Effect of Trimetazidine on Exercise Performance in Patients With Coronary Artery Ectasia

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SUMMARY

Coronary artery ectasia (CAE) is a rare form of coronary artery disease. It has previously been shown that nitrate derivatives induce exertional angina in patients with CAE. Furthermore, there is limited data about the effects of other anti-ischemic agents in CAE. The aim of this study was to investigate the effect of trimetazidine on exercise performance in patients with CAE.

The study population consisted of 56 patients with isolated CAE (32 males, mean age: 58 ± 9 years). The presence of myocardial ischemia was evaluated by treadmill exercise test. The exercise test was positive in 49 patients at baseline and in 27 patients during trimetazidine therapy (P < 0.01). The exercise test induced angina in all of the patients who had a positive test result. Significant ST depressions were observed in 42 and 23 patients before and after the treatment, respectively (P < 0.01). The extent of ST depression at peak exercise was significantly lower on trimetazidine (0.9 ± 0.5 vs 1.5 ± 0.6 mm, P < 0.01). With trimetazidine, the exercise duration increased from 7.8 ± 2.1 to 8.7 ± 2.4 min (P = 0.04) and cardiac work-load also increased from 8.9 ± 2.3 to 10.4 ± 2.1 mets (P < 0.01).

The results suggest that trimetazidine can relieve exercise-induced angina and improve exercise performance in patients with CAE. (Jpn Heart J 2003; 44: 463-470)

Key words: Coronary artery ectasia, Exercise, Trimetazidine, Angina

CORONARY artery ectasia (CAE) is defined as a luminal dilatation of the coronary artery larger than 1.5 times the adjoining normal segment.1) Its incidence has been reported to be 0.3-4.9% in several studies. The majority of CAE occurs as a result of coronary atherosclerosis (50%), although 20-30% of cases have been regarded as congenital in origin and 10-20% have been attributed to inflammatory or connective tissue diseases.1-4)

In some case reports and small studies, it has been shown that patients with CAE can present with exercise-induced angina pectoris due to myocardial ischemia without coincident significant coronary artery stenosis or other cardiac...
defect.\textsuperscript{2,4,5} Sometimes, myocardial infarction may occur as a complication due to thrombotic occlusion in an ectatic segment or microembolization into distal segments of ectatic arteries.\textsuperscript{6,7)}

In a recent study,\textsuperscript{4)} it has been shown that the administration of nitroglycerin, which works hemodynamically, induced angina pectoris in patients with CAE. Therefore, the study recommended that administration of nitrate derivatives be avoided in these patients.

To our knowledge, there is no evidence indicating the cellular anti-ischemic agent trimetazidine is useful in patients with isolated CAE. Therefore, the aim of the present study was to investigate the effect of trimetazidine on exercise performance in symptomatic patients with CAE.

\textbf{METHODS}

\textbf{Patients:} We have prospectively reviewed coronary angiograms of 2271 consecutive patients undergoing cardiac catheterization due to coronary or valvular heart disease at the Sevket Demirel Heart Centre between September 1999 and April 2001. This study was conducted prospectively and was completed in June 2001. In this study cohort, the incidence of CAE was 6.1\% (141 patients). A total of 85 patients with CAE were excluded. Many of the exclusions were due to concomitant obstructive coronary atherosclerosis narrowing the luminal diameter more than 50\% in the same or other coronary arteries (n = 53). Other reasons for exclusion causes were as follows: refusal of the study protocol (n = 3), atrial fibrillation requiring drug therapy (n = 6), left bundle-branch block (n = 4), right bundle-branch block (n = 2), unable to perform an exercise test (n = 5), ST segment depression more than 1 mm at rest ECG (n = 4), severe aortic stenosis and/or regurgitation (n = 5), and severe left ventricular hypertrophy (n = 3). The remaining 56 patients with isolated CAE constituted our study population. There were no associated coronary anomalies or other cardiac defects in the study patients. They had no evidence of connective tissue or inflammatory disease detected by means of clinical and/or laboratory investigation. The study patients were admitted to the hospital due to stable angina (n = 34) or unstable angina (n = 22).

After the patients had performed the basal exercise test, they were given trimetazidine at a dose of 20 mg tid for 4 weeks, after a 7-day washout period. All study patients gave informed consent.

\textbf{Coronary angiography:} Coronary angiography was routinely performed through femoral artery puncture. Coronary arteriograms were obtained in the left and right anterior oblique projections with cranial and caudal angulation for best visualization of the right and left coronary arteries. Antero-posterior view with slight
cranial angulation was also obtained for the left main coronary artery. Additional projections were performed in case of inadequate visualization of the coronary territory. Based on previous studies, coronary ectasia was defined as a diameter dilatation exceeding 1.5 fold of an adjacent normal diameter.\(^1\) If no adjacent normal segment could be identified, the mean diameters of the coronary segments in patients with normal coronary arteries were considered as normal values.

**Exercise test:** All study patients performed an exercise stress test by means of a standard Bruce Treadmill Protocol. All patients were suggested to attain the maximum work capacity and the target heart rate was considered as 100% of the age-predicted maximum heart rate. The individual maximum heart rate was calculated as 220 minus patient age. The test was terminated when the target heart rate was achieved or when severe chest pain, fatigue or dyspnea occurred, or when ectopic supraventricular tachycardia, complex ventricular arrhythmias (frequent couplets or triplets or ventricular tachycardia), hypotension, severe hypertension (systolic blood pressure \( \geq 230 \text{ mmHg} \)), or ST-segment depression \( \geq 3.0 \text{ mm} \) or ST-segment elevation \( \geq 1.0 \text{ mm} \) in a non-Q wave lead developed. During the exercise and recovery, three ECG leads (aVF, V\(_2\) and V\(_6\)) were monitored continuously, and blood pressure was measured at 2-minute intervals. Peak heart rate, exercise duration, maximum cardiac work-load (which is considered to be a metabolic equivalent, mets) and ST-segment depression were recorded. The ST segment changes were assessed by a single observer blinded to the angiographic findings of patients in terms of the criteria of the American Heart Association.\(^8\) ST-segment deviation was measured 60 ms after the J point compared with the resting value during peak exercise. The ST-segment deviation was considered significant if there was \( \geq 1.0 \text{ mm} \) ST elevation in a non-Q wave lead, or horizontal or downsloping ST-segment depression or \( \geq 1.5 \text{ mm} \) slow upsloping ST-segment depression in at least 3 consecutive beats. Also, the appearance of exercise-induced angina was considered significant for a positive exercise test. Before the test, all anti-ischemic and antihypertensive medications except for aspirin, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and diuretics were discontinued for two days. After the patients had undergone a baseline exercise test, they were given trimetazidine for 4 weeks, and the test was repeated.

**Statistical Analysis:** All data are presented as the mean \( \pm \) standard deviation and were analyzed by the \( t \)-test and Fisher’s exact test. A \( P \) value of \( < 0.05 \) was considered statistically significant.
RESULTS

This study included 56 patients with angiographically documented isolated CAE. Thirty-two patients were male and the mean age was $58.3 \pm 9.4$ (range, 45 to 65) years.

The clinical characteristics of the study population are shown in Table I. Coronary ectasias were located in the left main artery in 5 (9%) cases, left anterior descending artery in 20 (35.7%) cases, right coronary artery in 23 (41%) cases, and left circumflex artery in 8 (14%) cases.

The baseline exercise test was positive in 49 of the 56 patients. It caused significant ST segment depression of $1.5 \pm 0.6$ mm at $8.9 \pm 2.3$ mets and induced angina pectoris in 42 patients. Seven patients had angina pectoris without significant ST segment changes. After trimetazidine therapy, the exercise test was positive in 27 patients ($P < 0.01$). It provoked ST segment depression of $0.9 \pm 0.5$ mm at peak exercise at $10.4 \pm 2.1$ mets and angina pectoris in 23 patients. However, only 4 patients had exercise-induced angina without significant ST changes. The drug therapy significantly improved the exercise-induced angina ($P < 0.01$) and decreased the extent of ST segment depressions ($P < 0.01$). The achieved exercise duration on trimetazidine was significantly longer compared with the pretreatment duration ($8.7 \pm 2.4$ vs $7.8 \pm 2.1$ minute; respectively, $P = 0.04$). Similarly, cardiac work-load attained at the end of the test was significantly higher after trimetazidine therapy ($10.4 \pm 2.1$ vs $8.9 \pm 2.3$ mets, $P < 0.01$, Table II). The peak systolic and diastolic blood pressures were not changed after trimetazidine.

<table>
<thead>
<tr>
<th>Mean age (years)</th>
<th>58.3 ± 9.4</th>
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</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>32/24</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (25%)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>36 (64%)</td>
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<tr>
<td>Coronary artery ectasia</td>
<td></td>
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<tr>
<td>Left main artery</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>20 (35%)</td>
</tr>
<tr>
<td>Circumflex artery</td>
<td>8 (14%)</td>
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<tr>
<td>Right coronary artery</td>
<td>23 (41%)</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Beta-blockers</td>
<td>26 (46%)</td>
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<tr>
<td>Calcium antagonists</td>
<td>18 (32%)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8.8%)</td>
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</tbody>
</table>
(\(P = 0.79, P = 0.10\), respectively). Similarly, the heart rate achieved at peak exercise was also unchanged after the therapy (157.4 ± 8.6 vs 154.3 ± 11.7 beats/minute; respectively, \(P = 0.1\)).

**DISCUSSION**

Trimetazidine has anti-ischemic properties without affecting myocardial oxygen consumption and blood supply.\(^9\) In fact, this agent does not cause significant changes in heart rate and blood pressure or rate x pressure double product either at rest or during exercise.\(^9\) In ectatic coronary arteries, there is impaired coronary blood flow such as slow flow and delayed coronary antegrade filling of dye and segmental back-flow phenomenon.\(^4\) Therefore, it is reasonable that trimetazidine can be beneficial for patients with CAE.

The mechanism of action of trimetazidine has been attributed to prevention of intracellular adenosine triphosphate decrease,\(^10\) increase in adenosine levels,\(^11\) and protection against oxygen-free radical-induced toxicity by ischemia.\(^12\) It also shifts cardiac energy production from fatty acid oxidation to glucose utilization.\(^13\) The induced increase of adenosine leads to myocardial cell tolerance to ischemia, which is called myocardial preconditioning. For this reason, trimetazidine has been considered to be a pharmacological preconditioning agent by Patrizia et al.\(^11\)

To our knowledge, the current study is the first trial that evaluates the effect of trimetazidine in symptomatic patients with CAE. We observed that, after 4 weeks of treatment with trimetazidine, the cardiac work-load was improved and the duration of exercise was lengthened. We also showed that this therapy signif-
icantly improved exercise-induced angina and reduced the extent of ST segment depressions.

In a recent study, Kruger, et al reported that nitroglycerin aggravated exercise-induced myocardial ischemia in patients with isolated CAE. In their study, metabolic evidence of myocardial ischemia was evaluated by means of both ergometric stress testing (treadmill or bicycle) and coronary sinus lactate metabolism through coronary sinus pacing. After the administration of nitroglycerin, they documented that there was no improvement of angina pectoris and no reduction of ischemia-induced ST segment depression. In contrast, they observed a significant alteration of coronary sinus lactate metabolism. This paradoxical effect of nitroglycerin could have resulted from its hemodynamic effects. Contrary to the findings of Kruger, et al with nitroglycerin, we found beneficial effects of trimetazidine on exercise performance in these patients.

Several clinical studies have shown that trimetazidine alone or in combination with a beta-blocker or calcium channel blocker can significantly improve exercise tolerance and increase the ischemic threshold in patients with exercise angina due to coronary artery stenosis. In a multicenter study, Szwed, et al evaluated the efficacy and tolerance of trimetazidine in combination with an anti-anginal agent which works hemodynamically in patients with exercise-induced angina who were not sufficiently controlled with classical anti-anginal agents. The patients were given a 4-week regimen of trimetazidine (20 mg tid) as adjunctive treatment after a positive treadmill test. At the end of the treatment period, the duration of exercise lengthened from 443.7 to 486.6 sec ($P < 0.01$) and total work-load also increased from 9.4 to 10.6 mets ($P < 0.01$). In addition, a significant lengthening in the time to 1 mm ST depression and to the onset of angina was observed. The number of daily anginal episodes and nitrate consumption were significantly reduced as well ($P < 0.01$).

Trimetazidine is a novel anti-anginal agent for the treatment of angina induced by significant obstructive coronary artery stenosis. In the Trimetazidine European Multicenter Study, Detry, et al compared the effects of trimetazidine with those of propranolol in patients with stable angina. After 3 months, there were no significant differences between trimetazidine (60 mg/day) and propranolol (120 mg/day) with regards to the anginal attack rate per week, exercise duration, and time to 1 mm ST segment depression. In brief, the efficacies of trimetazidine and propranolol in patients with stable angina pectoris were comparable.

Using a combined therapy of trimetazidine and diltiazem in patients with stable angina induced by severe coronary artery stenosis, Machanda, et al showed that exercise time to angina, exercise duration, and maximum work-load at peak exercise were significantly improved compared with diltiazem alone.
Recently, Kurtoglu, et al reported that based on the TIMI frame count method, a one-month therapy of dipyridamole, which inhibits adenosine degradation, improved the coronary blood flow in patients with coronary slow flow. However, the patients had no concomitant coronary ectasia.\textsuperscript{16)}

**Study limitations:** First of all, the number of patients was insufficient to come to a conclusive statement that trimetazidine alone completely improves symptoms in patients with CAE. Secondly, we did not study the frequency of daily or weekly anginal attacks in the diaries of the patients. Also, four weeks of treatment may be inadequate to evaluate the efficacy of trimetazidine, although another study also has reported a similar treatment period.\textsuperscript{14)} In addition, we did not design the study to be a placebo-controlled, cross-over model. Finally, it is also possible that the second exercise test might have been a training procedure for angina pectoris in these patients.

In conclusion, this study suggests that trimetazidine can relieve exertional angina and reduce the extent of ST segment depression due to exercise-induced myocardial ischemia, and also can improve the exercise performance in patients with CAE. Its beneficial effects are likely attributed to an improvement of coronary flow or myocardial preconditioning through increasing plasma adenosine levels.

**REFERENCES**