Hyperglycemia Is Associated With Enhanced Thrombin Formation, Platelet Activation, and Fibrin Clot Resistance to Lysis in Patients With Acute Coronary Syndrome

ANETTA UNDAS, MD, PHD[1]
ILONA WIEK, MSC[2]
EWA STĘPIEŃ, PHD[2]
KRZYSZTOF ZMUDKA, MD, PHD[1]
WIESŁAWA TRACZ, MD, PHD[1]

OBJECTIVE — Acute hyperglycemia on admission for acute coronary syndrome worsens the prognosis in patients with and without known diabetes. Postulated mechanisms of this observation include prothrombotic effects. The aim of this study was to evaluate the effect of elevated glucose levels on blood clotting in acute coronary syndrome patients.

RESEARCH DESIGN AND METHODS — We studied 60 acute coronary syndrome patients within the first 12 h after pain onset, including 20 subjects with type 2 diabetes, 20 subjects with no diagnosed diabetes but with glucose levels >7.0 mmol/l, and 20 subjects with glucose levels <7.0 mmol/l. We determined generation of thrombin-antithrombin complexes (TATs) and soluble CD40 ligand (sCD40L), a platelet activation marker, at the site of microvascular injury, together with ex vivo plasma fibrin clot permeability and lysis time.

RESULTS — The acute coronary syndrome patients with no prior diabetes but elevated glucose levels had increased maximum rates of formation and total production of TATs (by 42.9%, $P < 0.0001$, and by 25%, $P < 0.0001$, respectively) as well as sCD40L release (by 16.2%, $P = 0.0011$, and by 16.3%, $P < 0.0001$, respectively) compared with those with normoglycemia, whereas diabetic patients had the highest values of TATs and sCD40L variables ($P < 0.0001$ for all comparisons). Patients with hyperglycemia, with no previously diagnosed diabetes, had longer clot lysis time (by ~18%, $P < 0.0001$) similar to that in diabetic subjects, but not lower clot permeability compared with that in normoglycemic subjects.

CONCLUSIONS — Hyperglycemia in acute coronary syndrome is associated with enhanced local thrombin generation and platelet activation, as well as unfavorably altered clot features in patients with and without a previous history of diabetes.

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Acute hyperglycemia occurs in up to 50% of all ST-segment elevation myocardial infarctions, whereas patients with diabetes represent ~25% of patients with ST-segment elevation myocardial infarctions (1). When glucose tolerance testing is performed, 65% of patients with myocardial infarction and a negative history of diabetes can be diagnosed with diabetes or impaired glucose tolerance (2). Acute hyperglycemia on admission has been reported to worsen the prognosis in myocardial infarction patients with and without known diabetes (3), including increased risk of in-hospital mortality in both groups (4).

Cardiovascular stress induces release of catecholamines, cortisol, and glucagons, leading to increases in glucose and free fatty acids that enhance hepatic gluconeogenesis and diminish peripheral glucose uptake. Unfavorable effects of high blood glucose levels in myocardial infarction involve impaired left ventricular function, increased incidence of the no-reflow phenomenon, and a tendency for arrhythmias (5). Several mechanisms implicated in the detrimental impact of hyperglycemia during acute myocardial ischemia have been postulated, i.e., enhanced oxidative stress, the activation of blood coagulation and platelets, stimulation of inflammation, and endothelial cell dysfunction (5). All of these have also been reported in type 2 diabetes (6,7).

Evidence for the prothrombotic effects of acute hyperglycemia in vivo is scanty. Exposure to 24-h selective hyperglycemia in healthy volunteers results in increased tissue factor procoagulant activity (8). Acute hyperglycemia activates platelet aggregation, enhances thrombin generation, and activates coagulation factor VII (9). It is not known whether acute hyperglycemia during myocardial infarction is potent enough to influence hemostasis. Moreover, hyperglycemia, both in diabetic patients and under in vitro conditions, is linked to unfavorably altered fibrin clot properties and reduced fibrinolysis compared with the results at normoglycemia (10,11). Recently, we have showed that in patients with acute myocardial infarction, a history of type 2 diabetes is associated with impaired plasma clot permeability and fibrinolysis (12). The effect of hyperglycemia on clot properties in acute myocardial infarction patients with no history of diabetes has not been investigated yet. The aim of the study was to evaluate potential prothrombotic alterations in acute myocardial infarction patients in relation to hyperglycemia, including thrombin formation, platelet activation, and fibrin network structure/function.

RESEARCH DESIGN AND METHODS

— Patients with acute myocardial infarction admitted to the cor-

From the [1]Institute of Cardiology, Jagiellonian University School of Medicine, Cracow, Poland; and the [2]John Paul II Hospital, Cracow, Poland.
Corresponding author: Anetta Undas, mmundas@cyf-kr.edu.pl.
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onary care unit within the first 12 h after the onset of chest pain were enrolled in the study. We recruited 20 consecutive acute myocardial infarction patients with a history of type 2 diabetes, who self-reported taking insulin or oral hypoglycemic drugs on a regular basis (the DM group) and 20 patients with a negative history of diabetes, who had a serum glucose level of ≥7 mmol/l on admission (the HG group). Twenty patients with glucose levels <7 mmol/l (the NG group) served as a reference group.

Inclusion criteria were typical chest pain and elevated cardiac troponin levels. Changes in electrocardiogram (ECG) recordings such as either ST-segment elevation ≥0.1 mV or ST-segment depression ≥0.1 mV in at least two contiguous ECG leads or normal ECG results were allowed. Exclusion criteria were as follows: cardiogenic shock, any acute illness, cancer, hepatic or renal dysfunction, a history of venous thromboembolism or stroke, anticoagulant therapy, and recent myocardial infarction (within the previous 3 months). All subjects received 300 mg aspirin 2–8 h before the study. Major adverse coronary events were recorded within the first 30 days after enrollment.

All subjects enrolled in the study provided written, informed consent. The University ethics committee approved the study.

Laboratory investigations

Blood samples were obtained from an antecubital vein using a 21-gauge butterfly needle within 15 min upon admission. The lipid profile, C-reactive protein (CRP), glucose, creatinine, platelet count, and cardiac troponin T were determined using routine laboratory methods. A1C was analyzed by high-performance liquid chromatography using a Variant II analyzer (Bio-Rad, Hercules, CA). A human-specific radioimmunoassay kit (Linco Research, St. Charles, MO) was used to measure plasma insulin levels. Fibrinogen was determined using the Clauss method. High-sensitivity CRP was measured by latex nephelometry (Dade Behring, Marburg, Germany). Blood samples for thrombin and platelet markers were centrifuged at 2,500*g* for 15 min, and plasma was stored at −80°C. Using commercially available enzyme-linked immunosorbent assays, we determined the following in plasma: interleukin-6 (IL-6) (R&D Systems, Abingdon, U.K.); thrombin-antithrombin complexes (TATs) and prothrombin 1.2 fragments (F1.2), markers of thrombin formation (Enzygnost, Dade Behring); and soluble CD40 ligand (sCD40L), a marker of platelet activation (R&D Systems). Routine laboratory data and hemostatic variables were also obtained after 30 days from the event.

Model of vascular injury

Measurements were performed in blood collected at 60-s intervals from a standardized skin incision, made using a Simplate IR device (Organon Teknika, Durham, NC) at the inflation of the sphygmomanometer cuff at 40 mmHg, as described previously (13–15). Blood was collected by means of heparinized tubes (Kabe Labortechnik, Numbrecht-Elsenroth, Germany) into Eppendorf tubes containing anticoagulants as described previously (14,15). After centrifugation at 3,000*g* at 4°C for 20 min, supernatants were frozen at −80°C. Both TAT (Dade Behring) and sCD40L (R&D Systems) were measured in the samples. Interassay and intra-assay coefficients of variation (CVs) were 5–7%. Thrombin formation and platelet activation were described as maximum velocity of both processes and total amounts of each marker produced within the first 6 min of bleeding (using the trapezoid rule) (14,15).

Clot permeability

Permeation properties of fibrin clots were assessed according to the method of Mills et al. (16). Briefly, tubes containing plasma clots formed upon addition of calcium chloride and human thrombin (Sigma) were connected via plastic tubing to a reservoir of 0.05 mol/l Tris-HCl, and its volume flowing through the gels was measured within 60 min. A permeation coefficient (K_s), which indicates the pore size, was calculated from the equation, as described (16). The interassay CV was 9.2%.

Plasma clot lysis assay

To determine lysis time, we used an assay by Lisman et al. (17) with some modifications. Briefly, citrated plasma was mixed (1:1) with HEPES buffer containing calcium chloride, diluted recombinant tissue factor (Innovin, Dade Behring), phospholipid vesicles, and recombinant tissue plasminogen activator (Boehringer Ingelheim). The turbidity of this mixture (100 μl) was measured at 405 nm at 37°C in a SpectraMax 340 kinetic microplate reader (Molecular Devices). Clot lysis time was defined as the time from the midpoint of the baseline to maximum turbid transition, to the final plateau phase. The interassay and intra-assay CVs were 8.1 and 6.2%, respectively.

Statistical analysis

The study was powered to have an 80% chance of detecting a 10% intergroup difference in maximum rate of TAT generation at the site of microvascular injury using a P value of 0.05, based on mean values in published articles (13–15). To demonstrate such a difference or greater, 12 patients were required in each group. The corresponding number of patients for local sCD40L release was calculated to be 12.

Continuous data are presented as means ± SD or as median (interquartile range). The Kolmogorov-Smirnov test was used to determine normal distribution. The significance of between-group differences was tested by ANOVA with Scheffe's adjustment. Post hoc comparisons were made using a Tukey test. The χ^2 test or Fisher's exact test was used to compare categorical variables. Pearson's correlations were used to identify associations between variables. A two-sided P value < 0.05 was considered statistically significant.

RESULTS — The three myocardial infarction groups did not differ with regard to demographic and clinical variables (Table 1). All three patient groups were enrolled after 5.2 ± 0.3 h of chest pain onset ($P = 0.9$). Patients with diabetes were treated either with insulin ($n = 8$; 40%) or with oral hypoglycemic agents ($n = 12$; 60%). Duration of the disease ranged from 0.5 to 11 (median 5) years. As expected, glucose levels were higher in both hyperglycemic groups and in patients with normoglycemia, whereas serum insulin and A1C were elevated in the DM group, with no difference between the HG and NG groups (Table 1). Higher cardiac troponin T was observed in the DM group than in the HG group (Table 1). In contrast to CRP, IL-6 levels were elevated by 86% both in the DM and HG groups compared with the NG group. Fibrinogen levels were 29% higher in the DM group than in the NG group, with similar values in both hyperglycemic groups (Table 1).

Bleeding time did not differ among the three groups (Table 1). The total volume of blood collected from wounds was similar in all groups (data not shown).

Table 1—*Comparisons of laboratory variables in the three groups of patients with acute coronary syndrome, based on a history of diabetes and glucose levels on admission*

	DM group	HG group	*P* value	NG group	*P* value*	*P* value†
n	20	20		20		
Age (years)	61 ± 10	60 ± 9	NS	61 ± 7	NS	NS
Men	14 (70)	16 (80)	NS	11 (55)	NS	NS
STEMI	11 (55)	11 (55)	NS	12 (60)	NS	NS
Hypertension	14 (70)	13 (65)	NS	14 (70)	NS	NS
Previous PCI	9 (45)	4 (20)	NS	7 (35)	NS	NS
Current smokers	14 (70)	13 (65)	NS	14 (70)	NS	NS
Hypoglycemic drugs	20 (100)	0 (0)	<0.0001	0 (0)	<0.0001	NS
Statins	16 (80)	5 (25)	0.0002	11 (55)	NS	NS
β-Blockers	17 (85)	16 (80)	NS	16 (80)	NS	NS
ACEIs	15 (75)	11 (55)	NS	14 (70)	NS	NS
Aspirin	20 (100)	20 (100)	NS	20 (100)	NS	NS
Diuretics	8 (40)	6 (30)	NS	7 (35)	NS	NS
Glucose (mmol/l)	9.74 ± 2.34	8.58 ± 0.87	NS	4.69 ± 0.68	<0.0001	<0.0001
Platelets (10^3/mm^3)	258.9 ± 49.3	249.5 ± 45.8	NS	253.5 ± 41.0	NS	NS
CRP (mg/l)	2.72 (0.9–6.5)	1.45 (0.77–4.11)	NS	1.9 (1.01–2.32)	NS	NS
IL-6 (ng/ml)	3.13 ± 1.19	3.13 ± 1.06	NS	1.68 ± 0.56	<0.0001	<0.0001
TnT (ng/ml)	2.98 ± 2.07	1.53 ± 1.42	0.028	2.92 ± 2.7	NS	NS
TnT max (ng/ml)	5.9 (2.7–13.2)	28.9 (5.9–49.7)	0.019	24.9 (7.5–41.9)	0.013	NS
Fibrinogen (g/l)	4.1 ± 1.08	3.17 ± 0.8	0.004	3.04 ± 0.7	0.002	NS
TC (mmol/l)	6.06 ± 1.08	5.42 ± 0.99	NS	5.42 ± 1.14	NS	NS
LDL cholesterol (mmol/l)	3.75 ± 1.06	3.31 ± 0.73	NS	3.41 ± 0.99	NS	NS
HDL cholesterol (mmol/l)	1.28 ± 0.7	1.21 ± 0.37	NS	1.23 ± 0.15	NS	NS
TGs (mmol/l)	1.97 ± 1.46	1.68 ± 1.06	NS	1.56 ± 0.44	NS	NS
sCD40L (pg/ml)	747.75 ± 283.72	619.95 ± 306.55	NS	339.75 ± 92.97	<0.0001	0.0003
TAT (μg/l)	6.58 ± 1.67	5.86 ± 1.73	NS	5.06 ± 1.84	0.0095	NS
F1.2 (nmol/l)	1.16 (0.97–1.89)	1.04 (0.88–1.19)	NS	0.91 (0.78–1.13)	0.016	NS
A1C (%)	6.81 ± 0.37	5.5 ± 0.36	<0.0001	5.47 ± 0.27	<0.0001	NS
Insulin (pmol/l)	154.985 ± 53.47	96.825 ± 31.12	0.0002	86.7 ± 31.15	<0.0001	NS

Data are means ± SD, *n* (%), or median (interquartile range). *Comparison (ANOVA, post hoc analysis) between the group of patients with diabetes and that with glucose levels <7.0 mmol/l (the NG group). †Comparison (ANOVA, post hoc analysis) between the group with no known history of diabetes, but elevated glucose levels on admission for an acute event (the HG group), and the group with glucose levels <7.0 mmol/l (the NG group). ACEI, angiotensin-converting enzyme inhibitor; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TnT, cardiac troponin T; TC, total cholesterol; TG, triglyceride.

Thrombin formation

Plasma TAT and F1.2 concentrations did not differ between the DM and HG groups. However, diabetic patients with acute myocardial infarction, but not those from the HG group, had higher plasma levels of F1.2 (by 27.5%) and TATs (by 30%) than those observed in the NG group (Table 1).

Time courses of TAT generation at the site of injury were similar regardless of the presence or absence of hyperglycemia (Fig. 1*A*). Maximum TAT levels were found at 6 min, with the highest values in the DM group (112.6 ± 10.4 nmol/l) and the lowest in the NG group (89.7 ± 9.1 nmol/l; $P = 0.006$). There was no difference between maximum TAT levels in bleeding time blood in the HG (96.1 ± 5.9 nmol/l) and NG groups ($P = 0.3$). A peak rate of TAT formation after vascular injury was higher in hyperglycemia (0.36 ± 0.03 for the DM group and 0.3 ± 0.03 nmol/l/s for the HG group, respectively) compared with patients with normoglycemia (0.21 ± 0.03 nmol/l/s; $P < 0.0001$ for both comparisons). However, TAT was also generated faster in the DM group than in the HG group ($P < 0.0001$). Total amounts generated after injury within 6 min were increased by 24.3% in diabetic patients with acute myocardial infarction compared with amounts in those with elevated glucose levels without a history of diabetes ($P < 0.0001$) as well as by 55.4% compared with amounts in those with normoglycemia during acute myocardial infarction ($P < 0.0001$) (Fig. 2*A* of the online appendix [available at http://dx.doi.org/10.2337/dc08-0282]).

None of the variables describing TAT formation at the site of vascular injury showed associations with plasma TAT levels, glycemia, insulinemia, age, or other clinical or laboratory variables in the three groups studied. Total formation of TATs within the first 6 min was associated with triglycerides in the HG group, but not in the other two groups ($r = 0.48$; $P = 0.03$). The maximum rate of TAT generation and TAT levels tended to be higher in patients whose blood was drawn after a longer time from pain onset only in the DM group ($r = 0.38$; $P = 0.1$ for both). Other variables showed no correlation with time from pain onset (data not shown).

Platelet activation

Plasma sCD40L levels were similar in the DM and HG groups. Compared with the normoglycemic patients, patients in both the DM and HG groups displayed higher plasma sCD40L levels by 120 and 82.5%, respectively (Table 1). Profiles of sCD40L release, reflected in its levels in blood obtained from bleeding time wounds, shared common kinetics in acute myocar-

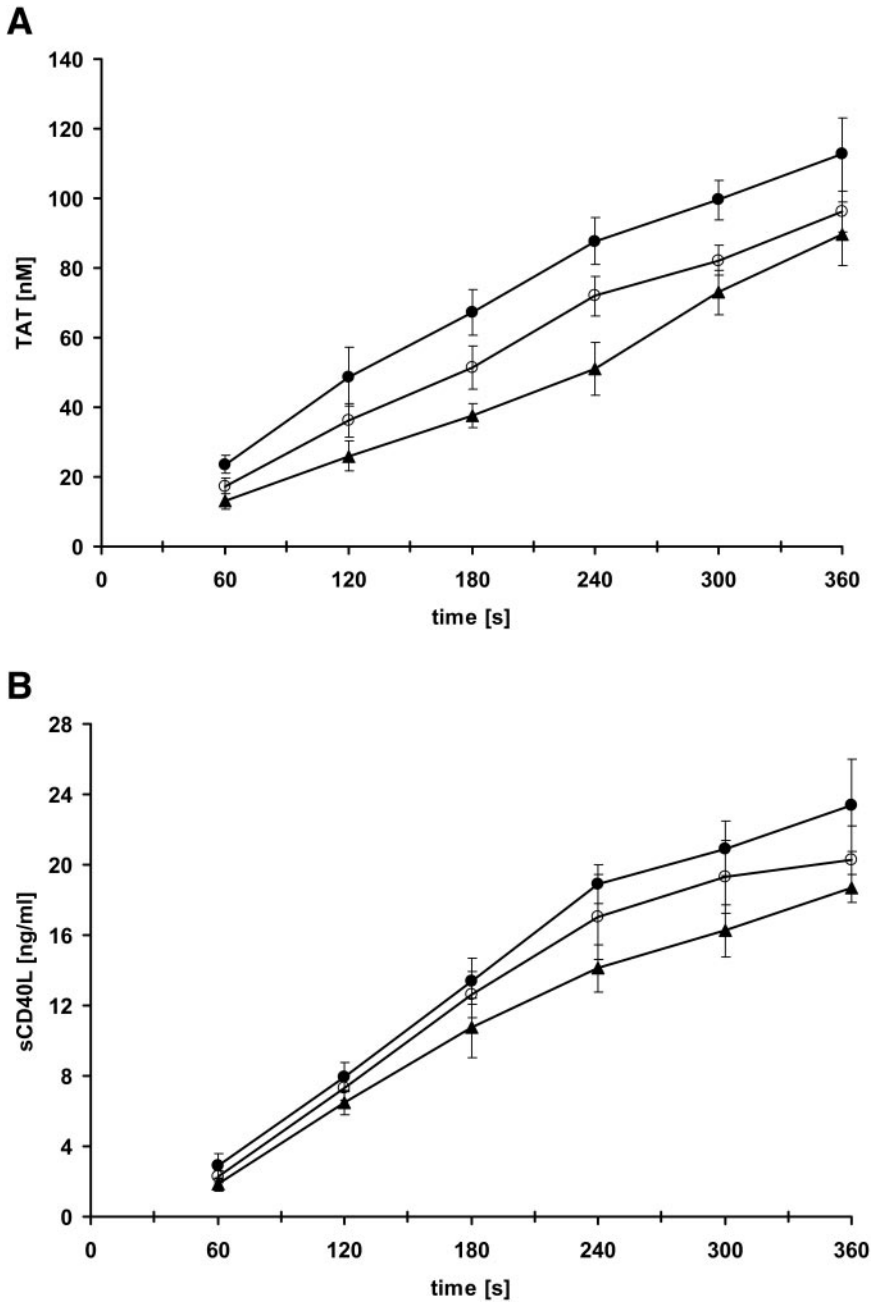

Figure 1— *Thrombin formation and platelet activation at the site of microvascular injury in patients with acute coronary syndrome.* A: *Concentrations of TATs in the 60-s bleeding time blood samples in 20 patients with documented diabetes (●), 20 patients with no history of diabetes but elevated glucose levels (○), and 20 patients with normoglycemia during the acute event (▲).* B: *Concentrations of sCD40L in the 60-s bleeding time blood samples in 20 patients with diabetes (●), 20 patients with no history of diabetes but elevated glucose levels (○), and 20 patients with normoglycemia during the acute event (▲). Values are plotted as means ± SEM.*

dial infarction patients, with the steepest increase in diabetic subjects (Fig. 1*B*). The highest local sCD40L value of 23.4 ± 2.6 ng/ml was observed in the DM group. A lower maximum sCD40L level of 20.3 ± 1.9 ng/ml ($P < 0.001$) was found in the HG group. Maximum rates of sCD40L release were higher in patients in the DM (0.087 ± 0.009 ng · ml^{-1} · s^{-1}) and HG (0.086 ± 0.01 ng · ml^{-1} · s^{-1}) groups than in individuals with normoglycemia (0.074 ± 0.012 ng · ml^{-1} · s^{-1}; $P < 0.001$ for both comparisons). There was no difference in this variable between the DM and HG groups ($P = 0.2$). The velocity of the sCD40L increase in shed blood was increased in the HG group compared with that in the NG group ($P = 0.011$).

Total release of sCD40L within the first 6 min was similar in the DM and HG groups. Both of these groups were characterized by increased amounts of sCD40L measured after injury (by 28 and 16.3%, $P < 0.001$, respectively) compared with the NG group (Fig. 2*B* of the online appendix).

In the DM group, the maximum rate of the sCD40L release showed no association with the duration of diabetes, insulin administration, age, or other clinical or laboratory variables with two exceptions. It was correlated with glucose ($r = 0.56$; $P = 0.01$) and with plasma TAT levels ($r = 0.53$; $P = 0.02$). No similar associations were observed in the two other groups. Total release of sCD40L within the first 6 min was associated with total cholesterol ($r = 0.47$; $P = 0.036$) and plasma sCD40L levels ($r = 0.48$; $P = 0.03$) but only in the HG group. Variables describing local sCD40L release showed no significant correlations with time from pain onset (data not shown).

Clot permeability

Lower clot permeability was found in patients with a prior history of diabetes compared with subjects from both the HG and NG groups (Table 2). However, K_s was similar in the HG and NG groups. K_s was correlated with fibrinogen in all

Table 2—*Fibrin clot permeability (K_s) and lysis time (t) in the three groups of patients with acute coronary syndrome, based on a history of diabetes and glucose levels on admission*

	DM group	HG group	*P* value	NG group	*P* value*	*P* value†
n	20	20		20		
K_s (10^{-9} cm^2)	6.1 (5.3–7.9)	7.5 (6.9–8.9)	0.02	7.6 (7.1–9.1)	0.006	NS
t (min)	127.9 (98.3–137.4)	116.1 (77.9–120.3)	0.001	98.5 (73.4–111)	<0.0001	<0.0001

Data are median (interquartile range). *Comparison between the DM and NG groups. †Comparison between the HG and NG groups.

groups (r from −0.36 to −0.51; $P < 0.05$). K_s was inversely associated with CRP only in the DM group ($r = -0.42$, $P = 0.03$), but showed no associations with lipids or thrombin or platelet parameters in venous or bleeding time blood in either group.

Fibrinolysis

Clot lysis time was the longest in the diabetic patients admitted for acute myocardial infarction and was significantly shorter in the HG group than in subjects with normoglycemia (Table 2). Lysis time showed correlations only with CRP in all three groups (r from 0.35 to 0.49; $P < 0.05$). No associations between lysis time and glucose or insulin levels were observed in any of the groups. There were no correlations of lysis time with thrombin generation or platelet activation in any of the patients and in the three groups or with time from the onset of myocardial infarction symptoms or troponin levels (data not shown).

Short-term outcomes

During a 30-day follow-up, there were three cardiovascular deaths (two in the DM group and one in the NG group). Recurrent myocardial ischemia was observed in six patients, two in each group. No intergroup differences in major adverse cardiovascular events were observed. Glucose levels determined 1 month after enrollment revealed that all normoglycemic subjects had still normoglycemia, whereas three subjects from the HG group had glycemia >7 mmol/l; exclusion of these patients did not alter the results for hemostatic variables (data not shown).

CONCLUSIONS — The current study shows that elevated glucose levels are associated with significantly augmented thrombin formation and platelet protein secretion in response to vascular injury not only in patients with type 2 diabetes but also in those with no prior history of diabetes and hyperglycemia during acute myocardial infarction. Moreover, we demonstrated that hyperglycemia observed in acute myocardial infarction results in hypofibrinolysis, regardless of a history of type 2 diabetes, whereas reduced clot permeability was found only in patients with previously diagnosed diabetes compared with normoglycemic individuals. Our findings indicate that not only diabetes but also hyperglycemia occurring in acute myocardial infarction patients with no prior diagnosis of diabetes produces several prothrombotic effects that may contribute to an increased risk for thrombotic complications after an acute coronary event. The impact of hyperglycemia in myocardial infarction patients appeared potent enough to be detected despite strong prothrombotic effects of coronary plaque injury during myocardial infarction. Our findings may also help explain a recent observation that glucose-insulin-potassium therapy, resulting in increased glucose levels, could be harmful within the first days of acute myocardial infarction (18).

Because efficient hemostasis occurs only at vascular lesions where tissue factor is exposed and platelets rapidly aggregate, measurements of hemostatic markers at the site of vascular injury are more sensitive than those in venous blood in the assessment of local thrombotic reactions (13,14,19). We did not observe elevated levels of thrombin or platelet markers in venous blood in diabetic patients compared with those from the HG group; the differences were detectable at the site of injury. Probable mechanisms for this effect of hyperglycemia involve enhanced activation of proinflammatory transcription factors that can increase tissue factor expression (20). Augmented local thrombin production in myocardial infarction patients with glucose >7.0 mmol/l was accompanied by increased platelet activation, reflected by elevated sCD40L levels in venous plasma and bleeding time blood. Of several soluble platelet activation markers, including β-thromboglobulin or P-selectin, sCD40L has been extensively studied in hyperglycemic subjects (8,9,21) and measured at the site of injury (19,22); ~95% of circulating sCD40L is platelet-derived (11,23). For these reasons, sCD40L was chosen as the platelet activation marker in the current study. Importantly, a similar increase in sCD40L release correlated with thrombin formation has been reported in patients with the metabolic syndrome (24).

Fibrin clot analysis revealed reduced lysis time in the DM and HG groups compared with that in subjects with glycemia <7 mmol/l, without any intergroup differences in clot permeability except for significantly higher permeability in diabetic subjects. Glycation of the fibrinogen molecules is largely responsible for altered fibrin clot features found at elevated glucose levels (10,11). We extended previous observations by showing a potent impact of diabetes on fibrin properties, easily detectable also in myocardial infarction patients despite the fact that acute myocardial ischemia itself is associated with deleterious clot alterations similar to those described in diabetic patients (12). A short-term increase in glucose levels does not modify fibrin structure, which explains the similar permeability observed in the HG and NG groups. Reduced lysis efficiency in the HG and DM groups indicates the presence of some glucose-mediated rapid mechanisms impairing fibrinolysis even if the extent of glycation is negligible. This effect could be explained by elevated plasminogen activator inhibitor 1 observed in hyperglycemia (5,6). It might be speculated that altered fibrin in hyperglycemia leads to lower binding affinity of both tissue plasminogen activator and plasminogen toward fibrin (11) and, as a consequence, impaired clot lysis in our assay.

One might suspect that insulin or oral hypoglycemic agents taken only by diabetic patients confounded the data interpretation. However, there is no evidence that in myocardial infarction patients such therapy alters thrombin formation or platelet activation. In terms of fibrin-modifying properties, insulin, gliclazide, and metformin have been shown to enhance clot lysis (25). We might speculate that susceptibility to lysis is probably even weaker in untreated diabetic patients with myocardial infarction. Another potential effect could be mediated by statins that were taken by a significantly lower percentage of the HG group before myocardial infarction. Because statins can reduce thrombin generation (13) and platelet activation (20) after injury in stable patients, both processes may have been relatively more vigorous in the HG group than in the DM and NG groups. However, no data support the view that statins are potent enough to suppress the massive activation of hemostasis observed in patients with acute myocardial infarction (26).

This study has limitations. First, the number of patients studied is limited. However, we matched the myocardial infarction patients with and without elevated glucose levels as well as those with normoglycemia well. Second, our analysis was based on a determination of each variable at a single time point. Third, results of oral glucose tests after myocardial infarction were not analyzed. However, lack of significant differences in A1C between the HG and NG groups speaks against the possibility that patients with undiagnosed diabetes before the acute

event were enrolled in the HG group. Finally, statistical associations reported here do not necessarily mean cause-effect relationships. Further studies are needed to elucidate this issue.

In summary, our findings demonstrate that acute hyperglycemia in acute myocardial infarction patients without a previous history of diabetes is associated with increased thrombin generation and platelet activation at the site of vascular injury as well as greater resistance to fibrinolysis. This study provides further insights into the relationship between hyperglycemia and thrombosis in myocardial infarction patients.

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