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Original Scientific Paper

In-hospital peak glycemia and prognosis in STEMI patients without earlier known diabetes

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Background Acute myocardial infarction is known as an acute metabolic stress, but clinicians currently have limited guidance regarding the evaluation and management of hyperglycemia after revascularization.

Methods and results We assessed the prognostic role of three different ranges of in-hospital peak glycemia (<140, 140–180, and >180 mg/dl) in 252 acute ST-segment elevation myocardial infarction patients without earlier known diabetes submitted to percutaneous coronary intervention consecutively admitted to our intensive cardiac care unit (ICCU). Patients with highest peak glycemia showed the highest intra-ICCU mortality (7/44, 15.9%), which was significantly higher with respect to the other two subgroups ($P=0.001$ and 0.034 , respectively). At backward stepwise logistic regression analysis, peak glycemia (odds ratio: 3.14; 95% confidence interval: 1.01–9.74, $P=0.047$) was an independent predictor of intra-ICCU mortality.

Conclusion In acute ST-segment elevation myocardial infarction patients without earlier known diabetes submitted to mechanical revascularization, the poorer in-hospital glucose control was associated with higher mortality; peak glycemia greater than 180 mg/dl was associated with the highest mortality, whereas patients with peak glycemia comprised between 140 and 180 mg/dl exhibited intermediate mortality rates. According to our data during hospitalization intensivists should achieve glucose control values less than 140 mg/dl, as peak glycemia resulted in the independent predictor of intra-ICCU mortality. *Eur J Cardiovasc Prev Rehabil* 17:419–423 © 2010 The European Society of Cardiology

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Keywords: acute ST-segment elevation myocardial infarction, in-hospital mortality, nondiabetic

Introduction

Acute myocardial infarction (AMI) is known as an acute metabolic stress whose components consists of a rapid rise in blood glucose mainly due to an increase in plasma catecholamines and plasma fatty-free acids [1]. Admission high blood glucose levels in patients with acute coronary syndrome (ACS) are common and are associated with an increased risk of death [2–4]. Most earlier studies have focused mainly on the prognostic value of admission glucose.

Despite a growing body of knowledge about the prognostic importance of elevated glucose in ACS

and some evidence of improved outcomes from tight glucose control in other critically ill populations [5,6], clinicians currently have limited guidance regarding the evaluation and management of hyperglycemia in the ACS setting, and in particular in the acute phase after revascularization.

It has been recently stated [2] that in ACS patients admitted to an intensive care unit (ICU), it is reasonable to consider intensive glucose control in those with significant hyperglycemia (i.e. plasma glucose > 180 mg/dl). In contrast, strategies for the management of patients with milder degrees of hyperglycemia are far to be elucidated. In particular, the precise goal of treatment has not yet been defined and the suggested range for plasma glucose is 90–140 mg/dl [2].

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The aim of this investigation was to assess the prognostic role of three different ranges of in-hospital peak glycemia (< 140, 140–180, and > 180 mg/dl) in 252 ST-elevation myocardial infarction (STEMI) patients without earlier known diabetes submitted to percutaneous coronary intervention (PCI) consecutively admitted, after mechanical revascularization, to our intensive cardiac care unit (ICCU).

Methods

In a prospective study, from 1 January 2006 to 31 July 2007, 252 consecutive patients with STEMI (within 12 h from symptoms' onset) and without earlier known diabetes were admitted to our ICCU, which is located at the tertiary center. In our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI [7]. STEMI patients are first evaluated by the Medical Emergency System staff in the prehospital setting and then directly admitted to the catheterization laboratory or transferred to it after a rapid stabilization in the first aid. After primary PCI, they are admitted to our ICCU. In the same period, 106 STEMI patients with diabetes were consecutively admitted to our ICCU but, because of diabetes, they were excluded from the study.

A successful procedure was defined as an infarct artery stenosis less than 20% associated with thrombolysis in myocardial infarction (TIMI) grade 3 flow. Failure PCI was defined as resulting in TIMI grade 0–2 flow, regardless the residual stenosis [8]. None of the patients were on any chronic anti-inflammatory agent.

Study population

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association [9].

On ICCU admission, soon after PCI, blood samples were obtained for glucose, cardiac biomarkers [creatinine phosphokinase (CPK): 20–160 U/l, CPK-myocardial band (MB): 0.5–3.6 ng/ml, Tn I < 0.15 ng/ml], and creatinine serum levels (0.6–1.5 mg/dl), C-reactive protein (< 9 mg/dl), erythrocyte sedimentation rate (ESR, 2–25 mm/h), leucocytes count (4000–10 000/ μ l), fibrinogen (200–450 mg/dl), lactic acid (0.6–1.7 mmol/l), hemoglobin A1c (HbA1c) values (< 6.5%), and *N*-terminal pro-B-type natriuretic peptide measurements (males: 0–50 years: < 88 pg/ml; > 50 years: < 227 pg/ml, females: 0–50 years: < 153 pg/ml; > 50 years < 334 pg/ml) [10,11]. Transthoracic two-dimensional echocardiography was performed on ICCU admission to measure the left ventricular (LV) ejection fraction. Glycemia was assessed three times a day throughout the ICCU stay. Patients were stratified into three groups according to peak glycemia: G1: less than 140 mg/l, G2: 140–180 mg/l, and G3: > 180 mg/l.

Intensive insulin therapy was administered in patients with significant hyperglycemia (i.e. plasma glucose > 180 mg/dl). The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed consent was obtained from all patients before enrollment.

Statistical analysis

Categorical data are expressed as frequencies and percentages; continuous data are reported as median (25–75th percentile). Univariate analysis (χ^2 , Fisher's exact test for categorical data; Mann–Whitney *U*-test and/or Kruskal–Wallis *H*-test for continuous data) was used to identify candidate variables for multivariate analysis using a threshold *P* value of less than 0.05. Backward stepwise logistic regression was performed to assess whether hyperglycemia was the predictor of in-hospital mortality. A *P* value of less than 0.05 was considered significant. Analysis was carried out using SPSS 11.5 statistical package (SPSS Inc., Chicago, Illinois, USA).

Results

Table 1 shows the clinical characteristics of STEMI patients included in the study, according to the peak glucose values. In our series, 12 patients (4.7%) presented with cardiogenic shock and eight patients with cardiac arrest (3.2%). Renal failure was present in 12 patients (4.2%). During the ICCU stay, most of the patients (152/252; 59.9%) exhibited peak glucose values less than 140 mg/dl. Higher peak glucose levels were associated with more advanced age (*P*=0.001), a higher incidence of renal failure (*P*=0.009), a higher Killip class (*P*=0.002), and a lower LV ejection fraction (*P*< 0.001). In the overall population, intra-ICCU mortality was 4.7% (12/252). Patients in G3 showed the highest intra-ICCU mortality (7/44, 15.9%), which was significantly higher with respect to the patients in both G1 (*P*=0.001) and G2 (*P*=0.034). No differences were observed among the three subgroups (Table 2) with respect to the extension of coronary artery disease, myocardial infarction location, TIMI flow post procedure, and incidence of PCI failure. Patients in G3 exhibited a higher incidence of TIMI flow 0–1 preprocedure.

Biochemical data are depicted in Table 3. Highest peak glucose levels were associated with the highest fasting glucose values (*P*< 0.001), CPK, CPK-MB, and Tn I (*P*=0.005, 0.001, and 0.003, respectively). None of the patients in G1 showed HbA1c values greater than 6.5%, whereas patients in G2 and G3 showed a higher incidence of HbA1c, that is, values greater than 6.5% (G2: 41.7%; G3: 81.1%, respectively). *N*-terminal pro-B-type natriuretic peptide levels were higher in G3 patients (*P*=0.003), and lactic acid (*P*< 0.001).

At backward stepwise logistic regression analysis, the following variables resulted as independent predictors of in ICCU mortality: age [odds ratio (OR): 1.12; 95%

Table 1 Clinical characteristics of patients included in the study

Variable frequency (%) or median (25–75th percentile)	Peak glycemia (g/dl)			P χ^2 or Kruskal–Wallis H test
	G1: <1.40 (n=151)	G2: 1.40–1.80 (n=57)	G3: >1.80 (n=44)	
Females/males	32/119 (21.2/78.8)	16/41 (28.1/71.9)	13/31 (29.5/70.5)	0.388
Age (years)	62 (55–73)	69 (62–76)	71 (59–78)	0.001
Weight (kg)	74 (65–82)	74 (66–84)	75 (65–82)	0.944
BMI (kg/m ²)	25.7 (23.5–28.0)	25.5 (23.8–29.7)	26.7 (23.7–28.6)	0.424
Hypertension	65 (43.0)	30 (52.6)	24 (54.5)	0.263
Dyslipidemia	58 (38.4)	30 (52.6)	18 (40.9)	0.177
Smoke				
No smoke	56 (37.3)	26 (45.6)	27 (61.4)	0.067
Earlier smoke	76 (50.7)	27 (47.4)	14 (31.8)	
Ever smoke	18 (12.0)	4 (7.0)	3 (6.8)	
Comorbidities	27 (17.9)	12 (21.1)	14 (31.8)	0.136
Renal failure	4 (2.6)	2 (3.5)	6 (13.6)	0.009
COPD	8 (5.3)	4 (7.0)	3 (6.8)	0.865
Earlier MI	16 (10.6)	5 (8.8)	9 (20.5)	0.146
Earlier angina	23 (15.2)	10 (17.6)	5 (11.4)	0.688
Earlier PCI	20 (13.2)	7 (12.3)	6 (13.6)	0.977
Earlier CABG	1 (0.7)	0	0	0.715
Killip class				
I	132 (88.0)	43 (75.4)	33 (75.0)	0.002
II	14 (9.3)	5 (8.8)	2 (4.5)	
III	1 (0.7)	3 (5.3)	1 (2.3)	
IV	3 (2.0)	6 (10.5)	8 (18.2)**	
AMI location				
Inferior	67 (44.4)	22 (38.6)	14 (31.8)	0.472
Lateral	9 (6.0)	6 (10.5)	3 (6.8)	
Anterior	75 (49.7)	29 (50.9)	27 (61.4)	
LVEF (%)	48 (40–52)	40 (35–48)	40 (26–47)	<0.001
Dead patients				
ICCU (2004–2007)	3 (2.0)	2 (3.5)	7 (15.9)**	0.001
Follow-up (n=152; 2004–2006)	5 (5.4)	0	1 (3.4)	0.401
Total (n=162; 2004–2006)	8 (8.4)	1 (3.1)	7 (20.0)	0.052

AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary-artery bypass graft; COPD, chronic obstructive pulmonary disease; ICCU, intensive cardiac care unit; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention. ** $P<0.01$.

Table 2 Angiographic data of patients included in the study

Variable frequency (%) or median (25–75th percentile)	Peak glycemia (g/dl)			P χ^2 or Kruskal–Wallis H test
	G1: <1.40 (n=151)	G2: 1.40–1.80 (n=57)	G3: >1.80 (n=44)	
Coronary artery disease				
No disease	2 (1.3)	0 (0.0)	0 (0.0)	0.571
1 vessel	55 (36.4)	24 (42.1)	14 (31.8)	
2 vessel	57 (37.7)	17 (29.8)	18 (40.9)	
3 vessel	36 (23.8)	14 (24.6)	12 (27.3)	
CABG	1 (0.7)	2 (3.5)	0 (0.0)	
Left main	8 (5.3)	5 (8.8)	2 (4.5)	0.583
Collateral branches	13 (8.6)	8 (14.0)	6 (13.6)	0.417
TIMI flow pre-PCI				
III	9 (6.0)	0 (0.0)	1 (2.3)	0.033
II	10 (6.6)	4 (7.0)	0 (0.0)	
I	19 (12.6)	6 (10.5)	12 (27.9)*	
0	113 (74.8)	47 (82.5)	31 (69.8)	
IRA				
RCA	58 (38.4)	21 (36.8)	10 (22.7)	0.443
CX	15 (9.9)	6 (10.5)	7 (15.9)	
LDA	76 (50.3)	28 (49.1)	26 (59.1)	
Left main	0 (0.0)	1 (1.8)	1 (2.3)	
CABG	2 (1.3)	1 (1.8)	0 (0.0)	
Stent implantation	137 (90.7)	53 (93.0)	37 (84.1)	0.305
TIMI flow postPCI				
III	140 (92.7)	51 (89.5)	39 (88.4)	0.598
II	8 (5.3)	4 (7.0)	4 (9.3)	
I	1 (0.7)	2 (3.5)	1 (2.3)	
0	2 (1.3)	0 (0.0)	0 (0.0)	
PCI failure abciximab	10 (6.6)	6 (10.5)	5 (11.4)	0.480

CABG, coronary artery bypass; CX, left circumflex artery; IRA, infarct-related artery; LDA, left descending artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction. * $P<0.05$.

Table 3 Biochemical data of patients included in the study

Variable frequency (%) or median (25–75th percentile)	Peak glycemia (g/dl)			P χ^2 or Kruskal–Wallis H test
	G1: <1.40 (n=151)	G2: 1.40–1.80 (n=57)	G3: >1.80 (n=44)	
Glycemia (g/l)	1.15 (1.03–1.23)	1.53 (1.47–1.64)	1.92 (2.28–2.34)	<0.001
HbA1c (%)	0	41.7	81.1	<0.001
NT-proBNP	1441 (418–2781)	1860 (584–3031)	3032 (948–4698)	0.003
Lactic acid	1.50 (1.00–1.90)	1.90 (1.60–2.30)	2.30 (1.73–3.50)	<0.001
CPK (U/l)	1572 (799–3015)	2371 (1356–4584)	2578 (1290–4518)	0.005
CK-MB (ng/ml)	172.0 (93.1–308.0)	297.0 (152.2–544.8)	291.0 (135.2–496.5)	0.001
Peak Tn I (ng/ml)	62.7 (33.0–129.0)	100.3 (55.9–224.5)	116.4 (51.9–199.8)	0.003
Creatinine (mg/dl)	1.00 (0.80–1.10)	1.00 (0.80–1.10)	1.10 (0.92–1.28)	0.003
Insulin resistance (HOMA>2)	62 (41.1)	36 (63.2)	36 (81.8)	<0.001

CK, creatine kinase; CPK, creatine phosphokinase; ESR, erythrocyte sedimentation rate; HbA1c; hemoglobin A1c; HOMA, homeostatic model assessment; MB, myocardial band; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

confidence interval (CI): 1.02–1.24, $P=0.021$]; LV ejection fraction (OR: 0.88; 95% CI: 0.80–0.96, $P=0.004$); Tn I (OR: 1.004; 95% CI: 1.000–1.008, $P=0.042$); and peak glycemia (OR: 3.14; 95% CI: 1.01–9.74, $P=0.047$).

Discussion

In patients with STEMI, hyperglycemia is common and frequently untreated [2]. Most earlier studies have focused predominantly on the prognostic value of admission glucose [2], whereas three earlier investigations suggest that hyperglycemia after hospital admission holds a more important prognostic significance than admission hyperglycemia. Suleiman *et al.* [12] observed that the addition of fasting glucose levels within 24 h of hospitalization to the admission glucose values improved the ability of the model to predict 30-day mortality rates. Svensson *et al.* [13] showed that hyperglycemia on arrival and hypoglycemia during hospitalization are both independently associated with worse adjusted all-cause 2-year mortality risk. Finally, Goyal *et al.* [14] assessed the effect of the change between 24 h and admission glucose levels and death, and documented that an increase in glucose values during the first 24 h of hospitalization was associated with higher 30-day and 180-day mortality rates.

Kosiborod *et al.* [15] documented that in elderly AMI patients, particularly those without recognized diabetes elevated glucose is common, rarely treated, and associated with increased mortality risk.

Moreover, in STEMI patients the benefits of treating hyperglycemia have not been established definitively and the target value of blood glucose to be achieved with treatment remains undefined [2]. Earlier randomized clinical trials of glucose control in ACS have been limited primarily to patients with known diabetes, and their results have been inconsistent due to the different patient selections, and the wide variation in glucose targets [16–21]. In contrast, studies in critically ill patients show that successful strict glucose control may result in better outcomes. In particular, a landmark study by van den Berghe *et al.* [5] showed that target-driven glucose control

with intensive insulin therapy (goal of whole blood glucose level of 80–110 mg/dl) reduced ICU mortality rates from 8.0 to 4.6% in surgical patients and in-hospital mortality rates from 10.9 to 7.2%. This improvement was more pronounced in patients with an ICU stay of more than 5 days. Obviously, as the significant differences in patient populations, the results of the studies carried out in critical illness by van den Berghe *et al.* [5] cannot simply be extrapolated to patients with ACS, mainly because many patients with ACS have ICU stays shorter than 3 days.

In contrast, in the recent guidelines [2], as the paucity of data on glucose control in ACS, intensive glucose control in patients with significant hyperglycemia (plasma glucose > 180 mg/dl) is considered reasonable (level of evidence B) regardless of earlier diabetes history, whereas in patients with milder degrees of hyperglycemia efforts to optimize glucose levels are suggested. Kosiborod *et al.* [22] documented that measures of persistent hyperglycemia during AMI are better predictors of mortality than admission glucose.

The main finding of this investigation, performed in nondiabetic STEMI patients submitted to mechanical revascularization, was that the poorer in-hospital glucose control was associated with higher mortality; in particular, peak glycemia greater than 180 mg/dl was associated with the highest mortality, whereas patients with peak glycemia comprised between 140 and 180 mg/dl exhibited intermediate mortality rates.

Acute glycemic variations are associated with a prothrombotic status related to several alterations of the hemostatic pathway, including lengthening of fibrinogen half-life, increased number of prothrombin fragments, factor VII, and in platelet aggregation [23]. Hyperglycemia *per se* induces a proinflammatory state, which includes both cellular and oxidative stress. At the cellular level, glucose is known to increase proinflammatory transcription factors (such as intranuclear nuclear factor-kappa B binding, activator protein-1, and early growth response-1) that are suppressed by insulin. In the presence of high glucose concentrations, several steps

of the glycolytic pathways can induce the release of toxic derivatives, including polyols derived from glucose, hexosamines from fructose-6-phosphate, advanced glycation products, and activators of the protein kinase C pathway from glyceraldehyde-3-phosphate. Vulnerability to glucose toxicity may also be due to increased generation of or deficient scavenging systems for radical oxygen species produced by activated glycolysis and oxidative phosphorylation. During hypoxia-reperfusion superoxide production is increased and when, in this setting, cells are also overloaded with glucose, high levels of superoxide (together with nitric oxide metabolites) contribute to mitochondrial dysfunction. This phenomenon supports the hypothesis that in STEMI patients even in the postrevascularization phase, glucose control should be optimized [23–26].

Our results are in agreement with the recent paper by Kosiborod *et al.* [25] who reported that based on the data of approximately 7800 patients with AMI glucose normalization after admission is associated with better survival in hyperglycemic patients.

Limitation of the study

The main limitation is represented by the small number size in this single-center study. However, the patient population is unselected and homogeneous comprising consecutive STEMI without earlier known diabetes patients all submitted to mechanical revascularization.

Conclusion

In STEMI patients without earlier known diabetes, peak glycemia was found to be an independent predictor for intra-ICCU mortality. In particular peak glycemia greater than 180 mg/dl was associated with the highest mortality, whereas patients with peak glycemia comprised between 140 and 180 mg/dl exhibited intermediate mortality rates. Thus, intensivists should consider intra-ICCU glucose control as a therapeutic goal, with a target less than 140 mg/dl.

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