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The Effect of Trimetazidine in the Treatment of Microvascular Angina

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Abstract. Although the pathophysiology of microvascular angina is unclear, intracellular metabolic changes are believed to be the main factors. Trimetazidine has an intracellular metabolic effect in coronary insufficiency. The effect of trimetazidine in microvascular angina is unknown. Thirty-five patients (8 men, 27 women, age 36–57 years, mean 43.9 ± 6.4 years) with microvascular angina were included in this study. The effects of trimetazidine (60 mg daily) were investigated in a placebo-controlled, double-blind study consisting of two 4-week treatment periods. Patients were assessed by symptom-limited exercise testing (Bruce protocol). Heart rate and systolic blood pressure at rest, peak exercise, and the time of 1 mm ST segment depression were not significantly different between placebo and trimetazidine treatment. Trimetazidine prolonged total exercise time and time to 1 mm ST depression compared with placebo. Maximum ST depression was less in patients with trimetazidine therapy than those with placebo. It is concluded that trimetazidine has a beneficial effect in cases with microvascular angina.

Introduction

Kemp et al. [1] were the first authors to report patients with angina and normal coronary angiograms. Since then there have been hundreds of publications that have tried to explain the etiology of chest pain in these patients and angiographically normal coronary arteries [2]. Coronary microvascular dysfunction [3], hormonal disturbance [4–6], abnormal vasomotricity of coronary microvessels [7–11], reduced coronary flow reserve [10,12,13], hyperinsulinemia [14–19], inappropriate adenosine release [20], and impaired endothelium function [21] are the notable responsible factors. With regard to these findings, some authors believe that microvascular angina develops because of different pathologies [22–24]. Because of many different findings, there is no consensus on the treatment for this condition. Calcium channel blockers [25], angiotensin-converting enzyme inhibitors [26], and aminophylline [20,27] were used for the treatment of this syndrome, however, treatment with nitrates was not effective [6,28,29].

Trimetazidine is a 1-(2,3,4 trimethoxybenzyl) piperazine dihydrochloride salt which displays antiischemic effects at the cellular level (preserve energy balance, prevent intracellular acidosis, and reduce free radical-induced injury) without inducing significant hemodynamic changes [30]. Its anti-anginal efficacy has been documented by several studies [31–33]. Beneficial effects have also been reported in patients having ischemic cardiomyopathy [33] after coronary artery bypass surgery [34] and angioplasty [35]. In this study, we evaluated the therapeutic effect of trimetazidine in patients with microvascular angina.

Patients and Methods

Thirty-five patients (27 women, 8 men, aged 36–57, mean 43.9 ± 6.4 years) with microvascular angina were included in this study. Microvascular angina was defined as typical exertional chest pain and positive exercise test results (>1 mm ST segment depression and chest pain, and completely normal coronary arteriogram). The systolic and diastolic blood pressures of all patients were at normal levels. According to electrocardiographic (ECG) data, echocardiographic and angiographic findings, none of the patients had valvular heart disease, mitral valve prolapse, coronary artery spasm, left ventricular hypertrophy, cardiomyopathy, or conduction disturbances. Patients were studied with the ambulatory ECG monitoring test and all 35 had episodes of horizontal or downsloping ST segment depression during 24-hour ambulatory monitoring.

Study Design

The effects of trimetazidine (60 mg daily) were investigated in a double-blind study with two 4-week treatment periods. After a 1 week of washout period, patients received placebo for 4 weeks; after another week of washout and patients received trimetazidine for another 4 weeks. They received no other drugs other than placebo or trimetazidine. Since all patients had normal coronary arteries, short-acting nitrates were not given. Patients were examined every week for anginal attacks. Exercise testings were performed at the end of placebo and trimetazidine treatment periods. The study protocol was approved by our University Medical School's Ethics Committee. The nature of the study was explained to each subject and written informed consent was obtained.

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Table 1. Heart rates, systolic blood pressures and rate-pressure products at rest, during maximum exercise, and time of the 1 mm ST segment depression and total exercise time (sec), time to 1 mm ST segment depression (sec) and maximum ST segment depression (mm) after the treatment with placebo or trimetazidine

	Trimetazidine	Placebo	p=
Resting values			
Heart rate (bpm)	72.54 ± 6.26	73.46 ± 7.26	0.89
Systolic blood pressure (mmHg)	121.19 ± 5.06	122.15 ± 6.38	0.75
Rate pressure product	8791.12 ± 1003	8962.78 ± 1185	0.83
1 mm ST segment depression			
Heart rate (bpm)	125.2 ± 12.2	127.0 ± 13.2	0.29
Systolic blood pressure (mmHg)	148.9 ± 9.8	150.1 ± 11.7	0.49
Rate pressure product	18642.2 ± 2341	19062.7 ± 2396	0.24
Peak exercise			
Heart rate (bpm)	146.0 ± 12.6	148.4 ± 14.1	0.58
Systolic blood pressure (mmHg)	164.2 ± 11.4	165.0 ± 10.8	0.80
Rate pressure product	23973.4 ± 2144	24486.0 ± 2876	0.75
Exercise time (seconds)	579.0 ± 140	357.2 ± 98	<0.0001
Time to 1 mm ST segment depression (seconds)	476.8 ± 123	275.6 ± 86	<0.0001
Maximum ST segment depression (mm)	1.54 ± 0.21	2.08 ± 0.32	<0.0005

(bpm = beats per minute).

Exercise Testing

Before the exercise test, patients were asked to rest in the sitting position for 15 minutes. Then they were invited to stand up and rest their heart rate, systolic and diastolic blood pressures, and rate products (heart rate × systolic blood pressure) were measured. All patients underwent the standard exercise testing (Bruce protocol). The end points of the test were target heart rate or progressive angina or fatigue. Complete ECG and blood pressure measurements were obtained before exercise, at 1-minute intervals during exercise, and a 3-minute intervals for 9 minutes of recovery. After signal averaging, the level of the ST segment 80 msec after the J point was measured in all 12 leads. The lead showing the maximal ST segment depression was selected for analysis. The total exercise time (seconds), time to 1 mm ST segment depression (seconds), and maximum ST depression (mm) were measured. Also heart rate (bpm), systolic blood pressure (mmHg), and rate pressure products were determined at resting, at time of 1 mm ST segment depression, and at time of peak exercise.

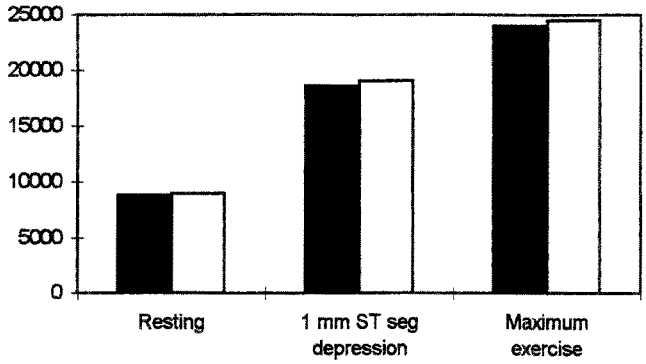

Fig. 1. Rate-pressure product during resting, 1 mm ST depression, and maximum exercise in the treatment with placebo (□) or trimetazidine (■).

Results

Ambulatory ECG was recorded and all of the 35 patients had episodes of horizontal or downsloping 1 mm ST segment depression or more. The number of episodes in 24 hours was 6.23 ± 3.92 and duration of episodes was 44.04 ± 23.34 minutes. Mean ST segment depression was 1.63 ± 0.43 mm. Before the placebo treatment, the number of anginal attacks per week was 17.78 ± 8.02. During placebo treatment, it was 16.08 ± 6.14; 16.24 ± 5.86; 16.76 ± 5.34, and 16.64 ± 5.92 at first, second, third, and fourth weeks, respectively. The changes were not significant. Before trimetazidine treatment the number of anginal attacks per week was 17.32 ± 6.02. During treatment it was 14.86 ± 5.32; 10.06 ± 4.26; 6.38 ± 3.76; 3.14 ± 2.62 at first, second, third, and fourth weeks, respectively. The changes at the second week and thereafter were significant ($p < 0.0001$). No differences were observed between placebo and trimetazidine groups in heart rate, systolic blood pressure, or rate-pressure product at resting, at time of 1 mm ST-segment depression, and at time of peak exercise (Table 1, Fig. 1). However, the time to 1 mm ST segment depression (476.8 ± 123 seconds vs 275.6 ± 86 seconds) and total time of exercise (579 ± 140 seconds vs 357.2 ± 98 seconds) were significantly ($p < 0.0001$ and $p < 0.0001$, respectively) longer in the trimetazidine group (Fig. 2). Furthermore, with trimetazidine, the maximum ST segment depression was significantly less ($p < 0.0005$) than with placebo (1.54 ± 0.21 mm vs 2.08 ± 0.32 mm) (fig. 3).

Discussion

The pathophysiology of microvascular angina is unclear. Many investigators believe that coronary microvascular dysfunction and intracellular metabolic changes are the main factors. According to the electromicroscopic study of Suzuki et al. [36], many endothelial nuclei in capillaries were swollen and the lumen of small arteries and arterioles were irregularly narrowed, with proliferated and deformed medial smooth muscle cells. The findings suggested that disturbances in the coronary microcirculation exist in patients with microvascular angina. However, recently, Wiedermann et al. [37] showed that coronary arteries were also

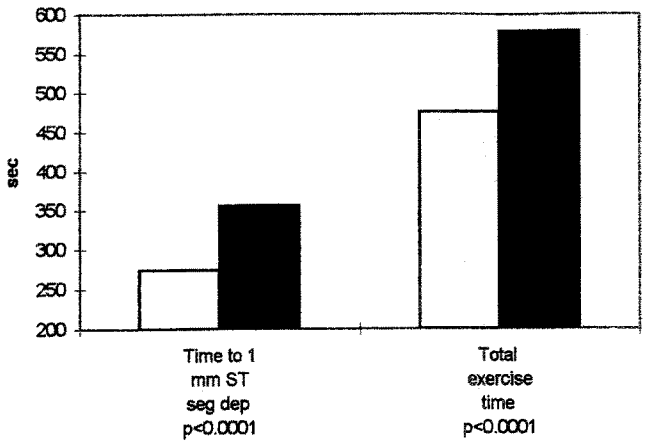

Fig. 2. Total exercise time and time to 1 mm ST segment depression in the treatment with placebo (□) or trimetazidine (■).

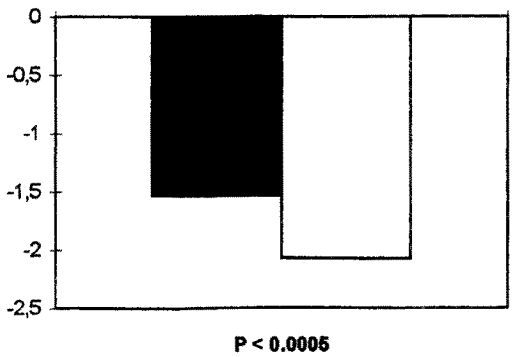

Fig. 3. Maximum ST segment depression (mm) in the treatment with placebo (□) or trimetazidine (■).

abnormal by intravascular ultrasound examination. As with the divergent concepts of etiologies, there is no consensus on the treatment of this syndrome. The aim of our study was to assess the value of long-term treatment with trimetazidine, which displays anti-ischemic effects at the cellular level, in comparison with placebo in cases with microvascular angina.

When comparing trimetazidine to placebo, we observed a beneficial effect on the increase in exercise tolerance and the delay of ischemic threshold. An increase in exercise duration and the time to 1 mm ST segment depression were shown without a significant change in heart rate, blood pressure, and consequent rate-pressure product. An unchanged rate-pressure product at peak exercise suggests that trimetazidine may exert its effect at cellular levels. The effect is similar to that in some studies in cases with stable angina pectoris [30–32]. Sellier et al. [31] showed that in patients with stable angina, trimetazidine improved exercise capacities and delayed the appearance of ischemic threshold without any chronotropic or vasomotor effects.

Initial pharmacological studies have indicated that trimetazidine prevents cellular changes associated with ischemia or hypoxia [33,38]. Recently, it has been shown that anti-ischemic effect of trimetazidine is at the cellular level. Trimetazidine reduces ischemia-induced acidosis and protects myocyte homeostasis. In maintaining the intracellular pH and ATP levels necessary for ATPase-depending pumps, trimetazidine prevents potassium leak and sodium and calcium accumulation in the cell. At a result, it is suggested that trimetazidine has the global cytoprotective effect [33,39,40].

In conclusion, compared with placebo, trimetazidine significantly improves exercise duration and time to 1 mm ST segment depression. Our study is the first on the literature that documented the benefical effect of trimetazidine in cases with microvascular angina.

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