L'exercice au-dessus du seuil ischémique et des marqueurs sériques de lésion myocardique

HISTORIQUE : Selon les lignes directrices actuelles relativement à l'entraînement à l'exercice chez les patients atteints d'une maladie cardiovasculaire, en présence d'ischémie induite par l'exercice, le rythme cardiaque pendant l'exercice devrait se situer au moins à 10 battements/min sous celui associé à une dépression du segment ST de 1 mm ou plus. Dans le cas des patients chez qui le seuil ischémique est relativement faible, cette recommandation n'assure pas un stimulus d'entraînement suffisant.
OBJECTIF : Documenter les effets d'une seule séance d'exercice au-dessus du seuil ischémique sur les marqueurs biochimiques de lésion myocardique chez des patients atteints d'une coronaropathie stable souffrant d'ischémie induite par l'exercice. Puisque la créatine kinase (CK) et ses isoenzymes MB (MB-CK) peuvent augmenter après l'exercice en raison d'une lésion du muscle squelettique, on a également mesuré la troponine T.
MÉTHODOLOGIE : Vingt et un patients atteints d'une coronaropathie documentée ont effectué deux séances d'exercice de 20 minutes. L'intensité de la première séance d'entraînement à l'exercice était établie à un rythme cardiaque inférieur au seuil ischémique (soit environ 10 battements/min de moins que celui associé à l'apparition d'une dépression du segment ST de 1 mm ou plus). L'intensité de la deuxième séance d'exercice était établie à un rythme cardiaque supérieur au seuil ischémique.
RÉSULTATS : Les mesures des analyses sanguines avant les séances d'exercice, puis six heures et 24 heures après, ne révélaient aucune augmentation des taux totaux de CK, de MB-CK ou de troponine. La valeur de toutes les mesures se maintenait bien en-dessous des limites inférieures associées à une atteinte myocardique.
CONCLUSIONS : Une période d'exercice de 20 minutes au-dessus du seuil ischémique n'entraîne pas de nécrose myocardique.

Exercise training has been shown to be beneficial in the treatment of patients with coronary disease and many other cardiovascular conditions (1,2). Current recommendations (3) for exercise training in coronary patients state that the intensity of training, as measured by the target heart rate, should be between 40% and 60% of the heart rate reserve or 65% to 85% of the maximal heart rate achieved on the pretraining symptom-limited exercise test. In the presence of exercise-induced ischemia, it is recommended that the heart rate during exercise training be at least 10 beats/min below the heart rate associated with an ST segment depression of 1 mm or greater. For patients with a relatively low ischemic threshold, this recommendation does not allow for a sufficient training stimulus, as demonstrated by Dressendorfer et al (4). However, very little research has been published on the subject of exercise training above the ischemic threshold in coronary patients (4,5).

Some animal studies have suggested that cellular necrosis may result from repetitive ischemia (6), while others have reported that brief repetitive ischemia episodes may be protective and result in a reduction of infarct size (7,8). Studies in coronary patients during coronary angioplasty have demonstrated a reduction in ST segment changes after repeated balloon inflations (9,10). This phenomenon in animal models and coronary patients is referred to as ischemic preconditioning.

The aim of the present study was to document the effects of a single session of exercise above the ischemic threshold on biochemical markers of myocardial injury in stable coronary patients with exercise-induced ischemia. Because creatine kinase (CK) and its MB isoenzyme (CK-MB) can increase after exercise because of skeletal muscle injury, troponin T was also measured. Elevated plasma troponin T is the most sensitive and specific marker of myocardial damage (11), and its levels increase rapidly after acute coronary syndromes but not after running a marathon (12).

METHODS

The study population consisted of 21 men with documented coronary artery disease defined as coronary stenosis of 70% or more of the lumen

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TABLE 1
Characteristics of study patients (n=21)

Characteristic	Value
Age, years	58±9
Previous myocardial infarction	8 (38)
Previous coronary artery bypass graft	4 (19)
Previous percutaneous transluminal coronary angioplasty	4 (19)
Angina (Canadian Cardiovascular Society class 1 or 2)	5 (24)
Left ventricular ejection fraction, %	55±6
Abnormal coronary angiogram	12 (57)
Positive myocardial perfusion scan	11 (52)
Antianginal medication	
Beta-blockers	10 (48)
Calcium channel antagonists	5 (24)
Nitrates	0 (0)

Data presented as n (%) or mean ± SD

diameter at coronary angiography; previously documented myocardial infarction; or a reversible perfusion defect on thallium or technetium-99 sestamibi scintigraphic exercise testing.

All patients demonstrated exercise-induced ST segment depression of 1 mm or greater during standard exercise testing using a ramp protocol (13). Patients with myocardial infarction, unstable angina, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty within the past three months, overt heart failure, history of hypertension with or without left ventricular hypertrophy on the resting electrocardiogram (ECG), serious arrhythmias or baseline ECG abnormalities that could interfere with the interpretation of the ST segment were excluded. Patients requiring digitalis were also excluded.

The ischemic threshold was defined as the heart rate at which a 1 mm horizontal or downsloping ST segment depression appeared on a baseline treadmill symptom-limited exercise test. Exercise testing was performed using a standard treadmill (Marquette Case 12; Marquette Electronics Inc, USA). Three ECG leads were continuously monitored and a complete ECG was recorded every 30 s to determine, as precisely as possible, the onset of ST segment depression (1 mm or greater). The ST segment was measured 0.08 s after the J point in three consecutive QRS complexes, with a flat baseline and R waves of equal amplitude.

Exercise sessions

Two 20 min exercise training sessions were scheduled at least 72 h apart. Both sessions were performed on the same treadmill used for the exercise test. The intensity of the first exercise training session was fixed at a heart rate below the ischemic threshold (ie, approximately 10 beats/min lower than the heart rate associated with the appearance of an ST segment depression of 1 mm).

The intensity of the second exercise session was fixed at a heart rate above the ischemic threshold (ie, at a heart rate associated with an ST segment depression of 1 mm or greater). The speed and grade of the treadmill were constantly adjusted to maintain the required exercise training heart rate and ST segment response at all times during both exercise training sessions. Patients were instructed to take all their medications, including antianginal agents, as usual on the days of the exercise test and exercise sessions.

Serum markers of myocardial injury

Blood samples for CK, CK-MB and troponin T were collected before, 6 h after and 24 h after each training session. CK and CK-MB levels were determined with reagents manufactured by Boehringer Mannheim (Germany) (normal lower than 195 U/L and 30 U/L, respectively). Troponin T was measured with an ELISA (Boehringer Mannheim) using polyclonal antibodies (normal lower than 0.1 ng/mL).

TABLE 2
Baseline exercise test results

Result	Value
Heart rate at rest, beats/min	64±1
Heart rate at ischemic threshold, beats/min	115±14
Systolic blood pressure at ischemic threshold, mmHg	176±20
Rate-pressure product at ischemic threshold, $\times 10^{-3}$	20.4±3.7
Maximal heart rate, beats/min	140±18
Maximal systolic blood pressure, mmHg	197±21
Maximal exercise tolerance (metabolic equivalents)	8.7±1.5
Maximal ST segment depression, mm	2.5±0.8

Data presented as mean ± SD

TABLE 3
Exercise test parameters below and above the ischemic threshold

Parameter	Below ischemic threshold	Above ischemic threshold	P
Heart rate, beats/min	91±13	120±20	<0.0001
Systolic blood pressure, mmHg	155±15	185±16	<0.0001
Rate-pressure product, $\times 10^{-3}$	14.5±2.9	21.8±4.8	<0.0001
Metabolic equivalents	3.4±0.7	5.1±1.2	<0.001
ST segment depression, mm	0.5±0.2	1.4±0.5	<0.001

Data presented as mean ± SD

Statistics

Results are expressed as the mean ± SD for continuous variables and as frequency (percentage) for categorical variables. Exercise test parameters and biochemical markers were compared between the two exercise sessions using paired *t* tests. Data at baseline, 6 h after and 24 h after training were compared using repeated measures ANOVA. $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

Twenty-one men with documented coronary disease (58±9 years of age), were included in the study. Patient characteristics are shown in Table 1. Although five patients reported Canadian Cardiovascular Society class 1 or 2 angina on exertion, no patient presented with angina during exercise testing or during the two exercise training sessions.

During the symptom-limited exercise test, the mean heart rate at the ischemic threshold was 115±14 beats/min and the systolic blood pressure was 176±20 mmHg (Table 2).

The mean heart rate during the exercise session below the ischemic threshold was 91±13 beats/min, corresponding to 65% of the mean maximal heart rate achieved during baseline symptom-limited exercise testing (Table 3). This heart rate was 24 beats/min lower than the heart rate at onset of ischemia. The mean level of ST segment depression was 0.5±0.2 mm. The total CK, CK-MB and troponin T did not increase after this exercise session at 6 h or at 24 h (Table 4).

The mean heart rate recorded during the exercise session above the ischemic threshold was 120±20 beats/min, corresponding to 85% of the maximal heart rate achieved during the baseline symptom-limited exercise test. This mean heart rate was 5 beats/min above the heart rate at the onset of ischemia. The mean level of ST segment depression during this exercise session was 1.4±0.5 mm and constant ECG monitoring confirmed that ST segment depression was 1 mm or greater at all times.

Blood test measurements at 6 h and 24 h after the exercise session above the ischemic threshold did not show any increase in total CK, CK-MB or troponin T. The troponin values were actually nearly identical between the exercise sessions below and above the ischemic threshold 6 h and 24 h after training. In fact, the value of all measure-

TABLE 4
Serum markers before and after exercise

	Below ischemic threshold	Above ischemic threshold
Before training		
CK, U/L	145±41	110±27
CK-MB, U/L	6±1	8±1
Troponin T, ng/mL	0.009±0.009	0.014±0.011
6 h post-training		
CK, U/L	151±36	127±32
CK-MB, U/L	9±2	8±1
Troponin T, ng/mL	0.015±0.008	0.014±0.012
24 h post-training		
CK, U/L	132±27	118±32
CK-MB, U/L	9±3	9±1
Troponin T, ng/mL	0.011±0.008	0.011±0.007

Data presented as mean ± SD. Normal ranges: creatine kinase (CK) 24 U/L to 195 U/L; CK-MB isoenzyme 0 U/L to 30 U/L; troponin T <0.1 ng/mL. No significant differences noted for all comparisons

ments remained well below the lower limits associated with myocardial damage (Table 4).

No clinical events occurred and no patient experienced angina during this session. No arrhythmias were noted.

DISCUSSION

In the present group of stable coronary patients with exercise-induced myocardial ischemia, exercise training above the ischemic threshold for a duration of 20 min did not result in elevated levels of CK, CK-MB or troponin T. In addition, no single patient showed an increase in any of the three serum markers of myocardial necrosis. The two exercise sessions were constantly monitored to ensure that the intensity of both sessions were continuously below or above the ischemic threshold. During the exercise session above the ischemic threshold, the mean ST segment depression was 1.4±0.5 mm, with continuous ECG monitoring always showing an ST segment depression of 1 mm or greater. All subjects were patients with proven coronary disease and, given that all known causes of false-positive exercise tests were excluded, the probability of ST segment depression representing true ischemia in this patient group is very elevated.

Because troponin T is a highly sensitive and specific marker of myocardial necrosis, it may be concluded that this exercise session above the ischemic threshold did not provoke myocardial necrosis.

As previously mentioned, current guidelines for exercise training in coronary patients state that in the presence of exercise-induced ischemia, the heart rate during exercise training should be at least 10 beats/min below the heart rate associated with an ST segment depression of 1 mm or greater (3). For patients with a relatively low heart rate at the onset of significant ST segment depression, this recommendation results in an insufficient training stimulus (ie, less than 40% to 60% of the heart rate reserve or less than 65% to 85% of the maximal heart rate achieved on the pretraining symptom-limited exercise test). Indeed, according to the results of one small study (4) in patients with exercise-induced ischemia, exercise training at the ischemic threshold provides a better training stimulus, and results in an improvement in aerobic capacity and lipid profile relative to training below the ischemic threshold. However, our study is the first to evaluate and demonstrate that a single training session above the ischemic threshold is safe and not associated with an elevation of serum markers of myocardial necrosis.

There are also theoretical benefits of exercise training above the ischemic threshold. As reviewed by Schwarz et al (14), it has been demonstrated in experimental animal studies that repeated and brief periods of ischemia are protective, and result in a reduction of infarct size. Also, long-term exercise training in pigs after gradual occlusion of the circumflex artery has been shown to improve myocardial function and coronary collateral reserve during exercise (15). Clinical studies in the catheterization laboratory in patients with significant coronary obstructions have shown less ST segment depression, less myocardial lactate production and less angina during the second balloon inflation, a phenomenon referred to as percutaneous transluminal angioplasty-related ischemic preconditioning (9,10). Although left ventricular function abnormalities of short duration have been described after brief episodes of exercise-induced ischemia, no evidence of chronic dysfunction has been described in this context (16).

Limitations

The present study has several limitations. First, only 21 men with coronary disease were included in the study, representing a small sample size. Second, the patient group was carefully selected and presented exercise-induced ischemia at an average heart rate of 115±14 beats/min and a normal left ventricular ejection fraction. Accordingly, the results cannot be generalized to all patients with coronary disease. Third, the ECGs during the exercise sessions in the present trial were continuously monitored to ensure that the intensity of exercise was respected at all times. This does not reflect the clinical practice of many cardiac rehabilitation programs. No significant ventricular arrhythmias were noted during the present study, but because the number of patients studied was limited, the potential for severe ischemia-induced arrhythmias during exercise above the ischemic threshold cannot be excluded.

CONCLUSION

In patients with stable coronary disease and exercise-induced ischemia, the measurements of CK, CK-MB and troponin T after a 20 min exercise session above the ischemic threshold do not show any increase. It can be concluded that a brief period of exercise above the ischemic threshold does not result in myocardial necrosis. The safety of chronic exercise training above the ischemic threshold will have to be demonstrated in larger studies before recommendations can be made for clinical practice.

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