Int J Diabetes & Metabolism (2005) 13: 88-92

Post-necrotic left ventricular dysfunction in Diabetes Mellitus: Effects of trimetazidine

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Abstract

The Index of Myocardial Performance (IMP) in 149 non-diabetic (group I) and 151 diabetic (group II) subjects who were treated for acute myocardial infarction was evaluated using two-dimensional Doppler echocardiography. Isovolumetric Contraction Time (ICT), Isovolumetric Relaxation Time (IRT) and Ejection Time (ET) were also measured. All patients in both groups received conventional, anti-ischaemic therapy (nitrates, ACE-inhibitors, and antiplatelet drug). In addition, 74 patients in group II (subgroup IIa) received an oral dose of 20 mg of trimetazidine, three times daily. The remaining 77 diabetics in group II were treated with conventional drugs alone (subgroup IIb). All diabetic patients (group II) also received an anti-diabetic (oral drug or insulin) treatment to keep their diabetes under control. Twelve months after the experiment, IMP was significantly ($p<0.001$) higher in diabetic patients (0.55±0.05) compared to non-diabetic controls (0.49±0.04). IRT was similar in both groups (81±15 ms vs 83±12 ms) and ET (275±27 ms vs 295±29 ms) was decreased in diabetics compared to the control group. The one-year follow-up showed a significant decrease in IMP in patients treated with trimetazidine (subgroup IIa) compared to those treated with conventional drugs (subgroup IIb alone). IRT values were lower in sub-group IIa compared to that of subgroup IIb. ICT returned towards the normal limits in both subgroups. Finally, ET decreased in subgroup IIa but increased in subgroup IIb compared to values obtained at the onset of treatment. In conclusion, trimetazidine when added to the conventional, anti-ischaemic therapy, seems to induce a more evident attenuation of post-AMI left ventricular dysfunction compared to those not given the drug.

Key words: *AMI, coronary heart disease, diabetes, echography, haemodynamics, trimetazidine,*

Introduction

Diabetes Mellitus (DM) is an independent risk factor for coronary artery disease (CAD).[1,2] Some findings indicate that CAD is more severe in diabetics than in the general population.[3,4] In DM, CAD is associated with abnormal coagulation resulting in the dysfunction of the coagulation processes, including increased platelet activation and aggregation, fibrinogen concentration, and circulating von Willebrand factor. In addition, DM induces alterations in myocardial fatty acid and in glucose metabolism. These factors increase the post-necrotic left ventricular dysfunction.[5] With respect to the metabolic derangement, Lopaschuk et al[6] have described the relationship between impaired myocardial carbohydrate/lipid metabolism and mechanical function during and after ischaemia in normal and diabetic heart. On the other hand, it is known that almost all patients with acute myocardial infarction (AMI) have impaired left ventricular function often evolving into heart failure.[7,8] Jaffe et al[9] reported an increased incidence in congestive heart failure after myocardial infarction of modest extent in diabetics compared to non-diabetic patients.

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Some drugs act on cardiac metabolism in both normal and diabetic subjects.[10] Trimetazidine is the first known metabolically active agent, acting at mitochondrial levels, that improves cardiac energy production by a metabolic switch, via inhibition of fatty acids oxidation towards activation of glucose oxidation, which protects the ischaemic heart.[11-13] TRIMPOL (TRIMetazidine in POLand) studies,[14,15] showed a decrease in the mean number of angina attacks, an improvement in exercise tolerance and a reduction in nitrate consumption during treatment with trimetazidine in combination with conventional drugs, for diabetics with CAD. Ranolazine is a similar drug used in the treatment of patients with severe chronic angina.[16] Contrary to the haemodynamic drugs, these substances act directly on heart metabolism and are the most promising therapeutic agents for the treatment of angina pectoris without coronary obstruction.[17,18]

Impaired ventricular function can be evaluated by Doppler echocardiography to calculate the Index of Myocardial Performance (IMP). This method was first employed by Tei et al. [19-21] The aim of this study was to compare the degree of left ventricular dysfunction in diabetics with AMI to non diabetic controls. The effects of trimetazidine when added to the conventional anti-ischaemic and antidiabetic drugs on

IMP and other time intervals of the cardiac cycle were also evaluated.

Subjects and Methods

One hundred and forty nine non-diabetic patients (98 M and 51 F) aged between 48 and 72 years with their first episode of AMI, but without signs of previous cardiovascular and/or respiratory diseases were enrolled (group I). One hundred and fifty one diabetics (102 M and 49 F), with ages ranged from 49 to 73 years with recent, first AMI and without other cardiac disease were included in the study (group II). For admission to study, both non-diabetic controls and diabetic patients needed to satisfy the following criteria: typical acute chest pain; acute ischaemic changes of ST-T tract in at least two continuous electrocardiographic leads; transient rise of troponine or creatinine-kinase that is significant for myocardial necrosis. Exclusion criteria were: atrial fibrillation; sinus tachycardia >100 beats/min; arterial pressure >130/80 mmHg and valvular diseases.

At hospital discharge, both controls and diabetics received an anti-thrombotic drug (Aspirin-100 mg or Clopidogrel-75 mg), an ACE-inhibitor (Lisinopril-5 mg), a nitroderivative drug and an oral hypoglycaemic agent or insulin-therapy if diabetic. The time-interval between AMI and the enrolment in the study was 10±3 days. All patients in the two groups underwent Doppler two-dimensional echocardiography, using a commercially available ultrasound machine (ATL 5000, HDI). LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were estimated from standard apical 4-chamber views. Ejection Fraction (EF) was measured according to Simpson's biplane disk method.[22] WMSI was calculated using criteria from the American Society of Echocardiography.[22] Three to five consecutive beats were measured and averaged. IMP was obtained from the inflow tract and outflow tract of left ventricle. The distance between the cessation of mitral flow to the onset of following mitral flow is the sum of Isovolumetric Contraction Time (ICT), Isovolumetric Relaxation Time (IRT) and Ejection Time (ET) and was defined as *a*. The distance between the onset and the end of aortic flow is ET and was defined as *b*. IMP was obtained according to the following formula:

$$\frac{a - b}{b}$$

ICT and IRT were also separately measured. After the baseline echocardiographic studies, group II patients were randomly assigned to trimetazidine therapy (subgroup IIa) or placebo (subgroup IIb) groups. The randomization criteria were: the clinical status, the ECG-AMI-extension, EF, WMSI, age, sex blood glucose-levels. The same Doppler evaluations were also performed in two subgroups of diabetics after 12 months. All of the echocardiographic examinations were repeated by the same sonographers, without the knowledge of subgroup assignment.

Statistical analysis

The means ± SD of IMP, ICT, IRT, and ET were calculated after AMI**,** in both the control group (group I) and diabetics (group II). These were compared using the Student-*t*-test for unpaired data. A p value < 0.05 was considered significant. The same evaluations were performed twelve months later in subgroups Ia and IIb patients.

Results

Haemodynamic and metabolic characteristics of non-diabetic controls (group I) and of all diabetic patients (group II) are reported in Table 1. The mean ± SD of the Doppler parameters recorded immediately after AMI in the two groups are shown in Table 2. IMP was significantly ($p<0.001$) higher in diabetic patients (0.55 ± 0.05) compared to non-diabetic controls (0.49 ± 0.04). This outcome appears to be dependent on the slight rise of ICT (71±11ms vs 62± 13 ms). IRT was similar in both groups (81±15 ms vs 83± 12 ms) and ET (275±27 ms vs 295 ± 29 ms) decreased in diabetics compared to that of the control group. The main metabolic and haemodynamic findings in the two subgroups of diabetic patients are depicted in Table 3. Patients in subgroup IIa included 74 patients (2 underwent CABG, other 3 underwent PTCA) while subgroup IIb comprised 77 diabetics (two underwent CABG; one had PTCA and 3 withdrew from the study).

The mean ± SD of IMP and other time points of the cardiac cycle recorded in the two subgroups of diabetic patients after one year are illustrated in Table 4. In diabetics receiving trimetazidine with conventional anti-ischaemic and anti-diabetic therapy (subgroup IIa), IMP was significantly lower ($p<0.001$) than in those treated with anti-ischaemic and antidiabetic drugs alone (0.44 ± 0.08 vs. 0.53 ± 0.07). ICT was similar in the two subgroups (45 ± 12 ms vs. 46 ± 11ms). In contrast, IRT was significantly increased ($p<0.05$) in subgroup IIb (111 ± 13 ms) compared to subgroup IIa (97±14ms). Moreover, ET was slightly reduced in subgroup IIb (280 ± 15 ms) compared to subgroup IIa (300 ± 17 ms).

Discussion

IMP evaluates "global" left ventricular function in a non-invasive manner. The rise in IMP has been described previously in many cardiovascular diseases, such as congestive heart failure,[23] systemic hypertension,[24] dilated cardiomyopathy,[25] cardiac amyloidosis[26] and myocardial necrosis. Szymanaskj et al[8] observed a clear increase in IMP in patients discharged from hospital after AMI. This increase in IMP decreases slowly in the course of time spanning over many months. Evaluating a group of 60 patients with AMI and 30 controls for approximately 12 months, Poulsen et al[21] showed that high IMP values slowly diminished with time. They showed that an index >60 reflects the severity of LV dysfunction, that could develop into CHF. In addition, Poulsen et al[21] contend that the simple non-geometric Tei index, assessed in the early phase of AMI, is able to detect left ventricular dysfunction and identify patients at risk for CHF.[7] Moreover, Moller et al[27] showed that IMP can predict cardiac death after the first AMI.

Table 1: Some metabolic and haemodynamic characteristics of non-diabetic and diabetic patients.

Clinical and metabolic aspects	**Group I (non-diabetics)**	**Group II (diabetics)**	***p value***
n	149	151	N.S.
M	98	102	N.S.
F	51	49	N.S.
Mean age (yrs.)	61±3	60±8	N.S.
BMI (kg/m^2)	26±3.2	26±8.1	N.S.
Systolic blood pressure (mmHg)	137±1.6	138±4.2	N.S.
Diastolic blood pressure (mmHg)	86±1.9	88±1.2	N.S.
LVEDV (ml)	116±11	119±10	N.S.
LVESV (ml)	62±12	64±15	N.S.
E.F.	0.49±0.09	0.46±0.07	N.S.
WMSI	1.81±0.5	1.98±0.6	N.S.
Heart rate (b/min)	79±2	81±6	N.S.
Blood glucose (mmol/l)	6.3±0.2	12.5±1.4	P<0.001
Total cholesterol (mmol/l)	4.3±0.02	4.6±0.05	N.S.
Triglycerides (mmol/l)	1.7±0.21	1.8±0.18	N.S.

BMI = Body Mass Index; LVEDV=Left Ventricular End-Diastolic Volume; LVESV=Left Ventricular End-Systolic Volume; E.F.=Ejection Fraction; WMSI= Wall Motion Score Index

Table 2: Early doppler-echocardiographic measurements of time intervals of cardiac cycle in non-diabetic vs. Diabetic patients

Doppler parameters	**group I**	**group II**	***p value***
IMP	0.49±0.04	0.55±0.05	*p<0.001*
ICT (ms)	62±13	71±11	*p<0.05*
IRT (ms)	83±12	81±15	*N.S.*
ET (ms)	295±29	275±27	*p<0.05*

IMP = Index of Myocardial Performance; ICT = Isovolumetric Contraction Time; IRT = Isovolumetric Relaxation Time; ET = Ejection Time (ET).

Table 3: Metabolic, haemodynamic and baseline echo-doppler time intervals of cardiac cycle values in diabetic patients with AMI treated with (Subgroup IIa) or without trimetazidine (Subgroup IIb).

	Subgroup IIa	Subgroup IIb	P value
Number	69	71	N.S
Male	52	53	N.S
Female	17	18	N.S
Mean age (yrs)	59 ± 4	61 ± 7	N.S
BMI (kg/m^2)	27 ± 2.1	26 ± 4.2	N.S
Systolic blood pressure (mmHg)	138 ± 1.8	139 ± 2.1	N.S
Diastolic blood pressure (mmHg)	87 ± 2.8	88 ± 3.2	N.S
Heart rate (b./min)	81 ± 3	82 ± 1	N.S
LVEDV (ml)	117 ± 12	120 ± 13	N.S
LVESV (ml)	63 ± 11	66 ± 0.9	N.S
EF	0.44 ± 0.07	0.42 ± 0.05	N.S
WMSI	1.81±0.9	1.86± 0.7	N.S
Blood glucose (mmol/l)	12.4±1.3	12.3±1.2	N.S
Total cholesterol (mmol/l))	4.5±0.03	4.9±0.06	N.S
Triglycerides (mmol./l.)	1.8±0.12	1.9±0.16	N.S
ICT (msec)	70±10	72±12	N.S
IRT (msec)	79±15	82±12	N.S
ET (msec)	278±26	272±27	N.S

Legend: B.M.I.=Body Mass Index; LVEDV=Left Ventricular End-Diastolic Volume; LVESV=Left Ventricular End-Systolic Volume; E.F.=Ejection Fraction; WMSI= Wall Motion Score Index. ICT = Isovolumetric Contraction Time; IRT = Isovolumetric Relaxation Time; ET = Ejection Time (ET).

Table 4 : Doppler values in diabetic patients with AMI treated with (Subgroup IIa) or without trimetazidine (Subgroup IIb).

	Subgroup IIa	Subgroup IIb	p value
IMP	0.44±0.08	0.53±0.07	p<0.001
ICT(msec)	45±12	46±11	N.S.
IRT (msec)	97±14	111±13	p<0.05
ET(msec)	300±17	280±15	p<0.001

IMP = Index of Myocardial Performance; ICT = Isovolumetric Contraction Time; IRT = Isovolumetric Relaxation Time; ET = Ejection Time (ET).

This is the first study that compares the outcome of IMP and of other time intervals of the cardiac cycle in diabetic patients with those of non-diabetics, both in the early and late phases post-AMI. In addition, IMP and other time intervals of the cardiac cycle were also evaluated in two diabetic subgroups: (i) those receiving the conventional anti-ischaemic therapy with trimetazidine (subgroup IIa) and (ii) those treated with both conventional anti-ischaemic therapy and a placebo (subgroup IIb).

Records of the early phases of the study showed that IMP was higher in diabetics compared to non-diabetic controls. In the early phase, ICT increased with a concomitant decrease in ET in diabetic groups compared to controls. However, IRT was similar in both normal and diabetic patients. Twelve months after AMI, IMP and ET remained unchanged from baseline values. ICT was reduced and IRT was clearly increased when compared to the values in the early phase of AMI. However, in subgroup IIa, IMP and ICT decreased significantly and ET increased slightly. The reduced glucose uptake in myocardial cells in diabetic patients with AMI seems to be the main cause of this outcome. The decrease in IMP and ICT and the increase in ET and IRT recorded in diabetics receiving trimetazidine in addition to conventional anti-ischaemic therapy (subgroup IIa) can be considered a consequence of the effects of trimetazidine. Furthermore, the significant rise in IRT in diabetic patients in subgroup IIb suggests a persistent diastolic ventricular dysfunction.[21]

It is well known that high levels of circulating fatty acids compensate for the reduced uptake of glucose in the myocardial cells of diabetic subjects. This change in the energy source favours fatty acid oxidation that provide between 90 and 100% of the heart's energy requirements, in comparison with normal hearts in which, fatty acid oxidation provides only 60-70% of the energy requirement.[28] However, the persistent fatty acid oxidation in diabetes induces an unfavourable ATP/O_2 consumption-ratio in respect to glucose oxidation, with a further reduction of energy availability.[4] Fatty acids are the major source of acetyl-CoA for the Tri-Carboxylic Acids (TCA) cycle and the oxidative production of ATP in diabetics.[28] However, fatty acids are not as efficient as glucose as a source of energy. In fact, their oxidation requires approximately 10% more oxygen to produce the equivalent amount of ATP than is required for glucose oxidation.[29] This difference in high-energy production compounds is trifling during the normal myocardial oxygenation, but can become inadequate for cardiac muscle affected by AMI. Trimetazidine is the prototype of the new class of 3-ketoacyl CoA thiolase inhibitors that does not produce any clinically significant changes in laboratory parameters but acts through the inhibition of 3-KetoAcyl-CoA-Thiolase (3-KAT), a mitochondrial enzyme modulating fatty acid oxidation which favours the oxidation of glucose. Mody et al[30] used PET to show that this novel antiangina agent does not alter the haemodynamic parameters of the heart but rather increases the total glucose utilization (oxidative and glycolytic) in the myocardium. In our study, trimetazidine probably induced a partial metabolic correction in the myocardial cells of diabetic patients and may thus be responsible for the lower values of IMP, IRT and ET.

The small number of patients and their limited uniformity (because the coronary angiography was not performed in all patients) are the most important limitations of the study. Only few diabetics underwent coronary angiography before or after AMI, because most of them did no have symptoms and signs of coronary disease. In addition, even if the coronary revascularization is the most important therapeutic measure in diabetics with CAD, in the present study, few patients underwent CABG or PTCA, because they were enrolled immediately for this study after the onset of AMI, to preserve the uniformity of their clinical status. Finally, patients receiving beta-blocker drugs were excluded to avoid compounding effects on the duration of IMP, ICT, IRT and ET. Nevertheless, our results confirm previous findings by our group that AMI in diabetics often evolves into left ventricular dysfunction.

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