Effects of Stress Hyperglycemia on Acute Myocardial Infarction

Role of inflammatory immune process in functional cardiac outcome

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OBJECTIVE — Stress hyperglycemia has been associated with increased mortality in patients with myocardial infarction (MI). We examined the association between plasma glucose levels, circulating inflammatory markers, T-cell activation, and functional cardiac outcome in patients with first MI.

RESEARCH DESIGN AND METHODS — Echocardiographic parameters, circulating levels of interleukin-18 (IL-18), C-reactive protein (CPR), and the percent of CD16-CD56, CD4/CD8, CD152, and HLA-DR expression were investigated in 108 patients with acute MI on admission to the emergency ward.

RESULTS — Our review found that 31 new hyperglycemic patients (glycemia ≥7 mmol/l) had higher infarct segment length ($P < 0.05$) and myocardial performance index ($P < 0.02$) and reduced transmitral Doppler flow ($P < 0.05$), pulmonary flow analysis ($P < 0.02$), and ejection fraction ($P < 0.05$) compared with 36 hyperglycemic diabetic patients and 41 normoglycemic patients. Plasma IL-18 and CRP were higher in the hyperglycemic than in the normoglycemic patients ($P < 0.005$), with the highest values in patients with new hyperglycemia ($P < 0.05$). Hyperglycemic patients had a higher percent of CD16+/CD56+ cells and CD4/CD8 ratio ($P < 0.01$), whereas they had lower CD152 expression (which has a negative regulatory function in T-cell activation) compared with normoglycemic patients ($P < 0.001$).

CONCLUSIONS — During MI, hyperglycemia is associated with increased levels of inflammatory markers, enhanced expression of cytotoxic T-cells, and reduced expression of T-cells, which are implicated in limiting the immune process. An increased inflammatory immune process seems a likely mechanism linking acute hyperglycemia to poor cardiac outcome in MI patients.

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An unusually high prevalence of glycosuria in nondiabetic patients who have acute myocardial infarction (MI) was noted as early as 1931 (1). Stress hyperglycemia after MI is associated with an increased risk of in-hospital mortality in patients with and without diabetes (2). Moreover, a positive association between hyperglycemia at the time of the event and subsequent mortality from MI has been reported (3). Although the mechanisms underlying this association are not fully understood, evidence that the use of insulin to lower glucose concentrations decreases mortality in diabetic patients who have MI (4) suggests that hyperglycemia is not simply an epiphenomenon of a stress response. Consequently, hyperglycemia at the time of MI may be an important and potentially modifiable risk factor for poor outcome.

A growing body of evidence suggests that MI is associated with local and systemic inflammation (5). Cell activation, which is mediated to some extent by immune mechanisms, is an important component of inflammatory reaction (6). Atherosclerotic plaques contain large numbers of activated T-cells, suggesting that immune mechanisms are important factors in the pathogenesis of the atherosclerotic background (6). Indeed, inflammatory cells infiltrate nearly all plaques, and culprit lesions of infarcted hearts appear to be particularly enriched in activated T-cells (7). This suggests that acute T-cell activation may play a role in plaque instability and the acute clinical manifestations of coronary atherosclerosis (7). Although circulating immune markers are also chronically elevated in patients with chronic stable angina, a transient burst of T-cell activation can be detected only in patients with unstable angina and MI (8), suggesting that immune factors might precipitate plaque complications such as thrombus formation and vasoconstriction at the site of the culprit lesions. Whether peripheral T-cell levels are increased and contribute to the poor outcome of acute coronary syndromes in diabetic and/or hyperglycemic patients is not known. This study was undertaken to examine whether the immune process during MI is influenced by diabetes and hyperglycemia. Specifically, we examined the association between stress hyperglycemia, T-cell activation, inflammatory markers, and echocardiographic parameters of

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Abbreviations: CRP, C-reactive protein; ECG, electrocardiogram; ET, ejection time; ICT, isovolumetric contracting time; IL-18, interleukin-18; IRT, isovolumetric relaxation time; MI, myocardial infarction; MPI, myocardial performance index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

functional cardiac outcome in patients with and without diabetes admitted for a first, uncomplicated MI to emergency wards.

RESEARCH DESIGN AND METHODS

Patients

The study group comprised 108 consecutive patients presenting with their first uncomplicated acute MI within 3–8 h after the onset of pain; they were all admitted into the emergency wards of three different hospitals in Campania, Italy, from July 2001 to October 2002. We defined acute MI according to criteria recommended by the American College of Cardiology (9). Thus, patients were diagnosed as having an acute MI if they had two values of serum troponin I >2.50 μg/l together with either typical symptoms of or electrocardiogram (ECG) changes indicating acute ischemia. Patients with interfering noncardiac diseases such as inflammatory disorders, malignancy, or infection were not eligible for the study. None of the patients were on any anti-inflammatory agent. Hyperglycemia was defined as an admission plasma glucose level of ≥126 mg/dl (≥7 mmol/l) (10). The normoglycemic study group included patients with a normal plasma glucose (<7 mmol/l) and no previous history of diabetes. Patients with hyperglycemia were subdivided into those with a previous history of diabetes (known diabetes) and those without such a history (new hyperglycemia). The study protocol was approved by the institutional ethics committee for human subjects. Written informed consent was obtained from all patients.

Study protocol

Measurements of brachial blood pressure, BMI, and plasma glucose levels were obtained on admission before patients started full medical therapy, including β-blockers and/or calcium antagonists, low-dosage aspirin, and continuous intravenous infusion of nitrates, heparin, and thrombolysis or primary percutaneous transluminal coronary angioplasty. Venous blood for troponin I levels was collected in EDTA-coated tubes immediately after a patient arrived at the emergency department. Troponin I was measured with an Opus Magnum device (Behring Diagnostics). A discriminator value of 2.0 μg/l was used for troponin I, as recommended by the manufacturer. In accordance with this recommendation, we found a 97.5 percentile of 2.0 μg/l in 87 healthy blood donors. Serum interleukin-18 (IL-18) was assayed using a high-sensitivity two-site enzyme-linked immunosorbent assay kit (R&D Systems). Plasma C-reactive protein (CRP) was determined using automated turbidimetry.

Flow cytometry

Fluorochrome-conjugated murine monoclonal antibodies specific for CD3, CD4, CD8, CD40 l (CD154), CD152, CD69, CD95, CD71, and CD25 (BD Pharmingen, Milan, Italy) were used in direct immunofluorescence techniques to define the immunophenotype of T-cells in the patient population immediately after a patient arrived at the emergency department. Fluorochrome-conjugated monoclonal antibodies of IgG1 and IgG2a isotypes specific for molecules unrelated to human leukocyte antigens (BD Pharmingen) were used to determine lymphocyte background fluorescence. Briefly, aliquots of 100 μl of venous whole blood from patients or control subjects were incubated for 20 min at 4°C with 20 μl of two or three different monoclonal antibodies conjugated to different fluorochromes (fluorescein isothiocyanate, phycoerythrin, or peridinin chlorophyll protein). Samples were then depleted of erythrocytes by incubation with 2 ml of fluorescence-activated cell sorter lysing solution (Becton Dickinson) at 4°C for 10 min. Leukocytes were then washed twice with PBS solution, resuspended in 0.3 ml of PBS, and analyzed on a FACScan® cytometer (Becton Dickinson). A minimum of 10,000 events was counted for each analysis. Analysis of surface marker coexpression by T-cells was performed on cells gated on the basis of CD3, CD4, or CD8 expression. Cells were considered positive for the examined surface antigen if they had fluorescence channel values >300 (corresponding to $>10^1$ on logarithmic scale). Results are expressed as the percent of positive cells and mean fluorescence intensity. All data were obtained with CellQuest software (Becton Dickinson).

Echocardiographic assessment

Patients enrolled in the study underwent two-dimensional echocardiography before starting full medical therapy. The study was performed using a standardized protocol and phased-array echocardiographs with M-mode, two-dimensional, and pulsed, continuous-wave, and color-flow Doppler capabilities. The ejection fraction was calculated from area measurements using the area-length method applied to the average apical area (11). Measurements were made with a computerized review station equipped with digitizing tablet and monitor screen overlay for calibration and measurement performance. The left ventricular internal dimension and interventricular septal were measured at the end diastole and end systole, and the wall motion score index was calculated according to American Society of Echocardiography recommendations (11). Doppler velocities and time intervals were measured from mitral inflow and left ventricular outflow recordings. Isovolumetric relaxation time (IRT) was the time interval from cessation of left ventricular outflow to onset of mitral inflow, the ejection time (ET) was the time interval between the onset and the cessation of left ventricular outflow, and the mitral early diastolic flow deceleration time was the time interval between the peak early diastolic flow velocity and the end of the early diastolic flow. The total systolic time interval was measured from the cessation of one mitral flow to the beginning of the following mitral inflow. Isovolumetric contracting time (ICT) was calculated by subtracting ET and IRT from the total systolic time interval. The ratio of velocity time intervals (vti) of mitral early (E) and late (A) diastolic flows (E_{vti}/A_{vti}) was calculated. The myocardial performance index (MPI) was calculated as (IRT + ICT)/ET.

Statistical analysis

Results are presented as means ± SD, unless otherwise stated. The Kolmogorov-Smirnov test showed that the data were not normally distributed. Differences among more than two matched samples were tested by Friedman's test, followed by Wilcoxon's matched-pairs signed-rank test, and differences among the study groups were tested by the Mann-Whitney-Wilcoxon rank-sum test or Fisher's exact test, as appropriate. $P < 0.05$ in the two-tailed test was regarded as significant.

RESULTS — Of the 108 study patients, 41 (38%) had glucose measure-

ments <7 mmol/l. The known diabetic group consisted of 36 hyperglycemic patients (33%) with a history of diabetes documented before admission. The newly diagnosed hyperglycemia group consisted of 31 (29%) patients with no prior history of diabetes who were found to have on admission a glucose level >7 mmol/l. Table 1 lists the baseline characteristics of the study subjects.

There were no differences in the mean age; sex distribution; smoking habits; levels of plasma cholesterol, triglycerides, or creatinine; or previous disorders among the three groups. Patients with known diabetes tended to have a greater BMI; however, this difference was not statistically significant. Systolic blood pressure and heart rate were slightly higher in diabetic patients. Although the use of diuretics and ACE inhibitors was higher in diabetic patients, the use of β-blockers and calcium channel−blocker therapy was similar in both groups. The MI therapy was similar in both groups (data not shown).

As expected, patients with known diabetes and new hyperglycemia had significantly higher plasma glucose levels compared with normoglycemic patients ($P < 0.01$). The admission plasma glucose level in patients with known diabetes (12.6 ± 1.2 mmol/l) was higher than that in the newly hyperglycemic group (11.7 ± 1.1 mmol/l), but the differences were not statistically significant. Of the 36 known diabetic subjects, 20 were being treated with insulin therapy, 12 with sulfonylureas, and 4 with metformin.

On admission, ECG findings were ST segment depression ($n = 27$, 25%), T wave inversion ($n = 37$, 34.3%), and ST segment elevation ($n = 27$, 25%). Despite the similar finding and extent of ST segment elevation on admission ECG in the three groups of patients (number of leads with ST elevation: normoglycemic, 2.5 ± 2.7; new hyperglycemia, 3.2 ± 2.3; known diabetic, 3.1 ± 2.2), troponin I levels were significantly higher in patients with new hyperglycemia and known diabetes than in normoglycemic patients ($P < 0.005$). Compared with known diabetic patients, patients with new hyperglycemia presented with higher levels of troponin I ($P < 0.01$). The newly hyperglycemic group had the highest troponin I levels, the normoglycemic group had the lowest levels, and the known diabetic group had intermediate levels (Fig. 1). There was no correlation between the time from the onset of symptoms and the admission troponin I levels ($r^2 = 0.005$, $P = 1$).

Table 1—*Patient characteristics, ECG findings, and echocardiographic parameters on admission*

	New hyperglycemia	Known diabetes	Normoglycemia
Patients (*n*)	31	36	41
Mean age (years)	57 ± 2	56 ± 4	59 ± 5
Sex (M/F)	13/18	19/17	22/19
BMI (kg/m^2)	26 ± 0.5	28 ± 0.4	25 ± 0.3
Waist-to-hip ratio	0.72 ± 0.05	0.72 ± 0.04	0.71 ± 0.05
Systolic blood pressure (mmHg)	128 ± 10*	126 ± 11*	119 ± 12
Diastolic blood pressure (mmHg)	83 ± 5	81 ± 6	80 ± 7
Heart rate (bpm)	79 ± 16*	78 ± 13*	70 ± 12
Blood glucose (mmol/l)	11.9 ± 1.7*	12.6 ± 1.3*	6 ± 0.9
Total cholesterol (mmol/l)	6.68 ± 0.03	6.82 ± 0.05	6.68 ± 0.04
HDL cholesterol (mmol/l)	1.22 ± 0.02	1.24 ± 0.03	1.29 ± 0.04
Triglycerides (mmol/l)	2.52 ± 0.11	2.61 ± 0.18	2.21 ± 0.16
Smokers (% [*n*])	22.5 (7)	22.2 (8)	24.4 (10)
Serum creatinine (μmol/l)	78.5 ± 2.7	79.2 ± 2.6	78.6 ± 2.3
Previous disorder (% [*n*])			
Angina pectoris	22.5 (7)	22.2 (8)	24.4 (10)
Hypertension	16.1 (5)	19.4 (7)	17.1 (7)
Hyperlipidemia	12.9 (4)	16.6 (6)	12.2 (5)
Active therapy (% [*n*])			
β-Blocker	3.2 (1)	5.5 (2)	2.4 (1)
Diuretic	3.2 (1)†	8.3 (3)*	2.4 (1)
ACE inhibitors	6.4 (2)†	13.9 (5)*	4.9 (2)
Calcium-channel blockers	6.4 (2)	5.5 (2)	7.3 (3)
Time from onset of pain to arrival in Emergency Department (h)	5.6 ± 1.6	5.4 ± 2.2	5.1 ± 2.9
ECG findings (% [*n*])	16.1 (5)	16.6 (6)	14.6 (6)
Normal	25.8 (8)	25 (9)	24.4 (10)
ST segment elevation	22.6 (7)	22.2 (8)	29.3 (12)
ST segment depression	35.5 (11)	36.1 (13)	31.7 (13)
T wave inversion			
Echocardiographic parameters			
Left ventricular mass index (g/m^2)	121.1 ± 8†	135 ± 9*	118.9 ± 7
Left ventricular internal diastolic diameter (m)	51.6 ± 3.3†	56.7 ± 3.9*	50.6 ± 2.7
Infarct segment length (%)	43.7 ± 2.1*†	38.9 ± 1.8*	30.6 ± 1.7
Ejection fraction (%)	34.8 ± 2.1*	35.5 ± 3.1*	44.6 ± 4.2
Wall motion score index	2.8 ± 0.3*†	2.1 ± 0.2*	1.4 ± 0.3
Myocardial performance index	0.58 ± 0.16*†	0.53 ± 0.11*	0.45 ± 0.19
Pulmonary venous flow (PVFs/PVFd ratio)	1.34 ± 0.4*†	1.51 ± 0.5*	1.60 ± 0.5
Mitral deceleration (ms)	151 ± 52*†	165 ± 58*	195 ± 24
Early/late diastolic ratio	0.9 ± 0.2*†	1.1 ± 0.4*	1.3 ± 0.3

Data are means ± SD. *$P < 0.01$ vs. normoglycemia; †$P < 0.01$ vs. known diabetes.

Echocardiographic/Doppler measurements are presented in Table 1. Hyperglycemic patients had higher infarct segment length ($P < 0.05$) and wall motion scores ($P < 0.01$), but lower ejection fraction ($P < 0.05$) than normoglycemic patients. Moreover, they had an increased MPI ($P < 0.02$) and reduced transmitral Doppler flow ($P < 0.05$) and pulmonary venous flow analysis ($P < 0.02$). Compared with known diabetic patients, patients with new hyperglycemia presented with higher infarct segment length ($P < 0.04$), wall motion score ($P < 0.05$), and MPI ($P < 0.04$), but lower transmitral Doppler flow ($P < 0.05$) and pulmonary venous flow analysis ($P < 0.05$). There

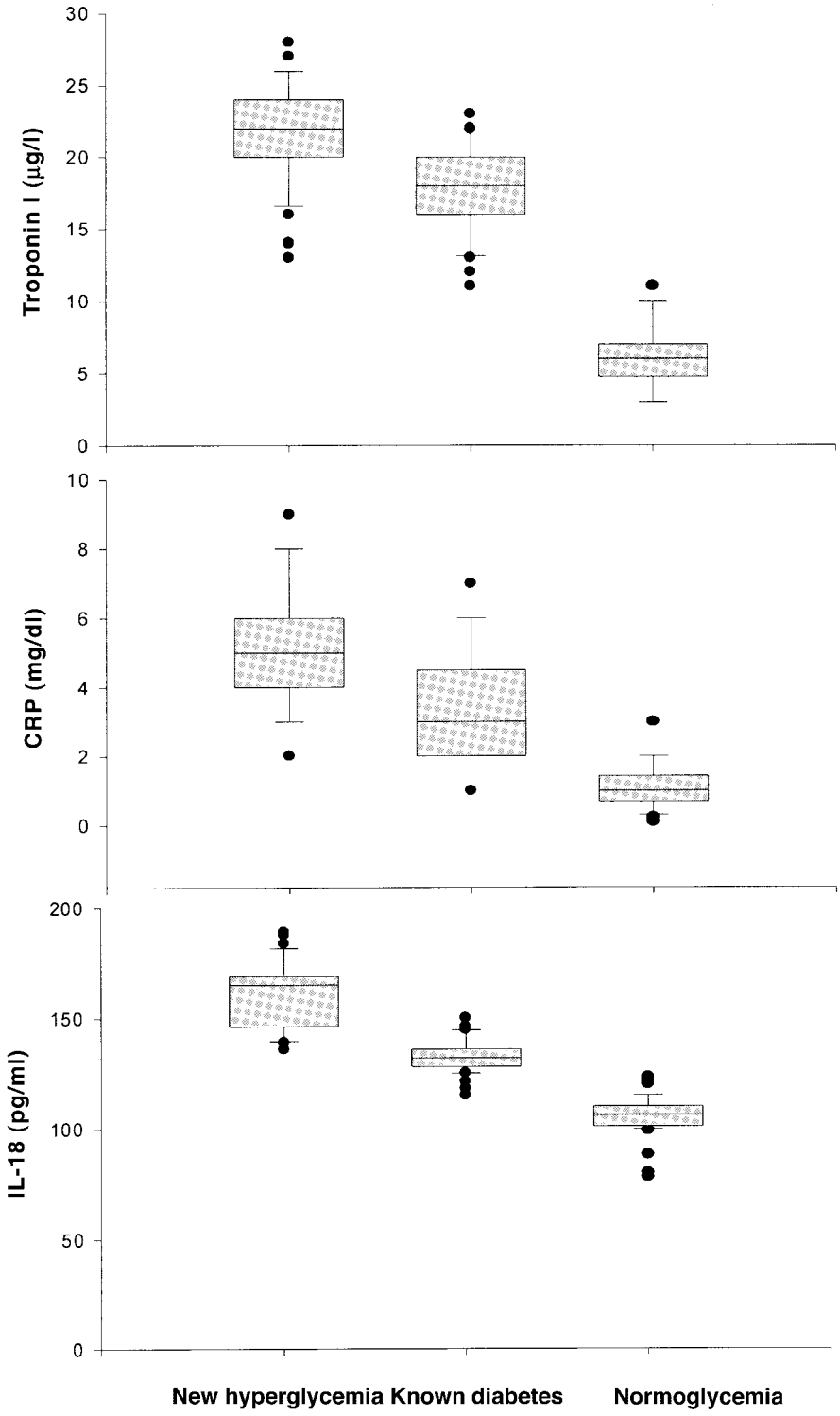

Figure 1—*Box plot showing troponin I, CRP, and IL-18 levels in newly hyperglycemic, known diabetic, and normoglycemic patient. This type of plot displays the 10th, 25th, 50th, 75th, and 90th percentiles as lines on a bar centered about the mean, and the 5th and 95th percentiles as error bars. The mean line and data points beyond the 5th and 95th percentiles can also be displayed.*

was no difference between diabetic patients treated with insulin or oral hypoglycemic therapy (data not shown).

Plasma IL-18 and CRP levels were higher in hyperglycemic than in normoglycemic patients ($P < 0.005$) (Fig. 1), with the highest values in patients with new hyperglycemia. Plasma glucose levels were correlated with IL-18 ($r = 0.20$, $P < 0.02$) and CPR ($r = 0.22$, $P < 0.01$).

Day-to-day variations in the expression of CD16/CD56, CD4/CD8, CD152, and CD4-CD8 HLA-DR antigens by lymphocytes, measured in five healthy control subjects on four consecutive days, were 1.8, 2.5, 3, and 5%, respectively, for each lymphocyte subtype. There were no significant differences among normoglycemic, new hyperglycemia, and known diabetic patients in the number of blood lymphocytes or monocytes. The percent of positive circulating lymphocytes CD16/CD56, CD4/CD8, and CD152 in the three groups of patients are shown in Fig. 2. Compared with normoglycemic patients, the hyperglycemic group had higher values of CD16/CD56 lymphocytes and CD4/CD8 ratio ($P < 0.01$), but a lower expression of CD152 ($P < 0.001$) (Fig. 1). Moreover, the percentage of CD16/CD56 lymphocytes and CD4/CD8 ratio was significantly higher and CD152 expression was more reduced in newly hyperglycemic patients than in known diabetic patients ($P < 0.05$) (Fig. 2). The percent of HLA-DR+ CD8 and CD4 lymphocytes was, on average, significantly more elevated in patients with new hyperglycemia (CD4, 19.7 ± 2.4%; CD8, 35.7 ± 4.2%) than in known diabetic patients (CD4, 15.9 ± 2.1%; CD8, 31.9 ± 3.4%; $P < 0.01$) (CD4, 3.8% [range, 1.4–5.8%]; CD8, 3.8% [range, 1.6- 5.4%]) or normoglycemic patients (CD4, 12.9 ± 1.9%; CD8, 25.3 ± 2.8%; $P < 0.001$) (CD4: 6.8% [range 2.3–10.5%]; CD8, 10.4% [range, 3.6–6.4%] $P < 0.001$).

CD152 expression had an inverse correlation with plasma glucose levels ($r = -0.24$, $P < 0.02$), infarct segment length ($r = -0.16$, $P < 0.04$), left wall motion score ($r = -0.18$, $P < 0.02$) and MPI ($r = -0.18$, $P < 0.03$). CD16/CD56 expression was positively correlated with plasma glucose levels ($r = 0.28$, $P < 0.01$), infarct segment length ($r = 0.18$, $P < 0.05$), and wall motion score index ($r = 0.18$, $P < 0.01$) (Table 1).

In multiple regression analysis, glucose levels were significant predictors of troponin I (adjusted $r^2 = 0.49$, $P < 0.005$), wall motion score index (adjusted $r^2 = 0.35$, $P < 0.005$), MPI (adjusted $r^2 = 0.33$, $P < 0.005$), CRP (adjusted $r^2 = 0.59$, $P < 0.001$), IL-18 levels (adjusted $r^2 = 0.41$, $P < 0.001$), and CD16+/CD56+

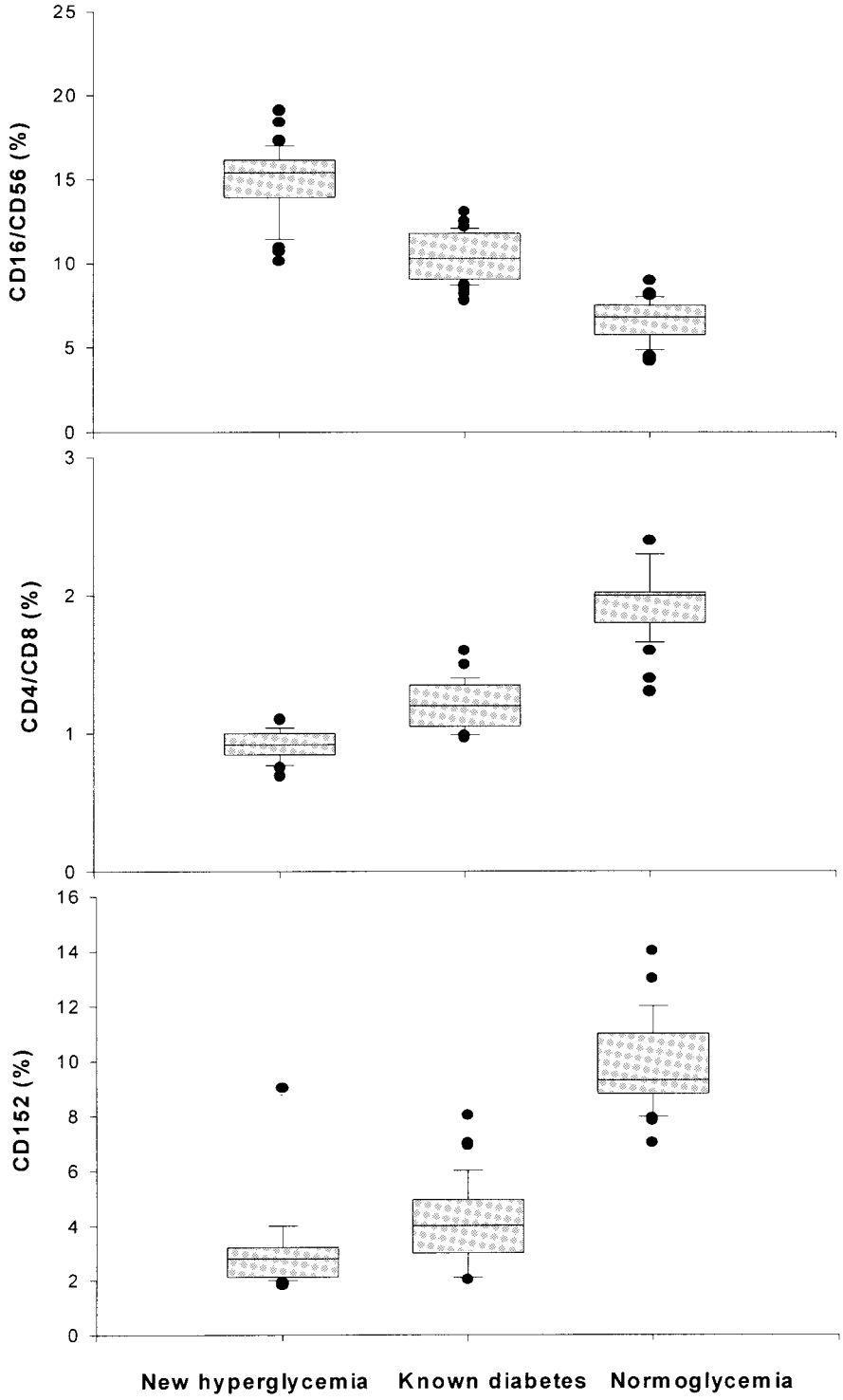

Figure 2—*Box plot showing percent of CD16/CD56, CD4/CD8, and CD152 lymphocytes in new hyperglycemic, known diabetic, and normoglycemic patients. See note regarding box plot in legend to Fig. 1.*

(adjusted $r^2 = 0.36$, $P < 0.005$); inclusion of age, sex, BMI, blood pressure, cholesterol and triglyceride levels, smoking status, previous disorders, and active therapy did not add explanatory information for our results.

At 3-month follow-up after the MI, 13 (41.9%) of the 31 new hyperglycemic patients had impaired glucose tolerance and 15 (48.4%) had diabetes.

CONCLUSIONS — To the best of our knowledge, there have been no studies investigating the association among glucose levels, troponin I, inflammatory markers, T-cell activation, and functional cardiac outcome in patients with acute MI. The main findings of our study demonstrate an association between inflammatory immune markers and functional cardiac outcome in patients with a first uncomplicated MI: stress hyperglycemia amplifies inflammatory immune reaction and worsens functional cardiac outcome.

In our study, hyperglycemia was associated with higher troponin I levels, probably as a consequence of more extensive myocardial damage. Consistent with this interpretation, we also found that patients with hyperglycemia presented with larger infarct size compared with normoglycemic patients. Although the relation between blood glucose levels and infarct size is not conclusive (12), a critical role for glucose has recently been demonstrated by the linear relation between blood glucose concentration and infarct size in diabetic or acutely hyperglycemic rats (13). The present results seem to confirm these findings, as hyperglycemia was positively correlated with both infarct segment length and wall motion score index increases. The increase in the MPI, which measures both systolic and diastolic parameters of ventricular function (14), indicates a worse functional outcome after MI in hyperglycemic patients. Moreover, the diminished diastolic filling time, the prolongation of mitral regurgitation, and the diminished effective ejection time in the hyperglycemic patients suggest that hyperglycemia may influence cardiac synchronization during MI. Studies have identified dyssynchrony between right and left ventricular contraction and relaxation as an independent predictor of heart failure and cardiac mortality in patients with heart failure (15). The results of the present study support an association between ventricular dyssynchrony and blood glucose levels in patients with MI. As for mechanisms behind this association, stress hyperglycemia may be responsible for more extensive cardiac damage.

More extensive myocardial damage may be linked to a greater inflammatory process and activated T-cells (16). Several

inflammatory markers have been associated with cardiovascular events, including cytokines and growth factors, which are released by activated macrophages that, together with T-cells, are major cellular components (16). We found that hyperglycemic patients had higher circulating levels of IL-18 and CRP compared with normoglycemic patients. IL-18 is a strong predictor of death from cardiovascular causes in patients with acute coronary syndromes (17). Interestingly enough, acute hyperglycemia in healthy subjects and patients with impaired glucose tolerance increases circulating cytokine concentrations, including IL-18 (18). Following this line of thought, it might be speculated that the detrimental effect of stress hyperglycemia in acute MI might also stem from its ability to increase circulating IL-18 and CRP levels. Consistent findings have supported CRP levels as being predictive of future cardiovascular events and death in initially healthy individuals, as well as in patients with unstable angina and in patients with MI (19). The positive correlation we found between blood glucose levels, CRP, and IL-18 also suggests that the increased inflammatory process may be a link between hyperglycemia and poor functional cardiac outcome in hyperglycemic patients during MI.

Lymphocyte activation seems to be necessary for the extension of the inflammatory process during acute MI (20). We saw evidence that circulating lymphocytes from patients with MI are activated and that the clinical outcome is related to the intensity of the immunological activation. Both CD4+ and CD8+ circulating lymphocytes from hyperglycemic patients with MI had higher expression of HLA-DR antigens compared with normoglycemic patients, suggesting that stress hyperglycemia is associated with enhanced T-cell activation. To reduce T-cell activation, the immune system has developed mechanisms to limit the immune process, including enhanced expression of CD152, which has a negative regulatory function in T-cell activation (21). We observed an impaired expression of CD152+ associated with worse cardiac outcome in hyperglycemic patients compared with normoglycemic patients. Thus, high glucose may interfere with the autoregulatory function of T-cell activation, which may be implicated in the prolongation of the inflammatory process and poor cardiac outcome. Interestingly enough, hyperglycemic patients also had an enhanced number of CD16/CD56 (natural killers) compared with normoglycemic patients. The recent demonstration of higher levels of natural killer cells in symptomatic plaques compared with asymptomatic plaques suggests a major role of these cells in atherosclerotic plaque destabilization, leading to acute coronary syndromes (22). Despite other controversial findings (23,24), the relation we observed between CD16/CD56 expression and the extent of ischemic injury suggests that natural killer lymphocytes may be an important feature of glucose-induced cardiac damage during MI.

In the current study, the levels of troponin I, inflammatory markers, expression of cytotoxic T-cell activation, and functional cardiac outcome were significantly better in diabetic patients, suggesting that stress hyperglycemia is more deleterious in nondiabetic than in diabetic patients. Patients with known diabetes are more likely to receive drugs treatment for hyperglycemia before MI. These treatments may lessen the rise in inflammatory markers and T-cell activation, promote myocardial uptake of glucose for anaerobic metabolism, and decrease coagulability because of reduced production of thromboxane A and plasminogen activator inhibitor 1 activity (25). The ability of insulin to inhibit cytokine release, CRP, and T-cell activation (26) may explain, at least in part, why the newly hyperglycemic patients had a poorer cardiac outcome compared with known diabetic patients, even though the latter group had higher plasma glucose levels. The inhibition of the inflammatory immune process by insulin may be one of the mechanisms responsible for the improved mortality seen with the glucose-insulin-potassium infusion during acute MI in patients with and without diabetes (4). Moreover, the use of intensive insulin therapy to maintain blood glucose at ≤110 mg/dl substantially reduced mortality in the intensive care unit, in-hospital mortality, and morbidity among critically ill patients admitted to the intensive care unit (27). However, the exact mechanisms by which morbidity and mortality were reduced remain largely speculative, as the effects of glycemic control cannot be distinguished from those of increased insulin levels. In our study, hyperglycemic patients with known diabetes treated with sulfonylurea or metformin did not exhibit differences in functional cardiac outcome and inflammatory-immune markers compared with patients treated with insulin. This observation is in line with data from the U.K. Prospective Diabetes Study that showed no difference in the number of deaths after MI or diabetes-related deaths among participants assigned to sulfonylurea, metformin, or insulin therapies (28).

The present study demonstrates an additional aspect of how hyperglycemia might contribute to poor cardiac outcome and favor cardiovascular death in MI patients with and without diabetes: stress hyperglycemia increases inflammatory markers such as CRP and IL-18, enhances the cytotoxic T-cell activity, and increases the immune stimulation by reducing the expression of T-cells implicated in the limitation of the immune process. An increased inflammatory immune process seems a likely mechanism linking acute hyperglycemia to poor cardiac outcome in MI patients.

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