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STRESS HYPERGLYCEMIA IN ACUTE MYOCARDIAL INFARCTION

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Summary. *Stress hyperglycemia represents increased blood glucose level that is result of activation of neurohormonal processes in organism exposed to stress. The aim of the paper is to analyze literature data on prognostic implications of admission hyperglycaemia in patients with acute myocardial infarction (AMI). Retrospective study included 543 patients with AMI hospitalised in Department for cardiovascular diseases in Niš, in period 2000-2005. The most logical explanation for connection of stress hyperglycemia and mortality is probably this: larger infarctions result in more pronounced sympathetic nervous system activation and catecholamine secretion. That leads to higher glycemia, on one hand, and higher mortality, on the other. In conclusion, both the medical literature and our own data suggest the quoad vitam prognostic value of hyperglycemia in AMI. Age, heart rate on admission and infarct size statistically significantly correlated with hyperglycemia and a trend for statistically significance was found for higher blood glucose values in women.*

Key words: *Acute myocardial infarction, stress hyperglycemia, prognosis*

Introduction

Stress hyperglycemia represents increased blood glucose level that is result of activation of neurohormonal processes in organisam exposed to stress. According to the American Diabetes Association (1) normal blood glucose level is less than 5.6 mmol/L (fasting glucose) and 6.1 mmol/L (2-h values in the oral glucose tolerance test (OGTT)). Increased glucose level during stress is result of sympatic nervous system activation and raised production of catecholamines (adrenalin and noradrenalin) and cortisol that stimulate processes of glyconeogenesis, glycogenolysis and lipolysis. These hormones are responsible for insulin resistance, on receptor and post receptor level, so there are in the same time hyperglycemia, hyperinsulinemia and insulin resistance (2-4).

Numerous studies have shown that stress hyperglycemia was common in acute critically illnesses, even in patients without diabetes mellitus (DM) (3-6). Stress hyperglycemia occurs in 5–30% of patients with apoplexia, myocardial infarction, sepsis, trauma and other critically illness (3) and it correlates with poor outcome (7).

First data about hyperglycemia in critically ill patients were recorded in 1855. by French psysiologist Claude Bernard (8).

Several studies have reported that stress hyperglycemia in the time of AMI, in patients with or without diabetes, was associated with increased both in-hospital (7,9–19) and long term mortality (10,11,20–23). It has been also shown that patients with stress hyperglycemia, but without previous diagnosis of diabetes, were at increased risk of congestive heart failure and cardiogenic shock (22) when compared to patients with DM (7). Some studies show that hyperglycemia, more than diabetes, is associated with poor prognosis of AMI (4,16,21,24,25), and diabetic patients have better prognosis than patients with stress hyperglycemia and blood glucose level in rang of diabetes (4,18,21). Lastly, blood glucose concentration was related to increased mortality in patients with ST - segment elevation myocardial infarction (STEMI) as well as in those with non-STEMI and regardless of whether patients received reperfusion therapy at the acute stage (22).

Elevated admission glucose appears more important than prior long-term abnormal glucose metabolism in predicting mortality in patients with suspected acute coronary syndrome (26).

Aim of the Paper

The aims of the paper are to analyze literature data on prognostic implications of admission hyperglycaemia in patients with AMI and to investigate interrelationship between blood glucose level and relevant clinical parameters in AMI.

Patients and Methods

Retrospective study included 543 patients with AMI hospitalised in Department for cardiovascular diseases in Niš, in period 2000-2005. Diagnosis of AMI was made by clinical, ECG, echocardiography and laboratory findings (troponin, CKMB). There was a slight predominance of men (54.88%), the average age was 63.8 ± 10.65 and mortality 9.01%.

DM was previously diagnosed in 21.7% of our patients and during this hospitalization in additional 4.1%. Impaired fasting glucose (IFG) was found in 19.2%.

Nineteen parameters were analyzed. Corellation test and descriptive statistical methodes were used.

Results

Figure 1. shows the values of admission glycemia in our patients.

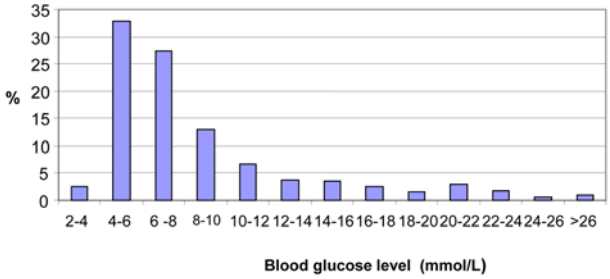


Fig. 1. Values of admision glycemia in our patients

Trend to statistical significance was found for hyperglycemia in women (correlation coefficient r = 0.0828, p = 0.590; fig. 2).

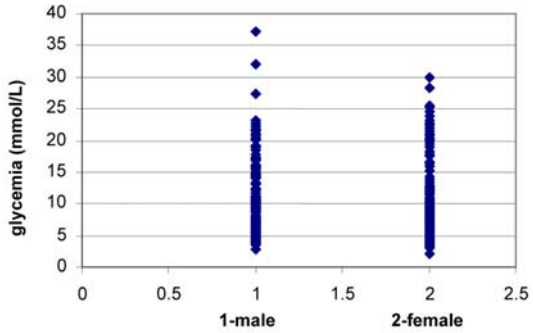


Fig. 2. Correlation between glycemia and gender

The significant positive correlation between glycemia and age was found (r=0.2245, p<0.0001; fig. 3).

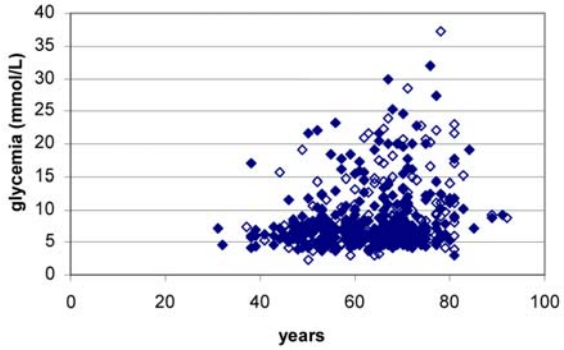


Fig. 3. Correlation between glycemia and age

Positive correlation of hyperglycemia with atrial fibrillation was found (r = 0.1134, p = 0.0100; fig. 4).

Hyperglycemia was in statistically significant correlation with heart rate on admission (r = 0.1274, p = 0.0071; fig. 5), with myocardial infarction size, as measured by troponin (r = 0.1680, p = 0.0472; fig. 6) as well as with mortality (r = 0.2845, p < 0.0001; fig. 7).

Glycemia was in negative correlation with smoking (r = -0.1557, p = 0.0472).

Fig. 4. Correlation between admission glycemia and presence of atrial fibrillation

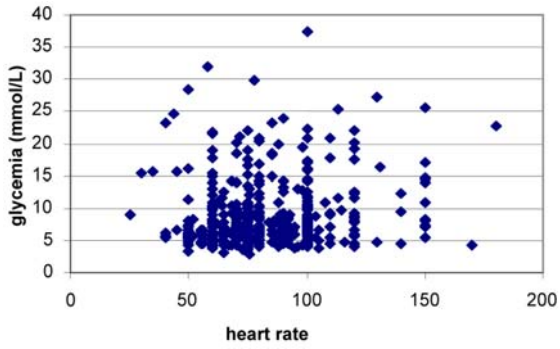


Fig. 5. Correlation between glycemia and heart rate on admission

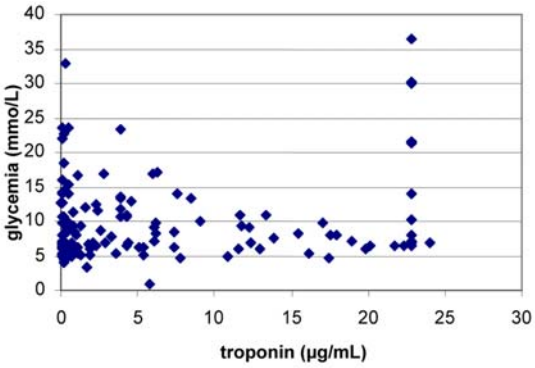


Fig. 6. Correlation between glycemia and infarction size measured by troponin

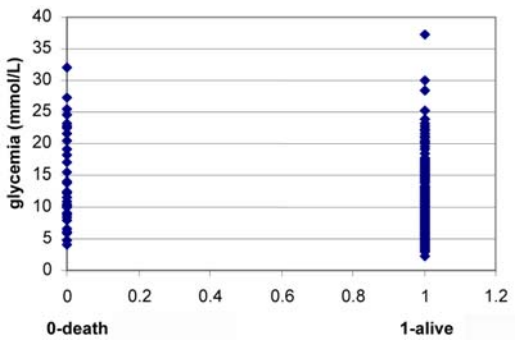


Fig. 7. Correlation between glycemia and mortality

Table 1 presents parameters that did not correlate with glycemia on admission.

Table 1. Non significant corellations with glycemia on admission

Parameter	p value
Hypertension	NS
Sistolic blood presure on admission	NS
Diastolic blood presure on admission	NS
Fibrinolitic's use	NS
Obesity	NS
Leukocites count	NS
Hematocrit	NS
Manifest infections	NS
Chronic obstructive lung disease	NS
Left ventricle size	NS
Left ventricle ejection fraction	NS

Discussion

Trend to statistical significance for higher prevalence of hyperglycemia in women could reflect more frequently recorded DM in women and worse prognosis of AMI (27).

Correlation with **gender** was investigated by several authors (10,13,15,19-21,28). In three studies (13,15,19,22) hyperglycemia correlated with female sex, while the opposite results -higher prevalence of hyperglycemia in males- were obtained in two studies (10, 21). Nordin *et al.* (20) and Marfella *et al.* (28) did not found any correlation.

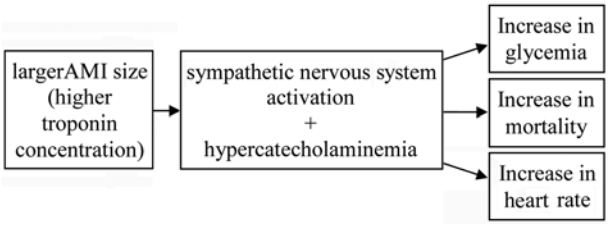
The obvious correlation of hyperglycemia with **age** is the result of glycoregulation alterations in older subjects. Our data are in agreement with other studies' results (10,15,16,19-22). Hyperglycemic patients in study of Salmasi *et al.* (29) were older, but not significantly.

A few studies investigated the relation between hyperglycemia and **heart rate** and it was found to be positive and statistically significant (13,21,28).

Negative correlation of hyperglycemia and **smoking** is an interesting finding. It can be explained by so-called smoking paradox, the fact that smokers have better prognosis in AMI and unstable angina pectoris (30). Global left ventricule function in AMI is better in smokers than in non smokers, resulting in lower both catheholamine and blood glucose levels.

Correlation of glycemia and **infarction size** was examined in several studies. Most of them estimated infarct size by values of creatine phosphokinase (15,19-21,31,32), aspartate aminotranferase and CKMB (33) and they almost all found positive correlation. In three studies infarction size was measured by troponin value. In work of Stubbs *et al.* (2) there was no correlation between these parameters, while the opposite result -significant correlation - was found in two studies (13,28). In study of Marfella *et al* (28) troponin was significantly higher in hyperglycemic patients. In addition, troponin was significantly higher in patients with stress hyperglycemia than in hyperglycemic diabetic patients.

The most logical explanation for connection of stress hyperglycemia and mortality is probably this (graph 1): larger infarctions result in more pronounced sympathetic nervous system activation and catecholamine secretion. That leads to higher glycemia, on one hand, and higher mortality, on the other. Between the first mentioned consequence of hypercatecholaminemia (stress hyperglycemia) and the infarction size (measured by troponin) we found statistically significant correlation.



Graph 1. Connection of stress hyperglycemia and mortality

We also found correlation between hyperglycemia and **mortality**, in concordance with literature data (7,10, 11,13,15,17,19-21,31,32).

Correlation between infarct size and mortality is well known. We were not able to measure plasma catecholamine levels, but Figure 1 illustrates probably the most rational explanation.

An additional argument - real involvement of sympatethic nervous system and catecholamines in these pathophysiological events – is correlation of heart rate (that catecholamines influence on) and hyperglycemia.

A few authors examined correlation of glycemia and blood pressure (**BP**). Significant correlation between glycemia and systolic BP was found in work of Marfella *et al.* (28). On the contrary, others did not found any significant relationship of these parameters (20,21).

In our work, suprice was, at first, missing correlation of glycemia on admission and systolic and diastolic BP on admission. Namely, according to higher glycemia as a consequence of hyperadrenergic condition in AMI, BP was expected to be higher, too. But, necrosis results in diminishing of left ventricle work, that leads to fall of BP. In other words, larger infarctions cause more pronounced sympathetic activation and catecholamine secretion. This leads to glycemia increase, but not BP increase, due to inability of damaged left ventricule to respond to stimulation with adequate rise in minute volume and, thus, in BP.

Relation of hyperglycemia and **hypertension** (as diagnosis, from medical history) was examined in a few studies. Our result (no correlation) is in keeping with some literature data (15,19,28), but not all (10,21).

Non significant correlation of hyperglycemia and **left ventricle ejection fraction**, found in our work, is in agreement with other authors' works (19,20). The single exception is the study of Marfella *et al.* (28).

Hyperglycemia is the marker of worse inhospital prognosis, but causality is questionable. Hyperglycemia can increase mortality by metabolic disturbances, but,

on the other hand, hyperglycemia is partially the consequence of hyperadrenergic condition, that directly aggravates the prognosis.

Hyperglycemia contributes to poor prognosis of AMI by several mechanisms. It was shown that stress hyperglycemia was associated with **increased inflammation** in humans (28,34,35). Patients with hyperglycemia have enhanced T-cell activation, both CD4+ and CD8+, as well as a large number of natural killer (NK) cells whose role in plaque instability is known (28). Hyperglycemic patients have higher circulation levels of CRP and IL-18 (28) and there are data that suggest IL-18 to be a strong predictor of death from cardiovascular causes in patients with acute coronary syndromes (36). There is a higher circulation level of TNF-α (4), which enhances generation of free radicals, causes dysfunction and apoptosis of endothelial cells (9) and, on the other hand, with adrenalin and noradrenalin, is responsible for insulin resistance that contributes again to hyperglycemia (4).

Hyperglycemic patients present more extensive myocardial necrosis than normoglicemic (2,3,10,13,15,19-21,28,32), suggesting that it may be associated with raised inflammation (37). Larger myocardial necrosis increase the risk of congestive heart failure and mortality and lead to greater production of stress hormones that elevate blood glucose level (7).

Hyperglycemia contributes to the production of reactive oxygen species and consequent **oxidative stress** (35); there are data about their role in atherosclerosis and acute cardiovascular events (14,38). Besides, superoxid anion inactivates both NO and prostacyclin which are potent vasodilatators and antiaggregans (39).

Acute blood glucose level increase in patients with AMI leads to **electrophysiological alteration** that may favour the occurrence of arrhythmias with potential fatal outcome (14). This is supported by the fact that hyperglycemia is arrhythmogenic, due to prolongation of QT interval, even in healthy subjects.

Hyperglycemia and insulin resistance increase lipolysis and **free fatty acids** generation (in **excess**) (7,9,34). They are toxic to ischaemic myocardium, damage cardiac-cell membranes and cause calcium overload. In this way they reduce myocardial contractility and induce arrhythmias and heart failure, that lead to poor outcome (40).

Hyperglycemia **activates thrombosis**. Namely, acute blood sugar level increase induces alteration in coagulation, such as shortening of fibrinogen half-life, increases of pro-thrombin fragments and factor VII, together with enhanced platelet aggregation (14,35).

The next potential mechanism for adverse outcome in patients with hyperglycemia during AMI is **osmotic diuresis**, that can result in hypovolemia and myocardial function decline (41).

Shen X *et al.* (42) found that elevated admission glucose levels in STEMI patients treated with primary percutaneous coronary intervention (PCI) are independently associated with **impaired microvascular flow**, which may contribute, at least in part, to the poor outcome.

In another work (43) hyperglycemia in patients with STEMI was an important predictor of impaired epicardial flow before reperfusion therapy has been initiated**.** In addition, Ishihara *et al*. (15) found that "no reflow phenomenon" occurred more frequently during PCI in patients with acute hyperglycemia.

Salmasi *et al*. (29) demonstrated abnormal LV filling, independent of LVEF, in normotensive subjects 2 months after AMI, which was proportional to severity of glucose intolerance.

Multivariate analysis in the paper of Kosuge *et al*. (44) showed that persistent hyperglycemia was independently associated with LV dysfunction, defined as a predischarge LV ejection fraction.

A little is known about the association between admission hyperglycemia and previously undiagnosed abnormal glucose tolerance. The study of Ishihara *et al*. (45) showed that, although abnormal glucose tolerance was common in non-diabetic patients with AMI, admission hyperglycemia did not represent abnormal glucose tolerance. Taking into account the considerably high prevalence of abnormal glucose tolerance among patients with AMI and no previous diagnosis of diabetes, OGTT could be routinely considered for the risk stratification (45).

The study of Skibchik *et al*. (46) revealed that measurement of glycosylated hemoglobin (HbA1c) level in patients with hyperglycemia during the acute period (first 1 to 3 days) of MI allows timely and adequate glucose-regulating therapy, lowering of diabetes hyper diagnostics, and thus, improvement of therapeutic tactics.

Conclusion

1. Both the medical literature and our own data suggest the *quoad vitam* prognostic value of hyperglycemia in acute myocardial infarction.

2. Age, heart rate on admision and infarct size statistically significantly correlated with hyperglycemia and a trend for statistically significance was found for higher blood glucose values in women.

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STRES HIPERGLIKEMIJA U AKUTNOM INFARKTU MIOKARDA

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Kratak sadržaj: *Stres hiperglikemija predstavlja povišnu koncentraciju glukoze u krvi, što je rezultat aktivacije neurohormonalnih procesa organizma izloženog stresu. Cilj rada je da analizuje podatke iz literature o prognostičkim implikacijama hiperglikemije pri prijemu pacijenata sa akutnim infarktom miokarda (AIM). Retrospektivna studija je uključila 543 bolesnika sa AIM, hospitalizovana u Klinici za kardiovaskularne bolesti u Nišu, u periodu od 2000-2005.g. Najlogičnije objašnjenje za povezanost hiperglikemije i mortaliteta je verovatno sledeće: veći infarkti uzrokuju izraženiju aktivaciju simpatičkog nervnog sistema i sekreciju kateholamina. To dovodi do povčenja glikemije - sa jedne strane i do većeg mortaliteta, sa druge. U zaključku, medicinska literatura i naši podaci sugerišu quoad vitam prognostičku vrednost hiperglikemije u AIM. Starost, frekvenca srca pri prijemu i veličina infarkta signifikantno korelišu sa hiperglikemijom, a trend ka statističkoj značajnosti je nađen za više vrednosti glikemije u žena.*

Ključne reči: *akutni infarkt miokarda, stres hiperglikemija, prognoza*