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ORIGINAL ARTICLE

Left Ventricular Remodeling after Anterior Myocardial Infarction in Diabetic Patients: Role of Oxidative Stress, Apoptosis, and Glucometabolic Status

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Background	There is relatively little known about the relevance and molecular mechanisms of diabetes mellitus (DM) on postinfarction left ventricular (LV) remodeling and dysfunction.
Purpose	1) To describe the process of postinfarction LV remodeling in diabetic patients and to detect its major determinants, 2) To evaluate the potential relations between postinfarction LV remodeling in diabetic patients and markers of oxidative stress, apoptosis, and glucometabolic status.
Patients & Methods	Seventy nine patients (67 men, age of 52.6 ± 8.48 years) admitted with their first anterior myocardial infarction (MI) who received fibrinolytic therapy and who had angiographically documented patency of all major coronary arteries were divided into a diabetic (Group I, n= 49) or a nondiabetic groups (Group II, n= 30). All patients had transthoracic echocardiography study on admission and 6 month thereafter. On admission, plasma levels of glucose, glycosylated hemoglobin (HbA1c), 8-iso-prostaglandin F_{2a} , (8-iso PGF_{2a}) as a marker of oxidative stress, and soluble Fas ligand (sFasL, a proapoptotic factor) were measured. On follow-up (Fu), plasma levels of HbA1c were determined.
Results	Both groups had similar LV end diastolic volume index (LVEDVI) at baseline (group I: 65.5 ± 18.8 ml/m ² , group II: 66.13 ± 21.9 ml/m ² ; p= 0.89) and at Fu (group I: 70.5 ± 21.6 ml/m ² , group II: 73.19 ± 27.0 ml/m ² , p= 0.62). Despite similar LV ejection fraction (LVEF) at baseline, patients in group I showed significant deterioration in LVEF (from $45.9 \pm 8.4\%$ to $42.17 \pm 11.0\%$, p= 0.001) whereas patients in group II showed significant improvement ($43.9 \pm 8.8\%$ to $48.47 \pm 13.2\%$, p= 0.001). Admission plasma 8-iso- PGF_{2a} levels were significantly high in group I than those in group II (184.24 ± 156.5 ng/dl, 90.65 ± 99.21 ng/dl, p= 0.0001). Admission plasma levels of sFasL in group I (66.28 ± 38.58 ng/dl) were significantly higher than those in group II (50.78 ± 33.7 ng/dl, p= 0.0001). There were no significant differences in the magnitude of increase in LVEDVI between different subgroups of diabetic patients when stratified according to baseline characteristics. By multivariate analysis, the independent predictors for LVEF deterioration in diabetic patients were: longer time to fibrinolysis (p= 0.02), higher Fu levels of HbA1c (p= 0.03), and higher admission levels of 8-iso- PGF_{2a} (p= 0.04).
Conclusions	1) Compared to nondiabetic patients, diabetic patients have: similar extent of postinfarction LV dilatation, significant global LV systolic dysfunction, excess oxyradical-mediated cellular damage, and elevated plasma levels of sFasL. 2) There is no associations between any clinical, echocardiographic, or biochemical variables and the degree of postinfarction LV dilatation in diabetic patients. 3) Delayed time to fibrinolysis, high oxidative stress in the acute phase of MI, and poor glycemic control at Fu, but not plasma levels of glucose or sFasL, are the major factors influencing the development of LV dysfunction in diabetic patients.
Key Words	Diabetes, remodelling, myocardial infarction, oxidative stress (Heart Mirror J 2007; 1(1): 13-21)

INTRODUCTION

Heart failure (HF) accounts for two thirds of the total mortality during the first year after MI in diabetic patients. However, the difference in HF rates between diabetic and nondiabetic patients remained constant despite improved therapeutic modalities (1-3).

There is general acceptance that left ventricular (LV) remodeling after MI plays a major role in the progression of HF (4). However, previous studies reported increased (4) similar (5), or even less (6) LV dilatation after MI in patients with diabetes mellitus (DM) than without. Moreover, there

is relatively little known about the relevance and molecular mechanisms of DM on postinfarction ventricular remodeling and dysfunction.

Experimental evidences have suggested an intimate link between oxidative stress and the development of postinfarction LV remodeling and dysfunction (7-9). Considering the fact that DM is a state of chronic oxidative stress (10-12) it may be reasonable to assume that diabetic patients are at higher risk for maladaptive remodeling after MI. However, no previous clinical study has been performed to study this potential relation.

It has been observed that there is an association between glucometabolic status on admission and the development of HF following MI (13). However, the impact of glucometabolic status on long-term LV remodeling following MI in diabetic patients is not clear.

More recently, interest has begun to focus on the role of apoptosis in postinfarction LV remodeling (14). Actually, the relevance of Fas pathway (one of the main regulatory pathways of apoptotic cell death) to the process of LV remodeling has been recently reported (15,16). However, whether the Fas pathway is related to the process of remodeling following MI in diabetic patients is still unclear.

The purposes of this study therefore were: 1) To describe the process of postinfarction LV remodeling in diabetic patients and to detect its major determinants, and 2) To evaluate the potential relations between postinfarction LV remodeling in diabetic patients and markers of oxidative stress, apoptosis and glucometabolic status.

PATIENTS AND METHODS

Study design and patients

This prospective study recruited consecutive patients admitted with their first anterior AMI to the coronary care units of the Cardiology Department of Kasr El-Eini Hospitals, Cairo University between August 2003 and September 2004. Only those patients who received fibrinolytic therapy (streptokinase: 1.5 million units by IV infusion) and who also had angiographically documented patency of the left anterior descending (LAD) coronary artery – and other major coronary arteries- at the time of hospital discharge were eligible to enter the study. All patients were discharged on the maximally tolerated doses of ACE inhibitors. For all enrolled patients, follow up (Fu) visits at 6 months were scheduled. Patients were asked to avoid the intake of multivitamin preparations (because of their antioxidant activity). All eligible patients had transthoracic echocardiography within 24 hours of hospital admission and at 6 months. On admission, plasma levels of glucose, glycosylated hemoglobin (HbA1c), 8-iso-prostaglandin F_{2a} , (8-iso PGF_{2a}) as a marker of oxidative stress, and soluble Fas ligand (sFasL; a proapoptotic factor) were measured. On Fu, plasma levels of HbA1c were also determined. Written informed consent was obtained from all enrolled patients.

The following exclusion criteria were applied: contraindications to fibrinolytic therapy or to ACE inhibitors, prior MI or coronary artery bypass grafting surgery (CABG), valvular regurgitation or stenosis beyond mild degree, serum creatinine $> 2\text{mg/dl}$, reinfarction or CABG during the study interval, and the presence of persistent atrial fibrillation or paced rhythm.

Definitions

Anterior ST elevation MI was defined as ST-segment elevation $\geq 2\text{mm}$ above the baseline in at least two adjacent electrocardiographic anterior precordial leads associated with a typical pattern of serum cardiac marker consistent with AMI (17). Diabetes mellitus was diagnosed if patients were treated by antidiabetic agents or there was documented elevation of fasting plasma glucose ($\geq 126\text{mg/dl}$) on at least two occasions during hospital stay (18). Hypertension: persistent elevation of systolic blood pressure $\geq 140\text{ mmHg}$ and/or diastolic blood pressure $\geq 90\text{mmHg}$ or taking antihypertensive medications (19). Dyslipidaemia was diagnosed if patients were treated by statins or if there was elevation of fasting total serum cholesterol ($\geq 200\text{mg/dl}$) or LDL- cholesterol ($\geq 130\text{mg/dl}$) during hospital stay (20). Heart failure was a clinical diagnosis defined by the presence of suggestive symptoms (e.g. orthopnea, paroxysmal nocturnal dyspnea, or episode of acute pulmonary oedema) in association with clinical signs (third heart sound, elevated jugular venous pressure, pedal edema). Early fibrinolysis was defined when streptokinase was given within the first 6 hours after symptom onset. Acute hyperglycemia was defined as admission plasma glucose $\geq 200\text{mg/dl}$ (18).

Antidiabetic therapy. During index hospitalization, diabetic patients were managed by subcutaneous insulin using a sliding scale tailored according to individual needs. During the study interval, no attempt was done to adjust or to modify the antidiabetic therapy which remained the responsibility of the attending physician.

Follow up visit. Beside echocardiographic examination and collection of blood samples, there was special emphasis on: compliance to medical treatment, concomitant medication usage, presence of anginal symptoms, evidences for reinfarction, and clinical features of HF.

Two-dimensional echocardiography. Studies were performed with commercially available imaging systems: Hewlett-Packard Sonos (1000) or ATL (HDI, 5000). The LV was divided according to the 16 – segment model as proposed by the American Society of Echocardiography (21). The following measurements were taken: 1) Left ventricular volumes were determined using the modified Simpson biplane formula. All volumes were normalized to body surface area to obtain end-diastolic volume index (LVEDVI) and LV end-systolic volume index (LVESVI), 2) Left ventricular ejection fraction (LVEF). Changes in LVEF from baseline to Fu were calculated as a percent change relative to the initial values (percent Δ EF). LVEF deterioration was

defined as percent $\Delta EF \geq 7\%$ (value approaching to the mean percent ΔEF in the overall population ± 1 SD), 3) Regional LV function was estimated via the wall motion score index (WMSI) = sum of wall motion scores / number of visualized segments, 4) Infarct size was estimated via the percent wall motion asynergy (% WMA) = [number of segments showing WMA / total number of segments evaluated] $\times 100$, 5) LV mass index was calculated using an equation suggested by Devereux and Reichek (22), 6) Sphericity index was calculated as LV short-axis / LV long-axis; both axes were measured at end diastole in the apical four chambers view, 7) Mitral regurgitation was quantified as the largest colour regurgitant jet area, 8) Diastolic dysfunction. Mitral inflow was assessed by pulsed Doppler. Diastolic dysfunction was diagnosed if there was impaired relaxation pattern (E/A ratio < 1), pseudonormalization pattern (E/A ratio of 1 to 1.5 that becomes reversed by Valsalva maneuver), or restrictive pattern (E/A > 2.0).

LV remodeling was defined as increase in LVEDVI $> 20\text{mL}/\text{m}^2$ at 6 Fu relative to the baseline study (value approaching to the mean LVEDVI increase in the overall population ± 1 SD; this value is also beyond the intraobserver variability).

Measurement reproducibility. This was assessed by measuring LVEDVI, LVESVI, and LVEF in 10 patients on two occasions.

Coronary arteriography. The LAD coronary artery was specifically analyzed to assess percent diameter stenosis (by a quantitative computer-assisted system) and TIMI grade flow (20). The artery was judged patent if there was TIMI grade 2 or 3 flow. In case of percutaneous intervention (PCI), the intervention was considered successful in case of achieving residual stenosis $< 20\%$ and TIMI grade 3 flow without being complicated with infarction.

Biochemical Analysis. Blood samples were collected into sterile Vacuttes® tubes, immediately centrifuged (2,500 rpm for 12 minutes) and plasma was stored in epindorf tubes at $< -20^\circ \text{C}$. Quantification of the plasma levels of 8-iso-PGF_{2α} was performed using BIOXYTECH® enzyme-linked immunoassay kit (OXIS Health Products, Inc. Portland, U.S.A). Quantification of plasma levels of sFasL was performed by using Quantikine® enzyme-linked immunoassay kit (R and D Systems Inc. Minneapolis, U.S.A). Levels of HbA1c were determined with Tina-quant® HbA1cII (Roche/Hitachi) kits using Hitachi-911 autoanalyser.

Statistical Analysis. This was performed using SPSS for Windows (version 11.0, SPSS Inc., Chigaco, Illinois). Continuous variables were presented as mean ± 1 standard deviation (SD) and categorical variables as numbers and percentages. For continuous values, comparisons between the groups were made by student t test and within groups by the paired t test. For categorical variables, comparisons were performed by chi-square test. Normal distribution

was evaluated by the Kolmogorov-Smirnov test. Bivariate correlations were analyzed by Spearman's test. ANOVA test was used to compare the means of different tertiles. Changes (Δ) in various echocardiographic measurements were calculated as Fu minus baseline values. Independent predictors for LVEF deterioration in diabetic group were determined by multivariate stepwise regression analysis model (with a forward stepwise approach). A p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Seventy nine patients (67 men and 12 women with a mean age of 52.6 ± 8.48 years) formed the study group. According to diabetic status, patients were divided into a diabetic group (Group I, n= 49) or a nondiabetic group (Group II, n= 30). Clinical and angiographic characteristics. There were no significant differences between the two groups (Table 1). Importantly, variables known to modify redox homeostasis (smoking, hypertension, HF, hyperlipidaemia, BMI, and age) were equally distributed between both groups. By design, all patients were discharged with patent LAD and other major coronary arteries.

Table 1. Clinical, angiographic, and biochemical characteristics.

Variables	Group I	Group II	p value
Clinical data			
Age (year)	53.08 \pm 7.13	51.9 \pm 10.42	0.55
Male	40 (82)	27 (90)	0.3
Hypertension	13 (27)	8 (27)	0.9
Current smoking	40 (82)	25 (83)	0.8
Dyslipidaemia	19 (39)	9 (30)	0.8
Previous angina	11 (22)	10 (33)	0.28
Fibrinolytic therapy			
Time to therapy (hours)	7.13 \pm 2.48	5.98 \pm 3.53	0.09
Early fibrinolysis	27 (55)	12 (40)	0.24
HF	5 (10)	3 (10)	0.97
BMI [†] (kg/m ²)	29.6 \pm 3.2	27.7 \pm 4.1	0.7
Angiographic data			
Time to angiography (day)	5.57 \pm 2.16	6.6 \pm 4.01	0.11
Patent LAD artery*	38 (77)	21 (70)	0.45
Diameter stenosis (%)	60.31 \pm 28.38	57.5 \pm 33.57	0.69
PCI to LAD artery	29 (60)	16 (53)	0.6
Time to PCI (day)	5.49 \pm 3.03	6.9 \pm 4.19	0.08
Biochemical data			
Admission plasma glucose (mg/dl)	190.91 \pm 54.1	110.5 \pm 29.3	0.0001
HbA1c (%)			
Baseline	8.42 \pm 1.23	5.63 \pm 0.54	0.0001
Fu	7.96 \pm 0.97	-	-
8-iso-PGF _{2α} (ng/dl)	184.24 \pm 156.5	90.65 \pm 99.2	0.0001
sFasL (ng/dl)	66.28 \pm 38.58	50.78 \pm 33.7	0.0001

Data are presented as the mean value \pm SD or number (%) of patients.

† BMI, body mass index.

* Defined as TIMI grade 2 or 3.

Of the 49 diabetic patients in group I, 38 patients (88%) had previously known DM and 11 patients (22%) had newly diagnosed DM at the time of index MI. The mean duration of DM was 6.51 ± 4.17 years. At the time of hospital discharge, 31 patients (64%) were taking oral hypoglycaemic agent, 12 patients (24%) were taking insulin, and 6 patients (12%) were on both.

At the time of hospital discharge, all patients were on ACE inhibitors and aspirin. Beta blockers were given to 78% and 80%, nitrate to 94% and 83%, and statins to 39% and 40% of patients in group I and II, respectively.

Average follow up time was 7.3 ± 0.9 month in group I and 7.35 ± 0.9 month in group II ($p= 0.6$). At Fu visit, 8 patients (16%) had clinical features of HF in group I and 3 patients (10%) in group II ($p= 0.4$). Of note, 6 patients (12%) discontinued ACE inhibitors in group I and three patients (10%) in group II ($p= 0.7$).

Biochemical data. The mean time of infarction to baseline analysis was 13.3 ± 4.61 hour in group I and 14.58 ± 5.81 hour in group II ($p= 0.28$). Table 1 summarizes the laboratory data of both study groups. As expected, group I had significantly elevated plasma levels of admission glucose ($p= 0.0001$) and HbA1c ($p= 0.0001$) compared with group II. Admission 8-iso-PGF_{2a} levels were significantly high among patients in group I ($p= 0.0001$).

Plasma levels of sFasL in group I were significantly higher than those in group II ($p= 0.0001$).

Echocardiographic measurements (Tables 2 and 3). The between group differences regarding LVEDVI and LVESVI at baseline and Fu were not different. During the study period, both groups exhibited further significant increase in LVEDVI when compared to baseline studies. Similar proportions (10%) of both groups had LV remodeling ($p= 0.13$). In group I, LVESVI at Fu increased significantly when compared to baseline value ($p= 0.002$). In contrast, patients in group II, showed no change ($p= 0.3$). Despite similar LVEF at baseline, patients in group I showed significant deterioration in their LVEF ($p= 0.001$) whereas patients in group II showed significant improvement ($p= 0.001$). Thus, at Fu, group I exhibited significantly lower LVEF compared with group II ($p= 0.02$).

It is notable that while nondiabetic patients exhibited significant improvement of regional LV function ($p= 0.01$), this improvement was marginal in nondiabetic patients ($p = 0.05$). However, WMSI at Fu was similar in the two groups ($p= 0.38$). Despite similar infarct size at baseline and at Fu, both groups showed significant reduction in infarct size thorough the study interval ($p= 0.04$ for group I and $p= 0.035$ for group II when compared to baseline values). Within and in-between group comparisons were comparable regarding LVMI, sphericity index, diastolic dysfunction, mitral regurgitation jet area and left atrial size.

Table 2. Changes in the LV measurements in both study groups.

Variables	Baseline	Fu	P
LVEDVI (ml/ m²)			
Group I	65.51 ± 18.8	70.51 ± 21.62	0.035
Group II	66.13 ± 21.9	73.19 ± 27.0	0.001
LVESVI (ml/ m²)			
Group I	35.46 ± 12.4	40.8 ± 15.75	0.002
Group II	37.53 ± 15.3	39.3 ± 21.92	0.33
LVEF (%)			
Group I	45.93 ± 8.4	42.17 ± 11.03	0.001
Group II	43.93 ± 8.82	48.47 ± 13.12	0.001
LVMI (gm/m²)			
Group I	109.66 ± 30.14	114.47 ± 28.69	0.3
Group II	113.47 ± 32.5	115.27 ± 34.58	0.6
Sphericity index			
Group I	0.467 ± 0.041	0.477 ± 0.078	0.36
Group II	0.46 ± 0.03	0.48 ± 0.07	0.21
% WMA			
Group I	51.148 ± 12.54	49.48 ± 12.42	0.04
Group II	52.5 ± 12.98	49.37 ± 13.96	0.035
WMSI			
Group I	1.79 ± 0.28	1.72 ± 0.34	0.05
Group II	1.77 ± 0.31	1.65 ± 0.36	0.01
Diastolic dysfunction			
Group I	23 (47)	26 (53)	0.8
Group II	12 (40)	15 (50)	0.8
Left atrium (cm)			
Group I	3.7 ± 0.37	3.82 ± 0.34	0.2
Group II	3.72 ± 0.4	3.8 ± 0.52	0.178
MR (cm²)			
Group I	0.78 ± 1.21	1.02 ± 1.6	0.2
Group II	0.66 ± 1.0	1.15 ± 1.79	0.07

Data are presented as the mean value ± SD or number (%) of patients.

Measurement reproducibility (intraobserver variability). The mean differences between measurements made at two time points were: 7.1 ± 5.6 ml/m² for LVEDVI, 6.3 ± 5.0 ml/m² for LVESVI, $2.0 \pm 3.1\%$ for LVEF, and $2.6 \pm 3.0\%$ for percent ΔEF.

Determinants of LV dilatation in diabetic patients. ΔLVEDVI was compared between subgroups of diabetic

patients according to baseline characteristics. There were no significant differences in ΔLVEDVI between subgroups of patients (Table 4).

Table 3. Echocardiographic measurements: Comparisons between both groups.

Variables	Group I	Group II	P
LVEDVI (ml/m²)			
Baseline	65.51 ± 18.8	66.13 ± 21.91	0.89
Fu	70.51 ± 21.62	73.19 ± 27.03	0.62
Δ	4.9 ± 16.1	7.06 ± 10.7	0.53
Δ ≥ 20 mL/m ²	5(10)	3(10)	0.13
LVESVI (ml/m²)			
Baseline	35.46 ± 12.4	37.53 ± 15.33	0.51
Fu	40.8 ± 15.75	39.32 ± 21.92	0.72
Δ	5.34 ± 11.6	1.79 ± 9.93	0.16
LVEF (%)			
Baseline	45.93 ± 8.42	43.93 ± 8.82	0.31
Fu	42.17 ± 11.03	48.47 ± 13.12	0.02
Δ EF	-3.76 ± 7.34	4.53 ± 6.7	0.0001
Percent Δ EF	-8.5 ± 15.72	9.26 ± 15.36	0.0001
LVMI (gm/m²)			
Baseline	109.66 ± 30.14	113.47 ± 32.50	0.59
Fu	114.47 ± 28.69	115.27 ± 34.58	0.91
Δ	4.81 ± 24.17	1.80 ± 21.86	0.58
Sphericity index			
Baseline	0.467 ± 0.04	0.467 ± 0.038	0.99
Fu	0.477 ± 0.078	0.48 ± 0.07	0.84
Δ	0.012 ± 0.77	0.014 ± 0.66	0.88
% WMA			
Baseline	51.14 ± 12.54	52.5 ± 12.98	0.64
Fu	49.48 ± 12.4	49.37 ± 13.96	0.64
Δ	-1.65 ± 5.52	-3.12 ± 7.9	0.33
WMSI			
Baseline	1.79 ± 0.28	1.77 ± 0.31	0.82
Fu	1.72 ± 0.34	1.65 ± 0.36	0.38
Δ	-0.06 ± 0.22	-0.12 ± 0.24	0.27
Diastolic dysfunction			
Baseline	23(47)	12(40)	0.6
Fu	26(53)	15(50)	0.8
Left atrium (cm)			
Baseline	3.73 ± 0.37	3.72 ± 0.4	0.92
Fu	3.82 ± 0.34	3.8 ± 0.52	0.84
Δ	0.09 ± 0.23	0.07 ± 0.3	0.8
MR (cm²)			
Baseline	0.78 ± 1.21	0.66 ± 1.0	0.63
Fu	1.02 ± 1.63	1.15 ± 1.79	0.75
Δ	0.23 ± 1.32	0.49 ± 1.47	0.43

Data are presented as the mean value ± SD or number (%) of patients.

Table 4. Comparisons between subgroups of patients in group I according to ΔLVEDVI.

Variable	Δ LVEDVI (ml/m ²)	P
Age (≥50 vs. <50 year)	5.3 ± 16 vs. 4.2 ± 16	0.8
Gender (Male vs. Female)	5.6 ± 12 vs. 2.1 ± 27	0.7
Hypertension (Yes vs. No)	6.0 ± 19 vs. 4.6 ± 15	0.7
Smoking (Yes vs. No)	4.3 ± 14 vs. 7.9 ± 23	0.5
Angina (Yes vs. No)	9.0 ± 11 vs. 4.0 ± 17	0.2
Time to fibrinolysis (> 6 h vs. < 6h)	5.6 ± 17 vs. 3.4 ± 10	0.6
Patent LAD artery (Yes vs. No)	5.1 ± 11 vs. 4.2 ± 22	0.8
Use of beta-blockers (Yes vs. No)	5.0 ± 18 vs. 5.3 ± 15	0.8
Baseline LVEF (≥ 40 % vs. < 40%)	6.1 ± 14 vs. 2.0 ± 20	0.4
Baseline 8-iso-PGF _{2α} (≥ 150 vs. < 150 ng/dl)	7.1 ± 15 vs. 3.5 ± 17	0.3
Baseline sFasL (> 50 vs. < 50 ng/dl)	4.6 ± 17 vs. 5.4 ± 15	0.5
Acute hyperglycemia (Yes vs. No)	5.1 ± 15 vs. 4.3 ± 20	0.8

Data are presented as the mean value ± SD

Determinants of postinfarction LVEF deterioration in diabetic patients (Table 5). Of the 49 patients of group II, 26 patients (54%) showed deteriorated LVEF, whereas the remainder 23 patients (46%) did not. By univariate analysis,

diabetic patients with deteriorated LVEF had longer time to fibrinolysis, higher plasma levels of HbA1c at admission and at Fu, higher admission plasma levels of 8-iso-PGF_{2α}, and greater absolute reduction in HbA1c during the study period. By multivariate analysis, the most powerful independent predictors were: longer time to fibrinolysis (p=0.02), higher Fu levels of HbA1c (p=0.03), and high levels of 8-iso-PGF_{2α} (p=0.04). According to this model, these three variables can explain 53% of the variation for LVEF deterioration in diabetic patients (R² = 0.53)

Table 5. Results of multivariate logistic regression analysis.

Variable	B	Odds ratio	CI (95%)	p
Time to fibrinolysis	0.527	1.7	1.1-2.7	0.002
Fu- HbA1c	-1.54	8.3	1.7-40.3	0.03
Baseline 8-iso-PGF _{2α}	0.156	1.6	1.2-2.4	0.04

R²: 0.53

The regression equation: [-11.9+0.527 time to fibrinolysis -1.54 HbA1c at Fu +0.156 PGF_{2α} at baseline

Postinfarction LV function and plasma tertile levels of baseline 8-iso-PGF_{2α} and HbA1c. By 1-way ANOVA test, a linear trend toward lower LVEF and greater LVESVI at Fu as well as lower percent Δ EF in higher tertiles of admission 8-iso-PGF_{2α} appeared (p=0.03, p=0.01, p=0.001, respectively). Moreover, these three echocardiographic measurements were significantly low among patients in the upper tertile than patients in the lower tertile. The relative risk of LVEF deterioration was 25.5 times (95% CI= 3.68-183.4) as high among patients in the upper tertile than those among the lower tertile. Similarly, when diabetic patients were grouped into tertiles according to HbA1c at Fu, there was a linear trend toward lower LVEF at Fu in higher tertiles (p=0.013). Furthermore, patients in the upper tertile (HbA1c >8%) exhibited lower LVEF (p=0.01) at Fu than patients in the lower tertile (HbA1c < 7.5 %) (Table 6). The relative risk of LVEF deterioration was 6.2 times (95% CI =1.27-30.1) patients in the upper tertile than those among the lower tertile.

Table 6. Analysis of variance in selected echocardiographic measurements according to admission 8-iso-PGF_{2α} tertiles.

Variable	8-iso-PGF _{2α} (ng/dl)			p*
	≤ 95 n= 15	96-224 n= 24	≥ 225 n= 10	
LVEF (%)				
Fu	46.4 ± 10	45.4 ± 9.4	36 ± 12†	0.03
%Δ EF	3 ± 12	-9.3 ± 16†	-19 ± 9.9‡	0.0001
Pts with ΔEF ≤ 7%	3 (20)	10 (53)	13 (87)‡	0.001§
LVESVI (ml/m²)				
Fu	32.8 ± 10	40 ± 13	49.7 ± 19#	0.01
Δ	4.3 ± 13.2	1.5 ± 5.7	10.3 ± 13	0.1
LVEDV (ml/m²)				
Fu	61.4 ± 15	78.5 ± 25	71.3 ± 20	0.09
Δ	4.9 ± 8.9	2.0 ± 18.9	8.7 ± 17.9	0.5

Data are presented as the mean value ± SD or number (%) of patients

*, comparing the group means around the overall mean (by 1-way ANOVA)

§, comparison by chi square test

‡, p=0.0001 (versus the lower tertile)

†, p=0.048 (versus the lower tertile)

#, p= 0.02 (versus the lower tertile)

NB: the mean time to fibrinolysis was comparable in all groups (p=0.06)

Oxidative stress and glucometabolic markers in diabetic patients. Poor glycaemic control at the time of AMI was associated with excess ROS-mediated damage as evident by two observations: First, at the time of AMI, diabetic patients with HbA1c > 8% had significantly elevated 8-iso-PGF_{2α} levels when compared to patients with HbA1c < 8% (240.3±156.4 ng/dl vs. 123.6±70.5 ng/dl, p= 0.002); second, baseline HbA1c levels showed significant positive linear correlation with 8-iso-PGF_{2α} (r= 0.55, p= 0.002) (Figure 1). Of note, there was no significant relation between 8-iso-PGF_{2α} and admission plasma glucose (r =0.1) or sFasL level (r =0.07).

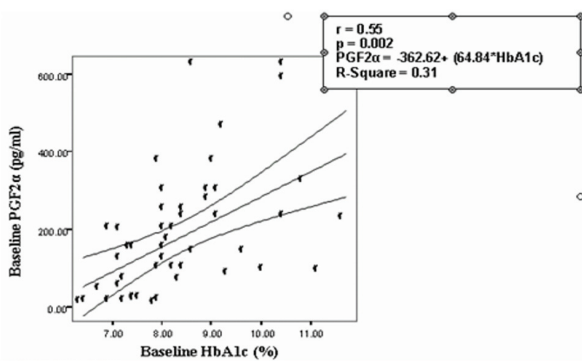


Figure 1. Scatterplot showing the linear correlation between HbA1c and 8-iso-PGF_{2α} at the time of the index MI

DISCUSSION

As far as we know, no previous clinical study was performed to study the impacts of oxidative stress, glucometabolic status, and apoptosis on postinfarction LV remodeling in diabetic patients.

Postinfarction left ventricular dilatation and function.

Our data suggest that classic LV dilatation occurred to the same extent in diabetic and nondiabetic patients. In agreement with these data, patients with and without DM had similar LV mass and shape. Global LV systolic function showed significant deterioration in diabetic patients whereas nondiabetic patients showed significant improvement. The changes in LVESVI (another index of systolic function) in diabetic patients similarly support these findings.

Previous studies. Previous studies reported conflicting data regarding postinfarction LV dilatation and function in diabetic patients (1,4,5,6,23). The discrepancy between studies can be attributed to the high prevalence of concomitant variables known to adversely affect the LV remodeling in diabetic patients (e.g., multivessel disease, prior infarcts, hypertension, and reinfarction). Furthermore, these studies were heterogeneous regarding the site and type of MI (e.g., inferior MI, non-ST-elevation MI) or the use of ACE inhibitors and B-blockers. Our study – by design – nullified the influence of these variables. Thus, the observed changes in the LV in diabetic patients can be attributed primarily to the effect of DM per se.

Mechanisms. One of the most consistent alterations in diabetic heart is the increased quantities of extracellular collagen in the noninfarcted area that may limit progressive dilatation after MI (23,24). Actually, collagen deposition is a prerequisite to prevent cardiac dilatation or even rupture after MI (25).

Although the conventional view of LV remodeling has held that progressive LV remodeling is detrimental, an alternative concept suggests that this process may be – within limit – adaptive and beneficial (27,28). LV dilatation allows the viable myocardium to maintain (or even to improve LVEF) through the operation of the Frank-Starling mechanism (28). Actually, one would have expected the low LVEF in diabetic patients at Fu to be associated with a greater LV dilatation to restore stroke volume. Of interest, the SAVE study has recently suggested that diabetic patients seem to have decreased capacity to remodel the LV after MI (6).

Our observation that diabetic patients had low LVEF supports the notion that structural, functional, and metabolic factors specific to DM place the LV at a higher risk for LV dysfunction (e.g., metabolic dysfunction, preexisting diabetic cardiomyopathy, autonomic neuropathy, endothelial dysfunction, excess cardiac apoptosis, activation of cardiac renin angiotensin system, and oxidative stress) (1,25,29,30). Of note, the improvement in regional LV function (reflected in WMSI) can be attributed to the presence of stunned but viable myocardial tissue capable of regaining function with time. This also explains the observed apparent decrease in the infarct size (as estimated by %WMA) throughout the study in both groups.

LV remodeling. Volume versus function. Our finding calls into question the use of LVEDVI as a surrogate marker for LV remodeling in diabetic patients. Instead, LV remodeling would be better quantified by measuring the LVEF in diabetic patients. Actually, cardiac remodeling is defined as a process that is manifested clinically with change in size, shape, and function of the heart (31).

LVEF is merely an arithmetic term based on LVEDV and LVESV and since LVEDVI was similar in our diabetic and nondiabetic patients, the low LVEF observed in our diabetic patients should be attributed primarily- if not exclusively- to greater LVESVI. Therefore, LVESVI may be a more meaningful index of LV remodeling in diabetic patients than LVEDVI and possibly than LVEF.

Time to fibrinolysis appeared as the strongest independent variable associated with deterioration in the LV function in diabetic patients. Earlier fibrinolysis is associated with increased myocardial salvage, smaller infarct size, and early IRA patency; all are factors known to be associated with better LV function (32,33).

Oxidative stress and postinfarction LV remodeling. 8-iso-PGF_{2α} is a novel sensitive, specific product that represents a stable in vivo index of lipid peroxidation that is mediated

-primarily if not exclusively- by oxidative stress 34,35). In the present study we demonstrated for the first time that oxidative stress within the acute phase of MI was an independent predictor of subsequent deterioration of the global LV systolic function in diabetic patients. This was further supported by the demonstration that high tertiles of baseline 8-iso-PGF_{2α} are significantly associated with lower LVEF and larger LVESVI at the end of the study.

Mechanisms. Cumulative evidence suggests that DM is a state of oxidative stress mediated by: 1) Increased reactive oxygen species (ROS) production via the mitochondrial electron transport chain, advanced glycosylation end products, and glucose autooxidation and by 2) Decreased concentrations of several antioxidants. 10,36,37,38 ROS can induce contractile dysfunction via several mechanisms: increased cytosolic Ca₂₊ causing excitation contraction uncoupling (39), impairment of oxidative phosphorylation⁴⁰, damage to the extracellular matrix with loss of mechanical coupling (39), induction of apoptosis (40,41) B-receptor downregulation (42), negative inotropism secondary to excess nitric oxide production and cytokine expression (43,44).

It is difficult to ascertain that the observed increase in ROS-mediated damage corresponds to a causal effect and is not merely a marker of advanced cellular changes accompanying LV dysfunction (i.e. an epiphenomenon). However, a causative role is strongly suggested by the studies that reported success of antioxidant therapy in preventing or retarding disease progression (8,9).

Our findings that LV dysfunction is closely linked to oxidative stress in the acute setting of MI may be explained by the concept that ROS is more relevant to initiation of the process rather than its accumulation (45). Interestingly, the cellular changes induced by an attack of ROS may continue or even progress with time even after resetting the redox homeostasis towards the normal state. This “memory” is explained by the ability of ROS to change gene expression (46), to alter signal transduction (47) and to induce sublethal cellular changes.

Our finding that oxidative stress is significantly related to LVEF but not LVEDVI may indicate that ROS may exert its effect mainly via functional rather than structural alterations. Actually, antioxidant agents were consistently reported to improve postinfarction LV function in rat models of MI. On the contrary, the effect of these agents on LV dilatation was inconsistent (8,9).

Oxidative stress and glucometabolic status. Our data also showed that poor glycaemic control at the time of AMI was associated with excess ROS-mediated damage. These findings prompted the thought that a mechanistic link may be present. Such a link is supported by a great deal of evidence suggesting that the oxidative stress is the unifying factor for the damaging effect of hyperglycaemia in diabetic patients (The common soil hypothesis) (12).

Glucometabolic status and postinfarction LV remodeling.

Our data showed that poor glycemic control (measured by HbA1c) on admission and at 6 months thereafter was significantly associated with deterioration of LV function in diabetic patients. However, only poor glycemic control at 6 months emerged as an independent risk factor for LV function deterioration by multivariate analysis. Poor glycemic control may be causally related to contractile dysfunction by several mechanisms: glucotoxicity, lipotoxicity, and abnormal gene expression (48,49).

In our study, plasma glucose (in terms of admission level or acute hyperglycemia) did not appear to have any significant influence on post infarction LV dilatation or dysfunction in diabetic patients. Some issues may partially explain this unexpected finding: 1) Patients with significant hyperglycemia are more likely to receive insulin on admission; this may bias the impact of hyperglycaemia on LV function, 2) There is an intrinsic difficulty in defining acute hyperglycaemia in diabetic patients because the baseline concentration of glucose is not known, 3) The new diagnostic criterion of DM (fasting plasma glucose \geq 126 mg/dl (18) may allow the recruitment of patients with less severe abnormalities of the glucose metabolism. Thus, the glucotoxicity of acute hyperglycemia on admission may not be apparent in our relatively small number of patients with short duration of Fu, 4) It is difficult to dissect the association between plasma glucose on admission and the concurrent long term glycemic control (reflected by HbA1c). It has been shown that admission blood glucose is largely determined by the previous metabolic control (50), and 5) Random admission plasma glucose may be influenced by prior meals or diurnal variations.

Role of sFasL-induced apoptosis. In the present study we demonstrated for the first time that plasma levels of sFasL were elevated in the acute phase of MI in diabetic patients compared with nondiabetic patients. sFasL may be induced by several stimuli, including hypoxia (51), reperfusion (52), and mechanical myocardial stretch (53). It is not clear how much of sFasL elevation in our diabetic patients was mediated by the acute infarction and how much was mediated by DM. There is no available answer to this question since there is no current clinical study that compared sFasL levels in diabetic patients with and without AMI.

Our data showed no significant relation between sFasL levels at the time of AMI and subsequent LV dilatation or dysfunction in diabetic patients. Some issues may partially explain this finding: 1) It should be noted that the levels of plasma sFasL change rapidly after the onset of MI. Time-course studies revealed that plasma sFasL levels decreased rapidly within three hours after the onset of MI (52). Thus, it is possible that in some of our patients plasma sFasL levels may have already returned to the basal levels when blood samples were taken, 2) Levels of plasma sFasL can rapidly increase in response to reperfusion or reocclusion of the infarct related artery (52). For logistic and methodological

reasons, the impact of both variables on plasma sFasL levels in our patients could not be accurately identified three. beside sFasL, the final outcome of the Fas pathway depends on other components (Fas, soluble Fas, Fas ligand, and procaspase (8). Thus, it is possible that the expression and activity of these downstream components have weakened or even nullified the potential impact of sFasL on postinfarction LV indices (4). It would be more appropriate to correlate postinfarction LV indices with sFasL levels in the coronary sinus (that reflect the maximum and the most active sFasL level in the heart) than in the peripheral venous blood (where sFasL is diluted), and 5. it is possible that Fas-induced LV changes have been attenuated by the effect of captopril (the most common used ACE inhibitor in our study). Actually, captopril has been reported to inhibit Fas-induced apoptosis in many cell types (54).

Study Limitations. 1) The exclusion of patients who died or those who had CABG, or recurrent MI eliminated some of the highest-risk patients for LV remodeling, 2) Echocardiographic Fu was not extended beyond 6 months. However, postinfarction remodeling has generally been regarded as a process that is completed over a period of months (55), 3) The success rate of fibrinolytic therapy in achieving reperfusion was not known in this study (a common problem in clinical practice). Nevertheless, the patency rates of LAD coronary artery in our diabetic and nondiabetic patients were similar (4). Myocardial viability – factor known to affect LV remodeling (56)– was not assessed in this study, 5) LVEF and LVESV are afterload dependent. Therefore, the absence of data on peak systolic pressure at the time of echocardiography is a limiting factor in the study.

CONCLUSION

1) Compared to nondiabetic patients, diabetic patients have similar extent of LV dilatation after MI. However, diabetic patients have significant global LV systolic dysfunction, 2) Diabetic patients have evidence of excess oxyradical-mediated cellular damage in the acute phase of MI when compared to nondiabetic patients, 3) There is no association between oxidative stress, glucometabolic status, or plasma levels of sFasL (or any other clinical variable) and the degree of postinfarction LV dilatation in diabetic patients, 4) Delayed time to fibrinolysis, high oxidative stress in the acute phase of MI, and poor glycemic control at follow up are the major factors influencing the development of LV dysfunction in diabetic patients.

RECOMMENDATIONS

1) In diabetic patients, postinfarction LV remodeling can be better quantified by measuring LVEF and LVESVI. Thus, treatment of diabetic patients after MI should be aimed at improvement of these indices, 2) Plasma level of 8-iso-PGF_{2α} may be a novel marker that can be clinically used to stratify diabetic patients in the acute phase of MI into low

and high risk groups regarding the future risk of developing LV dysfunction, 3) Early time to fibrinolysis and improving glycemic control should be one of the primary aims in diabetic patients, 4) Our findings may provide a rationale for antioxidant therapy during the acute phase of MI in diabetic patients. Additional mechanistic investigations may lead to the innovation of a causal antioxidant molecule that may inhibit, at an early stage, the molecular mechanisms leading to ROS generation, and, 5) Future studies should be designed to elucidate the potential relations between each member of the Fas pathway and various indices of postinfarction LV remodeling.

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