ORIGINAL ARTICLE

The effect of trimetazidine added to maximal anti-ischemic therapy in patients with advanced coronary artery disease

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Abstract

Background: *The purpose of the study was to assess the effect of trimetazidine administered for 20 days in 56 patients with ischemic heart disease treated with maximal tolerated doses of anti-ischemic drugs who were not candidates for percutaneous or surgical revascularization.*

Methods: *The efficacy of trimetazidine was evaluated by comparing exercise testing parameters before and after treatment, combined with the patient response to a questionnaire administered at baseline and following the treatment. We evaluated the duration of exercise, workload, double product, time to the occurrence of ischemic changes in ECG, the number of leads with diagnostic ST segment depression, and the magnitude of ST segment depression.*

Results: *After 20 days of trimetazidine treatment, an improvement in exercise testing parameters was seen in about 50% of patients, and the differences of the mean values were statistically significant. The patient response to the questionnaire administered following the treatment indicated a decreased frequency of anginal episodes and an increased exercise duration to the occurrence of angina in two thirds of patients, less requirement for nitrates in 40% of patients, and increased exercise tolerance in 50% of patients. In patients with subjective response to treatment, comparison of exercise testing parameters before and after treatment showed significant increase in the duration of exercise, time to ischemic changes in ECG, and the degree of ST segment depression during peak exercise. In patients with no subjective response to treatment, a statistically significant difference was seen in the double product only.*

Conclusions: *After 20 days of treatment with trimetazidine added to maximal anti-ischemic treatment in patients with refractory angina, an improvement in exercise testing parameters and subjective response to treatment were seen in about 40% of patients. In patients with subjective response to treatment, exercise testing parameters improved significantly compared to the baseline values.* (Cardiol J 2008; 15: 344–350)

Key words: stable angina pectoris, metabolic treatment, subjective and objective evaluation of treatment effects

Introduction

Percutaneous or surgical revascularization is the most effective strategy to improve myocardial perfusion. In some patients, however, neither percutaneous nor surgical revascularization is feasible, and the drug treatment including beta-blockers, calcium channel blockers and/or nitrates is not sufficiently effective. An intervention aimed at the metabolic pathways in ischemic myocardial cells is a promising therapeutic option in such patients. With normal myocardial perfusion and optimal oxygen supply, oxidation of fatty acids is the main source of energy in the heart (60–80%) but also the most oxygen-consuming process. Regarding other energy sources in the heart, lactate oxidation is the source of about 15% of energy used by the myocardium, another 15% comes from glucose oxidation, and less than 10% comes from anaerobic glycolysis. These proportions change if oxygen supply to myocardium is limited, with reduced energy production through beta-oxidation of fatty acids and glucose oxidation and limited rate of these processes. In contrast, anaerobic glycolysis becomes a major source of energy. Glycolysis and glucose oxidation become uncoupled, resulting in overproduction of lactate and protons and accumulation of acylcarnitine and acylcoenzyme A. The latter are strong detergents disrupting cell membranes and intracellular enzymatic processes. At the same time, pain resulting from myocardial ischemia leads to catecholamine release and resulting enhanced lipolysis. Thus, blood free fatty acid levels become elevated, leading to inhibition of glycolysis and further decrease in glucose oxidation [1–3]. A pharmacologic intervention targeted at the metabolic processes in myocardial cells should improve effectiveness of energy production, decrease the oxygen debt, and protect myocardial cells from the effects of ischemia. These effects are collectively called cytoprotection. One such cytoprotective drug is trimetazidine. Cytoprotective drugs are used as an adjunct to hemodynamic drugs and revascularization [4, 5].

The purpose of the study was to assess the clinical effectiveness of trimetazidine added to maximal individually tolerated doses of hemodynamic anti-ischemic drugs in patients with angina pectoris who were deemed not to be candidates for percutaneous or surgical revascularization. We evaluated the effect of trimetazidine on various exercise testing parameters and the subjective response to treatment using a questionnaire regarding quality of life and exercise tolerance.

Methods

Among our patients who underwent coronary angiography due to symptomatic ischemic heart disease (with Canadian Cardiovascular Society [CCS] class II or III symptoms), we selected 89 patients who were deemed not to be candidates for percutaneous or surgical revascularization due to diffuse lesions in the coronary vessels. Exclusion criteria included inability to perform an exercise test, anemia, valvular heart disease, and myocardial hypertrophy by echocardiography (defined as interventricular septum and/or posterior wall thickness > 12 mm). The study was approved by the Ethics Committee at the Nicolaus Copernicus University Collegium Medicum in Bydgoszcz. After the patients were informed about the purpose and the nature of the study and gave written consent for participation, their existing drug treatment was optimized. The optimization included adjusting medications according to the current European Society of Cardiology guidelines (aspirin, statin, angiotensin-converting enzyme inhibitor) and increasing doses and/or adding new hemodynamic anti-ischemic drugs (beta-blockers, calcium channel blockers, long-acting nitrates). Drug reducing myocardial oxygen requirement were individually adjusted depending on specific clinical contraindications, and the doses used were increased to maximal individually tolerated ones. Following drug treatment optimization within 2 to 6 weeks, anginal symptoms became adequately controlled in 33 of 89 originally recruited patients. Thus, the final study population included 56 patients with CCS class II or III symptoms persisting despite adequate hemodynamic treatment and a positive result of the exercise testing. The study group consisted of 15 women and 41 men aged 48 to 75 years (mean age 62.8 years). The participating women were slightly older than men (63.8 *vs.* 62.4 years).

All subject underwent an exercise test twice, initially after optimization of existing drug treatment, but before trimetazidine administration, and later after 20 days of treatment with 35 mg of trimetazidine (Preductal MR, Servier) given twice daily. The exercise testing was performed using a treadmill (Marquette Medical) according to the Bruce protocol, with 12-lead ECG recorded on a thermosensitive paper. ST segment deviations were measured manually. Criteria of termination of the exercise test included retrosternal chest pain, ST segment depression by ≥ 0.2 mV, ST segment elevation by ≥ 0.2 mV, significant ventricular arrhythmia (frequent ventricular ectopy, multifocal

Table 1. Exercise test parameters before and after 20 days of trimetazidine treatment.

Exercise test parameter	Mean pretreatment values	Mean values after 20 days of trimetazidine treatment	Difference	P
Total duration of exercise [s]	322.7	344.3	21.6	< 0.003
Duration of exercise to the occurrence of diagnostic ST segment depression [s]	226.4	275.9	49.5	< 0.0002
Peak workload [METs]	6.5	6.8	0.3	< 0.03
Double product	19,051	17,630	1421	< 0.02
ST segment deviation [mm]	−1.58	−1.29	0.29	< 0.0001

ectopy, ventricular salvoes, non-sustained ventricular tachycardia, sustained ventricular tachycardia, R-on-T ventricular ectopic beats), the occurrence of atrial fibrillation and/or flutter, intraventricular or atrioventricular conduction abnormalities, blood pressure elevation above 220 mm Hg systolic and/or 110 mm Hg diastolic, no increase or decrease in heart rate during exercise, no increase or decrease in blood pressure during exercise, and patient request. During the exercise test, the following parameters were evaluated: resting and maximal exercise-induced heart rate, resting and maximal exercise-induced systolic and diastolic blood pressure measured noninvasively, double product calculated as the maximal exercise-induced systolic blood pressure multiplied by the maximal exercise-induced heart rate, total duration of exercise, exercise duration to diagnostic ST segment depression, peak workload measured in metabolic equivalents (METs), the magnitude of ST segment depression in 12-lead ECG, and the number of leads with diagnostic ST segment depression.

Subjective evaluation of the quality of life and exercise tolerance was based on the response to a questionnaire administered at baseline and after 20 days of treatment with trimetazidine. In the questionnaire, patients were asked about the frequency of anginal episodes, exercise distance to the occurrence of angina, the number of flights of stairs climbed without anginal pain, the frequency of short-acting nitrate use, and whether they saw improvement, no change, or worsening of exercise tolerance and quality of life upon treatment.

Statistical analysis of the data included Student *t* test to compare mean values of normally distributed variables. P value of less than 0.05 was considered statistically significant. Wilcoxon test was used to compare dependent samples. Two-fraction test was used to compare proportions of response and no response to treatment as measured using pre- and post-treatment exercise test. Mann-Whitney test was used to compare distributions of samples.

Results

Our results regarding exercise test parameters are presented in Table 1. Total duration of the exercise test after 20 days of trimetazidine treatment increased in 69.6% of patients, did not change in 1.8% of patients, and decreased in 28.6% of patients. Mean total duration of the exercise test increased by 21.6 s (from 322.7 s to 344.3 s), and this difference was statistically significant (p < 0.003). Duration of the exercise test to the occurrence of diagnostic ST segment changes after 20 days of trimetazidine treatment increased in 46.4% of patients, did not change in 28.6% of patients, and decreased in 25% of patients. Mean duration of exercise to the occurrence of diagnostic ST segment changes was 226.4 s at baseline and increased to 275.9 s after 20 days of trimetazidine treatment. The difference of 49.5 s was statistically significant (p < 0.0002). Workload after 20 days of trimetazidine treatment compared to baseline increased in 41.1% of patients, did not change in 39.3% of patients, and decreased in 19.6% of patients. Mean workload before trimetazidine treatment was 6.5 METs, compared to 6.8 METs after trimetazidine treatment. The difference of 0.3 MET was statistically significant (p < 0.03). ST segment changes were measured manually in 12-lead ECG. Overall, we analyzed 672 leads at baseline and after 20 days of trimetazidine treatment. Of these, 235 leads showed changes compared to baseline. The number of leads with diagnostic ST segment changes decreased in 46.4% of patients, did not change in 41% of patients, and increased in 9.1% of patients. The degree of ST segment depression decreased in 51.1% of leads, did not change in 28.5% of leads, and increased in 20.4% of leads. Double product calculated as the maximal

Table 2. Comparison of the mean values exercise test parameters between patients with diabetes (n = 14) and patients without diabetes (n = 42).

Exercise test parameter	Patients with diabetes			Patients without diabetes			Test	
	n	Mean	SD	n	Mean	SD	t-Student	p
Mean increase in the total duration of exercise [s]	14	–0.27	48.0	42	29.2	55.1	–1.74	NS
Mean increase in the duration of exercise to the occurrence of ST segment changes [s]	14	28.0	78.7	42	55.3	96.9	–0.88	NS
Mean increase in the peak workload [METs]	14	0.87	3.76	42	0.40	1.15	0.70	NS
Mean decrease in the double product	14	–1818	4465	42	–1245	4057	–0.44	NS
Mean change of the ST segment depression [mm]	14	–0.28	0.82	42	–0.30	0.77	0.17	NS

exercise-induced systolic blood pressure multiplied by the maximal exercise-induced heart rate, reflecting adaptation of the cardiovascular system to exercise, decreased after 20 days of trimetazidine treatment. The mean value of the double product decreased from 19,051 to 17,630, and this difference was statistically significant ($p < 0.02$).

The exercise test parameters were compared between men and women, hypertensive and normotensives, and patients with and without diabetes. We found no significant differences in these parameters between both genders and between patients with and without diabetes, although a trend was seen towards more improvement of the exercise test parameters in patients with diabetes compared to patients without diabetes (Table 2). Among hypertensives, we found significantly higher number of ECG leads with decreased ischemic changes and lower number of ECG leads with diagnostic ST segment changes compared to normotensives.

Table 3 shows results of subjective evaluation of the effects of trimetazidine treatment. A questionnaire administered before and after 20 days of trimetazidine treatment included questions regarding the frequency of anginal episodes, exercise distance to the occurrence of angina, requirement for short-acting nitrates, and a subjective feeling of improvement.

Subjective improvement was reported by 71.4% of patients (n = 40). Overall, 66% of patients reported a decreased frequency of anginal episodes, 32% of patients reported no change in the frequency of anginal episodes, and one patient reported an increased frequency of anginal episodes following trimetazidine treatment. In addition, 60.7% of patients reported an increased exercise distance to the

Table 3. Subjective evaluation of the effects of trimetazidine treatment.

Parameter	Reported effect	Number of patients (%)
Frequency of anginal pain	**Lower**	**37 (66.1)**
	No change	18 (32.1)
	Increased	1 (1.8)
Exercise distance to the occurrence of angina	**Longer**	**34 (60.7)**
	No change	18 (32.1)
	Shorter	4 (7.1)
Short-acting nitrate use	**Lower**	**24 (42.8)**
	No change	30 (53.6)
	Higher	2 (3.6)
Exercise tolerance	**Better**	**29 (51.8)**
	No change	26 (46.4)
	Worse	1 (1.8)
Subjective improvement	**Yes**	**40 (71.4)**
	No	16 (28.6)

occurrence of angina, 32.1% of patients reported no change of the exercise distance to the occurrence of angina, and 7.1% of patients reported a decreased distance to the occurrence of angina. The requirement for nitrates following trimetazidine treatment decreased in 42.8% of patients, did not change in 53.6% of patients, and increased in two patients (3.6%). Subjectively reported exercise tolerance, expressed as the number of flights of stairs that could be climbed without anginal pain, increased in 51.8% of patients and did not change in 46.4% of patients. One patient reported that the exercise tolerance was worse following trimetazidine treatment compared to baseline.

Next, we compared the mean values of exercise test parameters between patients with subjective improve-

Table 4. Comparison of the mean values exercise test parameters between patients with subjective improvement and patients without subjective improvement.

Parametr	Patients with subjective improvement			Patients without subjective improvement			p
	n	Mean	SD	n	Mean	SD	
Mean increase in the total duration of exercise [s]	40	27.8	62.3	16	8.2	32.8	NS
Mean increase in the duration of exercise to the occurrence of ECG changes [s]	40	54.3	100.0	16	38.0	78.3	NS
Mean increase in the peak workload [METs]	40	0.34	1.30	16	0.17	0.62	NS
Mean decrease in the double product	40	−1135	4300	16	−2023	3924	NS
Mean change of the ST segment depression [mm]	162	−0.35	0.78	73	−0.16	0.78	NS

Table 5. Comparison of the exercise test parameters at baseline and after 20 days of trimetazidine treatment between patients with subjective improvement following trimetazidine treatment and patients without subjective improvement following treatment.

Parameter	Patients with subjective improvement			Test		Patients without subjective improvement			Test	
	n	Mean	SD	t-Student	p	n	Mean	SD	t-Student	p
Mean increase in the total duration of exercise [s]	40	27.8	62.3	2.71	0.01	16	8.2	32.8	1.03	NS
Mean increase in the duration of exercise to the occurrence of ECG changes [s]	40	54.3	100.0	3.30	< 0.003	16	38.0	78.3	1.88	NS
Mean increase in the peak workload [METs]	40	0.34	1.30	1.59	NS	16	0.17	0.62	1.13	NS
Mean decrease in the double product	40	−1135	4300	−1.60	NS	16	−2023	3924	−2.12	0.05
Mean change of the ST segment depression [mm]	162	−0.35	0.78	−5.69	< 0.0001	73	−0.16	0.78	−1.74	NS

ment following trimetazidine treatment (40 patients) and no such improvement (16 patients). We found no significant differences in any of the exercise test parameters between these two groups of patients (Table 4).

Among 40 patients reporting subjective improvement following trimetazidine treatment, we found an improvement during the exercise test regarding any of the parameters evaluated (total duration of the exercise test, duration of the exercise test to the occurrence of pain or ST segment changes, peak workload, magnitude of ST segment depression) in 22 of them (39.3% of all patients). We found no objective improvement in the remaining 18 (32.1%) patients who reported subjective improvement following trimetazidine treatment.

Among 16 patients reporting no subjective improvement following trimetazidine treatment, we found no improvement in the evaluated parameters of the exercise test in 11 (19.6%) of them, and in 5 of these patients (8.9%) parameters of the exercise test improved following trimetazidine treatment.

In patients with subjective response to treatment, comparison of exercise testing parameters before and after treatment showed significant increase in the duration of exercise, time to ischemic changes in ECG, and the degree of ST segment depression. In patients with no subjective response to treatment, a statistically significant difference was seen only in the mean value of the double product (Table 5).

Discussion

Patients with ischemic heart disease who are not candidates to revascularization that cannot be adequately controlled in terms of anginal pain using optimal drug treatment (with maximal individually tolerated doses of drugs decreasing myocardial oxygen requirement) are a special group of patients. Indeed, cytoprotective therapy is most commonly used in such patients in clinical practice. This is a heterogeneous group of patients in terms of the metabolic state of the myocardium, with different size of the hibernated myocardium and different degree of the collateral circulation. Thus, the effects of metabolic treatment may vary in such a population. The effectiveness of trimetazidine added to standard anti-ischemic treatment has been confirmed in many studies [6–8]. In our study, we evaluated the effectiveness of 20-day treatment with trimetazidine added to maximal individually adjusted anti-ischemic regimen. We used both objective (exercise test parameters) and subjective (questionnaire) measures to evaluate the effect of treatment, comparing results of both evaluations. Comparison of the exercise test parameters before and after 20 days of trimetazidine treatment revealed that all evaluated parameters (total exercise duration, peak workload, duration of the exercise to the occurrence of diagnostic ST segment changes, severity of the ischemic changes, and the number of ECG leads showing signs of myocardial ischemia) improved following trimetazidine treatment in about 50% of patients, and the differences were statistically significant. Many studies showed the effectiveness of trimetazidine treatment compared to placebo [9, 10]. In our study, we tried to verify subjective evaluation of the effects of trimetazidine treatment in an objective way, comparing exercise test parameters between patients with subjective improvement or no subjective improvement following treatment. Among patients who reported improvement (71.4% of the study population), two subsequent exercise tests differed significantly in regard to total duration of exercise, duration of exercise to the occurrence of diagnostic ECG changes, and the magnitude of ST segment depression, with better results following 20-day trimetazidine treatment. Among patients who reported no subjective improvement (28.6% of the study population), a statistically significant difference was seen in the double product only. Decreased value of the double product was most commonly the effect of lower maximal exercise-induced heart rate, indirectly suggesting better exercise tolerance despite no such improvement being reported by the patient. Improvement of quality of life and left ventricular function following trimetazidine treatment were also reported by other authors [11].

Another interesting finding was a significantly higher reduction of in the number of ECG leads with diagnostic ST segment changes during exercise test following 20-day trimetazidine treatment in patients with hypertension (by 58%) compared to patients without hypertension (by 33%; p < 0.001). In these patients, the mean change of ST segment depression following trimetazidine treatment was –0.76 mm compared to +0.786 mm in patients without hypertension (p < 0.02). Exercise-induced ST segment depression diagnostic for myocardial ischemia that occurs without significant lesions in the coronary arteries is a common finding in patients with hypertension. This may by explained by myocardial hypertrophy and inadequate perfusion of increased myocardial muscle mass, or small vessel disease (endothelial dysfunction). However, patients with left ventricular hypertrophy were not included in the present study. Can trimetazidine treatment lead to improved endothelial function? There are only few data on this issue in the literature but one study showed decreased endothelin release by endothelial cells following trimetazidine treatment [12].

Diabetes leads to changes in the myocardial cell metabolism, as well as disturbed ion transport. Animal studies showed impaired glucose transport to cardiomyocytes. This favors anaerobic glycolysis, resulting in lactate accumulation and lactic acidosis. This in turn delays cardiomyocyte function recovery following an ischemic episode, decreasing the likelihood that affected heart cells will survive. In addition, glucose and lactate oxidation rate is reduced in patients with diabetes due to impaired ability of mitochondria to oxidize pyruvate, resulting from increased acetyl-coenzyme A and free fatty acid levels. Concomitant impairment of calcium transport also contributes to decreased myocardial contractility [13]. Patients with diabetes comprised 25% of our study population. In these patients, we found a trend towards improvement of exercise test parameters compared to patients without diabetes that did not reach statistical significance. Similar results were obtained in TRIMPOL I study and in the study by Ribeiro et al. [14]. Fragasso et al. [15] found improved glucose metabolism parameters (increased total tissue glucose disposal, lower blood fasting glucose level, improvement in insulin sensitivity) in patients with diabetes treated with trimetazidine. Perhaps the duration of trimetazidine treatment in our study was too short to show statistical significance of the observed differences.

We found concordant subjective and objective improvement in 39.3% of patients treated with trimetazidine. In addition, objective but not subjective improvement was seen in 8.9% of patients. Thus, overall 48.2% of the studied patients benefited from trimetazidine treatment.

Limitations of our study included short duration of follow-up (although many studies showed early benefits of trimetazidine treatment), no placebo control group or crossover placebo control, and the specific way questions in the questionnaire regarding subjective effects of trimetazidine treatment were constructed. The responding patients did not give quantitative data on short-acting nitrate use but only compared current and previous nitrate use which may lack adequate precision.

Conclusions

1. In approximately 40% of patients with ischemic heart disease who are not candidates to myocardial revascularization, 20-day trimetazidine treatment improved both exercise test parameters and subjective symptoms related to myocardial ischemia.
2. In patients with subjective improvement following trimetazidine treatment, exercise test parameters improved significantly compared to the pretreatment values.
3. Short duration of trimetazidine treatment and probably also some "metabolic heterogeneity" of the studied population may explain lack of benefits of trimetazidine treatment in some patients.

Acknowledgements

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