THE EFFECT OF TRIMETAZIDINE TREATMENT ON TISSUE DOPPLER PARAMETERS IN PATIENTS WITH ISCHEMIC DILATED CARDIOMYOPATHY

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ABSTRACT

Introduction: The aim of this study was to evaluate the effects of additional trimetazidine treatment on Tissue Doppler parameters in patients with ischemic dilated cardiomyopathy.

Material and Methods: Forty patients with ischemic DCM (left ventricular ejection fraction (LVEF) <40% left ventricular end diastolic diameter (LVEDD) >55 mm) were studied. Patients were randomized into either conventional therapy plus trimetazidine (n:20 patients, 20 mg three times daily) or conventional therapy alone (n:20 patients). After 6 months of follow-up, Tissue Doppler echocardiographic analyses of the patients were reviewed and compared with the initial data.

Results: There were no significant differences between two groups with respect to sex, height, weight, body surface area, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left atrial and right ventricular diameter. After 6 months of trimetazidine treatment, IVRT and late diastolic myocardial velocities were decreased and E/A ratios increased significantly from all measured territories. Although early diastolic myocardial velocities (E) from septal and inferior walls decreased significantly, anterior and lateral E velocities did not show any statistically significant difference. Systolic myocardial (S) velocities form inferior and lateral walls increased significantly, while septal S velocity showed a significant decrease. Anterior S velocity did not show any statistically significant difference after 6 months of trimetazidine treatment. In contrast, no changes were found in tissue Doppler parameters of control group after six months except for a significant decrease in lateral S velocity.

Conclusions: Trimetazidine is an effective adjunctive treatment in patients with ischemic dilated cardiomyopathy.

INTRODUCTION

Trimetazidine (1-[2,3,4-trimethoxy-benzyl]piperazine dihydrochloride) is an effective and well-tolerated anti ischemic drug that possesses anti-ischemic properties without any hemodynamic effects, acting primarily by optimizing cardiac energy metabolism. It inhibits mitochondrial long chain 3-ketoacyl coenzyme A thiolase which results in decreased fatty acid oxidation and increased glucose utilization in cardiac cells. Transition from fatty acid oxidation renders the heart dependent on the oxidation of glucose for contractile energy. Preferential glucose usage during ischemia results in decreased intracellular concentration of sodium and calcium in cardiac cells which subsequently decreases hydrogen ion concentration leading to protection of cellular membranes.

These metabolic alterations may have positive impact on cardiac efficiency and function. Besides from these effects, trimetazidine also has been shown to exhibit antioxidative properties and has been suggested to decrease the loss of intracellular potassium ions and membrane content of peroxidated lipids during acute and chronic ischemic conditions. It improves endothelium-dependent vasodilatation via a decrease in plasma malondialdehyde and lipid hydroperoxide levels in patients with ischemic cardiomyopathy. Overall, trimetazidine has demonstrated several positive effects in studies of ischemic heart patients, such as improvement in clinical symptoms of angina pectoris, reduced left ventricular end diastolic and end systolic volumes, decreased hospitalization rates and all cause mortality.
Heart failure remains one of the major causes of death worldwide. It is chronic, progressive disease which requires lifelong medical therapy and associated with high mortality and morbidity. Despite the improvements in medical and interventional therapies, 90-day mortality rates are reported as high as 9.8% (11). Ischemic dilated cardiomyopathy (IDCMP) is the leading cause of heart failure, representing 12% of the total deaths, fourth most common cause of disease burden, according to the statistics of the WHO. Conventional medical therapy of the IDCMP includes ACE-inhibitors, beta-blockers, aldosterone antagonists, diuretics. The aim of this study was to determine whether the addition of trimetazidine therapy has any impact on left ventricular systolic function in patients with IDCMP by using tissue Doppler imaging technique.

**MATERIAL AND METHODS**

**Patients:** Forty patients (31 males and 9 females) were enrolled in this study. Forty consecutive patients who were diagnosed as ischemic DCM, using Transthoracic Echocardiography (LVEF <40% and LVEDD >55 mm) were included in the study. Exclusion criteria were advanced heart failure (NYHA III/IV), atrial fibrillation, primary valvular disease, active myocarditis or a history of myocarditis, clinical or echocardiography features consistent with an obstructive, hypertrophic or restrictive cardiomyopathy, pericardial disease, diabetes mellitus, primary hepatic, renal, neurological, pulmonary or endocrine disease. All patients had Cardiac Catheterization. Patients who had noncritical coronary artery disease were classified as ‘idiopathic’ DCM and excluded from the study.

**Baseline evaluation and follow-up:** At the time of entry physical examination, medical history and symptoms of the patients were recorded. Transthoracic echocardiography examination was performed using a commercially available ultrasound system (Acuson Sequoia, 3.5MHz transducer) in the left lateral decubitus position. LVEF was derived from apical four chamber view according to the modified Simpson rule. Left atrial (LA), left ventricular end-diastolic (LVEDD), left ventricular end-systolic (LVESD) and right ventricular dimensions were measured from the M-mode tracings of the Parasternal long axis view. Tissue Doppler echocardiography velocities were obtained by using a commercially available software package (Acuson, DTI package) that utilized 2 mm pulse wave Doppler sample gate. The myocardial velocities were measured from septal, lateral and anterior, inferior walls from the apical four chamber and two chamber views, respectively. For each patient, peak early diastolic (E'), atrial (A'), systolic tissue velocities (S') and isovolumic relaxation time (IVR'T) were measured. The mean values were obtained by averaging at least six consecutive beats. E'/A'<1 and IVR'T>100 msc was accepted as diastolic dysfunction. All patients received acetylsalicylic acid, B-blocker, ACE inhibitor. Patients who have NYHA class III–IV heart failure symptoms received spironolacãone. Patients were randomly assigned to receive 20 mg of trimetazidine three times daily in addition to their current regimen. Twenty patients were included in study group and the rest were included in the control group. After 6 months control echocardiographic measurement was done.

All the data are presented as mean±SD unless otherwise specified. Student’s t test was used to compare the variables that show normal distribution. The paired r test was used to assess the variations of the echocardiographic variables in two groups. ANOVA test was used to assess the differences between changes of the parameters in the groups. A p value <0.05 was considered statistically significant.

**RESULTS**

Forty patients with ischemic DCM were enrolled and randomly assigned in the study (Trimetazidine group, n: 20; Control group, n: 20). The mean age of the study and control groups were 58.73 ± 9.00 and 58.15 ± 12.44 years, respectively. There were no significant differences between two groups with respect to sex, height, weight, body surface area, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial (LA) and right ventricular (RV) diameter. Table 1 describes the clinical and echocardiographic parameters of the study and control groups. Patients were followed up for 6 months.

**Table 1** Clinical and echocardiographic parameters of the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Study Group</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD %</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>58.12 ± 12.44</td>
<td>58.73 ± 9.00</td>
<td>NS</td>
</tr>
<tr>
<td>Female n, (%)</td>
<td>4 (20)</td>
<td>5 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Male n, (%)</td>
<td>16 (80)</td>
<td>15 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.55 ± 9.84</td>
<td>165.77 ± 9.63</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.2 ± 11.09</td>
<td>72.77 ± 16.25</td>
<td>NS</td>
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<tr>
<td>BSA (m²)</td>
<td>1.78 ± 0.17</td>
<td>1.81 ± 0.20</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.67 ± 0.78</td>
<td>7.04 ± 0.78</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>5.63 ± 0.85</td>
<td>5.86 ± 0.85</td>
<td>NS</td>
</tr>
<tr>
<td>LA (cm)</td>
<td>4.53 ± 0.64</td>
<td>4.92 ± 0.72</td>
<td>NS</td>
</tr>
<tr>
<td>RV (cm)</td>
<td>2.84 ± 0.44</td>
<td>2.91 ± 0.51</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>30.5 ± 7.14</td>
<td>30.31 ± 6.7</td>
<td>NS</td>
</tr>
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BSA: Body surface area, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LA: Left atrial diameter, RV: Right ventricular diameter, EF: Ejection fraction

**Table 2** Tissue Doppler values of the two groups on study entry

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
</table>
| IVRT sep (cm)               | IVRT lat (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT ant (ms) | IVRT inf (ms) | IVRT antconst
The initial tissue Doppler findings of the two groups are presented in Table 2. There was no significant difference between two groups with respect to initial tissue Doppler findings at study entry. We compared the initial and final echocardiographic variables of each patient; mitral and lateral annular early diastolic (E'), late diastolic (atrial, A'), systolic tissue velocities (S'), isovolumic relaxation time (IVRT), E'/A' ratio. After 6 months of trimetazidine treatment, IVRT and late diastolic myocardial velocities were decreased and E/A ratios increased significantly from all measured territories. Although early diastolic myocardial velocities from septal and inferior walls decreased significantly, anterior and lateral early diastolic myocardial velocities did not show any statistically significant difference. Systolic myocardial velocities form inferior and lateral walls increased significantly, while septal systolic myocardial velocity showed a significant decrease. Anterior systolic myocardial velocity did not show any statistically significant difference after 6 months of trimetazidine treatment. In contrast, no changes were found in tissue Doppler parameters of control group after six months except for a significant decrease in lateral systolic velocity. Table 3 and 4 show tissue Doppler values of the study and control groups at the study entry and after 6th months, respectively.

DISCUSSION

The result of the present study documented that the adjunct of 6 month-trimetazidine treatment to standard optimal medical therapy improves diastolic and systolic functions of the chronically dysfunctional myocardium. IVRT, late diastolic velocities significantly decreased and E/A ratios significantly increased in all measured myocardial walls. Furthermore, S velocities from inferior and lateral walls showed a significant increase. By contrast after six months patients receiving placebo had almost no change in the Tissue Doppler parameters.

Ischemic DCM is the most common type of dilated cardiomyopathy and characterized by dilated left (and/or right) ventricle with impaired systolic function. Although medical, surgical and nonsurgical device therapies continues to improve, it remains an important cause of mortality and morbidity worldwide13.

Trimetazidine is representative of a group of pharmaceutical compounds which exerts it anti-ischemic effect independent of changes in heart rate or blood pressure. The anti-ischemic effect of trimetazidine is obtained at the cellular level by shifting cardiac energy metabolism from fatty acids to glucose and increasing ATP production. Drug exerts its action by inhibiting the activity of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase which leads to reduction of myocardial ischemia and to an improvement in cardiac efficiency14,15.

The effect of trimetazidine on cardiac functions has been also shown in other studies. A recent metaanalysis revealed that trimetazidine therapy increased total exercise time, NYHA functional class, LVEF and decreased LVESD, LVDD, left ventricular end-systolic volume and serum BNP level15. In another randomized clinical trial has shown that trimetazidine treatment improves NYHA functional class, exercise capacity, quality of life, and left ventricular function in chronic heart failure patients, irrespective of etiology. Trimetazidine produceda significant decrease in BNP levels from baseline to
13 months. It increases the efficiency of oxygen use during ischemic conditions by shifting the metabolism to a more efficient fuel source, glucose, instead of fatty acids. That change improves myocardial oxygen consumption efficiency within the range of 16% to 26% (17). Much evidence now supports the concept that any shift in substrate preference away from fatty acid metabolism to glucose metabolism is an effective therapy to treat heart failure22–25. Patients with chronic heart failure and reduced ejection fraction were randomized to receive either placebo or treatment with trimetazidine. After six months of follow-up, patients treated with trimetazidine had improved their ejection fraction more than 9% and their functional capacity had increased. The cardiovascular changes associated with drug therapy occurred in the absence of obvious hemodynamic changes, and was most likely attributable to improved cardiomyocyte cell metabolism.

In systolic heart failure patients receiving optimal medical treatment, 3 months trimetazidine treatment associated with clinical improvements, increased left ventricular function and paralleled by significant reduction in resting energy expenditure (REE). It is possible that trimetazidine exerts its beneficial cardiac effects via modulation of the peripheral metabolism23. A prospective trial compared the conventional therapy plus trimetazidine with conventional therapy alone in a group of 42 patients with ischemic heart failure and reduced left ventricular ejection fraction (<55%). QTc interval was measured at study entry and after 1 month. Trimetazidine shortened QTc interval in patients with ischemic heart failure. In another study24, patients with chronic heart failure either randomized to trimetazidine three times daily in addition to standard therapy or continued their usual therapy. Sixty-one patients enrolled in the study, were evaluated at baseline and every 6 months thereafter with physical examination, echocardiography, and 6-minute walking test until completion of the study protocol. Trimetazidine added to recommended medical treatment significantly reduced the primary endpoints of all-cause mortality, total number of hospital admissions for heart failure and improved patient functional status. In trimetazidine-treated patients, a significant increase of the left ventricle ejection fraction was also detected. It is therefore concluded that long-term trimetazidine significantly reduces all-cause mortality and heart failure hospitalization in patients with ischemic cardiomyopathy.

Fragasso et al.25 reported that patients with diabetes and ischemic cardiomyopathy, trimetazidine improved left ventricular function, symptoms, glucose metabolism and endothelial function. Rosano et al.25 also showed that in diabetic patients with ischemic heart disease trimetazidine added to standard medical therapy had beneficial effect on left ventricular volumes and on LVEF compared to placebo.

Our study also revealed that 6 month Trimetazidine treatment improved diastolic and systolic functions of the left ventricle and supported the concept that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by trimetazidine is an effective adjunctive treatment in patients with ischemic dilated cardiomyopathy.

References


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