ORIGINAL ARTICLE

The role of metabolic therapy with trimetazidine in effort tolerance in patients with ischemic heart disease

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ABSTRACT

Aim To investigate whether or not additional treatment of ischemic heart disease with trimetazidine could improve effort tolerance and overall quality of life of patients with ischemic heart disease.

Methods The study included 200 patients with ischemic heart disease. The sample was divided into 2 randomly selected groups: experimental and control group. The diagnostic procedures included: trade-mill test according to Bruce protocol, heart ultrasound for assessment of ejection fraction, test for the assessment of quality of life and subjective problems (Short Form SF 36). Patients were tested for time of discharge from hospital, after 6 and 12 months, including re-evaluation of the overall condition of the previous period.

Results Patients have been tested for the tolerance of effort with the measurement Metabolic Equivalent of TASK (METs), which is the equivalent of physical labor. Patients treated with trimetazidine since the time of hospital discharge achieved an average of 3.68, after 6 months 5.68, and after 12 months 7.79 METs. The control group achieved 3.68, 3.59 and 3.87 METs, respectively. Using Mann-Whitney test no difference at discharge time ($p=0.880$), but after six and twelve months there was some difference ($p<0.001$). Results of ejection fraction measured by echocardiography were similar. No difference between the two groups with regard to time of discharge ($p=0.821$, but $p<0.001$ after six and twelve months, respectively).

Conclusion Patients treated with conventional therapy including trimetazidine have better tolerance to effort and better ejection fraction on heart ultrasound examination in comparison with those treated without trimetazidine, so trimetazidin improve the metabolic balance of heart muscle.

Key words: METs, ergometry, echocardiography, quality of life with heart ischemia

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INTRODUCTION

Ischemic heart disease could be result of chronic inappropriate perfusion of myocardium through coronary arteries or consequence of previous myocardial infarction. The main difference between these two conditions is global ischemic status of whole myocardium, in chronic ischemic heart disease cases, without regional hypokinesia, or inappropriate coronary supply in a zone suffered by infarction with regional hypokinesia (1).

Heart failure is one of the most common diseases worldwide. Population of any country worldwide is prone to suffering of heart failure. In developed countries heart failure occurs in late phases of life, but in underdeveloped countries heart failure occurs earlier. It is known that if a person does not suffer from any other disease, he/she will die from heart failure (2).

Physiologically, cardiomyocytes are replaced with connective tissue in elderly people. This process is known as cardiac remodelling (3). If there are no other diseases, atherosclerosis develops in blood vessels and in the heart at the same time. The dynamic of this process is affected by many factors, including metabolic, genetic, dietary, physical activity, hormonal, and many others (4). Primary cardiomyopathy in the early phase of life is possible, but it is uncommon. The most common secondary cardiomyopathy is ischemic one with previous myocardial infarction, or without it (5).

Trimetazidine as a metabolic drug in combination with standard therapy in ischemic heart disease acts by selectively inhibiting KAT enzymes and reducing oxidation of fatty acids, stimulating glycolysis with the formation of a higher amount of ATP (6). It proves acidosis in the cell by increasing the calcium concentration, increasing the metabolic rate of phospholipids. At the same time it protects the cell membrane from oxidative stress caused by beta-oxidation of fatty acids, increases myocardial contractility, prevents myocardial apoptosis (through MAPKYAKT pathway), reduces cardimyocytes sensitivity to oxygen radicals and reduces the occurrence of interstitial myocardial fibrosis (through ROS / CTGF pathway) (7)

Heart failure could be asymptomatic for a few months or a few years. The first symptoms of heart failure will develop during an effort, in the beginning just during great effort, but later with limited effort too (8). The NYHA classification has been very useful for many years and can be some orientation for diagnosis and treatment of heart failure. In European population 6-10% of elderly individuals older than 65 years suffer from heart failure. Death related to heart failure has cardiovascular origin of the disease.

In normal physiology of the heart, more than 60% of metabolic energy for heart work comes from beta oxidation of fatty acids. Five percent is from metabolic turnover of lactic acids and about 35% from glycolysis. This is very different from skeletal muscles where most energy is generated by glycolysis (9)

Improvement of metabolic state of the heart production of energy will be the best idea to improve heart function at all. Metabolic support is an idea that has existed for a few decades, but in the last three decades metabolic therapy was introduced for improvement of the overall heart metabolic status. One of the most commonly used metabolic drugs is trimetazidine. To analyse whether metabolic therapy improves effort tolerance and quality of life we performed this study (10,11).

The aim of this study was to investigate whether or not additional treatment of ischemic heart disease with trimetazidine could improve effort tolerance and overall quality of life of patients with ischemic heart disease.

PATIENTS AND METHODS

Patients and study design

The study was performed at the Department of Cardiology in University Clinical Centre (UKC) in Tuzla during 2017. The study included 200 patients with ischemic heart disease randomly divided into two groups. The first one, experimental group, was treated with conventional therapy and metabolic drug trimetazidine in the dose of 35 mg daily for all patients. The second group was treated only with conventional therapy, without trimetazidine. At the and of the study, after one year, in the experimental group 95 patients were completely followed up (47 females and 48 males), and in the control group 84 (44 females and 40 males).

All patients signed informative consents. The study was approved by Etic Committee of UCC Tuzla.

Methods

Patients were examined for conventional risks of ischemic heart disease, including blood cell

count, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL), cholesterol, triglycerides, urea, creatinine, and fasting blood glucose.

Patient's tolerance to effort was examined by trade-mill stress testing according to Bruce protocol (12). For all patients echocardiography was performed with the measurement of ejection fraction (EF) (13-15).

The ergometry test and measurement of ejection fraction on echocardiography, as well as analysis of quality of life considered with standardized questionnaires, were performed at the time of discharge from hospital, after 6 months and after 12 months.

Standardized and authoritative questionnaires were used for a realistic assessment of all aspects of quality of life, including personal satisfaction with their love life, the feeling of existence of life energy, emotional state, mood or depression, especially parameters of the physical effort. In laboratory diagnostic conditions, the Bruce protocol of ergometry, and on the other hand, tolerance to the effort that affects the possibility of daily activities, such as walking up the stairs, were analysed. Gradation was applied as follows: easily climbing to the third floor up the stairs represents a good tolerance to effort, fatigue already at the beginning of the second floor, as moderate restriction, and fatigue already at the first floor as a significant limitation for climbing the stairs.

Quality of life was assessed with standardized questionnaire, short version (Short Form SF 36) (16,17).

Patients were assessed after discharge from hospital, after six months and after twelve months.

Statistical analysis

The data were assessed using Kolmogorow-Smirnov test with nonparametric Mann-Whitney test of sum of rank. The results of quality of life questionnaire were calculated by nonparametric Fisher exact test, if the frequency was less than 5, otherwise by χ^2 test. $p<0.05$ was used as statistically significant.

RESULTS

All 200 patients were followed up during the period of twelve months. Some patients were lost from the follow-up, and at the end, 95 patients in the experimental group were followed up during the entire period of twelve months. In the control group 84 were followed up completely.

On the day of discharge from hospital, there was no difference between the patients in the effort tolerance by measure of the achieved METs, 3.6774 METs inthe experimental and 3.6838 in the control group (p=0.880). After six months of the treatment, the trade-mill showed statistically significant difference, e. g. patients of experimental group had better tolerance to effort ($p<0.001$). Greater tolerance to effort was recorded after 12 months, 7.77 METs and 3.87 METs, respectively) (Figure 1).

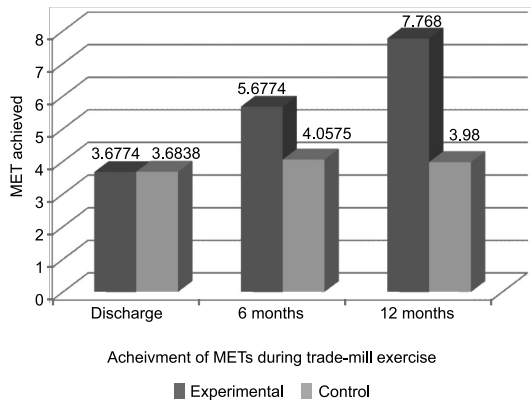

Figure 1. Achievment of Metabolic Equivalent of TASK (METs) in ergometry, trade-mill exercise testing according to Bruce protocol in three periods of assessement

On the date of discharge, average EF was nearly the same in both groups: experimental 0.5469 and control 0.5828 (p=0.821), but after six and twelve months it was better in the experimental group ($p<0.001$) (Figure 2).

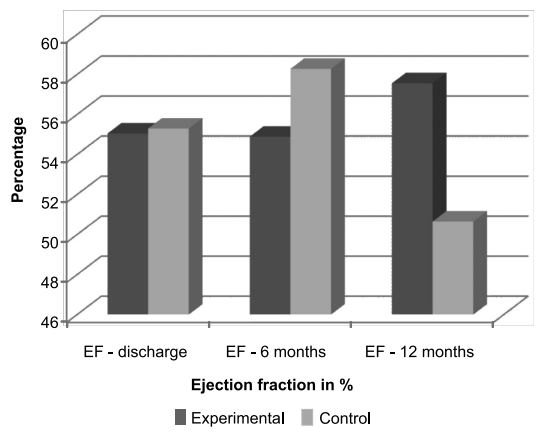

Figure 2. Ejection fraction (EF) (%) in three periods of assessement

Complete laboratory examination for the parameters, which could influence results of ergo-

Table 1. Limitation while moving up the stairs on several floors

Limitation while moving up stairs	No (%) of patients					
	Before therapy		6-month therapy		12-month therapy	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
No limitation	1 (1)	5 (5)	1 (1.05)	1 (1.19)	11 (11.82)	2 (2.5)
Medium limitation	12 (12)	31 (31)	28 (29.47)	24 (28.57)	41 (44.09)	26 (32.5)
Severe limitation	87 (87)	64 (64)	66 (69.47)	59 (70.24)	41 (44.09)	52 (65)
Total	**100**	**100**	**95**	**84**	**93**	**80**
p	**<0.001**		**0.932**		**0.001**	

metry and EF, were performed. Red blood cell count was not different in the groups on the date of discharge from hospital. An average Hb in the experimental group was 137.90 g/L (±18.44), and in the control group 138.84 (±18.59) (p=0.374). Total cholesterol in the experimental group was in average 4.93 mmol/L (±1.81), and in the experimental group 5.01 mmol/L (±1.136) (p=0.126).

Better condition for moving up the stairs on several floors was found in the group treated with tremetazidine than in patients with only conventional therapy (Table 1).

DISCUSSION

Our results were compared with those in recent literature in the assessment of effort tolerance and quality of life. One of the most important studies related to trimetazidine is TRMPOL II. In this study, 12-week treatment with trimetazidine plus metoprolol significantly improved treadmill exercise test results and reduced all symptoms of ischemic heart disease, compared with the patients treated with metoprolol and placebo. The patients were with stable angina pectoris. This improvement was achieved without any hemodynamic changes in these patients, whose angina was not controlled only with metoprolol in the therapy. In this study trimetazidine showed good tolerability, no serious side effects were reported (18). In some other studies a combination of thimetazidine and conventional therapy was tested with calcium channel blocker, beta blocker etc. The results showed the benefit of combination of trimatazine with conventional therapy (19-21).

The positive effect of trimetazidine to cardimyocytes has not yet been fully understood. It is not quite clear whether it can be attributed to direct cytoprotective actions, change of tissue pH and by reduction of myocardial cell acidosis. Reduction of calcium overload was seen including increase of intracellular ATP levels, increase and preservation of the antioxidant capacity (22). As a result of these actions protection against oxygen-free radical induced toxicity was done (23).

In our study it was clear that addition of triemtazidine to conventional anti-ischemic therapy improves body capacity to effort, improves complete myocardial metabolism with preservation of systolic heart function measured by ejection fraction. The results of effort tolerance were the same as noted in recent literature (24-26).

It is known that good resolution of myocardial injury after myocardial infarction is essential for preservation of cardiac compensation. If the reparation of myocardium, after myocardial infarction is not well done, substantial quantity of fibrous tissue and scar may be replacement for injured myocardial tissue. In these situations substantial regional hypokinesia could be seen (27). On the other hand, if the scar tissue is very powerful, diastolic heart dysfunction could be found. In this situation heart failure with preserved ejection fraction may occur (28).

To evaluate complete patients' ability for everyday practice, a modified and abbreviated questionnaire was developed. Assessment of patient's ability to go upstairs showed better condition in patients treated with trimetazidine than without it.

In conclusion, the result of this study has shown that addition of trimetazidine to conventional therapy improves ischemic cardimyocytes metabolism with improvement of patient's ability for effort, improved ejection fraction resulting in overall improvement of quality of life.

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TRANSPARNCY DECLARATION

Competing interest: None to declare.

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