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Original Article

Metabolic intervention with trimetazidine improves intracardiac hemodynamics and reduces re-hospitalizations in patients with advanced heart failure

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Abstract: Objectives: We tested whether management with metabolic cytoprotective and antiischemic agent trimetazidine may reduce readmissions in advanced heart failure (HF) patients through the possible improvement of left ventricular ejection fraction (LV EF) and filling pressure. Methods: This was a single-center prospective open-label study. The study population included initially 40 patients with advanced HF and EF <30%, NYHA III-IV functional class, significant restriction of physical activity and at least 1 hospitalization during the last 12 months. After discharge patients were assigned to additional treatment with trimetazidine 80 mg/daily dose (20 patients) or standard guideline-based pharmacological therapy (20 patients). After enrollment patients underwent a total of four outpatient clinical and echocardiographic examinations (baseline before discharge, 2 weeks, 1, 3 and 6 months after the discharge). The echocardiographic assessment of EF and LV filling pressure by Tissue Doppler were performed blindly. Results: At 6 months, trimetazidine-treated patients had an improvement of LV EF (from 23.7% to 25%) as compared to controls (from 22.5% to 22.6%). Tissue Doppler study showed a decrease of LV filling pressure in trimetazidine treated group from 15.1 at baseline to 13.7 after 6 months of treatment. In the control group, LV filling pressure remained unchanged (from 16.78 to 16.7) (P<0.001). The rate of hospitalizations for cardiovascular causes was reduced at 6 months (83.3% vs 70.0%). Conclusions: Treatment with trimetazidine 80 mg/daily in addition to standard guideline-based therapy for 6-months decreased hospitalization, improved systolic function and LV filling pressure in advanced HF patients.

Keywords: Advanced heart failure, trimetazidine, rehospitalization, left ventricular ejection fraction, left ventricular filling pressure

Introduction

Advanced heart failure (HF) represents the extreme of HF and is characterized by persistent HF symptoms and progressive myocardial dysfunction, despite the guideline-recommended treatment. Patients with advanced HF have frequent hospital readmissions and poor quality of life [1, 2]. Poor tolerance to guideline-recommended medical therapy in such patients is the frequent need to undergo definitive treatment.

Alterations of myocardial energetic metabolism in patients with chronic HF contribute to systolic dysfunction and myocardial remodelling.

In several studies, it was shown that myocardial energy metabolism is altered in advanced stages of HF with reduced mitochondrial oxidative metabolism and downregulation of glucose and fatty acid oxidation [3-6]. Current treatment of HF targets fluid overload and neurohumoral overactivation. Several studies have suggested that the metabolic agent trimetazidine improves functional capacity in patients with HF with reduced ejection fraction (HFrEF) and mortality through selective inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase and increase of glucose oxidation [7-10]. In our previous studies, we reported, that trimetazidine improves left ventricular (LV)

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function and functional capacity at 6-months follow-up [11].

Patients with advanced HF have poor outcomes and limited opportunities for guideline-recommended pharmacotherapy due to compromised hemodynamics, high number of comorbidities and fragility. Treatment of such patients represents a challenge, because of low blood pressure, severely reduced EF, and resistance to diuretics. Cumulated data on the beneficial effects of trimetazidine in HFrEF suggest, that in advanced HF patients with chronic reduction of coronary blood flow and inability to adjust myocardial performance for peripheral metabolic needs, metabolic intervention with trimetazidine may improve clinical state and myocardial performance [9, 12, 13].

Apart from this, taking into consideration, that glucose oxidation may exert less ATP utilization compared to fatty acid oxidation, such an adaptive approach of pharmacotherapy may have a beneficial influence in severe forms of HF [14]. However, at present, it is not evident whether the improvement of the metabolic state of ischemic myocardium seen with trimetazidine in myocardial systolic dysfunction may occur also in advanced HF with poor prognosis. Therefore, we aimed to study the impact of such metabolic intervention with trimetazidine on important LV echocardiographic indices and outcomes in HF patients with high-risk profile and high NYHA class.

Materials and methods

Study population

The study population included initially 40 patients with advanced HF and EF <30%, NYHA III-IV functional class, significant restriction of physical activity and having at least 1 hospitalization during the last 12 months. All patients had sustained NYHA III-IV functional class symptoms despite receiving maximally tolerated guideline-recommended medical therapy. Comorbidities and clinical data of patients were obtained from patient examination and hospital medical records. During hospitalization, patients received appropriate therapeutic interventions, including inotropes, intravenous diuretics, and iron supplementation. After the discharge patients were assigned to trimetazidine (20 patients) or standard guideline-recommended pharmacologic therapy (20 patients) groups. The number of patients was determined based on prior studies with trimetazidine conducted with a similar design.

One patient from trimetazidine group dropped out of the study due to low adherence to medical treatment. Both echocardiographic and study endpoint assessment were performed blindly.

Study design

This was a single-center prospective open-label study. After group allocation 40 patients were included and 38 completed the study. All patients underwent outpatient visits with a total of four examinations (baseline before the discharge, 2 weeks, 1, 3 and 6 months after the discharge). At each visit careful clinical examination and cardiovascular and lung ultrasound were performed for the congestion assessment according to the hospital protocol for advanced HF patients, which was previously described and applied for HF patients follow-up monitoring [15]. Physical examination was performed by trained heart failure physicians. LVEF was measured at discharge and at 6 months follow-up. All echocardiographic measurements were performed according to American Society of Echocardiography guidelines [16, 17]. LV Filling pressure and inferior vena cava assessment to evaluate congestion status were performed by experienced HF specialists and trained echocardiography physicians in accordance with European Society of Cardiology Heart Failure Association (ESC HFA) and American Society of Echocardiography (ASE) guidelines [17]. The study protocol was discussed and approved by the Ethics Committee of Yerevan State Medical University. The informed consent was obtained from all patients prior to their enrollment in the study. Patients were allocated into two homogeneous groups. Diuretic treatment modification at outpatient visits was allowed during the study depending on clinical, echocardiographic and lung ultrasound-based congestion signs at outpatient visits. Patients were empirically allocated to receive trimetazidine added to baseline therapy or continue without the additional trimetazidine therapy. Group A (n=18 patients) received additional trimetazidine modified form at a dose of 80 mg once daily for 6 months in addition to conventional guideline-recommended treatment of HF. Group B (n=20 patients)

Table 1. Baseline characteristics of the patients in trimetazidine-treated and control groups

	Trimetazidine group (n=18)	Control group (n=20)
Mean age	65.44 ± 9.77	65.90 ± 10.79
Male	11 (61.1%)	15 (75%)
Female	7 (38.9%)	5 (25%)
CHF (NYHA II)	1 (5.56%)	4 (20%)
CHF (NYHA III-IV)	17 (94.4%)	16 (80%)
Previous MI	13 (72.2%)	19 (95%)
Diabetes mellitus	5 (27.78%)	7 (35%)
Chronic kidney disease (GFR <30 ml/min)	1 (5.56%)	0 (0%)
Revascularization	6 (33.3%)	7 (35%)
LV EF (%)	23.7 ± 5.79	22.50 ± 5.50
SBP (mmHg)	125.59 ± 26.03	117.50 ± 20.74
DBP (mmHg)	78.82 ±16.16	76.00 ± 12.31
LA volume index	54.55 ± 29.09	46.22 ± 23.24
E/e' ratio	15.1 ± 6.00	16.78 ± 6.02
Beta-blockers	18 (100%)	20 (100%)
RAAS inhibitors	14 (77.7%)	19 (95%)
Intravenous diuretic doses	5 (27.8%)	7 (35%)
Aldosterone antagonists	16 (88.9%)	19 (95%)
Digoxin	1 (5.56%)	0 (0%)

Parametric data are expressed as mean ± SD, non-parametric data as number of patients (%). CHF - chronic heart failure; NYHA - New York Heart Association; GFR - glomerular filtration rate; LV EF - left ventricular ejection fraction; SBP - systolic blood pressure; DBP - diastolic blood pressure; LA - left atrium; RAAS - renin-angiotensin-aldosterone system.

received conventional HF treatment including renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, loop diuretics, and mineralocorticoid receptor antagonists.

Statistical analysis

Data were analyzed by a commercially available IBM_22.0.0 SPSS statistical package (IBM, Armonk, NY, USA). Continuous variables with normal distribution are expressed using mean and standard deviation (SD), while categorical variables are presented as numbers and percentages. All *p*-value estimates were obtained from 2-tailed tests and results were deemed statistically significant at $P<0.05$. Due to the non-randomized nature of the study, the propensity score (PS) was performed in order to minimize selection bias between the groups. The Kaplan-Meier test was used to compare death and rehospitalization probability and the Mantel-Cox log rank test was used to compare mean survival time between groups.

Results

Of 40 patients who were enrolled 38 completed the protocol. One patient on the trimetazidine arm was excluded from the study because of non-adherence to the study protocol and one patient died in the same group. The cause of death was cardiovascular.

Both groups were comparable at baseline with regards to their clinical characteristics, hemodynamics, echocardiographic evaluation and distribution of their concomitant treatment (**Table 1**). There were no statistical differences with regards to main HF characteristics, namely EF, hemodynamics, and left ventricular filling pressure in both groups.

The relatively higher percentage of RAAS inhibitors treatment in the control group may be explained by a better tolerance of these patients to medications with hemodynamic effects.

In the trimetazidine group increase in LVEF was observed after 6-month of follow-up compared to controls (**Figure 1**). Decrease of LV filling pressure was observed in both groups but was more significant in the trimetazidine group (**Figure 2**).

Changes in echocardiographic parameters are presented in **Figures 1** and **2**.

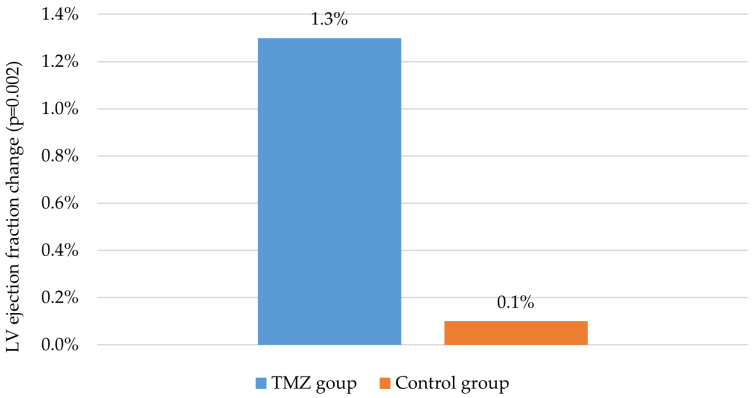

Figure 1. Changes in echocardiographic LV EF in the trimetazidine and control groups during the follow-up. TMZ - trimetazidine; LV EF - left ventricular ejection fraction.

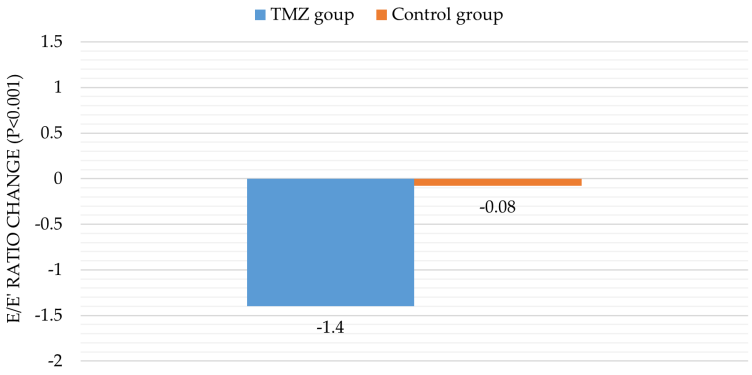

Figure 2. Changes in E/e' ratio in the trimetazidine and control groups.

After 6-month of treatment, a statistically significant decrease in E/e' ratio was observed in the trimetazidine group compared to controls.

The case processing analysis summary showed that the number of events was two times less in the trimetazidine group compared to controls (**Table 2**).

During the follow-up period reduction of HF hospitalization was observed in trimetazidine group expressed by only 5 HF decompensation-related hospitalizations among 3 patients in trimetazidine treated group and a total of 7 hospitalizations (6 HF decompensations, 1 stroke) among 6 patients in the control group (**Figure 3**). Treatment modification with loop diuretics to prevent decompensation and rehospitalisation with an increase of diuretic doses and switch to intravenous diuretics was performed in 5 patients in trimetazidine group and 7 patients in control group.

After a 6-months follow-up period, the effect on mortality was neutral (**Figure 4**).

Discussion

In this small cohort of patients with high-risk HF, we demonstrated the potential efficacy of trimetazidine therapy by moderate, but statistically evident improvement of LVEF and filling pressure parameters. There was also a decrease in rehospitalizations in the trimetazidine group compared to controls, although effects on mortality were neutral.

To the best of our knowledge, this is the first study evaluating the effect of trimetazidine on LV filling pressure.

The results of our study have clinical significance since the increased E/e' ratio reflects elevated left atrial pressure and plays an important role in the progression of HF [18]. Pathophysiologic explanation of such clinical improvement with a decrease in hospitalizations may be associated with a beneficial metabolic effect on myocardial energetic profile and improvement of systolic function, proven previously in several studies and meta-analysis [8, 11, 19, 20].

Patients with advanced HF remain at high risk of death and hospitalizations despite the advances in treatment during the last decades.

HF treatment in patients with advanced HF is challenging due to low systolic blood pressure, higher NYHA functional class and low EF [21]. Pharmacological agents available for long-term treatment of patients with high-risk profiles have several limitations with regard to hemodynamics and the tolerability influences, side effects, particularly in renal failure patients. Non hemodynamic approach with purely metabolic mechanism of action with minimal side effects and optimal patient compliance becomes very important in this cohort of patients. To the best of our knowledge, our study was the

Table 2. Case processing summary table for hospitalizations

	Number of patients	Number of hospitalized patients	Number of non-hospitalized patients	Percent of non-hospitalized patients
Trimetazidine group	18	3	15	83.3%
Control group	20	6	14	70.0%
Total in both groups	38	9	29	76.3%

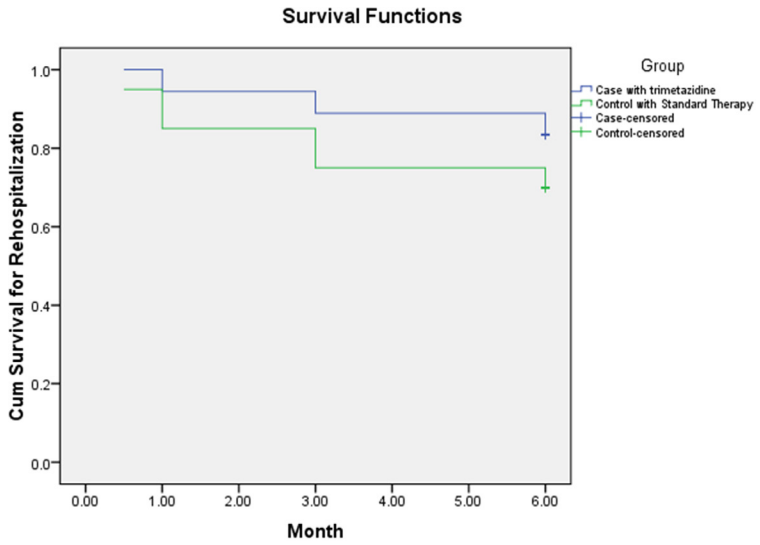

Figure 3. Kaplan-Meier curve showing reduction of hospitalizations in trimetazidine-treated group compared to controls.

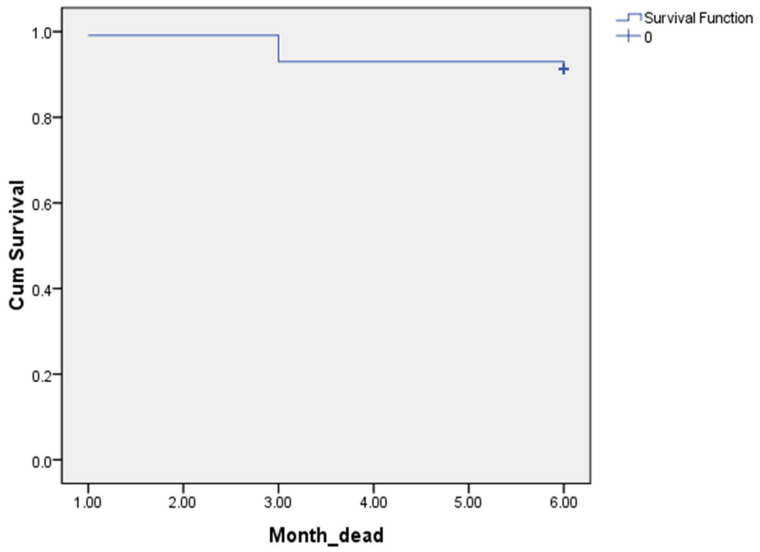

Figure 4. Kaplan-Meier curve showing the effects on mortality in the groups.

first aiming to evaluate the metabolic intervention by trimetazidine in patients with advanced HF.

Trimetazidine is widely used antianginal medication that has been demonstrated to reduce the number of ischemic events and improve exercise tolerance in patients with chronic coronary artery disease including those with diabetes, and systolic dysfunction [22-26]. It has been shown to improve ejection fraction in patients with systolic dysfunction and to enhance the response to dobutamine stress test in individuals with post-ischemic left ventricular dysfunction [27-29].

Our small study in patients with advanced HF included ischemic patients with high prevalence of diabetes mellitus and chronic kidney disease. In patients with chronic HF, the influence of trimetazidine on mortality was shown in several studies with long follow-up periods [30, 31].

The beneficial effects of trimetazidine on mortality, hospitalizations, and left ventricle function could be related to the peculiar mechanism of action of the drug. Trimetazidine exerts myocardial antiischemic effect independently from changes in oxygen supply-to-demand ratio. The antiischemic effect of trimetazidine is obtained on a cellular level by shifting the energy substrate reference from fatty acid oxidation by rapidly restoring the phosphorylation processes, protecting cardiac cells against intracellular acidosis, preventing the intracellu-

lar accumulation of sodium and calcium ions, and finally by reducing oxidative damage [32-34]. All these properties contribute to protection of the myocardial cell against necrotic and apoptotic cell death. Our study was the first showed such effect in patients with advanced HF with compromised hemodynamics and frequent hospitalizations.

There were no trimetazidine treatment-related adverse events experienced by any of the patients.

Limitations

The limitations of our study were the small number of patients and the relatively short period (6 months) of follow-up, which did not allow us to assess mortality and long-term benefits compared with that observed with other HF treatment medications with proven effects.

Nevertheless, the effect of trimetazidine was studied in patients with advanced HF patients, who were outpatients and not on device therapy.

Part of the patients was on intermittent intravenous furosemide intervention which might influence the clinical course, although the number of such patients was comparable in both groups.

Conclusions

Treatment with trimetazidine 80 mg/daily dose in addition to standard guideline-recommended therapy, over a 6-month period, decreased hospitalizations, improved LV systolic function and LV filling pressure in patients with advanced HF patients. The use of trimetazidine was associated with good tolerance. An improvement of LV function parameters indicated that the addition of trimetazidine to standard treatment in advanced HF can promote the functional improvement through the beneficial effects on systolic function and diastolic filling pressure. Such effects lead to a decrease in frequently observed hospitalizations in this cohort of patients.

Disclosure of conflict of interest

None.

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