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Trimetazidine improves left ventricular function in diabetic patients with coronary artery disease: a double-blind placebo-controlled study

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Abstract

Background: Patients with diabetic cardiomyopathy have an impaired myocardial glucose handling and distal distribution of coronary atherosclerosis. Trimetazidine, an anti-ischemic metabolic agent, improves myocardial glucose utilization though inhibition of fatty acid oxidation. Aim of the present study was to evaluate whether the metabolic effect of trimetazidine on left ventricular function in patients with diabetic cardiomyopathy.

Methods: 32 patients (24 males and 8 females, mean (SE) age = 67 ± 6 years) with type 2 diabetes and ischemic cardiomyopathy were randomized to receive either trimetazidine (20 mg, t.d.s.) or placebo (t.d.s.) for six months in a randomized parallel study. Patients performed an echocardiogram at baseline and after 6 months.

Results: Demographic data were comparable between the two groups. After six month baseline left ventricular end-diastolic diameters increased from 62.4 ± 1.7 to 63 ± 2.1 mm in the placebo group, while decreased from 63.2 ± 2.1 to 58 ± 1.6 mm ($p < 0.01$ compared to baseline) in the trimetazidine group. Compared to baseline, left ventricular ejection fraction increased by 5.4 ± 0.5% ($p < 0.05$) in the trimetazidine group while remained unchanged in the placebo group -2.4 ± 1.1% (NS), $p < 0.01$ between groups. A significant improvement in wall motion score index and in the E/A wave ratio was detected in patients treated with trimetazidine, but not in those receiving placebo.

Conclusion: in diabetic patients with ischemic heart disease trimetazidine added to standard medical therapy has beneficial effect on left ventricular volumes and on left ventricular ejection fraction compared to placebo. This effect may be related to the effect of trimetazidine upon cardiac glucose utilization.

Introduction

Diabetes mellitus is an important risk for future cardiovascular events in patients with and without ischaemic heart disease. Indeed, diabetic patients without overt coronary artery disease have a similar prognosis than non-diabetic patients with coronary disease and diabetic patients with

coronary disease have a cardiovascular death rate double than that of non-diabetic patients, this influence being independent of age, sex, hypertension and cholesterol levels [1]. The reduced survival of diabetic patients with angina is the result of accelerated atherogenesis with involvement of peripheral segments of major coronary arteries and peripheral branches and of changes in myocardial glucose utilization [2,3]. The involvement of distal coronary artery branches, in patients with diabetes, reduces regional coronary perfusion and causes diffuse hibernation of myocardium that together with the abnormal glucose utilization decreases left ventricular function.

The anti-ischemic medical therapy of coronary diabetic patients does not differ from that of non diabetic patients. Until recently, the antianginal drugs available to control symptoms and myocardial ischemia have all been haemodynamic agents that eliminate or reduce angina attacks principally by decreasing myocardial oxygen demand and by improving, in some instances, myocardial perfusion [4]. The haemodynamic agents are often used in combination. However, there is conflicting evidence for the efficacy of combination treatment [5,6]. Metabolic agents represent a new therapeutic approach that directly modify the use of energy substrates in the heart, lessening ischaemic injury and improving cardiac performance during ischaemia [7]. Due to their purely metabolic mode of action, free from any haemodynamic effect, anti-ischemic agents such as trimetazidine provide independent benefit in ischaemia when used as monotherapy and additional benefit when used in combination with a conventional agent. Clinical trials have shown that combined haemodynamic and metabolic treatment is more effective than combined haemodynamic therapy on the control of myocardial ischemia and is well tolerated [8-10].

There is a large body of evidence to suggest that the metabolic agent trimetazidine is an effective anti-ischemic agent in patients with chronic stable angina [4,7,11,12]. However, until recently it was not clear whether trimetazidine can improve the mechanical efficiency of chronically dysfunctional myocardium, and whether this potentially beneficial effect could translate into improvements in left ventricular function as well as functional capacity. Because of its metabolic point of action and its beneficial effect on glucose utilization trimetazidine may exert a protective effect on the dysfunctional myocardium of diabetic patients with coronary artery disease. This effect may then translate into an improvement of myocardial contractility of hybernated area.

Aim of the present study was to evaluate the effect of a 6 month therapy with trimetazidine on left ventricular function of diabetic patients with coronary artery disease and reduced left ventricular function.

Methods

Study population

The study population included 51 patients with type 2 diabetes, chronic stable angina on optimal medical therapy and with the following characteristics: proven coronary artery disease by either coronary angiography or previous myocardial infarction or hospitalisation for unstable angina; good acoustic window; left ventricular function <50%; written informed consent. Type 2 diabetes was defined according to the American Diabetes Association guidelines [13].

Patients with clinically significant findings on physical examination or presence of known clinically significant disease that would interfere with study evaluation, uncontrolled diabetes mellitus (HbA1c > 9%), recent (<3 months) unstable angina and/or acute myocardial infarction, arrhythmia (Lown IV); cardiac surgery, percutaneous coronary interventions, stroke or transient ischemic attack in the previous 6 months, presence of cardiac conduction abnormalities that would prejudice the evaluation of regional left ventricular function as those with inadequately controlled arterial hypertension (blood pressure > 160/95 mmHg), uncorrected hypokalemia; primary valvular, congenital heart disease, myocardial, pericardial or endocardial disease; kidney or liver dysfunction were excluded from the study. Patients with history of intolerance or allergic response to study drug and those unable to comply with the protocol or refusing the examination related to end-point and those scheduled to undergo myocardial revascularization procedures were also excluded.

During the study period patients therapies routinely used for the treatment of myocardial ischemia (e.g. acetylsalicylic acid, anti-platelet drugs, anticoagulants, hypolipidaemic agents, anti-anginal therapy) and heart failure were continued.

Study design

The study design was double blinded, randomized, parallel, placebo controlled. After a baseline evaluation of all inclusion and exclusion criteria, patients entered a run in phase up to six weeks, at the end of which patients underwent a baseline echocardiogram and were then randomised to receive either trimetazidine (20 mg t.d.s.) or matching placebo (t.d.s.) for 6 months. The trans-thoracic echocardiogram was repeated at the end of the treatment period. Patients received a diary card to report the occurrence of episodes of chest pain and use of tri-nitroglycerin tablets.

Study of left ventricular function

All patients underwent trans thoracic echocardiogram following the guidelines of the American Society of

Table 1: Baseline Clinical Characteristics of Study Patients

	All Patients	Trimetazidine	Placebo
Mean age (years)	65.4 ± 6.3	65.6 ± 5.7	65.2 ± 7
Male	24	11	13
Female	8	5	3
BMI	25.4 ± 3.2	25.7 ± 3.3	25.2 ± 3.3
Baseline glucose	164.6 ± 26.2	166.9 ± 21.9	162.2 ± 30.4
Triglycerides at baseline	238.1 ± 59.5	231.3 ± 43.7	244.9 ± 72.9
Triglycerides at randomisation	185.7 ± 46.4	180.5 ± 34	191 ± 57
Cholesterol at baseline	264.5 ± 27.8	263.3 ± 29.3	265.2 ± 27.2
Cholesterol at randomisation	198.3 ± 20.8	197.8 ± 21.9	198.8 ± 20.4
HBA1c	7.6 ± 0.8	7.7 ± 1	7.5 ± 0.6
Prior MI	18	9	9
Prior CABG	7	4	3
Prior PTCA	12	6	8
Carotid Atherosclerosis	12	7	5
Coronary atherosclerosis			
1 vessel disease	1	0	1
2 vessel disease	14	6	8
3 vessel disease	16	9	7
any vessel + graft	1	1	0
distal disease	23	12	11
USE OF DRUGS AT RANDOMISATION			
Aspirin/ticlopidine	18	12	14
Clopidogrel	6	6	4
Anticoagulants	6	5	6
Digitalis	28	13	15
Diuretics	31	16	15
Nitrates	18	8	10
B-blockers	23	11	12
Ca-antagonists	14	9	6
ACE-I	29	14	15
ARB	4	2	2
Statins	30	14	16
Oral hypoglycaemics	25	12	13
Insulin	7	4	3

Clinical features of study patients. Clinical characteristics, incidence of previous myocardial infarction or revascularization procedures in patients randomized to trimetazidine or placebo. No significant differences were detected between groups. BMI = body mass index, MI = myocardial infarction, CABG = coronary artery by-pass grafting, PC I = percutaneous coronary interventions.

Echocardiography, using the parasternal and the apical views to calculate dimensions and evaluate global and regional left ventricular function [14].

Image analysis

All echocardiograms were performed using an Acuson Sequoia 512 echocardiograph (Acuson Corporation, Mountain View, Ca, USA) and stored on videotape or onto electronic files. The echocardiograms were analysed by two experienced investigators blinded on clinical data. In case of discrepancy, a third investigator analysed the examination.

End-diastole was defined as the frame coinciding with the peak R wave of the QRS complex on the ECG. End-systole was defined as the frame at the end of the T wave. Left ventricular end diastolic and end systolic diameters were obtained from the parasternal long axis view. A biplane algorithm was used to calculate left ventricular volumes. Left ventricular end-diastolic volume and end-systolic volumes were obtained from the apical four- and two-chamber views using a modified Simpson's rule, from which ejection fraction was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume.

Regional left ventricular function was evaluated according to the guidelines of the American Echocardiographic Society using a 16-segment model. Each segment of interest was visually graded using a semiquantitative scoring system, where 1 = normal, 2 = hypokinetic, 3 = akinetic and 4 = dyskinetic. A global wall motion score index (WMSI)

Table 2: Baseline Echocardiographic Parameters

	Trimetazidine	Placebo
LA (mm)	52.6 ± 2.1	51.9 ± 1.7
LVEDD (mm)	63.2 ± 2.1	62.4 ± 1.7
LVESD (mm)	41.1 ± 1.5	39.5 ± 1.3
LVEF (%)	32.3 ± 5.3	32.8 ± 2.3
LV Wall Motion Index Score	1.37 ± 0.2	1.38 ± 0.3
E/A	0.68 ± 0.1	0.64 ± 0.12

Baseline echocardiographic parameters in patients randomized to trimetazidine or placebo. No significant differences in echocardiographic and Doppler measures were found between the two groups at baseline.

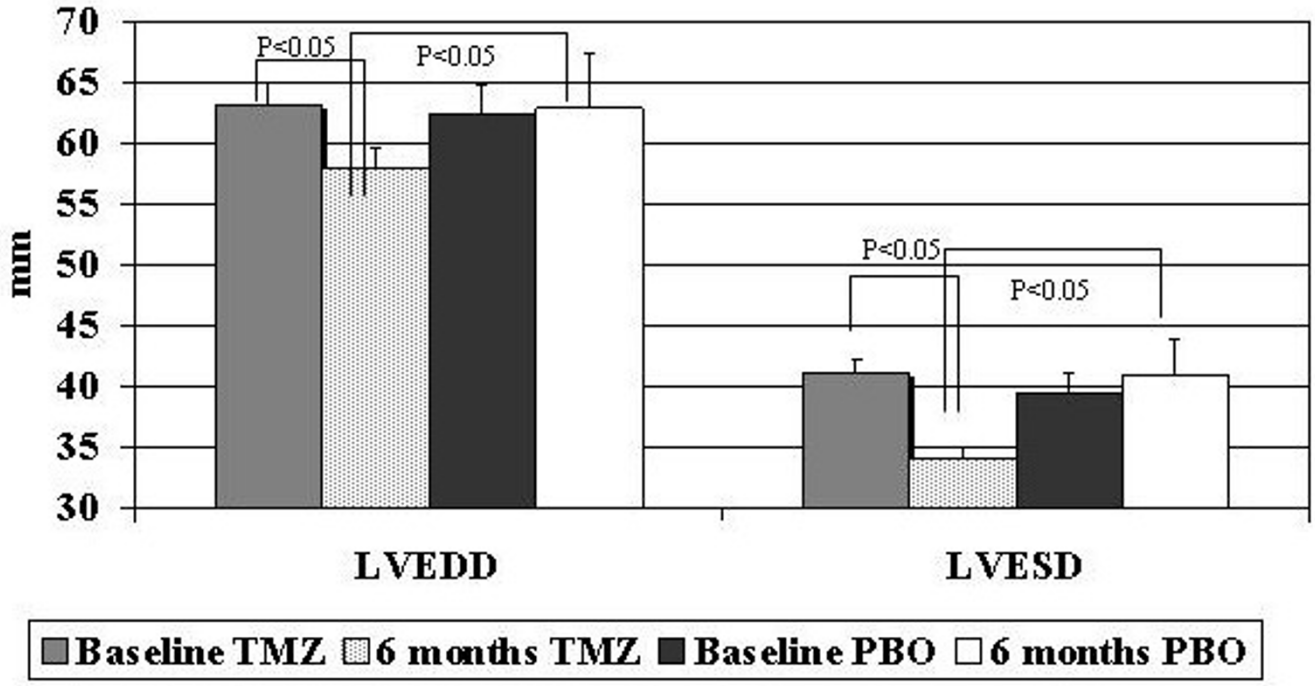

Figure 1
Effect of six month therapy with trimetazidine or placebo on top of usual medical care in patients with type 2 diabetes. Trimetazidine significantly reduced left ventricular end diastolic (LVEDD) and end systolic (LVESD) diameters compared to both baseline examination and placebo. TMZ = Trimetazidine, PBO = Placebo

was then calculated as the sum of the scores for each segment.

Statistical analysis

Values are given as mean ± 1 SD or as percentages where appropriate. Differences in mean values between groups were assessed using either the two tailed Student's t-test for paired samples (parametric variables) or Wilcoxon signed rank test (for non parametric variables). The effects of treatment on echocardiographic parameters relative to respective pretreatment values withing groups were analyzed using the analysis of covariance for repeated measurements using baseline values as costant covariates. All calculated p value are 2-tailed and considered as significant when <0.05.

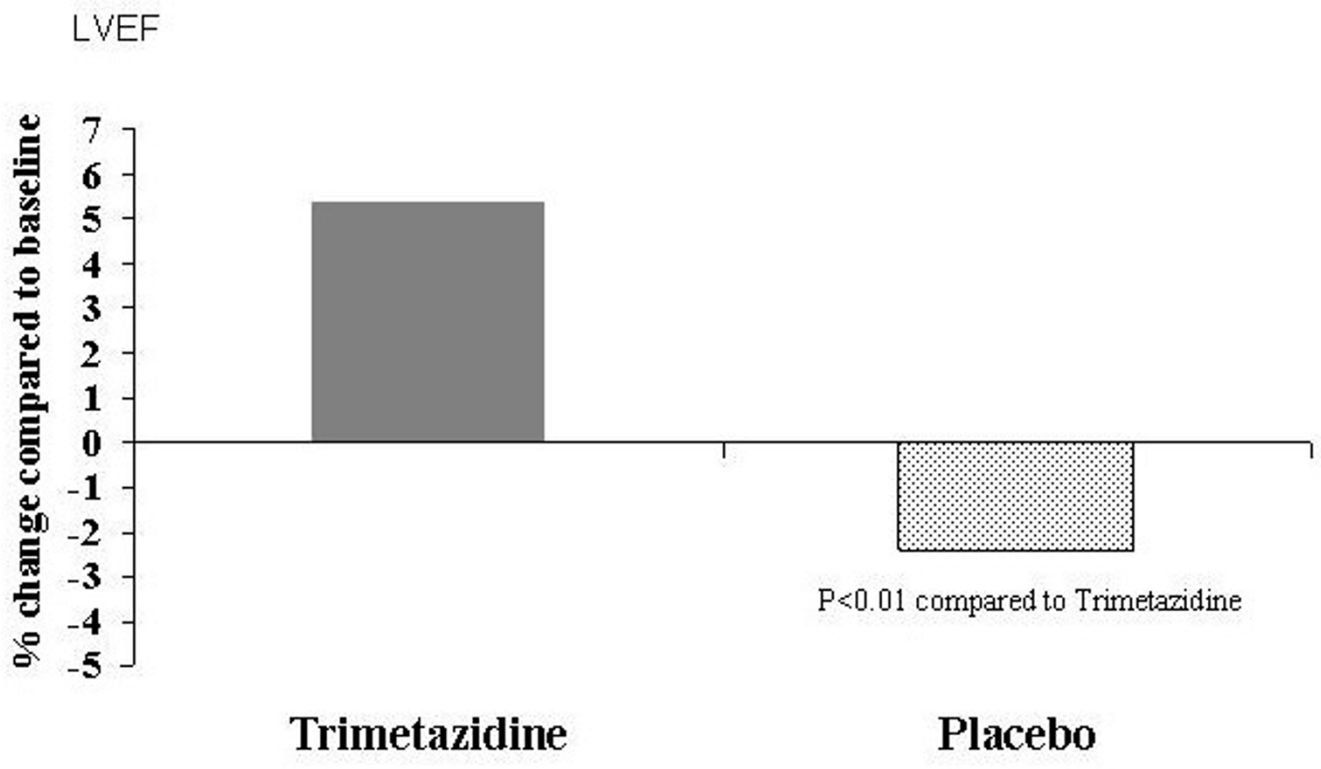

Figure 2
Effect of six month therapy with trimetazidine or placebo on left ventricular ejection fraction (LVEF). A significant improvement in LVEF was detected in patients receiving trimetazidine while a decrease of LVEF was noted in patients allocated to standard care and placebo

Results

From a total of 51 patients with diabetes mellitus and coronary artery disease 32 (24 men, 8 women, mean age 65.4 ± 6.3 years) met the inclusion criteria and entered the study. Eleven patients were excluded because scheduled to undergo either percutaneous or surgical myocardial revascularization procedures, three because of uncontrolled diabetes mellitus and five because unable or unwilling to attend the follow up examination. Patients randomised to trimetazidine or placebo had similar clinical and angiographic characteristics (table 1), 18 patients have had an acute myocardial infarction in the past, 7 have undergone coronary artery surgery and 12 have undergone percutaneous coronary intervention. The majority of patients had multivessel coronary atherosclerosis often with involvement of peripheral branches. Ten patients were taking statins at baseline examination, in 4 of them it was needed either to adjust the dose of statins or change statin therapy, the remainder 22 patients were started on statin therapy. Use of cardiovascular drugs at randomisation was similar in patients randomized to either treatment. Baseline echocardiographic characteristics were also similar in the two groups (Table 2). Blood pressure and heart rate remained unchanged with trimetazidine and placebo (SBP 2 ± 3 vs 4 ± 5 mmHg, DBP -1 ± 4 vs 3 ± 42 mmHg, HR -2 ± 7 vs 4 ± 9 bpm, trimetazidine vs placebo respectively). One patient in the placebo group did not perform follow up examination because he was hospitalised for an acute ischemic syndrome and was therefore excluded from the analysis.

After six months, compared to patients treated with placebo, diabetic patients treated with trimetazidine showed a significant reduction of left ventricular diastolic and systolic diameters (63.2 ± 2.1 to 58 ± 1.6 mm -8% vs 62.4 ± 1.7 to 63 ± 2.1 mm 1, 6%, $p < 0.05$; 41.1 ± 1.5 to 34 ± 1 mm vs 39.5 ± 1.3 to 41 ± 0.9 mm, $p < 0.05$ respectively, table 2, figure 1), while no significant changes compared to pre-treatment values were detected in the placebo group. A significant decrease in left ventricular end-diastolic volume index (-3.7 ± 1.9 ml/m^2, $p < 0.04$ compared to baseline and placebo) and end-systolic volume index (-2.2 ± 1.1 ml/m2, $p < 0.04$ compared to placebo and baseline) was noted in patients treated with trimetazidine,

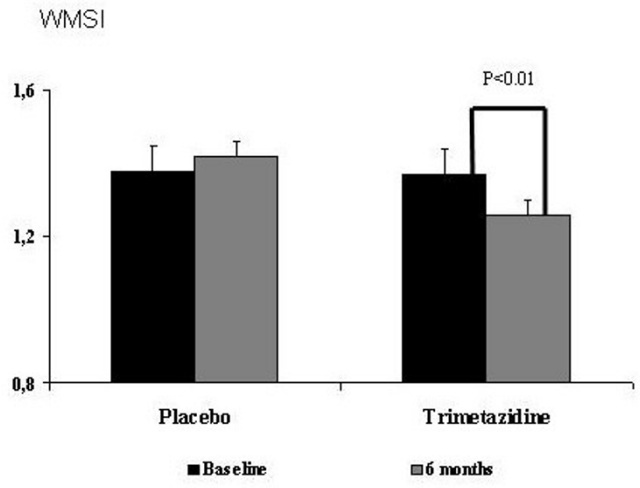

Figure 3
Effect of six month therapy with trimetazidine or placebo on wall motion score index (WMSI). A significant improvement in WMSI was detected in patients receiving trimetazidine while no change was noted in patients allocated to standard care and placebo

while an increase in left ventricular end-diastolic volume index (1.9 ± 1.1 ml/m^2) and end systolic volume (0.48 ± 0.4 ml/m^2) was found in the placebo group. Patients treated with trimetazidine showed an improvement in left ventricular ejection fraction (5.4 ± 0.5%), while a decrease (-2.4 ± 1.1%) was noted in patients treated with placebo (Figure 2). The wall motion score index significantly decreased in patients treated with trimetazidine (from 1.37 ± 0.2 to 1.26 ± 0.16, $p < 0.01$) while it remained unchanged in patients treated with placebo (from 1.38 ± 0.3 to 1.42 ± 0.21, Figure 3). Left ventricular diastolic function evaluated trough E/A on mitral flow significantly improved in patients treated with trimetazidine (from 0.68 ± 0.1 to 0.89 ± 0.3, while it remained unchanged in patients treated with placebo (Figure 4).

Discussion

The present study shows that the adjunct of trimetazidine to standard anti-anginal therapy improves left ventricular systolic and diastolic function of chronically dysfunctional myocardium in patients with type 2 diabetes, coronary artery disease and depressed left ventricular function suggesting that the adjunct of targeted cardiac metabolic therapy to usual care improves areas of hybernated myocardium.

Trimetazidine is representative of a new group of metabolic agents with a myocardial anti-ischaemic effect achieved independently of changes in the oxygen supply-to-demand-ratio [4]. Unlike other classical antiischaemic drugs, trimetazidine neither reduces oxygen consumption nor increases oxygen supply and, as a consequence, no significant changes in heart rate or blood pressure have been observed in this as in other studies with such a drug [4,11]. The anti-ischemic effect of trimetazidine is obtained at a cellular level by shifting the energy substrate preference from fatty acid oxidation to glucose oxidation, secondary to selective inhibition of 3-ketoacylCoA thiolase (3-KAT) [15]. Since more ATP is produced per oxygen consumed when glycogen is a substrate, compared with fatty acids, less oxygen is required for a given amount of work [16]. In experimental in vitro studies, trimetazidine has been shown to have a cardioprotective effect during myocardial ischaemia because of a more rapid restoration of phosphorylation processes, protection of cardiac cells against the accumulation of hydrogen ions, and prevention of the intracellular accumulation of sodium and calcium ions [16,18]. Because of the preferential promotion of glucose and pyruvate oxidation, trimetazidine improves the activity of the sodium-potassium ATPase and the calcium uptake pump of the sarcoplasmic reticulum, that are respectively responsible of left ventricular systolic depolarisation and diastolic relaxation. In the present study the improvement of left ventricular function was paralleled by a similar improvement of left ventricular diastolic compliance assessed by trans-mitral flow velocities, suggesting that the experimental evidence of an improvement of sarcoplasmic Ca pump does translate into an effect on diastolic function. The results of this study are in agreement with those of Belardinelli et al [17] and of Lu et al [12] that have shown an improvement of left ventricular function in patients with ischemic cardiomyopathy but neither of the two studies evaluated the effect of trimetazidine on left ventricular function of diabetic coronary patients.

Because of the peculiarity of the anatomic and metabolic characteristics of ischemic diabetic cardiomyopathy a pure haemodynamic therapy may prove to be successful in controlling symptoms, that often is not a major issue in these patients, but may be unsuccessful in avoiding the decline of left ventricular function because of diabetic cardiomyopathy. In the present study patients randomized to placebo, and receiving usual care, showed a trend towards a decline of left ventricular performance while the opposite was observed in those patients receiving trimetazidine on top of usual care. In all patients usual care included maximal anti-anginal therapy plus control of glycaemic status and aggressive lipid lowering therapy.

Traditional drugs for chronic stable angina act by reducing the use of ATP through suppression of heart rate and blood pressure or by increasing aerobic formation of ATP by increasing coronary blood flow. Partial inhibition of

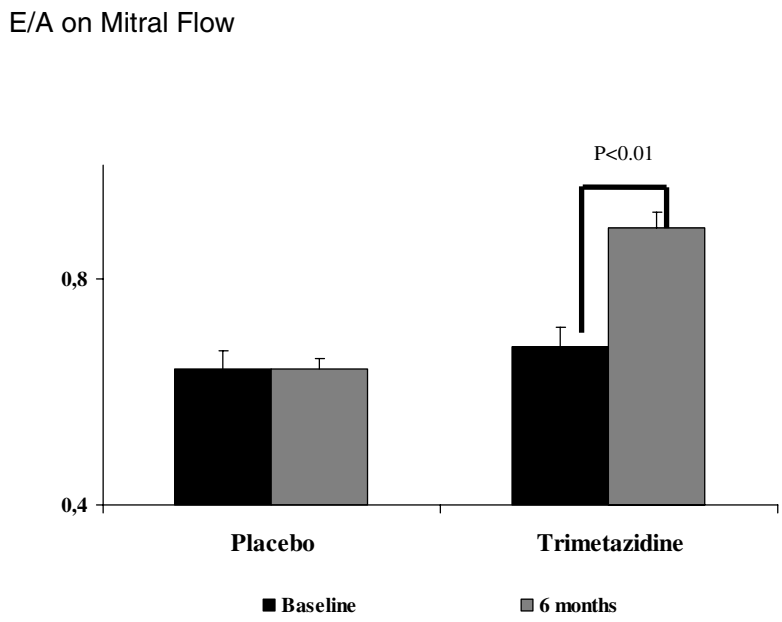

Figure 4
Effect of six month therapy with trimetazidine or placebo on left ventricular diastolic function evaluated by the E/A wave ratio on mitral Doppler flow. A significant improvement in diastolic function was noted in patients receiving trimetazidine while no change was noted in patients allocated to standard care and placebo

fatty acid oxidation increases glucose and pyruvate oxidation and decreases lactate production, resulting in higher pH and improved contractile function during ischaemia. The metabolic and functional effects of metabolic agents is of particular relevance in patients with diabetes mellitus in whom glucose metabolism is impaired and myocardial metabolism is shifted towards a preferential utilization of fatty acids. Diabetic alterations of myocardial metabolism result mainly from malfunctions of acetyl-CoA-carboxylase, carnitine-palmitoyl-transferase-1 and Pyruvate-dehydrogenase inducing an overshot of fatty acid oxidation that inhibits glucose oxidation [18]. As a consequence of these metabolic derangements, in patients with diabetic cardiomyopathy, aerobic glycolysis is more promptly shifted to anaerobic glycolysis under ischemia with a consequent reduced production of energy substrates and accumulation of lactate and acid metabolites that in turn induce reduction of myocardial efficiency. By inhibiting fatty acid oxidation, trimetazidine, improves myocardial glucose utilization both at rest and during ischemia. Therefore, the metabolic effect of trimetazidine translates into a reduced total ischemic burden and into a greater mechanical efficiency of hybernated myocardium thereby improving left ventricular function [19-21]. The anti-ischemic effect of trimetazidine has been proven by the TRIMPOL-1 study group in diabetic patients receiving background anti-ischemic treatment [22]. In the TRIMPOL-1 study it has been shown that, trimetazidine exerts its anti-ischemic effect without influencing either blood pressure or heart rate. The present study is in agreement with previous observations suggesting that does not affect haemodynamic parameters. This study is novel in that no previous observation has suggested a beneficial effect of trimetazidine on left ventricular function that is an important determinant of long term survival in patients with ischemic heart disease.

In conclusion, adjunctive therapy with trimetazidine to standard treatment of diabetic patients with ischemic cardiomyopathy improves systolic and diastolic function suggesting that metabolic therapy may be particularly useful in these patients. Further studies will be necessary to

evaluate whether this effect on left ventricular function translates into a chemical relevant effect on long term survival

List of abbreviations

ACE: angiotensin converting enzyme

ARB: angiotensin receptor blocker

BMI: body mass index

DBP: diastolic blood pressure

CABG: coronary artery by-pass grafting

HbA1c: glycated haemoglobin

HR: heart rate

GTN: tri-nitroglycerin

LA: Left atrial

LV: left ventricular

LVEDD: left ventricular end diastolic diameters

LVESD: left ventricular end systolic diameters

LVEF: left ventricular ejection fraction

MI: myocardial infarction

NS: not significant

PC I: percutaneous coronary interventions

PBO: Placebo

SBP: systolic blood pressure

t.d.s.: three times a day

TIA: transient ischemic attack

WMSI: global wall motion score index

TMZ: Trimetazidine

Competing interests

None declared.

Authors' contributions

All authors were involved in the conceptual design of the study, in the evaluation of the results and in the preparation of the manuscript. B. S., C.V., M.F. and G. R. were involved in performing the clinical trial in all its components.

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