THE EFFECT OF STRESS INDUCED-HYPERGLYCEMIA ON HOSPITAL TREATMENT OUTCOME IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITH ST SEGMENT ELEVATION

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Elevated glucose level on admission in the number of emergency conditions, including acute myocardial infarction (AMI), is linked to worse outcomes, regardless of the current treatment.

The introduction of primary percutaneous coronary intervention (PPCI) in therapy of AMI patients with ST segment elevation (STEMI) has improved the treatment of these patients. However, there are contradictory evidences regarding the impact of stress-induced hyperglycemia on the treatment outcome. The present study is aimed to indentify the effect of stress-induced hyperglycemia on in-hospital prognosis of patients with STEMI treated with AIM-PPCI.

Prospective study included 116 patients with a diagnosis of first AMI-STEMI treated with PPCI at the Department of Cardiovascular Diseases, Clinical Center Niš in the period 2010-2011. Immediately after establishing the diagnosis, the patients with adequate medicament preparation were transferred into the angiography room for the coronary stent implantation. Laboratory analysis of the whole blood samples were done immediately after admission and in the next 24 hours.

Receiver operator characteristic (ROC) analysis revealed that stress-induced hyperglycemia (glucose 11.2 mmol/L, an area under the curve of 0.812) is a delimiting factor for distinguishing the outcome and survival of patients on admission. The group of patients without stress-induced hyperglycemia had mortality rate about five times less (1/79 - 1.2%) than the group of patients with stress-induced hyperglycemia (5/37 - 13.5%), p=0.041. Comparing these groups with the incidence of DM, stress-induced hyperglycemia had no significant effect on mortality in the group without DM (1/54 vs. 3/26, ns) and in the group with DM (1/25 vs. 1/11, ns).

The cut-off value of glucose, obtained by ROC curve, is 11.2 mmol/L for stress-induced hyperglycemia in patients with STEMI treated with PPCI. This value could determine a significant gradient of risk: patients with glycemia <11.2 mmol/L on admission had almost five times lower risk of mortality in hospital than those with the level of glucose ≥ 1.2mmol/L. Stress-induced hyperglycemia has an equally bad effect on hospital survival in the groups with and without DM. Acta Medica Medianae 2012;51(3):18-23.

Key words: stress-induced hyperglycemia, primary percutaneous coronary intervention, acute myocardial infarction
of patients, which was difficult to assess based only on the value of fasting blood glucose (4). Taking in account that two-thirds of disorder of glucose metabolism or DM in AMI patients could not be revealed by the fasting blood glucose test, the current recommendation is the application of the OGTT (5). The importance of hyperglycemia in AMI was not only due to high prevalence, but also due the harmful effect. Hyperglycemia was strongly associated with poor outcome in acute coronary syndromes (ACS) (6-9). However, there were various methodological problems for more efficient utilizing hyperglycemia as a predictor of poor in-hospital outcomes in acute myocardial infarction. One of them was the lack of agreement which value of glucose should be considered as stress hyperglycemia (SHG) (10). Despite the fact that the introduction of PPCI in the therapy of AIM significantly reduced AIM mortality, impaired glucose metabolism still adversely affect both short and long-term prognosis in this group of patients.

**Aim**

The main objective of this prospective study was to analyse blood glucose on admission and its influence on in-hospital prognosis of patients with acute myocardial infarction (STEMI) treated with PPCI at the Clinic for Cardiovascular Diseases, Clinical Center Niš. At the same time, the effect of stress-induced hyperglycemia on in-hospital survival of patients with diagnosis of DM was analysed.

**Materials and methods**

**Patients' selection**

The study included 116 patients with a diagnosis of first AMI (STEMI) treated in the coronary care unit at the Department of Cardiovascular Diseases, Clinical Centre Niš, in the period 2010-2011. The patients with diagnosed cardiogenic shock and pulmonary edema, as well as the patients requiring the rescue PCI after failed fibrinolysis, were excluded from the study. The criteria for selecting patients for PPCI treatment were: persistent retrosternal pain (≥ 30 min and up to 12 hours), elevated ST segment (≥ 0.1mV in at least two adjacent limb leads or ≥ 0.2mV in pericardial leads or acute bundle branch block). All patients received standard preparation for PCI: 300 mg aspirin, 600 mg clopidoogrel and 0.5/kg/TT-iv enoxiparina with gastroprotection (in accordance with the guidelines for the management of STEMI AMI). Patients also received: iv nitroglycerin, beta blockers, statins, ACE inhibitors, anti-arrhythmic drug and atropine (iv), if required, and in the absence of contraindications. Coronary angiography with stent implantation was performed in the angiography room under sterile conditions, by femoral artery punctation. After interventions, the patients were turned back to the coronary care unit to have their treatment continued. Two hours after the procedure, the patients received low molecular weight heparin, depending on the operator estimation in the angiography room. All patients received aspirin (300mg), clopidoogrel (75mg), along with other therapies in the absence of contraindications (beta-blocker, ACE inhibitor, statin and mononitrile) until hospital discharge. Laboratory analysis of the whole blood samples were done immediately after admission and in the next 24 hours in the central laboratory of the Clinical Center Niš (Abbott AxSYM System device). Patients with previously diagnosed DM were considered those who were on diet, oral hypoglycaemic agents or taking insulin therapy. All the patients, with and without the diagnosis of DM, were treated with short-acting insulin sc in the case of blood glucose level over 11mmol/L. Newly diagnosed DM patients were considered those with the value of glycemia on admission above 11.1mmol/L and fasting glycemia, 7.0mmol/L in first 24 hrs. Echocardiographic analysis, including also the left ventricular ejection fraction, was done on the Aloka Pro Sound 4000.

**Statistical analysis**

The results were statistically analysed using the Student’s t test, chi square test, one-way and multeway ANOVA and were tabularly or graphically presented. SPSS 15.0. software package was used for data processing and for obtaining Receiver operator characteristic (ROC) curve.

**Results**

1. Epidemiological risk factors: the impact on patients survival

Age and sex distribution of patients on admission are shown in Table 1. There were significantly more male patients in the examined group. The incidence of the coronary heart disease risk factors is shown in Table 2. The early and newly diagnosed diabetes mellitus was found in 36 patients (31%). Besides older age, gender, presence of diabetes mellitus, tobacco smoking had also adverse effect on the treatment outcome (Table 3).

2. The level of blood glucose and treatment outcome

Receiver operator characteristic (ROC) analysis revealed the glucose level of 11.2 mmol/L as a delimiting factor for distinguishing the outcome and survival of patients in hospital (Figure 1). The cut-off value of glucose of 11.2 mmol/L for stress hyperglycemia had the under curve area of 0.812; 95% confidence interval (95% CI) was 0.878 to 1.000 and standard error (SE) was 0, 0532, with p<0.0001. There was significantly higher mortality (p<0.05) in the whole group of patients and negative effect on the treatment outcome in patients with stress hyperglycemia (Table 4).
Table 1. Age and gender

<table>
<thead>
<tr>
<th>Patients (n=116)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.3 ± 10.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>72 (62) &lt;0.001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>44 (38) ns</td>
</tr>
</tbody>
</table>

Table 2. CHD (coronary heart disease) risk factors

<table>
<thead>
<tr>
<th>CHD risk factors</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>95 (82.7)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>85 (74.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36 (31.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>46 (39.6)</td>
</tr>
</tbody>
</table>

Table 3. CHD risk factors and in-hospital death (univariate logistic regression analysis)

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.109</td>
<td>1.051-1.171</td>
</tr>
<tr>
<td>Gender</td>
<td>2.893</td>
<td>1.152-7.269</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.857</td>
<td>0.628-5.496</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.059</td>
<td>0.376-2.979</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.833</td>
<td>1.123-7.15</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.267</td>
<td>0.103-0.69</td>
</tr>
</tbody>
</table>

Table 4. Outcomes with respect to stress hyperglycemia

<table>
<thead>
<tr>
<th>Survivors</th>
<th>Dead</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress hyperglycemia + (glycemia ≥ 11.2 mmol/l)</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>Stress hyperglycemia - (glycemia &lt; 11.2 mmol/l)</td>
<td>63</td>
<td>1</td>
</tr>
</tbody>
</table>

3. The treatment outcome of patients with and without DM depends on stress hyperglycemia and other parameters

Hyperglycemia due to stress was significantly more prevalent in the elderly patients and in tobacco smokers. Patients with stress hyperglycemia in both groups had higher myocardial damage (higher troponin value and lower EF) but the equal mortality rate as the patients with and without stress hyperglycemia regardless of the existence of DM (Table 5).

Discussion

Stress hyperglycemia represents the elevation of plasma glucose levels as a result of neuro-humoral activation in the body under stress. It is more frequent (30%) in the critically ill patients, patients without prior DM and those with CVI, sepsis, trauma, representing the marker for poor outcome (11).

The underlaying mechanisms of the harmful effect of stress hyperglycemia on the worse outcome of AMI include:

- inflammation
- oxidative stress
- prolonged QT interval
- increased production of free fatty acids
- activated platelets
- condition of the insulin resistance
- progressive endothelium dysfunction
- disturbed microcirculation in the myocardium (no-reflow phenomenon) (12).

However, one of the arising questions is whether the stress hyperglycemia is only a marker of excessive production of adrenaline and cortisol or a marker for directly damaged myocardium leading to lower EF, as one of the main indicators for both short- and long-term prognosis of patients. It is assumed that in excessive stress conditions with severe degree of endothelial dysfunction there is, on the one side, the anti-insulin preponderance of stress hormones, and, on the other side, reduction of sensitivity of insulin receptors and glucose utilization in the cells (worsening of endothelial dysfunction). This certainly leads to a more pronounced metabolic disturbances and energy deficiency of cells, particularly cells of ischemic myocardium. Thus hypoglycemia, regardless of the presence of diabetes mellitus, could be viewed as a surrogate marker of endothelial dysfunction, as well the marker of the hyperactivity of the cortico-medullary zone of adrenal gland and sympathetic nervous system. Taking in consideration that substrate for these disorders is hypothalamic dysfunction induced by peripheral stimulation, it could be assumed that hyperglycemia could also correlate with other indicators of cardiac function, such as the BNP (13).

Table 5. Clinical, biochemical characteristics and outcomes with respect to diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>Diabetics n=36 (31%)</th>
<th>p</th>
<th>Nondiabetics n=80 (69%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (X±SD)</td>
<td>58.2±11.1</td>
<td>65.4±8.2</td>
<td>&lt;0.05</td>
<td>54.1±10.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (60.3)</td>
<td>8 (72.6)</td>
<td>ns</td>
<td>25 (46.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>15 (60.3)</td>
<td>7 (63.3)</td>
<td>ns</td>
<td>34 (62.9)</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (54.1)</td>
<td>6 (54.5)</td>
<td>ns</td>
<td>41 (76.2)</td>
</tr>
<tr>
<td>Anterior myocardial infarction (%)</td>
<td>5 (20)</td>
<td>3 (27.2)</td>
<td>ns</td>
<td>19 (35.1)</td>
</tr>
<tr>
<td>Stress glycemia (X±SD)</td>
<td>6.3±1</td>
<td>14.0±4.4</td>
<td>&lt;0.001</td>
<td>6.3±0.9</td>
</tr>
<tr>
<td>Ejection fraction (X±SD)</td>
<td>43.1±7</td>
<td>44.7±8</td>
<td>ns</td>
<td>46.3±5</td>
</tr>
<tr>
<td>Troponin I (X±SD)</td>
<td>8.77±6</td>
<td>10.2±4</td>
<td>ns</td>
<td>10.2±3</td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td>-</td>
<td>2 (8.0%)</td>
<td>ns</td>
<td>1 (1.8%)</td>
</tr>
</tbody>
</table>
The reperfusion therapy, according to the recommendations, is the main treatment for patients with STEMI, while primary PCI is considered more effective, not only due to recanalisation of occluded coronary arteries, but also because of significantly better survival of patients with STEMI, compared to fibrinolytic therapy. 25% to 50% of patients with established epicardial flow (TIMI 3) had disturbed microcirculate flow (no-reflow) and slower resolution of ST elevation, associated with remodeling and poor outcome (14). In our group of patients, the existence of the DM adversely influenced the outcome of treatment, along with gender (male), age and tobacco consumption (Table 3).

The most important finding of this study is that the value of hyperglycemia on admission (stress hyperglycemia) had adverse effect on the treatment outcome of the patients with acute myocardial infarction (STEMI). ROC analysis revealed that the value of blood glucose (11.2 mmol/L) on admission could delimit good and poor in-hospital outcome (Figure 1). Dividing the patients into two groups, particularly those with glycemia below and above the value of the so-called stress hyperglycemia (>11.2mmol/L), irrespective of DM diagnosis on admission, we found that hyperglycemia had adverse effect on hospital survival (Table 4).

As a potential prognostic parameter in AMI, stress hyperglycemia, has the advantage, due to availability for analysis in the smallest health care organizations, to be easily and quickly obtained in HMP.

There is a possibility that stress hyperglycemia is not only a marker, but also a causal factor (15, 16), inferred from the pathophysiological analysis (17,18) and the finding that the artery patency after AMI fibrinolysis is associated with glycemia on admission, independently of clopidogrel administration (19). In this case, the values of glycemia that are associated with the best prognosis should be determined, and whether achieving that goal provides a better prognosis (20). The benefits of insulin therapy in order to normalize glycemia in acute coronary syndrome are due to:
- coronary vasodilation
- improving endothelial function
- anti-inflammatory effect
- antithrombotic effect-(21).

Thus, a possibility of resolving the problems of no-reflow phenomenon as well as better microcirculation after the successful re-opening of the epicardial vessels either by medication or PPCI is provided. However, only three randomized controlled studies had the primary aim to examine whether better glycemic control improves prognosis in AMI (22). The solution to the problem requires additional randomized clinical trials, but it is considered that the control of hyperglycemia with insulin to the target value of glucose of 6.11mmol/L is a useful therapy for this group of patients (23).

**Conclusion**

1. The threshold of stress-induced hyperglycemia which affected the outcome of patients with acute myocardial infarction (STEMI) treated with PPCI was 11.2mmol/L or higher.
2. The values above 11.2mmol/L have worsening effect on the outcome in the entire group of respondents irrespective of the presence of DM.
3. Before starting PPCI in patients with plasma glucose value above 11.2mmol/L on admission, hyperglycemia should be corrected by insulin in order to decrease the possibility of no-reflow phenomenon and better predictor of the outcome in these patients.
References


**UTICAJ HIPERGLIKEMIJE USLED STRESA NA ISHOD BOLNIČKOG LEČENJA BOLESNIKA SA AKUTNIM INFARKTOM MIOKARDA SA ST ELEVACIJOM**

Aleksandar Stojković, Miloje Tomašević, Nebojša Krstić, Zoran Perišić, Milan Pavlović, Sonja Šaling-JMartinović, Svetlana Apostolović, Lazar Todorović, Goran Koračević, Gordana Nikolić, Vladimir Miloradović i Violeta Irić-Ćupić

Povišena glikemija pri prijemu, u brojnim urgentnim stanjima, uključujući akutni infarkt miokarda (AIM), pogoršava ishod lečenja bez obzira na savremenu terapiju. Uvođenjem primarne perkutane koronarne intervencije (PPCI) u terapiju AIM sa ST segment-elevacijom (STEMI) poboljšano je lečenje ove grupe bolesnika. Kontradiktorna su saopštenja u literaturi oko uticaja hiperglikemije usled stresa na ishod lečenja, pa je cilj istraživanja bio analiza uticaja hiperglikemije usled stresa na hospitalnu prognozu bolesnika sa AIM-STEMI lečenih PPCI.


Receiver-operator characteristic (ROC) analizom pokazano je da je najbolja vrednost hiperglikemije usled stresa pri prijemu, za razgraničavanje onih koji će preživeti i onih koji će umrijeti u bolnici, 11.2 mmol/L, sa površinom ispod krivulje 0.812. U grupi bez hiperglikemije usled stresa umrlo je približno pet puta manje bolesnika (1/79-1.2%) nego u grupi sa hiperglikemijom usled stresa (5/37 -13.5%), p=0.041. Prisustvo hiperglikemije je podjednako loše uticalo na prognozu bolesnika bez obzira na prisustvo ili odsustvo dijabetes melitusa. Smrtnost u grupi bez DM sa hiperglikemijom ili bez nje bila je slična (3/26 vs. 1/54, ns) kao i u grupi sa DM (1/11 vs. 1/25, ns).

Najbolja granična (cut-off) vrednost za hiperglikemiju usled stresa kod bolesnika sa AIM STEMI lečenih PPCI je 11.2mmol/L, dobijena je ROC krivom, a determiniše značajan gradijent rizika: bolesnici sa glikemijom <11.2mmol/L pri prijemu imali su skoro pet puta manji rizik od umiranja u bolnici od onih sa koncentracijom glikoze ≥11.2mmol/L. Pojava hiperglikemije usled stresa podjednako je loše uticala na bolničko preživljavanje u grupama sa i bez DM. Acta Medica Medianae 2012;51(3):18-23.

**Ključne reči:** hiperglikemija usled stresa, primarna perkutana koronarna intervencija, akutni infarkt miokarda