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Determinants of C-peptide levels and acute insulin resistance/sensitivity in nondiabetic STEMI role of Killip class

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ABSTRACT

The alterations in glucose homeostasis in the early phase of nondiabetic ST-elevation myocardial infarction (STEMI) are complex, involving not only hyperglycemia but also the development of acute insulin resistance (as part of the stress response) as assessed by the Homeostatic Model Assessment index (HOMA). No data is so far available on C-peptide values in the acute phase of STEMI in patients without previously known diabetes. The aims of the present investigation, performed in 782 consecutive STEMI patients without previously known diabetes, were as follows: a) to assess the determinants of C-peptide levels; b) to address the relation between acute insulin-resistance and Killip class; and c) to investigate the prognostic role of C-peptide for early mortality. In our series, 729 patients (93.2%) were in Killip I–II (group A), while 53 patients (6.8%) were in Killip classes III–IV (group B). Group B showed higher levels of admission glycemia, insulin and C-peptide ($p < 0.001$, $p = .022$ and $p < 0.001$ respectively), together with higher values of HOMA-index and log-HOMA ($p < 0.001$ and $p < 0.001$, respectively) and reduced HOMA-%B ($p = 0.014$). Left ventricular ejection fraction was inversely correlated with C-peptide, insulin and admission glycemia ($p < 0.001$, $p = 0.018$ and $p < 0.001$, respectively). At logistic regression analysis C-peptide and insulin values were not associated with in-ICCU death.
According to our data, the development of acute insulin resistance in the early phase of STEMI can be viewed as an adaptive mechanism to stress (represented by acute myocardial ischemia), similar to other acute critical conditions, related to the severity of stress (that is to the hemodynamic impairment).

Introduction

In the setting of acute myocardial infarction [1], hyperglycemia is not simply a marker of pre-existing diabetes or glucose intolerance but it may represent a stress response to myocardial injury mainly related to acute catecholamine release [2,3]. In patients with ST elevation myocardial infarction (STEMI) several studies addressed the glucose stress response [4] by investigating the prognostic role of glucose values measured on admission and throughout hospital stay [5–8].

However, the alterations in glucose homeostasis in the early phase of STEMI are far more complex, including also the development of acute insulin resistance which has been so far investigated only by few studies by means of the Homeostatic Model Assessment (HOMA index) [9,10]. No data is so far available on C-peptide values in the acute phase of STEMI in patients without previously known diabetes, taking into account that C-peptide is a robust measure of insulin secretion but not of insulin action [11], differently from HOMA index.

Since in critically ill patients the severity of insulin resistance is associated with the severity of illness [12], we hypothesized that in non-diabetic STEMI patients advanced Killip classes were associated with a more severe acute insulin resistance.

The aims of the present investigation, performed in 782 consecutive STEMI patients without previously known diabetes, were as follows: a) to assess the determinants of C-peptide levels; b) to address the relation between acute insulin-resistance and Killip class; and c) to investigate the prognostic role of C-peptide for early mortality.

Methods

From 1st April 2009 to 31st December 2012, 782 consecutive patients with STEMI (within 12 h from symptoms' onset) and without previously known diabetes were admitted to our Intensive Cardiac Care Unit (ICCU), which is located at a tertiary center (where primary percutaneous coronary intervention-PCI- can be performed 24/24 h 7 days/week). In our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI [13–16]. After primary PCI, they are admitted to our ICCU.

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association [13,16].

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On ICCU admission, after PCI, in a fasting blood sample the following parameters were measured: glucose (g/l), glycated hemoglobin (%), insulin (mU/l), C-peptide (mU/l), troponin I (Tn I, ng/ml), uric acid (mg/dl), NT-pro Brain Natriuretic Peptide (NT-pro BNP) (pg/ml), leukocytes count ($*10^3$/μl), fibrinogen (mg/dl) and hs-C-Reactive protein positivity (hs-CRP) (normal values < 9). Intensive insulin therapy was administered in patients with significant hyperglycemia (that is plasma glucose > 180 g/l) [4].

The presence of comorbidities was determined by taking the patients' history directly and Charlson index was calculated [17].

Indexes of insulin-resistance/sensitivity

Criteria used for the definition of insulin resistance are in accordance with the recently published guidelines proposed by the European Group of the study of Insulin Resistance (EGIR) [18]. The Homeostatic Model Assessment index (HOMA) was calculated according to the following formula: {[fasting insulin (μU/ml)] × [fasting glucose (mmol/l)]}/22.5. Subjects whose values exceeded the sex-specific 75th percentile (i.e. 1.80 for women and 2.12 for men) were considered to have insulin resistance (HOMA-IR) [10,18]. Log (HOMA-IR) has been also calculated since it is considered useful for evaluation of insulin-resistance in individuals with glucose intolerance, mild to moderate diabetes and other insulin-resistant conditions [19,20].

Beta-function has been evaluated by the following index [21]: HOMA-%B = (20 × FPI) / ((FPG-3.5) where FPI is the fasting plasma insulin and FPG is the fasting plasma glucose [19,21–24].

Transthoracic 2-dimensional echo-cardiography was performed on ICCU admission in order to measure left ventricular ejection fraction (LVEF).

The primary outcome was in-ICCU death.

The study protocol was in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Informed singed consent was obtained in all patients before enrollment.

Statistical analysis

Data have been stored in a dedicated data-base and analyzed with IBM SPSS Statistics 20 for Microsoft® Windows® (SPSS-IBM, USA). Continuous data are reported as mean ± SD or median (interquartile range, IR) as needed; comparisons between patients admitted in Killip classes I–II and III–IV were performed by means of Student's *t*-test or Mann–Whitney *U*-test, respectively. Categorical data are reported as frequencies (percentages); between-group comparisons were made with chi-square test. Correlations between some relevant anthropometric, clinic and laboratory data with admission glucose, insulin and C-peptide have been assessed with Spearman's rho. Logistic multivariable regression analysis was used to investigate the impact of age, peak TnI, glucose, creatinine and C-peptide on in-ICCU death. Candidate variables were chose as those considered relevant for the outcome, taking into account the number of events. Nevertheless, both models resulted slightly overfitted. Hosmer–Lemeshow goodness-of-fit test and Nagelkerke pseudo-R^2 were reported for logistic models. Statistical significance has been fixed at a two-tailed p value less than 5%.

Results

Table 1 depicts the clinical characteristics of the overall study population. In our series, the incidence of PCI was 4.9%, and in-ICCU mortality and 1-year discharge mortality rates were 2.7 and 4.2%, respectively. As shown in Table 2, 729 patients (93.2%) were in Killip I–II, while 53 patients (6.8%) were in Killip classes III–IV. Patients in Group B showed a higher Charlson index (p < 0.001), more frequently anterior myocardial infarction (p = 0.041) and a 2-and 3-vessel coronary artery disease (p = 0.017), together with a higher incidence of PCI failure (p < 0.001) and a lower admission EF (p < 0.001). A higher in-ICCU mortality rate was observed in Group B (p < 0.001). Higher values of Tn I, creatinine (admission, peak and discharge), NT-pro BNP, uric acid were observed in Group B, together with a higher inflammatory activation (as indicated by increased values of leukocytes and CRP positivity). When compared to patients in Group A, patients in Group B showed significantly higher levels of admission glycemia, insulin and C-peptide (p < 0.001, p = .022 and p < 0.001 respectively), together with higher values of HOMA-index and log-HOMA (p < 0.001 and p < 0.001, respectively) and reduced HOMA-%B (p = 0.014). No difference was observed in HbA1C values between the two subgroups.

Table 1
Clinical characteristics.

All patients	
Age (years), mean ± SD 65.5 ± 13.3	
	Males/Females, n (%) 578/204
(73.9/26.1)	
BMI (Kg/m2), mean ± SD 26.1 ± 3.6	
History of, n (%)	
Smoking 506 (64.7)	
COPD 65 (8.3)	
Previous PCI 93 (11.9)	
Previous AMI 92 (11.8)	
Hypertension 347 (44.4)	
Comorbidities, n (%)	
0 71 (9.1)	
1–2 571 (73.0)	
>2 140 (17.9)	
	Charlson index (units), mean ± SD 1.0 (1.0–2.0)
1.67 ± 1.26	
AMI location, n (%)	
anterior 393 (50.3)	
inferior 336 (43.0)	
Other 53 (6.8)	
Coronary artery disease, n (%)	
1-vessel 337 (43.1)	
2-vessel 278 (35.5)	
3-vessel 167 (21.4)	
Left main involvement, n (%) 44 (5.6)	
PCI failure, n (%) 38 (4.9)	
EF (%), mean ± SD 44.5 ± 9.3	
Time door-to-balloon (minutes), median (IR) 210 (150 to 300)	
In-hospital mortality, n (%) 21 (2.7)	

COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; BMI: body mass index; AMI: acute myocardial infarction; LM: left main coronary artery; and EF: ejection fraction.

As shown in Table 3, LVEF was inversely correlated with C-peptide, insulin and admission glycemia (p < 0.001, p = 0.018 and p < 0.001, respectively). Similarly age showed an indirect correlation with C-peptide, insulin and admission glycemia (p = 0.011, p = 0.073 and p < 0.001, respectively).

At logistic regression analysis (Table 4) C-peptide and insulin values were not associated with in-ICCU death.

Discussion

Homeostasis model assessment (HOMA), developed in 1985 [23], is a model of interactions between glucose and insulin dynamics that are used to yield an estimate of insulin sensitivity and beta-cell function [23]. The HOMA index assumes a feedback loop between the liver and beta-cell [19–23]; i.e., the relation between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion [19,21]. Thus, deficient beta-cell function reflects a diminished response of beta-cell to glucose-stimulated insulin secretion. While the euglycemic hyperinsulinemic clamp is time consuming, labor intensive and requires an experienced operator to manage the technical difficulties, HOMA index is feasible in all clinical conditions and information provided by this test is promptly available for