Lactate in the acute phase of ST-elevation myocardial infarction treated with mechanical revascularization A single-center experience

American Journal of Emergency Medicine (2012) **30**, 92–96

ELSEVIER

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

Lactate in the acute phase of ST-elevation myocardial infarction treated with mechanical revascularization A single-center experience ☆

Chiara Lazzeri MD*, Serafina Valente MD, Marco Chiostri MD, Claudio Picariello MD, Gian Franco Gensini MD

Intensive Cardiac Coronary Unit, Heart and Vessel Department, Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy

Received 26 August 2010; revised 3 October 2010; accepted 9 October 2010

Abstract

Aims: The prognostic role (if any) of lactate for early mortality in patients with ST-elevation myocardial infarction (STEMI) submitted to primary percutaneous coronary intervention (PCI) is so far not elucidated. We therefore assessed whether lactic acid (LA) was a prognostic predictor for early mortality in 807 patients with STEMI submitted to primary PCI consecutively admitted to our intensive cardiac care unit (ICCU) from January 1, 2006, to December 31, 2009.

Result: Higher levels of LA were found in older patients ($P = .025$) and were associated with a progressive decline in estimated glomerular filtration rate ($P < .001$) and in ejection fraction ($P < .001$). The increase in LA values paralleled the progressive increase in glucose values, peak glycemia, troponin I, N-terminal pro–brain natriuretic peptide, and uric acid ($P < .001$, $P < .001$, $P < .001$, $P = .018$, and $P = .006$, respectively). The in-ICCU mortality rate was highest in the third LA tertile ($P < .001$). Lactate levels were independent predictors for in-hospital mortality only in patients with Killip classes III to IV (odds ratio [OR], 1.17; 95% confidence interval [CI], 1.05-1.30, $P = .003$). In addition, age (OR, 1.11; 95% CI, 1.03-1.19, $P = .006$) and leukocytes (OR, 1.17; 95% CI, 1.03-1.33, $P = .015$) were independent predictors for in-hospital mortality when adjusted for PCI failure.

Conclusion: In patients with STEMI submitted to primary PCI, blood lactate is a prognostic marker for early mortality only in the subgroup with advanced Killip class. The degree of hemodynamic impairment (as indicated by Killip class), of myocardial ischemia (as inferred by troponin I), and glucose values are the main factors influencing lactate concentrations in the early phase of STEMI.

1. Introduction

Hyperlactatemia is known as a marker of the metabolic stress response and its severity is associated with increased mortality in critically patients [1-3]. Lactate

☆ No disclosures.

* Corresponding author. Tel.: +39 55 7947518; fax: +39 55 7947518.
E-mail address: lazzeric@libero.it (C. Lazzeri).

0735-6757/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajem.2010.10.008

levels, commonly used in intensive care settings as a diagnostic and prognostic tool, have been equated mainly with inadequate tissue oxygenation. Despite that most studies have been performed in patients with signs of clinical shock, elevated blood lactate levels have been associated with a higher mortality even in hemodynamically stable patients because they may indicate occult hypoperfusion [4-6].

Few studies investigated the prognostic role of lactate in patients with acute ischemic heart disease. Chiolero et al [7] described hyperlactatemia in patients in cardiogenic shock (CS) in the early postoperative period after heart surgery and concluded that hyperlactatemia could mainly be related to increased tissue lactate production. Koreny et al [8] observed that peak serum lactate was a significant univariate predictor of in-hospital mortality in patients who develop acute renal failure during the first 24 hours of CS after acute myocardial infarction. Contrasting are the data on the prognostic role of lactate in these patients. Geppert et al [9] found, in a retrospective study in 38 CS patients, that interleukin-6 concentrations (and not lactate) were an independent predictor of 30-day mortality. Conversely, in 45 consecutive patients with CS complicating STEMI and submitted to optimal treatment (represented by percutaneous coronary intervention [PCI] and stent implantation, use of glycoprotein IIb/IIIa inhibitors, intra-aortic balloon pump, mechanical ventilation, and ultrafiltration, when needed), we documented [10] that hyperlactatemia (>6.5 mmol/L) was an independent indicator of in-hospital mortality.

The prognostic role (if any) of lactate for early mortality in patients with ST-elevation myocardial infarction (STEMI) submitted to primary PCI is so far not elucidated. We therefore assessed whether lactic acid (LA) was a prognostic predictor for early mortality in 807 STEMI patients submitted to primary PCI consecutively admitted to our intensive cardiac care unit (ICCU) from January 1, 2006, to December 31, 2009.

2. Methods

2.1. Study population

From January 1, 2006, to December 31, 2009, 807 consecutive patients with STEMI (within 12 hours from symptoms' onset) were admitted to our ICCU, which is located at a tertiary center.

In our hospital, in Florence, the reperfusion strategy of patients with STEMI is represented by primary PCI [10-12]. 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 emergency department. After primary PCI, they are admitted to our ICCU.

A successful procedure was defined as an infarct artery stenosis less than 20% associated with Thrombolysis In Myocardial Infarction grade 3 flow. Failure PCI was defined as resulting in Thrombolysis In Myocardial Infarction grade 0 to 2 flow, regardless the residual stenosis [10,11].

The diagnosis of STEMI was based on the criteria of the American College of Cardiology/American Heart Association [12].

On ICCU admission, after PCI, in a fasting blood sample, the following parameters were measured: glucose (g/L), troponin I (ng/mL), uric acid (mg/dL) [13], N-terminal pro–brain natriuretic peptide (NT-proBNP) (pg/mL) [11], leukocyte count ($\times 10^3/\mu$L), fibrinogen (mg/dL), erythrocyte sedimentation rate, glycated hemoglobin (%), cholesterol (mg/dL), triglycerides (mg/dL), alanine aminotransferase (U/L), aspartate aminotransferase (U/L). Creatinine (mg/dL) was also measured to calculate glomerular filtration rate (mL min^{-1} 1.73 m^{-2}). Glucose values and troponin (Tn I) were measured 3 times a day (ie, at 6:00 AM, 12 noon, and 6:00 PM, respectively) and peak glucose and peak Tn I were considered [14], respectively. Blood lactate was collected on ICCU admission.

Transthoracic 2-dimensional echocardiography was performed on ICCU admission to measure left ventricular ejection fraction.

In-ICCU mortality was considered as outcome.

The study was approved by an appropriate ethical committee, and all patients gave informed consent to participate.

3. Statistical analysis

Data have been processed by means of the SPSS 13.0 statistical package (SPSS Inc, Chicago, Ill). A P value less than .05 was considered statistically significant. Data are reported as frequencies (percentages) and medians (95% confidence interval [CI]) and analyzed by means of χ^2 (or Fisher exact text, when appropriate) and Mann-Whitney U test, respectively. Moreover, the study population has been divided by tertiles of LA levels to investigate which variables differed between the 3 subgroups by means of Kruskal-Wallis or χ^2. A linear regression analysis investigated the correlation of insulin vs glycemia. By means of 2 multivariable backward linear regression analyses, we explored the adjusted correlations of LA with clinical and biochemical variables; the respective final models have been reported. Logistic regression analysis was carried out considering as outcomes intra-ICCU mortality. In this multivariable analysis, candidate variables were chosen as those that resulted significantly different at univariable analysis and/or clinically relevant. Backward procedure (probability for entry, .05; probability for removal, .10) was repeated until all variables in the model reached statistical significance.

4. Results

Our population comprises 807 consecutive patients with STEMI submitted to primary PCI (Table 1). Males were more frequent (73.2%), and anterior myocardial infarction was the most frequent localization (56.4%). The incidence of PCI failure was 7.1% and the in-ICCU mortality rate was 6.1%. Tertiles of LA are shown in Table 2. Higher levels of LA were found in older patients (P = .025) and were associated with a progressive decline in estimated glomerular filtration rate (P < .001) and in ejection fraction (P < .001). Killip classes III to IV and a higher incidence of PCI failure were more frequent in the highest LA tertile (P < .001 and P < .001, respectively). The increase in LA values paralleled the progressive increase in glucose values, peak glycemia, Tn I, NT-proBNP, and uric acid (P < .001, P < .001, P < .001, P = .018, and P = .006, respectively). The highest values of leukocytes and of fibrinogen were detectable in the third LA tertile (P < .001 and P = .010, respectively). The in-ICCU mortality rate was highest in the third LA tertile (P < .001). As depicted in Fig. 1, admission lactate was significantly higher in patients in Killip classes III to IV in respect to those in Killip classes I to II. Table 3 shows the variables significantly correlated with lactate at multivariable linear regression analysis.

At multivariable backward logistic regression analysis, in the overall population, the following variables were independent predictors for in-ICCU mortality when adjusted for age and uric acid: Tn I (odds ratio [OR], 1.004; 95% CI, 1.001-1.007; P = .004), NT-proBNP (100 U/step) (OR, 1.009; 95% CI, 1.002-1.016; P = .014), leukocytes (1000/mL) (OR, 1.218; 95% CI, 1.039-1.428; P = .015) (Hesmer-Lemershow goodness-of-fit χ^2, 3.222; P = .920. pseudo r^2, 0.455).

Table 4 shows multivariable backward logistic regression analysis according to Killip classes. Lactate levels were independent predictors for in-hospital mortality only in patients with Killip classes III to IV (OR, 1.17; 95% CI, 1.05-1.30; P = .003), In addition, age (OR, 1.11; 95% CI, 1.03-1.19; P = .006) and leukocytes (OR, 1.17; 95% CI, 1.03-1.33; P = .015) were associated with in-hospital mortality when adjusted for PCI failure (pseudo r^2, 0.37; Hesmer-Lemershow goodness-of-fit χ^2, 3.25; P = .917).

Table 1 Clinical characteristics of 807 patients with STEMI included in the study

	Median (25th-75th percentile) or frequency (%)
Age (y)	68 (58-77)
Male/female (%)	591/216 (73.2%/26.8%)
History of	
Diabetes mellitus (n [%])	175 (21.7%)
Smoking (n [%])	496 (61.5%)
COPD (n [%])	69 (8.6%)
Previous PCI (n [%])	104 (12.9%)
Previous MI (n [%])	114 (14.1%)
Hypertension (n [%])	421 (52.2%)
Estimated GFR (mL min^{-1} 1.73 m^{-2})	77.7 (62.5-92.1)
AMI location (n [%])	
Anterior	455 (56.4%)
Inferior	291 (36.1%)
Other	61 (7.6%)
Coronary artery disease (n [%])	
No disease	1 (0.1%)
One-vessel	304 (37.7%)
Two-vessel	285 (35.3%)
Three-vessel	217 (26.9%)
LM involvement (n [%])	58 (7.2%)
CABG involvement (n [%])	10 (1.2%)
PCI failure (n [%])	42 (5.2%)
Admission EF (%)	45 (35-50)
Latency (min)	240 (175-345)
In-hospital mortality (n [%])	49 (6.1%)

COPD indicates chronic obstructive pulmonary disease; MI, myocardial infarction; GFR, glomerular filtration rate; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; EF, ejection fraction.

5. Discussion

In the present investigation performed in a large series of patients with STEMI submitted to mechanical revascularization, we documented, for the first time, that lactate values are independent predictor for in-ICCU mortality only in the subgroup of patients in advanced Killip classes. Moreover, we observed that the degree of hemodynamic impairment (as indicated by Killip class), of myocardial ischemia (as inferred by Tn I), and glucose values are the main factors influencing lactate concentrations in the early phase of STEMI.

The mechanisms regulating the rates of lactate production vary in different disease states. During exercise, hyperlactatemia clearly results from imbalance between oxygen delivery and energy requirements. In critically ill patients, the genesis of hyperlactatemia is quite more complex, including regional hypoperfusion, an inflammation-induced up-regulation of glycolysis, alterations in lactate-clearing mechanisms, and the increased work of breathing [15]. In patients with CS, a marked increase in endogenous lactate production was reported and lactate clearance was nonsignificantly different in these patients from that of healthy subjects [7,16]. In our investigation, the relationship between Killip class, peak Tn I, and lactate strongly suggests that in patients with STEMI submitted to PCI, lactate levels may be mainly related to hemodynamic impairment and thus to increased lactate production. According to our data, in STEMI treated with mechanical revascularization, the prognostic role of lactate stems from its relation with hemodynamic derangement because it was an independent predictor for early mortality only in patients with advanced Killip class, even when adjusted for PCI failure. In this

Table 2 Tertiles of LA in our population

	First tertile (≤1.3 mmol/L; n = 278)	Second tertile (1.3-1.9 mmol/L; n = 272)	Third tertile (>1.9 mmol/L; n = 257)	*P* Kruskal-Wallis *H* or χ^2
Males/females	199/79 (71.6/28.4%)	213/59 (78.3/21.7%)	179/78 (69.6/30.4%)	.059
Age (y)	66.5 (57.0-76.0)	67.5 (58.0-76.0)	71.0 (59.5-79.0)	.025
BMI (kg/m^2)	25.7 (23.3-27.6)	26.3 (24.4-28.4)	26.0 (23.8-28.4)	.008
Estimated GFR (mL min^{-1} 1.73 m^{-2})	84.0 (67.5-98.7)	76.6 (64.8-89.9)	70.7 (49.8-88.1)	<.001
AMI anterior (%)	143 (51.4%)	157 (57.7%)	155 (60.3%)	.102
Killip class				<.001
I-II	264 (94.6%)	249 (91.9%)	188 (73.2%)	
III-IV	15 (5.4%)	22 (8.1%)	69 (26.8%)	
EF (%)	45 (40-52)	45 (38-50)	40 (35-50)	<.001
PCI failure	5 (1.8%)	13 (4.8%)	24 (9.4%)	.002
Glucose (g/L)	1.21 (1.06-1.45)	1.32 (1.12-1.62)	1.66 (1.31-2.30)	<.001
Peak glucose (g/L)	1.38 (1.21-1.65)	1.54 (1.27-1.97)	1.86 (1.50-2.54)	<.001
HbA_{1c} >6.5% (n = 568)	34 (21.0%)	34 (21.3%)	46 (27.9%)	.249
Peak Tn I (ng/mL)	63.35 (27.89-133.60)	89.50 (36.78-158.50)	106.00 (49.87-239.04)	<.001
NT-proBNP (pg/mL)	1398 (553-3306)	1188 (496-3000)	1932 (595-6047)	.018
Uric acid (mg/dL)	5.3 (4.1-6.5)	5.5 (4.5-6.5)	5.8 (4.8-6.8)	.006
ESR (mm/h)	30 (15-46)	25 (15-42)	30 (15-48)	.154
Leucocytes (×10^3/μL)	10.3 (8.4-12.6)	10.9 (9.0-14.0)	12.7 (10.2-16.1)	<.001
hs-CRP positivity	119 (51.1%)	101 (43.0%)	114 (56.2%)	.020
Fibrinogen (mg/dL)	401 (341-506)	380 (322-453)	384 (312-470)	.010
ALT (U/L)	31 (20-48)	35 (22-57)	45 (28-79)	<.001
AST (U/L)	75 (34-158)	85 (44-184)	107 (56-248)	<.001
GGT (U/L)	25 (18-43)	31 (21-55)	33 (22-56)	<.001
Length of stay (h)	52 (47-75)	51 (47-75)	62 (43-96)	.215
In-hospital mortality	2 (0.7%)	7 (2.6%)	40 (15.6%)	<.001

BMI indicates body mass index; GFR, glomerular filtration ratio; AMI, acute myocardial infarction; EF, ejection fraction; HbA_{1c}, glycosylated hemoglobin; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase.

context, it was observed that in patients with acute myocardial infarction, blood lactate was a predictor of shock development [17].

Beside, in our series, lactate concentrations were related also to glucose values, which are known as prognostic indicators for early mortality in patients with STEMI [14,18,19]. Lactate is the end product of glucose metabolism, but in disease states, hyperglycemia alone is not enough to modify blood lactate concentrations. Although lactate increases after glucose administration in healthy and surgical subjects [20-22], Lund et al [23], who studied surgical patients to longer intraoperative times and greater degree of stress, did not find any increase in circulating lactate concentrations after intravenous glucose administration. In patients with severe sepsis and CS, Revelly et al [16] observed that endogenous glucose production was markedly increased, but it was not influenced by lactate infusion. In this context, the counterregulatory response, as well inflammatory mediators, may have contributed to glycolysis and increased lactate production.

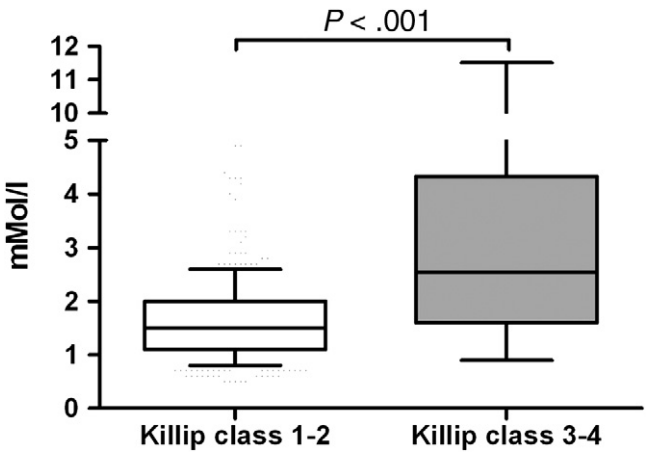

Fig. 1 Lactate values according to Killip class.

Table 3 Multivariable linear regression analysis

	Outcome: admission lactate			
	Unstandardized	SE	Standardized	*P*
Killip class	0.58	0.18	0.21	.001
Admission glycemia	1.06	0.20	0.30	<.001
Peak Tn I	0.003	0.001	0.217	<.001
Constant	0.56	0.95		.56

r^2 = 0.320; *P* < .001.

Table 4 Multivariable backward logistic regression analysis according to Killip classes

	Killip class I-II		
	OR	95% CI	*P*
Age (1-y step)	1.11	1.02-1.20	.014
Tn I	1.006	1.003-1.009	<.001
Leukocytes (1000/mL step)	1.20	1.01-1.40	.033
	Killip class III-IV		
	OR	95% CI	*P*
Lactate (1 mmol/L step)	1.17	1.05-1.30	.003
Age (1-y step)	1.11	1.03-1.19	.006
Leukocytes (1000/mL step)	1.17	1.03-1.33	.015

Adjusted for EF and glycemia.
Pseudo r^2, 0.49; Hesmer-Lemershow goodness-of-fit χ^2, 5.35; $P = .720$.
Adjusted for PCI failure.
Pseudo r^2, 0.37; Hesmer-Lemershow goodness-of-fit χ^2, 3.25; $P = .917$.

Although lactate metabolism is far to be completely understood in acute myocardial ischemia, the tight connection between glucose and lactate metabolism we observed in patients with STEMI may underscore the clinical relevance of glucose management in these patients [18] also taking into the potential role of acute insulin resistance and insulin therapy [24].

In conclusion, according to our data, in patients with STEMI submitted to primary PCI, blood lactate is a prognostic marker for early mortality only in the subgroup with advanced Killip class. The degree of hemodynamic impairment (as indicated by Killip class), of myocardial ischemia (as inferred by Tn I), and glucose values are the main factors influencing lactate concentrations in the early phase of STEMI.

References

[1] Khosravi H, Shshpori R, Stelfox HT, Kirkpatrick AW, Laupland B. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. Crit Care 2009;13:R90.

[2] Cerovic O, Golubovic V, Spec-Marn A, Kremar B, Vidmar G. Relationship between injury severity and lactate levels in severely injured patients. Intensive Care Med 2003;29:1300-5.

[3] Nguyean HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32:1637-42.

[4] Jansen TC, van Bommel J, Woodward R, Mulder PG, Bakker J. Association between blood lactate levels, Sequential Organ Failure Assessment subscores, and 28-day mortality during early and late intensive care unit stay: a retrospective observational study. Crit Care Med 2009;37(8):2369-74.

[5] Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Med 2007;33(11):1892-9.

[6] Meregalli A, Oliveira RP, Friedman G. Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. Crit Care 2004;8(2):R60-5 [Epub 2004 Jan 12].

[7] Chiolero RL, Revelly JP, Leverve X. Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery. Crit Care Med 2000;28:3784-91.

[8] Koreny M, Karth GD, Geppert A, Neunteufl T, Priglinger U, Heinz G. Siostrzonek P. Prognosis of patients who develop acute renal failure during the first 24 hours of cardiogenic shock after myocardial infarction. Am J Med 2002;112(2):115-9.

[9] Geppert A, Dorninger A, Delle-Karth G, Zorn G, Heinz G, Huber K. Plasma concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. Crit Care Med 2006;34(8):2035-42.

[10] Valente S, Lazzeri C, Vecchio S, Giglioli C, Margheri M, Bernardo P, et al. Predictors of in-hospital mortality after percutaneous coronary intervention for cardiogenic shock. Int J Cardiol 2007;114 (2):176-82.

[11] Valente S, Lazzeri C, Chiostri M, Giglioli C, Sori A, et al. NT-proBNP on admission for early risk stratification in STEMI patients submitted to PCI. Relation with extension of STEMI and inflammatory markers. Int J Cardiol 2009;132(1):84-9.

[12] Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28(20):2525-38.

[13] Lazzeri C, Valente S, Chiostri M, Sori A, Bernardo P, Gensini GF. Uric acid in the acute phase of ST elevation myocardial infarction submitted to primary PCI: its prognostic role and relation with inflammatory markers: a single center experience. Int J Cardiol 2010; 138:206-16.

[14] Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF. In hospital peak glycemia and prognosis in STEMI patients without previously known diabetes. Eur J Cardiovasc Prev Rehabil 2010;17(4):419-23.

[15] Gutierrez G, Williams JD. The riddle of hyperlactatemia. Crit Care 2009;13:176.

[16] Revelly JP, Tappy L, Martinex A, Bollmann M, Cayeux MC, Berger MM, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. Crit Care Med 2005;33:2235-40.

[17] Mavric Z, Zaputovic L, Zagar D, Matana A, Smokvina D. Usefulness of blood lactate as a predictor of shock development in acute myocardial infarction. Am J Cardiol 1991;67:565-8.

[18] Deedwania P, Kosiborod M, Barrett E, et al. American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity and Metabolism. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2008;117(12):1610-9.

[19] Lazzeri C, Chiostri M, Sori A, Valente S, Gensini GF. Postprocedural hyperglycemia in ST elevation myocardial infarction submitted to percutaneous coronary intervention: a prognostic indicator and a marker of metabolic derangement. J Cardiovasc Med (Hagerstown) 2010;11(1): 7-13.

[20] Obata K, Ogata M, Matsumoto T, et al. The effects of glucose on plasma amino acids and pyruvate during upper abdominal surgery. Anesth Analg 1993;76:357-61.

[21] Jackson RA, Hamling JB, Sim BM, et al. Peripheral lactate and oxygen metabolism in man: the influence of oral glucose loading. Metabolism 1987;36:144-50.

[22] Prando R, Cheli V, Buzzo P, et al. Blood lactate behavior after glucose load in diabetes mellitus. Acta Diabetol Lat 1988;25:247-56.

[23] Lund J, Stjernostrom H, Bergholm U, et al. The exchange of blood-borne amino acids in the leg during abdominal surgical trauma: effects of glucose infusion. Clin Sci 1986;71:487-96.

[24] Lazzeri C, Sori A, Chiostri M, et al. Prognostic role of insulin resistance as assessed by homeostatic model assessment index in the acute phase of myocardial infarction in nondiabetic patients submitted to percutaneous coronary intervention. Eur J Anaesthesiol 2009;26 (10):856-62.