EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Cardioprotective Effect of Trimetazidine during Thrombolytic Therapy in Patients with Acute Myocardial Infarction

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We studied the cardioprotective effect of anti-ischemic drug trimetazidine in the thrombolytic therapy of acute myocardial infarction. Trimetazidine (60 mg/day) effectively inhibits lipid peroxidation and moderates reperfusion damage to the myocardium assessed by ECG, *QRS* index of damaged heart, and release of creatine phosphokinase into circulation.

Key Words: *acute myocardial infarction; thrombolytic reperfusion; lipid peroxidation; trimetazidine*

Efficiency of the therapy of acute myocardial infarction (AMI) to a great extent depends on early restoration of blood supply to ischemic myocardium [3,4]. At the same time, pharmacological correction of metabolic changes in cardiomyocytes in the affected region is an important factor in the fight for patient's life [6].

The key elements in the pathogenesis of acute myocardial ischemia are disturbances of ATP synthesis in mitochondrial respiratory chain, the development of acidosis, increased production of free oxygen radicals, and disturbances in ionic homeostasis in cardiomyocytes [9,10]. Routine drug therapy of AMI is aimed at reducing oxygen demand and/or increasing oxygen supply to the myocardium. Some new pharmacological preparations produce a complex metabolic effect on cardiomyocytes [8]. Trimetazidine produces an anti-ischemic effect in patients with chronic coronary insufficiency [5,11]. The anti-ischemic effect of trimetazidine is determined by improvement of energy metabolism via activation of aerobic glycolysis [7]. However, the protective effect of trimetazidine during the development of ischemic and oxidative damage in myocardial infarction or during reperfusion procedures was not studied [12].

Our aim was to evaluate of efficiency of trimetazidine in combination with thrombolytic therapy (TLT) in patients with AMI.

MATERIALS AND METHODS

The controlled randomized study (envelope method) included 79 AMI patients. In all patients efficient recanalization of coronary arteries was achieved after intravenous bolus injection of 750,000 U streptokinase. The patients were subdivided into control (n=39) and experimental (n=40) groups with similar demographic and clinical parameters (Table 1). In both groups, the percent of patients with infarction of the anterior or posterior wall of the left ventricle were approximately equal: in control group they were 50 and 50%, and in the experimental group they were 49 and 51%, correspondingly. Trimetazidine (40 mg/kg) was administered to patients of the experimental group 20 minutes before the start of TLT and then daily in a dose of

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60 mg/day throughout the hospital period. Written consent was obtained from all patients of the experimental group. Patients of the control group (n=39) were not treated with trimetazidine and received inhibitors of platelet aggregation, anticoagulants, β-adrenoblockers, ACE inhibitors, and nitrates when indicated.

The severity of the disease was assessed according to incidence of postinfarction anginal attacks, the need for nitrates for arresting these attacks, and the degree of acute cardiac insufficiency according to T. Killip classification. The intensity of oxidative stress after attaining thrombolytic reperfusion was assessed by plasma MDA concentration [14]. The size of necrotic zone was evaluated by two independent methods: ECG recording (Cardimax FX-326U cardiograph) throughout the hospital period with calculation of *QRS* index of affected myocardium [13] and repeated measuring of total plasma creatine phosphokinase (CPK) activity using Biocon kits (first 3 days after the onset of AMI). At the moment of enlisting the patients into the study, the groups were comparable in age, coronary anamnesis, AMI localization, its initial size, and the degree of cardiac insufficiency.

The data were processed statistically using dispersion analysis with two-sample Student's t test.

RESULTS

Trimetazidine produced no effect on the degree of acute cardiac insufficiency in AMI patients. At the same time, the incidence of anginal attacks and the need for nitrates in patients of the experimental group were lower than in the control group (0.90±0.13 *vs.* 3.4±0.6, and 2.0±0.5 mg/day *vs.* 10.0±2.0 mg/day, p<0.001, respectively).

It was established that blood flow recovery after TLT did not prevent necrotic damage to the myocardium in the basin of the occluded artery [2]. Actually, high CPK activity in the serum of control patients persisted for 48 h after recanalization (Fig. 1). The peak of CPK activity was attained by the 15th hour of the reperfusion period. *QRS* index also increased (by 1.7 times) as early as on reperfusion day 1 (Fig. 2) and continued to increase throughout the observation period. These data on the one side confirm damage to cardiomyocytes, and on the other side attest to involvement of myocytes of "stunned" and "hibernated" myocardium into the necrotic zone, despite restoration of coronary blood flow [6].

Trimetazidine had no effect on the dynamics of CPK activity in the first hours after recanalization, but after 12 h the differences between the examined groups became significant (Fig. 1). Moreover, in the experimental group the increase of *QRS* index was less pronounced (Fig. 2), which also attested to beneficial effect of trimetazidine on cardiomyocyte viability in the basin of the infarction-related artery.

TABLE 1. Clinical Parameters of Examined Patients (M±m)

Index	Control (n=39)	Trimetazidine treatment(n=40)
Percentage of men	79	73
IHD duration, years	4.6±1.1	4.8±0.9
Age, years (range)	56.04±8.84 (36-72)	55.94±9.31 (37-76)
Period from the onset of MI, h		
prior to admission	2.5±0.8	2.3±0.9
prior to thrombolytic therapy	3.6±0.9	3.3±0.8
prior to reperfusion	4.2±1.1	4.7±0.3
Percentage of patients subjected to coronary ventriculography, %	65	55

Recanalization of the coronary artery is known to provoke reperfusion damages. The pathogenesis of reperfusion damage is related to activation of LPO processes [1]. In our study, initial content of MDA was 9.74±0.64 μmol/liter (Table 2). In the control group MDA content increased 1.4-fold as early as 12 h after resumption of blood flow and returned to the initial level only on days 19-21. In the experimental group the maximum concentration of MDA was almost 2-fold lower than in the control group (Table 2).

These findings confirm cytoprotective potency of trimetazidine. The use of this drug in the treatment of AMI in combination with enzymatic recanalization of

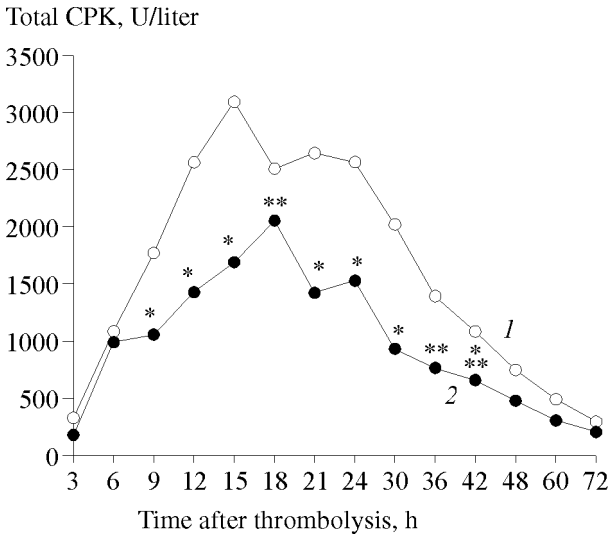

Fig 1. Dynamics of total creatine phosphokinase (CPK) activity in plasma of control patients (*1*) and in experimental group treated with trimetazidine (*2*). Here and in Fig. 2: *p<0.001, **p<0.01, ***p<0.05 compared to the control.

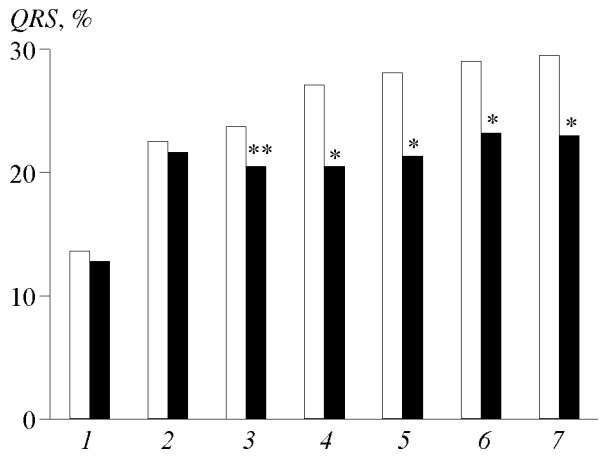

Fig 2. Effect of trimetazidine on the time-course of *QRS* complex. Light and solid bars correspond to control and experimental patients treated with trimetazidine, respectively. *1*) before thrombolysis, *2-7*) 1, 2, 3, 6, 12, and 21 days after thrombolytic therapy.

TABLE 2. Dynamics of MDA Concentration (% of Initial Value) in Patients after Thrombolytic Therapy during Hospital Period

Period from onset of MI	Control (n=30)	Experimental group (n=25)
6 h	100	100
12 h	143	100*
1 day	142	112*
2 day	95	124**
3 day	84	109***
14-16 day	100	67*
19-21 day	90	67**

Note. *p<0.001, **p<0.01, ***p<0.05 compared to the control.

coronary artery effectively prevented reperfusion damage to cardiomyocytes and restricted the necrotic area. Trimetazidine alleviates clinical course of AMI. However, the absence of significant differences in the severity of cardiac insufficiency between the examined groups suggests that trimetazidine has no time to stabilize energy metabolism in the myocardium during the acute phase of myocardial infarction.

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