The glucose dysmetabolism in the acute phase of non-diabetic ST-elevation myocardial infarction: from insulin resistance to

Acta Diabetol
DOI 10.1007/s00592-011-0325-6

ORIGINAL ARTICLE

The glucose dysmetabolism in the acute phase of non-diabetic ST-elevation myocardial infarction: from insulin resistance to hyperglycemia

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Received: 2 June 2011 / Accepted: 31 August 2011

Abstract In the setting of acute myocardial infarction, hyperglycemia and acute insulin resistance may represent a stress response to myocardial injury mainly related to acute catecholamine release. By measuring glucose values and insulin resistance (Homeostatic Model Assessment index—HOMA), we evaluated in 356 non-diabetic patients with ST-elevation myocardial infarction (STEMI) undergone mechanical revascularization: (a) the acute glycometabolic response by evaluating insulin resistance, glucose levels, and their combination and (b) whether insulin resistance and increased glucose values (and their combination) are able to affect in-Intensive Cardiac Care Unit (ICCU) mortality and complications. In the overall population, 226 (63.5%) patients showed glucose values ≤140 mg/dl (group B), while 130 patients had glucose values >140 mg/dl (group A) (36.5%). Within group B, insulin resistance (as inferred by positive HOMA index) was present in 125 patients (55.3%), whereas 101 patients (44.7%) exhibited normal values of HOMA index. Within group A, 109 patients (83.8%) were insulin resistant, while 21 patients (16.2%) had normal values of HOMA index. At multivariable analysis, glucose values were independently associated with in-ICCU mortality (OR: 7.387; 95% CI 2.701–20.201; $P < 0.001$) and complications (OR: 1.786; 95% CI 1.089–2.928; $P = 0.022$). In the early phase of STEMI, the acute glycometabolic response to stress is heterogeneous (ranging from no insulin resistance to glucose levels >140 mg/dl and, finally, to the combination of increased glucose values and insulin resistance). Increased glucose values are stronger prognostic factors since they are independently associated with in-ICCU mortality and complications.

Keywords STEMI · Insulin resistance · Hyperglycemia · Prognosis · Non-diabetic · PCI

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), hyperglycemia is common and, though frequently untreated, associated with an increased risk of death [4–7]. In these patients, increased glucose values hold a prognostic role when measured not only on admission [4] but also throughout hospital stay [8–10]. We recently observed [11] that glucose serum levels, measured after mechanical revascularization, were independent predictors of in-hospital mortality in STEMI patients without previously known diabetes undergone primary percutaneous coronary intervention (PCI).

Insulin resistance is known to be part of the glycometabolic response to stress, but few studies assessed the role of insulin resistance, evaluated by means of Homeostatic Model Assessment (HOOMA index), in the early phase of acute myocardial infarction [12, 13]. In non-diabetic STEMI patients undergone PCI, we reported that insulin resistance, as assessed by HOMA index, is quite common and helps in the early risk stratification, since it represents an

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Published online: 09 October 2011

independent predictor for in-hospital mortality [14]. Thus, the glycometabolic response to acute myocardial ischemia appears to be quite complex and, so far, poorly understood.

In critically ill patients [15], it has been reported that insulin resistance may develop in the absence of hyperglycemia probably thanks to the fact that increased endogenous production of insulin is responsible for normal glucose values [15].

In the present investigation, performed in consecutive STEMI patients undergone mechanical revascularization and without previously known diabetes, we investigated the acute glycometabolic response in the early phase by evaluating insulin resistance, as assessed by HOMA index, glucose levels, and their combination. Furthermore, we investigated the different role(s) (if any) of insulin resistance and increased glucose values (both isolated and in combination) in affecting in-Intensive Cardiac Care Unit (ICCU) mortality and adverse events (acute pulmonary edema and arrhythmias).

Methods

Study population

From June 30, 2008, to June 30, 2009, 356 consecutive patients with STEMI (within 12 h from symptoms' onset) and without previously known diabetes were admitted to our ICCU, which is located at a tertiary center and prospectively enrolled in our study. The Florence health district (approximately 800,000 inhabitants—Metropolitan Florence area) includes five community hospitals and one teaching hospital (Azienda Ospedaliero-Universitaria Careggi). In the latter, a Heart and Vessel Department runs three ICCUs and operates high volume programs for PCI. Regarding cardiac emergencies, Careggi hospital is also the referring center for four community hospitals (the furthest being 50 km away from Careggi), located in the so-called area Vasta. In our hospital, in Florence, the reperfusion strategy of STEMI patients is represented by primary PCI [16–18]. STEMI patients are first evaluated by the Medical Emergency System staff in the pre-hospital 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.

A successful procedure was defined as an infarct artery stenosis <20% associated with TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow. Failure PCI was defined as resulting in TIMI grade 0–2 flow, regardless the residual stenosis [19].

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association [20].

Blood samples were driven on ICCU admission, after mechanical revascularization, in a fasting state. The following parameters were measured: glucose (mg/dl), troponin I (ng/ml), insulin (mU/l), uric acid (mg/dl), high-sensitivity C-reactive protein (mg/dl) (normal values <9), NT-pro-brain natriuretic peptide (NT-BNP) (pg/ml) [16], and fibrinogen (mg/dl). Blood samples were collected bedside and analyzed at the Central Laboratory in our Azienda Ospedaliera Careggi by routine laboratory methods. Plasma glucose levels were measured with the glucose-oxidase method [21] and plasma insulin levels with a double antibody RIA method [22]. All biomarkers were measured according to the assay guidelines provided by the manufacturers of the instruments and assay kits: cTnI, Dade Behring Stratus CS and Dimension RxL; NT-proBNP, Roche Elecsys 2010; hsCRP, Dade Behring Dimension. Creatinine (mg/dl) was also measured in order to calculate glomerular filtration rate (ml/min/1.73 m^2) [23].

The study population was divided in two subgroups according to glycemia on ICCU admission: group A (glycemia $>$ 140 mg/dl) and group B (Glycemia $\leq$ 140 mg/dl). The cut-off of glycemia 140 mg/dl was chosen according to guidelines [4]. Within each subgroup, patients were subdivided according the presence or absence of insulin resistance as inferred by positive HOMA index.

Transthoracic 2-dimensional echocardiography (performed using a Toshiba machine model SSA 270 HG equipped with a 2.5-or 3.75-MHz transducer) was performed on ICCU admission in order to measure left ventricular ejection fraction (LVEF, according to Teicholz's method [24]); wall cinetic alterations and the presence of valvular disease and of pericardial fluid were also investigated.

In-ICCU mortality and in-ICCU complications (acute pulmonary edema and arrhythmias) were considered as outcomes.

Definition of insulin resistance

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) [25, 26]. HOMA was calculated according to the following formula: {[fasting insulin (microU/ml)] $\times$ [fasting glucose (mmol/l)]}/22.5 [27]. 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) [14, 28].

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

Statistical analysis

Data have been entered in a dedicated database and processed by means of SPSS 13.0 statistical package (SPSS Inc. Chicago, IL). A two-tailed P value < 0.05 was considered statistically significant. Data of glycemia subgroups are reported as frequencies (percentages) and medians (25–75th percentile) and were analyzed by Fisher's exact test for categorical variables with any field including <6 patients, or χ^2 test for the other categorical variables, and Mann–Whitney U test (continuous variables that resulted almost all non-normally distributed at one-sample Kolmogorov–Smirnov test). Multivariable logistic regression analyses were performed in an explorative manner to find predictors for both mortality and complications. For each outcome, a backward stepwise procedure was performed using $P > 0.10$ of the likelihood ratio test for exclusion.

Results

Clinical characteristics and angiographic data

Table 1 shows the clinical characteristics of STEMI patients included in the study. In the overall population, 226 (63.5%) patients showed glucose values ≤140 mg/dl (group B), while 130 patients had glucose values >140 mg/dl (group A) (36.5%). Within group B, insulin resistance (as inferred by positive HOMA index) was present in 125 patients (55.3%), whereas 101 patients (44.7%) exhibited normal values of HOMA index. Within group A, 109 patients (83.8%) were insulin resistant, while 21 patients (16.2%) had normal values of HOMA index. In group B, patients with insulin resistance showed higher values of BMI and higher incidence of dyslipidemia when compared to those without ($P = 0.004$ and $P = 0.014$, respectively). No difference was detectable

Table 1 Clinical characteristics of patients included in the study

Variable frequency (%) or median (25–75th percentile)	Glycemia > 140 mg/dl ($n = 130$) Group A			Glycemia ≤ 140 mg/dl ($n = 226$) Group B		
	No insulin resistance ($n = 21$)	Insulin resistance ($n = 109$)	P Fisher's exact test or Mann–Whitney U test	No insulin resistance ($n = 101$)	Insulin resistance ($n = 125$)	P Fisher's exact test or Mann–Whitney U test
Females/males	6/15 (28.6/71.4%)	35/74 (32.1/67.9%)	1	30/71 (29.7/70.3%)	22/103 (17.6/82.4%)	0.039
Age (years)	65 (56–80)	70 (60–78)	0.127	64 (56–76)	61 (54–70)	0.420
BMI (kg/m^2)	23.5 (22.5–25.6)	25.8 (24.2–28.0)	<0.001	24.9 (22.8–27.1)	26.6 (25.0–28.7)	0.004
Hypertension	10 (47.6%)	53 (48.6%)	1	38 (37.6%)	43 (34.4%)	0.676
Dyslipidemia	9 (42.9%)	46 (42.2%)	1	31 (30.7%)	59 (47.2%)	0.014
Smoke						
No smoke	4 (19.0%)	54 (49.5%)	0.015	31 (30.7%)	38 (30.4%)	1
Previous smoke/ever smoke	17 (81.0%)	55 (50.5%)		70 (69.3%)	87 (69.6%)	
Comorbidities	2 (9.5%)	8 (7.3%)	0.664	2 (2.0%)	4 (3.2%)	0.694
Renal failure	0	5 (4.6%)	1.000	1 (1.0%)	4 (3.2%)	0.384
COPD	2 (9.5%)	7 (6.4%)	0.638	8 (7.9%)	6 (4.8%)	0.409
Previous MI	4 (19.0%)	16 (14.7%)	0.741	17 (16.8%)	11 (8.8%)	0.103
Killip class						
I	14 (66.7%)	83 (76.1%)	0.597	91 (90.1%)	110 (88.0%)	0.692
II	1 (4.8%)	8 (7.3%)		6 (5.9%)	12 (9.6%)	
III	1 (4.8%)	4 (3.7%)		1 (1.0%)	1 (0.8%)	
IV	5 (23.8%)	14 (12.8%)		3 (3.0%)	2 (1.6%)	
AMI location						
Inferior	8 (38.1%)	40 (36.7%)	0.755	44 (43.6%)	53 (42.4%)	0.721
Lateral	2 (9.5%)	6 (5.5%)		7 (6.9%)	6 (4.8%)	
Anterior	11 (52.4%)	63 (57.8%)		50 (49.5%)	66 (52.8%)	
LVEF (%)	40 (32–46)	40 (35–48)	0.769	45 (38–52)	45 (39–52)	0.701

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *MI* myocardial infarction, *AMI* acute myocardial infarction, *LVEF* left ventricular ejection fraction

between the two subgroups with regard to myocardial infarction (MI) location, Killip class, and left ventricular ejection fraction. In group A, patients with insulin resistance showed higher values of BMI and lower incidence of previous smokers/ever smokers ($P < 0.001$ and $P = 0.015$, respectively). MI location, Killip class, and left ventricular ejection fraction did not significantly differ between the two subgroups.

Table 2 depicts angiographic data in our population. No differences were detectable with regard to severity of coronary artery disease and the incidence of PCI failure.

In the early phase of STEMI, patients without previously known diabetes showed different behaviors in regard to the glycemic response to acute stress. These imply increased glucose values associated or not with insulin resistance. The latter was more common in patients with higher BMI values and a higher incidence of dyslipidemia.

Biochemical data

Biochemical data are shown in Table 3. In group B, patients with insulin resistance showed higher values of NT-pro-BNP, lactic acid, and Tn I ($P = 0.012$, $P = 0.003$, and $P = 0.015$, respectively). In group A, no differences were detectable in the considered variables between patients with insulin resistance and those without.

Among patients with glucose values <140 mg/dl, those who showed insulin resistance had a higher infarct size (as indicated by peak Tn I).

Overall complications were as follows: 35 patients had arrhythmias (atrial fibrillation/atrial flutter: 22; ventricular tachycardia: 8; and AV block: 5) while 20 patients pulmonary edema and 24 patients cardiogenic shock. Patients with glycemia >140 mg/dl and insulin resistance showed a higher incidence of in-ICCU complications when compared to patients with glucose values <140 mg/dl and insulin resistance (34/109—31.2% vs. 25/125 —20.7%; $P = 0.025$). In-ICCU mortality rate was significantly higher in patients with glycemia >140 mg/dl and insulin resistance when compared to those with glucose values ≤140 mg/dl and insulin resistance (7/109—6.4% vs. 0; $P = 0.004$). Patients with glycemia >140 mg/dl and no insulin resistance exhibited a higher mortality rate when compared to patients with glucose values ≤140 mg/dl and no insulin resistance (4/21—19.0% vs. 1—1.0%; $P = 0.003$).

As shown in Table 4, among patients without insulin resistance, group A showed a higher Killip class ($P < 0.001$), higher values of HbA1c ($P = 0.036$), lactic acid ($P = 0.004$), and a higher mortality rate ($P = 0.003$). Among patients with insulin resistance, group A was older ($P < 0.001$), showed a higher Killip class ($P < 0.001$) and a lower LVEF ($P < 0.001$), and had higher values of HbA1c ($P < 0.001$), NT-pro-BNP ($P < 0.001$), lactic acid

Table 2 Angiographic data

Variable frequency (%) or median (25–75th percentile)	Glycemia > 140 mg/dl ($n = 130$) Group A			Glycemia ≤ 140 mg/dl ($n = 226$) Group B		
	No insulin resistance ($n = 21$)	Insulin resistance HOMA positive (>1.80 donne, >2.18 uomini) ($n = 109$)	*P* Fisher's exact test or Mann–Whitney *U* test	No insulin resistance ($n = 101$)	Insulin resistance HOMA positive (>1.80 donne, >2.18 uomini) ($n = 125$)	*P* Fisher's exact test or Mann–Whitney *U* test
Coronary artery disease						
No disease	0	0	0.622	1 (1.0%)	0	0.713
1-vessel	10 (47.6%)	40 (37.0%)		47 (46.5%)	59 (47.2%)	
2-vessel	6 (28.6%)	33 (30.6%)		33 (32.7%)	39 (31.2%)	
3-vessel	5 (23.8%)	35 (32.4%)		20 (19.8%)	27 (21.6%)	
CABG	0	1 (0.9%)	1	0	1 (0.8%)	1
IRA						
RCA	7 (36.8%)	33 (30.8%)	0.016	38 (38.8%)	38 (30.4%)	0.270
CX	1 (5.3%)	8 (7.5%)		10 (10.2%)	20 (16.0%)	
DA	9 (47.4%)	65 (60.7%)		49 (50.0%)	67 (53.6%)	
Left main	2 (10.5%)	0		0	0	
CABG	0	1 (1%)		0	0	
PCI failure	2 (9.5%)	9 (8.4%)	1	1 (1.0%)	4 (3.2%)	0.384

CABG coronary artery by-pass graft, *IRA* infarct-related artery, *RCA* right coronary artery, *CX* circumflex artery, *DA* descending artery, *PCI* percutaneous coronary intervention

Table 3 Biochemical data

Variable median (25–75th percentile)	Glycemia > 140 mg/dl ($n = 130$) Group A			Glycemia </=140 mg/dl ($n = 226$) Group B		
	No insulin resistance ($n = 21$)	Insulin resistance ($n = 109$)	*P* Fisher's exact test or Mann–Whitney *U* test	No insulin resistance ($n = 101$)	Insulin resistance ($n = 125$)	*P* Fisher's exact test or Mann–Whitney *U* test
HbA1c (%)	6.0 (5.6–6.4)	6.0 (5.7–6.6)	0.737	5.7 (5.4–6.1)	5.8 (5.5–6.0)	0.622
NT-pro-BNP (pg/ml)	1,984 (1,022–7,646)	1,735 (595–4,061)	0.395	760 (294–738)	1,373 (562–2,461)	0.012
Lactic acid	2.0 (1.1–3.6)	2.2 (1.5–2.7)	0.865	1.1 (0.8–1.8)	1.4 (1.1–1.9)	0.003
C-reactive protein positivity	13 (68.4%)	65 (63.1%)	0.797	57 (60.6%)	52 (43.3%)	0.013
Peak Tn I (ng/ml)	88.3 (27.7–425.5)	115.6 (64.5–224.0)	0.972	58.8 (24.1–138.3)	83.8 (43.0–173)	0.015
eGFR ml/min/1.73 m^2	86.2 (70.2–104.2)	74.8 (56.4–92.2)	0.902	87.3 (73.1–107.1)	91.3 (73.3–104.9)	0.073
Uric acid (mg/dl)	5.2 (4.2–6.2)	5.7 (4.8–6.8)	0.128	5.3 (4.2–6.2)	5.4 (4.5–6.5)	0.184
Fibrinogen (mg/dl)	404 (330–535)	379 (320–486)	0.321	383 (329–434)	382 (324–448)	0.676

NT-pro-BNP N terminal-pro-brain natriuretic peptide, *Tn I* troponin I, *eGFR* estimated glomerular filtration rate

($P < 0.001$), peak Tn I ($P = 0.021$), and C-reactive protein ($P = 0.003$), lower values of eGFR ($P < 0.001$), and a higher mortality rate ($P = 0.004$).

Multivariate analysis

At backward logistic regression analysis, the following variables resulted independent predictors for in-ICCU complications (when corrected for HOMA index): NT-pro-BNP values (OR: 1.012; 95% CI 1.004–1.020; $P = 0.003$), Tn I (OR: 1.003; 95% CI 1.001–1.004; $P = 0.022$), and glucose values (OR: 7.387; 95% CI 2.701–20.201; $P < 0.001$). Hosmer and Lemeshow test: 2.516; $P = 0.961$.

At backward logistic regression analysis, the following variables resulted independent predictors for in-ICCU mortality (when corrected for HOMA index): Killip class (OR: 1.456; 95% CI 1.075–1.971; $P = 0.015$), ejection fraction (OR: 0.965; 95% CI 0.936–0.994; $P = 0.018$), and glucose values (OR: 1.786; 95% CI 1.089–2.928; $P = 0.022$). Hosmer and Lemeshow test: 9.318; $P = 0.316$.

When assessing the prognostic impact of the glycemic response to stress, only glucose values were independent predictors for both in-ICCU complications and mortality.

Discussion

The main finding of the present investigation is that, in STEMI patients without previously known diabetes undergone mechanical revascularization, the acute glycometabolic response to stress is, in the early phase, complex and quite heterogeneous (ranging from no insulin resistance to glucose levels >140 mg/dl and, finally, to the combination of increased glucose values and insulin resistance). In fact, in our series, insulin resistance despite glucose levels ≤140 mg/dl was detectable in about one-third of the entire population. In this subgroup, insulin resistance can be related not only to pre-existing conditions (such as dyslipidemia and increased BMI) but also to "factors" strictly related to the acute phase: increased infarct size (as indicated by higher Tn I levels) and a more severe systemic derangement (as indicated by increased NT-pro-BNP levels and higher lactic acid values).

Our data are in agreement with previous studies performed in non-critically ill patients. In these investigations, isolated insulin resistance without over hyperglycemia was associated with increased inflammation, coagulation abnormalities [29–31], and severity of illness [32].

In presence of insulin resistance [33], the ischemic myocardium is forced to utilize free fatty acids (FFA) more than glucose for an energy source because myocardial glucose uptake is impaired and, in this setting, it is more prone to a metabolic crisis (since the hypoxic myocardium becomes less energy efficient). We recently [14] showed that insulin resistance (assessed by HOMA index) represents an independent predictor for early mortality. More recently, Garcia et al. [34] observed that hyperinsulinism was the most important factor associated with the

Table 4 Comparison between patients with insulin resistance and those without

Variable median (25–75th percentile)	No insulin resistance ($n = 122$)			Insulin resistance ($n = 234$)		
	Glycemia > 140 mg/dl ($n = 21$) Group A	Glycemia ≤ 140 mg/dl ($n = 101$) Group B	*P* value	Glycemia > 140 mg/dl ($n = 109$) Group A	Glycemia </=140 mg/dl ($n = 125$) Group B	*P* value
Clinical data						
Females/males	15/6	71/30	0.918	74/35	103/22	0.010
	71.4/28.6	70.3/29.7		67.9/32.1	82.4/17.6	
Age (years)	65 (56–80)	64 (56–76)	0.679	70 (60–78)	61 (54–70)	<0.001
BMI(kg/m^2)	23.5 (22.5–25.6)	24.9 (22.8–27.1)	0.397	25.8 (24.2–28.0)	26.6 (25.0–28.7)	0.051
Killip class						
I–II	15 (71.5%)	97 (96.0%)	<0.001	91 (83.5%)	122 (97.6%)	<0.001
III–IV	6 (28.5%)	4 (4.0%)		18 (16.5%)	3 (2.4%)	
AMI location			0.857			0.671
Inferior	8 (38.1%)	44 (43.6%)		40 (36.7%)	53 (42.4%)	
Lateral	2 (9.5%)	7 (6.9%)		6 (5.5%)	6 (4.8%)	
Anterior	11 (52.4%)	50 (49.5%)		63 (57.8%)	66 (52.8%)	
LVEF (%)	40 (32–46)	45 (38–52)	0.008	40 (35–48)	45 (38–52)	<0.001
Coronary artery disease			0.932			0.158
No disease	0 (0.0%)	1 (1.0%)		–	–	
1-vessel	10 (47.6%)	47 (46.5%)		41 (37.6%)	59 (47.2%)	
2-vessel	6 (28.6%)	33 (32.7%)		33 (30.3%)	39 (31.2%)	
3-vessel	5 (23.8%)	20 (19.8%)		35 (32.1%)	27 (21.6%)	
PCI failure	2 (9.5%)	1 (1.0%)	0.076*	9 (8.4%)	4 (3.2%)	0.085
Biochemical data						
HbA1c, median (IR), (%)	6.0 (5.6–6.4)	5.7 (5.4–6.1)	0.036	6.0 (5.7–6.6)	5.8 (5.5–6.0)	<0.001
NT-pro-BNP, median (IR), (pg/ml)	1,984 (1,022–7,646)	760 (294–738)	0.051	1,735 (595–4,061)	1,373 (562–2,461)	<0.001
Lactic acid, median (IR), mmol/l	2.0 (1.1–3.6)	1.1 (0.8–1.8)	0.004	2.2 (1.5–2.7)	1.4 (1.1–1.9)	<0.001
C-reactive protein positivity, *n* (%)	$13_{/19}$ (68.4%)	57/94 (60.6%)	0.524	65/103 (63.1%)	52/120 (43.3%)	0.003
Peak Tn I, median (IR), (ng/ml)	88.3 (27.7–425.5)	58.8 (24.1–138.3)	0.062	115.6 (64.5–224.0)	83.8 (43.0–173)	0.021
eGFR, median (IR), (ml/min/1.73 m^2)	86.2 (70.2–104.2)	87.3 (73.1–107.1)	0.724	74.8 (56.4–92.2)	91.3 (73.3–104.9)	<0.001
Uric acid, median (IR), (mg/dl)	5.2 (4.2–6.2)	5.3 (4.2–6.2)	0.833	5.7 (4.8–6.8)	5.4 (4.5–6.5)	0.367
Fibrinogen, median (IR), (mg/dl)	404 (330–535)	383 (329–434)	0.248	379 (320–486)	382 (324–448)	0.592
Mortality, *n* (%)	4 (19.0)	1 (1.0)	0.003*	7 (6.4)	0 (0.0)	0.004*

IR interquartile range (25–75th percentile)

BMI body mass index, *AMI* acute myocardial infarction, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *Hb A1c* glycated hemoglobin, *NT-pro-BNP* N terminal-pro-brain natriuretic peptide, *eGFR* estimated glomerular filtration rate

* Fisher's exact test

occurrence of new cardiovascular events at long-term follow-up in Colombian patients with acute myocardial infarction, thus empathizing the prognostic role of insulin resistance even at long term.

In acute coronary syndromes, insulin-resistant patients are known to be more prone to hyperglycemia [35, 36]. In our series, glucose values (when corrected for HOMA index) are independently associated with in-ICCU

mortality (thus confirming previous data by others and us) [4–11] and with in-ICCU complications.

The complexity of the glycometabolic response to stress during acute myocardial infarction, as well as the scarcity of data on this topic, can be inferred by still existing controversies on how to manage increased glucose values in patients with acute coronary syndromes. According to recent guidelines [4], it is reasonable to consider intensive glucose control in patients with significant hyperglycemia (that is plasma glucose >180 mg/dl), but strategies for the management of patients with milder degrees of hyperglycemia are far to be elucidated. We recently [37] observed that in non-diabetic STEMI patients, the poorer in-hospital glucose control was associated with higher mortality; peak glycemia >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. No recommendation is so far available on whether (and, if so, how) to treat STEMI insulin-resistant patients.

In a recent paper [27] we observed that, in the early phase of STEMI patients without previously known diabetes, insulin secretion and acute insulin resistance can be strictly related to BMI, while the degree of inflammatory activation, myocardial damage, and age are able to influence glucose values.

The results of the present investigation further extend previous findings documenting that glucose values have a stronger prognostic role for early death, since only glucose values (and not HOMA index positivity) were independently associated with in-ICCU mortality.

Limitations

A possible limitation of our study may be represented by the methodology of HOMA index approach in assessment of insulin resistance, since it was proposed mainly for stable patients. However, Holzinger et al. [38] in a group of 30 critically ill medical patients (continuously sedated and ventilated) documented that HOMA index, though indicating insulin resistance, did not correlated with the *M*-values and concluded that the euglycemic hyperinsulinemic clamp, which reflects stimulated insulin sensitivity, remains the gold standard technique for quantifying insulin resistance in critically ill patients. However, euglycemic hyperinsulinemic clamp is time-consuming, labor intensive and requires an experienced operator to manage the technical difficulties, so it is known to be not appropriate for routine clinical applications [39]. On the other hand, HOMA index, which reflects basal insulin sensitivity and responsiveness, has been recently used to estimate insulin resistance in critically ill patients with acute renal failure [40].

In conclusion, according to our data, in STEMI patients without previously known diabetes undergone mechanical revascularization, the acute glycometabolic response to stress in the early phase is heterogeneous (ranging from no insulin resistance to glucose levels >140 mg/dl and, finally, to the combination of increased glucose values and insulin resistance). Increased glucose values are stronger prognostic factors since they are independently associated with in-ICCU mortality and complications. Further studies are needed to better elucidate the role of insulin resistance alone and to assess whether insulin-resistant STEMI patients deserve a peculiar therapeutic strategy despite normal glucose values.

Conflict of interest We have no conflict interests to declare.

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