Effects of Intravenous Theophylline on Exercise-Induced Myocardial Ischemia. I. Impact on the Ischemic Threshold

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Objectives. Theophylline has been shown to delay the onset of myocardial ischemia and to prolong exercise duration. The present study was done to evaluate the mechanisms and actions of intravenous theophylline on the onset of ischemia and exercise duration.

Background. The ischemic threshold may be altered by the differential coronary vasodilation induced by endogenous adenosine. Theophylline is a competitive receptor antagonist of adenosine and may have a potential as an anti-ischemic medication.

Methods. A double-blind, placebo-controlled crossover trial using an infusion of intravenous theophylline (8.0 ± 2.0 mg/liter) or placebo before exercise in 12 patients was done. Oxygen uptake, heart rate, blood pressure and heart rate-blood pressure product were determined at the onset of ≥0.1-mV ST segment depression and angina pectoris, as well as at peak exercise. The extent of myocardial ischemia was evaluated by electrocardiographic criteria and quantitation of thallium-201 images at peak exercise.

Results. When compared with placebo, theophylline significantly delayed time to the onset of exercise-induced ischemia. Ischemia occurred at a higher heart rate-blood pressure product and oxygen uptake. Exercise duration was prolonged but was not associated with greater ischemia, as determined by oxygen uptake, ST segment depression, angina pectoris and size of thallium-201 defect.

Conclusions. It is concluded that theophylline favorably alters myocardial ischemia not only by delaying its onset but also by enabling it to occur at a higher threshold without causing deleterious effects during exercise. The mechanism for the increased ischemic threshold may be through the inhibition of adenosine and the coronary steal phenomenon.

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Traditionally, models of the determinants of myocardial ischemia have been based on the relations between myocardial oxygen demand and supply. Situations in which myocardial oxygen demand is increased result in ischemia when not accompanied by a concomitant increase in myocardial oxygen delivery. This concept implies the existence of a fixed ischemic threshold dependent on demand alone in the presence of a fixed supply secondary to coronary artery stenosis (1). However, other factors are also operative because the ischemic threshold has been shown to be variable (2-8). Recent evidence suggests that work loads and myocardial oxygen uptake at the onset of ischemia can be altered during differing exercise conditions. For example, Garber et al. (6) found that ischemia, as measured by electrocardiographic (ECG) changes and symptoms, occurs at lower work loads when a slowly progressing exercise protocol is used. These studies imply that ischemia may occur at lower thresholds during normal daily activities than would be predicted by standard Bruce protocol exercise testing, an observation confirmed in numerous ambulatory ECG studies (3-5,7). Hence, factors other than myocardial demand may alter the ischemic threshold. One possibility is the role of differential vasodilation produced by vasoactive substances such as adenosine (9-13).

Adenosine is a powerful coronary vasodilator endogenously released in response to myocardial ischemia to promote increased myocardial blood flow (12,13). However, the vasodilating effects of adenosine in the presence of existing coronary disease result in a preferential increase in coronary blood flow to areas of myocardium that are not supplied by stenotic coronary artery vessels and therefore may exaggerate ischemia. The inhibition of adenosine may prevent or delay this coronary steal phenomenon at a given work load and thereby raise the ischemic threshold (10).

Agents such as methylxanthines that inhibit adenosine may be effective in reducing or delaying ischemic events without altering the determinants of myocardial oxygen demand. Such compounds may produce alternate avenues of...
therapy to the traditional classes of drugs (that is, beta-adrenergic blocking agents, calcium antagonists and nitrates). In confirmation of this concept, the methylxanthine theophylline has been shown to delay the onset of exercise-induced ischemia and to prolong exercise duration (14–17). Unfortunately, little is known regarding the mechanisms of the effects of theophylline, particularly in relation to the action of adenosine. In addition, data from other studies have suggested that theophylline may exert deleterious effects on the myocardium that may limit its clinical utility (18–20).

The present study was undertaken to evaluate the effects of theophylline on exercise-induced myocardial ischemia and to further explore the mechanisms of these actions. The influence of theophylline on the onset of ischemia and peak exercise was evaluated by determining clinical variables, hemodynamic effects, oxygen uptake and comparative thallium-201 imaging (21,22).

Methods

Patient selection. Patients referred for exercise thallium-201 studies were screened for inclusion in this study. Patients who were in a clinically stable condition and who met the following criteria were eligible for study entry: 1) exercise-induced horizontal or downsloping ST segment depression ≥0.1 mV, 2) reversible thallium-201 defect by both qualitative and computer-assisted quantitative criteria, and 3) post-test likelihood of significant coronary artery disease ≥95% (23).

Patients were excluded from the study if any of the following were present: 1) ECG evidence of left ventricular hypertrophy, left bundle branch block or other baseline ST segment abnormalities rendering the exercise ECG uninterpretable; 2) known allergies to theophylline or current therapy with theophylline or other bronchodilators; 3) asthma or reactive airways disease; 4) digoxin therapy.

Study design. The study was a randomized, double-blind, placebo-controlled, crossover trial of intravenous theophylline using a replicated 2 × 2 Latin square design. After obtaining informed consent, subjects completed two baseline exercise tests and two exercise tests with thallium-201 imaging, which were preceded by an intravenous infusion of either theophylline or placebo.

Calcium channel antagonists and beta-blocking agents were withdrawn for 48 h before testing. Nitrates, other than sublingual, were withheld on the day of testing. The exercise studies were administered 7 to 10 days apart.

Procedures and analysis. Exercise testing. The exercise tests were administered at the same time in the morning for a given patient after a minimum of a 4-h fast. The exercise tests were symptom limited and used the standard Bruce protocol (24). Twelve-lead ECGs were recorded during each minute of exercise and until return to baseline after exercise. Oxygen uptake was measured during each minute of exercise. Tests were terminated because of ST segment depression ≥0.4 mV, complex ventricular arrhythmias, induced hypotension, progressive limiting angina or fatigue (24).

Medication protocol. After preparation for ECG monitoring and determination of baseline blood pressure and heart rate, each patient was randomized to a 30-min infusion of theophylline (5 mg/kg ideal body weight as the ethylene-diamine salt, aminophylline) or an equivalent volume of saline placebo in 100 ml of saline solution. Ideal body weight was calculated as follows: for men, 30 kg + 2.3 kg for every inch (2.54 cm) over 5 feet (1.52 m); for women, 45.5 kg + 2.3 kg for every inch over 5 feet (25). During the infusion, three ECG leads and patient symptoms were monitored, and the blood pressure and 12-lead ECG were recorded every 10 min. Exercise testing immediately followed the drug infusion.

Oxygen uptake methods. Oxygen uptake was measured during each exercise test by open circuit indirect calorimetry with an Ametek S-3A oxygen analyzer, a Beckman LB-2 carbon dioxide (CO₂) analyzer, and a Hewlett-Packard heated digital pneumotach (model 47303A). Measurements of oxygen uptake were made using a Douglas bag method with collection of 30-s mixed expired air samples (26). Before each test, the volume measurements were confirmed using a 3-liter syringe, and the oxygen and CO₂ analyzers were calibrated by using a gas with known concentrations of oxygen and carbon dioxide (about 15% O₂, 4% CO₂), verified by the micro-Scholander technique (27).

Thallium-201 imaging. Patients received an injection of 2.5 to 3.0 mCi thallium-201 1 min before the end of exercise after the placebo and theophylline infusions. Planar imaging was begun within 10 min using three standard views: anterior, 35° left anterior oblique and 70° left anterior oblique. Patients returned approximately 4 h later for delayed imaging.

Data analysis and interpretation. The ECGs were analyzed without knowledge of patient identity or treatment by consensus of two experienced cardiologists. For each subject, the lead showing the greatest ST segment depression was determined on the first test and was utilized on all subsequent tests. Data extracted from the ECGs included the time of onset of 0.1 mV horizontal or downsloping ST segment depression, ST segment depression at peak exercise, total exercise duration and time to onset of angina pectoris.

The thallium-201 images were analyzed visually and with computer-assisted quantitation. Images were interpreted by consensus by three experienced observers without knowledge of the drug protocol or patient identity. Thallium-201 images from normal patients and patients not participating in the study were included to reduce bias. The left ventricular images were divided into 15 segments; each segment was scored on a scale of 0 to 3 (0 = normal, 1 = slight photon emission reduction, 2 = moderate photon emission reduction, 3 = background or absent activity). Scoring of 15 segments resulted in a range of 0 to 45/patient (28).
with a computer-assisted method (29). An operator-
determined ellipse was fitted around the left ventricular
region of all three initial images. The images were realigned
to fit within the ellipse, and weighted background subtrac-
tion was performed. Thallium-201 activity profile scores
were derived and normalized to the hottest 9-point smoothed
pixel within the ellipse of the initial images. The left ventric-
ular activity was subdivided into five segments of equal
length around the perimeter. Mean normalized segmental
thallium-201 activity was then determined (30). Application
of this procedure to all three stress planar images resulted in
a possible range of 0% to 30% per patient.

**Theophylline assay.** Whole blood samples were collected
at peak exercise in a tube without additive and immedi-
ately spun at 1,200 × g for 15 min. The supernatant was extracted
and frozen immediately. Samples were stored at −10°C until
assayed (<1 month). Theophylline was assayed by using
the theophylline two-part rate test with a Kodak Ektachem
clinical analyzer (model 400). Duplicate serum samples
(10 µl) were analyzed with the methodology described by
Kodak (publication MP2-46).

**Data analysis strategy.** Statistical analyses were per-
formed by using a repeated measures approach to the
analyses of variance (31). When indicated, post-hoc testing
was performed with the Tukey HSD test (32). Data are
reported as the mean value ± SD. The significance level was
set at p < 0.05.

### Results

Twelve men met the study criteria and completed the
entire protocol. All patients had a history of stable angina
pectoris, and seven had evidence of prior myocardial infarc-
tion. All patients were receiving anti-ischemic medications,
and 11 were taking more than one drug.

**Effects of theophylline on exercise ischemia.** The mean
theophylline level at peak exercise in these patients was
8.0 ± 2.0 mg/liter. The effects of theophylline on exercise
variables are illustrated in Table 1. Theophylline signifi-
cantly delayed the time of onset of both ECG changes and
angina pectoris and significantly increased the total exercise
duration. Oxygen uptake was significantly greater at peak
exercise after theophylline administration. There were no
significant differences between the baseline and placebo
values for any of the exercise variables measured.

Eight patients experienced angina pectoris during the
exercise protocol. The time to the onset of angina was
significantly delayed after theophylline infusion, whereas
there were no significant differences between the anginal
responses at baseline and with placebo (Table 1). The onset
of angina occurred at a significantly higher heart rate,
systolic blood pressure and heart rate-systolic blood
pressure product after theophylline infusion (Fig. 1). The oxygen
uptake at the onset of angina was also significantly greater
after theophylline infusion.

### Table 1. Effect of Theophylline on Exercise-Induced Ischemia

|                | Baseline | Placebo | Theophylline | p Value
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<tr>
<td>Onset of ST ↓</td>
<td>4.0 ± 1.5</td>
<td>3.9 ± 1.5</td>
<td>5.7 ± 2.4*</td>
<td>&lt; 0.001</td>
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<td>(n = 12)</td>
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<tr>
<td>Onset of angina</td>
<td>4.8 ± 1.6</td>
<td>5.1 ± 1.0</td>
<td>6.7 ± 1.7*</td>
<td>&lt; 0.001</td>
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<td>(n = 8)</td>
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<tr>
<td>Exercise duration (min)</td>
<td>7.0 ± 1.8</td>
<td>7.6 ± 1.4</td>
<td>8.5 ± 1.8*</td>
<td>&lt; 0.05</td>
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<td>(n = 12)</td>
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<tr>
<td>VO₂ at maximal exercise</td>
<td>18.2 ± 2.9</td>
<td>19.5 ± 2.7</td>
<td>20.9 ± 3.5*</td>
<td>&lt; 0.01</td>
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<td>(n = 12)</td>
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*p < 0.05 compared with placebo and baseline; **p < 0.01 compared with baseline. Values are expressed as mean
value ± SL. n = number of patients; ST ↓ = ≥0.1 mV horizontal or downsloping ST segment depression; VO₂ =
oxxygen uptake (mL/kg per min).

**Figure 1.** Effects of intravenous theophylline on
the onset of angina pectoris in eight patients. Significant
difference between theophylline (T) and both placebo (P)
and baseline (B): *p < 0.05; **p < 0.01. VO₂ = oxygen consumption (ml/kg per min). Blood pressure is expressed in mm Hg,
heart rate in beats/min and heart rate—blood pressure product in arbitrary units.
A similar evaluation was made for the onset of ECG changes (12 patients, Fig. 2). As with the onset of angina, the heart rate, systolic blood pressure, rate-pressure product and oxygen uptake at the onset of ECG changes were significantly greater with theophylline infusion than with either placebo or at baseline.

Effects of theophylline on thallium-201 imaging. The effects of theophylline on the location and extent of ischemia were evaluated using thallium-201 imaging at peak exercise (Table 2). After both placebo and theophylline infusions, all patients had either completely reversible (n = 7) or partially reversible (n = 5) defects. Visual assessment performed in blinded fashion revealed no differences in either the severity or the extent of the defects based on the number of segments involved. Computerized quantitative analysis confirmed no significant differences in the percentage of abnormal myocardial images between theophylline- and placebo-treated patients.

The side effects of the theophylline infusion were monitored. During and after the theophylline infusions, there was no increase in the number of ventricular ectopic beats, baseline heart rate or: blood pressure (Table 1) or symptoms such as nausea, headache and vomiting.

Discussion

This double-blind, placebo-controlled crossover trial was performed to evaluate the effects of theophylline on exercise-induced myocardial ischemia. Theophylline not only delayed the onset of exercise-induced ischemia but also prolonged exercise duration. The clinical data suggest that the mechanism of impaired ischemia is through competitive inhibition of adenosine. The delay in the onset of ischemia during exercise was not associated with adverse effects or increased chronotropic demand, as shown by oxygen uptake, symptoms, ECG criteria and thallium-201 imaging at the completion of exercise but was associated with a higher ischemic threshold.

Comparison with recent published reports. This study confirms and extends the findings of recent reports (14-17) that theophylline delays the onset of exercise-induced myocardial ischemia. Crea et al. (14) reported increased time to the onset of both angina and ECG changes in a group of patients using a single-blind protocol with acute administration of intravenous theophylline and in 20 patients given an oral dosage (14). In a similar study by Crea et al. (17), exercise duration was prolonged. The present study also demonstrated a delay in the onset of ischemia while illustrating that ischemia was not exacerbated at the completion of the longer exercise period, as confirmed by ECG changes, angina or oxygen uptake. In addition, the thallium-201 defect size, previously shown to be dependent on work load, was unaltered by the theophylline infusion (33). These data provide strong evidence that ischemia was not negatively affected by theophylline.

Ischemic threshold. An important finding of this study was the higher ischemic threshold after administration of theophylline. If the mechanism of adenosine action is a coronary steal phenomenon, inhibition of this maldistribution of blood flow by theophylline should allow a proportionally greater flow to stenotic vessels at a given oxygen demand. Thus, a work load that was previously demonstrated to provoke ischemia should now be ischemia free, as we have shown in this study. Such a phenomenon was recently suggested by Cannon (10) and is demonstrated in the current findings by the higher rate-pressure product and oxygen uptake at the onset of either angina or ECG changes with theophylline.

Clinical implications. The effects of theophylline on the ischemic threshold have important clinical implications. Recent evidence (2-8) has demonstrated considerable variability in the occurrence of ischemia not only during daily activities but also under differing laboratory conditions. A consistent finding of these studies has been a lowered ischemic threshold with lesser activities such as walking than with more vigorous exercise (3,7). Furthermore, such ischemia at lower work levels is often silent and therefore unrecognized. New information (34) also suggests that standard medical therapies may be ineffective in treating such
ischemia. Thus, any medication, such as theophylline, that raises the ischemic threshold may provide more benefit to patients during daily activities than is provided by a drug that simply delays the onset of ischemia.

The present trial was performed using one intravenous dosage of theophylline (8 mg/liter) compared with placebo. The dosage chosen was subtherapeutic for the treatment of reactive airways disease but was well within the range that would be expected to inhibit adenosine and reverse the ischemic effects of intravenous diprydiamole for radionuclide imaging (14,35,36). Additional studies are needed to evaluate whether differing doses of theophylline will also have beneficial effects on ischemia or whether chronotropic and proarrhythmic effects are limiting.

Conclusions. Moderate concentrations of theophylline favorably delay the onset of exercise-induced myocardial ischemia at a higher ischemic threshold without negatively affecting ischemia at peak exercise. The impact on the ischemic threshold suggests that the mechanism of the anti-ischemic effects of theophylline may be competitive inhibition of adenosine.

References