

ORIGINAL ARTICLE

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Improved left and right ventricular functions with trimetazidine in patients with heart failure: a tissue Doppler study

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Abstract Downregulation of glucose and fatty acid oxidation occurs in heart failure (HF). Trimetazidine reduces fatty acid oxidation and increases glucose oxidation. In this single-blind study, trimetazidine, 20 mg three times per day ($n = 51$) or placebo ($n = 36$) was added to treatment of 87 HF patients receiving optimal HF therapy. Etiology of heart failure was coronary artery disease in 35 patients (68.6%) in the trimetazidine group and 22 (62.9%) in the placebo group. Fourteen (27.5%) patients in the trimetazidine group and 11 (31.4%) patients in the placebo group had diabetes. Peak systolic velocity (Vs), and the peak early diastolic (Vd) and late diastolic (Va) velocities of various segments left and right ventricles (RV) were obtained with tissue Doppler imaging (TDI) and averaged. Patients were re-evaluated three months later. Significant increases in mean left ventricular ejection fraction (LVEF) ($33.3\% \pm 5.6\%$ to $42.4\% \pm 6.3\%$, $P < 0.001$ and $30.6\% \pm 8.2\%$ to $33.2\% \pm 6.6\%$, $P = 0.021$) and LV and RV myocardial velocities and mitral and tricuspid annular TDI velocities were observed in both groups. However, compared to placebo, increments in LVEF ($9.1\% \pm 4.2\%$ vs. $2.5\% \pm 1.4\%$, $P < 0.001$) and myocardial velocities were significantly higher with trimetazidine ($P < 0.001$ for LV Vs, Vd, Va; $P = 0.035$ for RV Vd; and $P < 0.001$ for RV Va and Vs). Increase in LVEF with trimetazidine was significantly correlated with presence of diabetes ($r = 0.524$, $P < 0.001$). With trimetazidine LVEF increased significantly more in diabetic patients compared to nondiabetics ($P < 0.001$). Also, patients having both diabetes and ischemic HF tended to have greater improvement in LVEF compared to ischemic HF patients without diabetes ($P = 0.063$). Addition of trimetazidine to current treatment of HF, especially for those who are diabetic, may improve LV and RV functions.

Key words Tissue Doppler imaging · Ejection fraction · Myocardial velocity

Introduction

Failure of the myocardium in heart failure appears to be caused to some degree by alterations in substrate metabolism.¹ Myocardial energy metabolism may be normal in the early stages of heart failure, but as failure progresses mitochondrial oxidative metabolism is reduced and glycolysis is increased with downregulation of glucose and fatty acid oxidation. Reducing free fatty acid (FFA) oxidation and at the same time increasing glucose oxidation improves cardiac contraction and slows the progression of left ventricular (LV) failure.² Trimetazidine acts as a partial inhibitor of fatty acid oxidation and in turn stimulates glucose oxidation.^{3,4} Improvement in LV systolic function with trimetazidine in heart failure patients, especially those with diabetes, has been reported in several studies.^{5–11}

Tissue Doppler imaging (TDI), which records systolic and diastolic velocities within the myocardium and at the corners of the annulus, has been shown to provide accurate quantification of regional and global LV function.^{12–14} Several studies have demonstrated the clinical importance of TDI in patients with CHF.^{15–17} In this study we aimed to investigate the effects of trimetazidine on left and right ventricular functions using myocardial tissue Doppler velocities in patients with heart failure.

Patients and methods

In this prospective, single-blind and single-center study, 87 heart failure patients with New York Heart Association (NYHA) functional class II or III already being treated with optimal heart failure treatment including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, beta-blockers, spironolactone and digitalis in the case of no contraindication, and furosemide according

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to patients' symptoms, were included. Following baseline echocardiographic examination trimetazidine, 20 mg three times per day ($n = 51$) or placebo ($n = 36$) was added to the therapy and patients were re-evaluated 3 months later. Exclusion criteria were: NYHA class IV, acute myocardial infarction within 3 months, atrial fibrillation, LV ejection fraction (LVEF) $> 40\%$, severe valvular heart disease, alcoholic cardiomyopathy, pacemakers, renal failure (serum creatinine > 2.0 mg/dl), chronic lung disease or any systemic disorder, and use of additional drugs like antiarrhythmics and nonsteroids. The study was approved by Yuzuncu Yil University Medical Faculty Ethics Committee according to the Declaration of Helsinki, and patients gave written informed consent.

The echocardiographic examination was performed at rest, with the patient in the left lateral decubitus position, using a commercially available echocardiographic device (Vivid 3, General Electric, Piscataway, NJ, USA) with a 3-MHz transducer, by two experienced echocardiographers who were blinded to the clinical data. Using M-mode echocardiography, long-axis measurements were obtained at the level distal to the mitral valve leaflets according to current recommendations.¹⁸ Left ventricular ejection fraction was calculated via modified biplane Simpson method from apical four- and two-chamber views. Pulmonary artery systolic pressure (PASP) was calculated from tricuspid insufficiency flow in the parasternal short axis and apical four-chamber view, and the highest tricuspid regurgitation velocity was taken into account. The pulsed Doppler sampling volume was placed between the tips of the mitral valve leaflets to obtain maximum filling velocities. Early diastolic flow (E), atrial contraction signal (A) and E deceleration time (DT) were measured. Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal. Power output of the LV, in watts, was calculated as the product of mean arterial pressure and cardiac output. A conversion factor of 2.22×10^{-3} was used to convert the values from mmHg \times ml to watts.¹⁹

Tissue Doppler imaging was acquired to assess diastolic function and myocardial regional function. The pulsed wave spectral mode was used for TDI. Filters and baselines were corrected when the velocity ranged between -20 and 20 cm/s. From the apical four-chamber view with a 5-mm sample volume, early (Em and Et) and late (Am and At) diastolic velocities and systolic velocities (Sm and St) of lateral mitral annulus and lateral tricuspid annulus were measured. Myocardial velocities were recorded from basal, mid, and apical segments of the anterior, anteroseptal, lateral, posterior, and inferior walls of left ventricle (LV) and basal and mid segments of right ventricle (RV). Peak systolic velocity (Vs), and the peak early diastolic (Vd) and late diastolic (Va) velocities were measured. Patient-based LV and RV myocardial function was derived as the average value of tissue Doppler velocity data from all regions described above, and were reported separately for systole and early and late diastole.

All measurements were made off-line on three separate beats and then averaged for all parameters. There was no

significant variation in intra- and interobserver data. During the entire echocardiographic study, a single-lead electrocardiogram was continuously recorded.

Statistics

Data are presented as mean \pm standard deviation (SD). Using an SPSS package 10.0 (SPSS, Chicago, IL, USA) differences in mean values between groups were assessed using one-way analysis of variance (ANOVA). Categorical variables were compared by chi-square test. The significance of changes in parameters after treatment was analyzed by repeated measurements of ANOVA with two factors. One-way ANOVA test followed by Tukey HSD post hoc analysis was used to assess the effects of diabetes and ischemic origin of HF on the change in LVEF. The Spearman test was used to analyze the correlations. A two-tailed P value of less than 0.05 was considered significant.

Results

Baseline clinical characteristics of the study population are given in Table 1. All the patients had a history of coronary angiography. Etiology of heart failure was coronary artery disease in 35 patients (68.6%) in the trimetazidine group and in 22 (62.9%) in the placebo group. Functional class was improved from NYHA 3 to NYHA 2 in 24 patients in the trimetazidine group and 5 patients in the placebo group ($P < 0.001$). Significant increases in mean LVEF, cardiac output, and LV power output, and significant decreases in LV volumes and PASP were observed in both groups. Reductions in IVRT and DT were observed only in the trimetazidine group (Table 2). There were no significant differences between baseline and post-treatment values of heart rates and systolic and diastolic blood pressures. There were significant improvements in LV and RV myocardial velocities and mitral and tricuspid annular TDI velocities (Table 3). Differences between baseline and third month values of LVEF and mean myocardial velocities were calculated. The increments for LVEF and myocardial velocities were significantly higher in the trimetazidine group than in the placebo group (Table 4). Correlation analysis, within the trimetazidine group, revealed that increase in LVEF was significantly correlated with presence of diabetes mellitus ($r = 0.524$, $P < 0.001$) but not with coronary artery disease ($r = 0.043$, $P = 0.763$). For patients treated with trimetazidine, the amount of increase in LVEF was not significantly different between ischemic and nonischemic patients ($8.6\% \pm 3.6\%$ vs $10.2\% \pm 5.1\%$, $P = 0.203$) whereas it was significantly higher in diabetic patients compared to nondiabetics ($12.8\% \pm 4.5\%$ vs $7.7\% \pm 3.1$, $P < 0.001$). Analysis of variance with Tukey HSD test for post hoc analysis also revealed that the increase in LVEF was not significantly different between ischemic and nonischemic HF patients ($P = 0.999$). However, LVEF increased significantly more in diabetic patients compared to nondiabetics

Table 1. Baseline clinical characteristics of the study population

	Trimetazidine group (n = 51)	Placebo group (n = 36)	P value
Age (years)	59.4 ± 9.5	56.6 ± 13.6	0.136
Male sex	37 (72.5%)	21 (58.3%)	0.176
Coronary artery disease	35 (68.6%)	22 (62.9%)	0.646
Diabetes mellitus	14 (27.5%)	11 (31.4%)	0.810
Hypertension	28 (54.9%)	16 (45.7%)	0.511
History of smoking	34 (66.7%)	22 (59.5%)	0.509
Body mass index (kg/m ²)	25.6 ± 3.0	24.8 ± 4.4	0.108
Symptom duration (months)	25.4 ± 23.1 (3–120)	28.3 ± 43.4 (2–120)	0.627
NYHA class 2	25 (49.0%)	17 (47.2%)	1.0
NYHA class 3	26 (51.0%)	19 (52.8%)	
Systolic BP (mmHg)	121.5 ± 18.1	118.4 ± 21.2	0.726
Diastolic BP (mmHg)	80.4 ± 12.1	79.7 ± 10.2	0.731
Heart rate (beats/min)	71.2 ± 9.0	72.2 ± 8.6	0.646
Carvediolol	41 (80.3%)	28 (77.8%)	0.793
Metoprolol succinate	4 (7.8%)	6 (16.7%)	0.185
ACE inhibitor	33 (64.7%)	21 (58.3%)	0.655
ARB	14 (27.4%)	13 (36.1%)	0.482
Digitalis	33 (64.7%)	18 (48.6%)	0.189
Spirolactone	45 (88.2%)	31 (86.1%)	0.786
Furosemide	36 (70.5%)	23 (62.2%)	0.492
Statin	27 (52.9%)	19 (52.9%)	1.0

NYHA, New York Heart Association; BP, blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

Table 2. Comparison of baseline and third month echocardiographic parameters of the study population

	Group	Baseline	Third month
LVEF (%)	Trimetazidine	33.3 ± 5.6	42.4 ± 6.3 ^{ab}
	Placebo	30.6 ± 8.2	33.2 ± 6.6 ^c
LVDV (cm ³)	Trimetazidine	165.3 ± 46.3	152.3 ± 45.0 ^{ab}
	Placebo	172.2 ± 53.7	162.3 ± 45.7 ^c
LVSV (cm ³)	Trimetazidine	109.1 ± 38.3	86.7 ± 34.3 ^{ab}
	Placebo	115.2 ± 50.1	98.3 ± 34.0 ^c
PASP (mmHg)	Trimetazidine	24.4 ± 10.8 ^b	21.7 ± 7.7 ^{ab}
	Placebo	37.3 ± 16.3	35.2 ± 13.0
E (cm/s)	Trimetazidine	60.7 ± 15.4 ^b	60.0 ± 12.0 ^b
	Placebo	66.1 ± 14.2	66.0 ± 12.2
A (cm/s)	Trimetazidine	78.7 ± 17.1	71.6 ± 19.1 ^{ab}
	Placebo	80.8 ± 19.9	80.7 ± 16.1
DT (ms)	Trimetazidine	259.2 ± 60.9 ^b	247.2 ± 54.9 ^{ab}
	Placebo	226.5 ± 42.0	227.6 ± 35.1
IVRT (ms)	Trimetazidine	134.8 ± 22.5 ^b	128.1 ± 20.7 ^{ab}
	Placebo	122.2 ± 28.7	122.4 ± 22.9
Heart rate (beats/min)	Trimetazidine	71.2 ± 9.0	73.2 ± 10.27
	Placebo	72.2 ± 8.6	74.1 ± 11.6
Systolic BP (mmHg)	Trimetazidine	121.5 ± 18.1	122.6 ± 16.6
	Placebo	118.4 ± 21.2	116.8 ± 18.4
Diastolic BP (mmHg)	Trimetazidine	80.4 ± 12.1	78.3 ± 16.8
	Placebo	79.7 ± 10.2	77.6 ± 12.8
Cardiac output (l/min)	Trimetazidine	4.1 ± 0.9	4.6 ± 1.2 ^a
	Placebo	4.1 ± 1.1	4.5 ± 1.3 ^a
LV power output (W)	Trimetazidine	0.93 ± 0.31	1.02 ± 0.35 ^c
	Placebo	0.94 ± 0.40	1.03 ± 0.39 ^c

LVEF, left ventricular ejection fraction; LVDV, left ventricular diastolic volume; LVSV, left ventricular systolic volume; PASB, pulmonary artery systolic pressure; DT, deceleration time; IVRT, isovolumetric relaxation time; BP, blood pressure

^aSignificant vs baseline ($P < 0.01$); ^bsignificant vs placebo ($P < 0.05$); ^csignificant vs baseline ($P < 0.05$)

Table 3. Tissue Doppler analysis of lateral mitral and lateral tricuspid annuli and mean values of left and right ventricular myocardial velocities

	Baseline	Third month
Em (cm/s)		
Trimetazidine	6.2 ± 1.9 ^b	7.1 ± 1.8 ^{ab}
Placebo	4.5 ± 1.2	4.8 ± 1.4 ^c
Am (cm/s)		
Trimetazidine	6.8 ± 3.1 ^b	7.3 ± 2.5 ^{ab}
Placebo	4.5 ± 1.6	4.9 ± 1.4 ^a
Sm (cm/s)		
Trimetazidine	5.4 ± 1.6 ^b	6.7 ± 1.3 ^{ab}
Placebo	4.6 ± 1.4	4.8 ± 1.4
E/Em		
Trimetazidine	10.7 ± 4.5 ^b	8.7 ± 2.2 ^{ab}
Placebo	13.6 ± 5.3	12.9 ± 5.8
Mean LV Vd (cm/s)		
Trimetazidine	4.6 ± 0.9 ^b	6.0 ± 1.1 ^{ab}
Placebo	4.1 ± 0.4	4.3 ± 0.4 ^c
Mean LV Va (cm/s)		
Trimetazidine	4.9 ± 1.1 ^b	6.0 ± 1.2 ^{ab}
Placebo	4.4 ± 1.3	4.7 ± 1.4 ^c
Mean LV Vs (cm/s)		
Trimetazidine	4.5 ± 0.8 ^b	5.7 ± 0.8 ^{ab}
Placebo	4.2 ± 0.9	4.5 ± 1.0 ^c
Et (cm/s)		
Trimetazidine	7.5 ± 3.1 ^b	8.4 ± 2.9 ^{ab}
Placebo	9.2 ± 4.1	9.6 ± 3.9 ^a
At (cm/s)		
Trimetazidine	11.1 ± 5.2	13.0 ± 4.0 ^{ab}
Placebo	10.7 ± 4.0	11.0 ± 3.9 ^c
St (cm/s)		
Trimetazidine	9.8 ± 4.1 ^b	11.2 ± 3.2 ^{ab}
Placebo	8.9 ± 2.0	9.3 ± 1.9 ^c
Mean RV Vd (cm/s)		
Trimetazidine	7.9 ± 3.0 ^b	8.7 ± 2.8 ^{ab}
Placebo	7.1 ± 3.3	7.5 ± 3.3 ^c
Mean RV Va (cm/s)		
Trimetazidine	10.6 ± 4.3	12.7 ± 4.5 ^{ab}
Placebo	10.6 ± 4.7	10.9 ± 4.6
Mean RV Vs (cm/s)		
Trimetazidine	9.3 ± 3.7 ^b	10.7 ± 3.6 ^{ab}
Placebo	7.7 ± 2.3	8.1 ± 2.3 ^c

Em, Am, and Sm, early and late diastolic and systolic velocities of lateral mitral annulus; LV, left ventricle; Et, At, and St, early and late diastolic, and systolic velocities of lateral tricuspid annulus; Vd, Va, and Vs, early and late diastolic, and systolic myocardial velocities

^aSignificant vs baseline ($P < 0.01$); ^bsignificant vs placebo ($P < 0.05$); ^csignificant vs baseline ($P < 0.05$)

($P < 0.001$). Also, patients having both diabetes and ischemic HF tended to have greater improvement in LVEF compared to ischemic HF patients without diabetes ($P = 0.063$).

Discussion

In this prospective study we showed that trimetazidine added to optimal heart failure treatment has improved functional status and left and right ventricular functions based on tissue Doppler velocities in patients with heart failure of both ischemic and nonischemic origin. Despite recent advances, chronic heart failure is a difficult condition to manage in clinical practice. Trimetazidine, a specific partial inhibitor of fatty acid oxidation, has been reported to exert anti-ischemic properties without affecting myocardial oxygen consumption and blood supply.²⁰ The potential beneficial effect of trimetazidine in LV dysfunction was first described by Brottier et al.⁵ They reported improved LV function in patients with severe ischemic cardiomyopathy after 6 months' treatment with trimetazidine.⁵ Further studies subsequently validated these findings.⁶⁻⁹ Although different results have been reported, chronic administration of trimetazidine in addition to conventional therapy, in overall terms, has improved functional class and LV functions of heart failure patients.²⁰⁻²⁴ Accordingly, we found significant improvements in functional class and LV function of optimally treated heart failure patients after addition of trimetazidine. Although to a lesser extent, we have also observed significant improvement in LVEF with placebo. This finding may be incidental or may be related with better follow-up and adherence to medical treatment.

Tissue Doppler imaging is an echocardiographic method that allows quantitative assessment of regional myocardial tissue velocities directly from the myocardium.¹⁴ This method offers the advantage of qualitative assessment of both systolic and diastolic regional ventricular function. We have observed that addition of trimetazidine to optimal heart failure treatment resulted in improvement of NYHA class and LV functions. Although our study is a short-term

Table 4. Comparison of changes in mean left ventricular ejection fraction and myocardial velocities between patients treated with trimetazidine and placebo

	Trimetazidine group (n = 51)	Placebo group (n = 36)	P value
LVEF	9.1 ± 4.2	2.5 ± 1.4	<0.001
Mean LV Vd (cm/s)	1.4 ± 0.8	0.3 ± 0.3	<0.001
Mean LV Va (cm/s)	1.1 ± 0.8	0.3 ± 0.3	<0.001
Mean LV Vs (cm/s)	1.1 ± 0.6	0.3 ± 0.3	<0.001
Mean RV Vd (cm/s)	0.7 ± 1.6	0.4 ± 0.3	0.035
Mean RV Va (cm/s)	2.0 ± 2.3	0.3 ± 0.3	<0.001
Mean RV Vs (cm/s)	1.4 ± 1.3	0.4 ± 0.3	<0.001

LVEF, left ventricular ejection fraction; LV, left ventricle; RV, right ventricle; Vd, Va, and Vs, early and late diastolic, and systolic myocardial velocities

study, the finding of improved myocardial velocities may reflect early positive remodeling and will be possibly responsible for the chronic benefits to clinical status.

Beneficial effects of trimetazidine were reported in patients with both ischemic and nonischemic heart failure.²¹ According to our results, it seems that trimetazidine was effective in treating patients with heart failure of both ischemic and nonischemic origin. However, we found a better response to trimetazidine in diabetic patients. Approximately 60%–90% of adenosine triphosphate (ATP), the most essential myocardial energy source, is produced by beta-oxidation of FFA while the glucose metabolism produces 10%–40%.²⁵ Glucose oxidation is less energy demanding, using fewer oxygen molecules per produced ATP molecule, which is important during myocardial ischemia.²⁶ Glucose utilization is hampered in the diabetic patient, particularly during periods of stress, during which energy production is shifted almost exclusively toward beta-oxidation.²⁷ Thus the myocardial metabolism is likely to be unfavorable in heart failure patients with diabetes. Due to decrease in insulin sensitivity and elevation of FFA metabolism in diabetes, pharmacologic agents that inhibit fatty acid oxidation may be especially useful in diabetic patients.¹ Kantor et al. showed that trimetazidine has a very modest inhibitory effect on the rate of fatty acid oxidation in the rat heart (~15%), but causes a doubling in the rate of glucose oxidation.³ Beneficial effects of trimetazidine in diabetic patients with ischemic left ventricular dysfunction were also observed in clinical studies.^{10,11}

We observed that trimetazidine was associated with a significant decrease in E/Em ratio and significant increases in systolic and diastolic velocities of lateral mitral annulus. It has been previously shown that an increased ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus (E/Em) obtained by TDI correlates with LV filling pressure and is a powerful predictor of clinical outcome.^{12,28} Systolic and diastolic velocities of mitral annular TDI have also been shown to correlate with LVEF and exercise capacity.^{13,17}

To our knowledge, there is no other study in the literature that examines the effects of trimetazidine on RV functions. In patients with LV heart failure, RV TDI is a sensitive indicator of RV dysfunction and can help to establish prognosis. Right ventricular velocity of tricuspid annular systolic motion was significantly lower in patients with LV systolic heart failure than in healthy subjects.²⁹ It has been demonstrated that RV TDI systolic velocity was an independent predictor of outcome in patients with LV heart failure.³⁰ The positive effects of trimetazidine on RV TDI parameters found in our study may contribute to functional improvement of heart failure patients.

Limitations

The small number of patients is the major limitation of our study. However, though not conclusive, it is of sufficient importance and interest to identify the need for a large-scale multicenter placebo-controlled trial.

Conclusion

Addition of trimetazidine to standard current treatment of heart failure, especially in diabetics, may improve functional class and left and right ventricular functions.

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