Admission hyperglycemia in patients with acute coronary syndrome complicated by cardiogenic shock

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Abstract

Background: Many reports showed that for patients with acute coronary syndrome (ACS) increased admission blood glucose (ABG) level is associated with adverse outcomes. Although scientific reports on this issue are still inconsistent, many recent studies confirm that hyperglycemia is also an unfavorable prognostic factor in patients with ACS complicated by cardiogenic shock (CS). The aim of this study is to determine if hyperglycemia on admission can be a predictor of in-hospital death in patients with ACS complicated by CS.

Methods: The study population consisted of 40 patients with ACS complicated by CS admitted to the Intensive Cardiac Therapy Clinic from January 2010 to May 2013 and treated with primary percutaneous coronary intervention. A control group was selected among patients with uncomplicated ACS.

Results: Patients with CS had significantly higher levels of ABG (15.4 ± 6.26 vs. 7.97 ± 2.28 mmol/L, p < 0.01) in comparison with the control group. There was no statistically significant correlation between the level of glucose on admission and in-hospital mortality. Average ABG in patients who survived and in those who died were respectively 15.42 ± 5.61 vs. 15.40 ± 6.87 mmol/L, p > 0.05. Comparison in groups depending on ABG level and calculations with use of receiver-operating characteristics curves showed no relationship between the level of ABG and patients’ deaths.

Conclusions: Hyperglycemia on admission is a clinical feature of patients with ACS who develop CS, however its prognostic value requires further studies. (Cardiol J 2015; 22, 3: 290–295)

Key words: cardiogenic shock, hyperglycemia, myocardial infarction

Introduction

The most serious disease of the cardiovascular system is acute myocardial infarction (AMI). Although numerous clinical complications are associated with AMI, none are more potentially devastating or carry a worse prognosis than cardiogenic shock (CS) [1]. It occurs in 5% to 8% of patients hospitalized with AMI. This translates into approximately 40,000–50,000 cases per year in the United States and approximately 60,000–70,000 cases in Europe [2]. Despite advances in treatment during the last two decades, CS still remains the major cause of death with hospital mortality rates approaching 50% [2–5]. Appropriate monitoring, risk stratification and intervention from first medical contact can be undertaken after the onset of AMI symptoms only when we focus on identifying patients who are at high risk of CS development. Therefore, looking for simple, easily and
fast measurable prognostic factors of this deadly complication risk could be the next milestone in saving patients with myocardial infarction.

Hyperglycemia is an independent predictor of death in many acute states like trauma, head injury, stroke or acute coronary syndrome (ACS). It causes harm to critically ill through a variety of mechanisms including concurrent activation of inflammatory process and producing a hypercoagulable state [6].

It has been shown that for patients with AMI, increased admission blood glucose (ABG) level has been associated with adverse outcomes including death [7]. The prevalence of admission hyperglycemia (glucose levels ≥ 7.8 mmol/L) in different epidemiological studies ranges from 51% to > 58% of patients hospitalized with AMI [8]. Increased glucose level on admission is an independent factor of more impaired initial flow in the infarct-related artery and occurrence of no-reflow phenomenon [9]. In addition, patients with hyperglycemia have higher Killip class, a larger infarct and worse left ventricular (LV) function [10]. Also higher incidence of CS has been observed among hyperglycemic patients with AMI [11, 12]. Although, scientific reports on this issue are still inconsistent, many recent studies confirm that hyperglycemia is an unfavorable prognostic factor in AMI patients complicated by CS [11, 13–15].

Since measurement of blood glucose (BG) level is simple and fast, it is highly important whether hyperglycemia on admission can be an independent predictor of death in patients with CS.

The aim of this study is to determine if hyperglycemia on admission can be a predictor of in-hospital death in patients with ACS complicated by CS.

Study population

The population of our prospective study consisted of 40 patients with ACS complicated with CS (CS [+ ] group), admitted to the Intensive Cardiac Therapy Clinic during the period from January 2010 to May 2013 and treated with primary percutaneous coronary intervention (PCI). A control group (CS [– ] group) was selected among age-, gender- and infarct location-matched patients with uncomplicated ACS. All patients enrolled in the study were transported to the hospital by ambulance directly from home or another location of the event. The main criteria for exclusion from the study were: shock from non-cardiac causes, transfer from other hospitals, prehospital cardiac arrest.

Study protocol

We used the contemporary definition of AMI to confirm the diagnosis of ST elevation myocardial infarction (STEMI): typical clinical symptoms, persistent ST segment elevation ≥ 0.2 mV in two of V_2–V_4 leads or ≥ 0.1 mV in two of other contiguous leads or new left bundle branch block in electrocardiography (ECG) and elevation of myocardial necrosis markers (troponin T, creatinine kinase-MB fraction) [16]. The diagnosis of non-STEMI (NSTEMI) was made on the basis of typical chest pain and elevated biochemical markers of myocardial necrosis after exclusion of elevation of ST-segment in ECG [17]. CS diagnosis was based on clinical findings (cold, clammy skin, oliguria or anuria) and hemodynamic criteria including systemic systolic blood pressure < 90 mm Hg or decrease by 30 mm Hg compared to baseline lasting for at least 30 min without the use of inotropic support or intraaortic balloon pump. Patients with CS as a result of mechanical complications of AMI (acute mitral valve regurgitation, ventricular septal rupture) and other causes of hypotension such as arrhythmias, hypovolemia, vasovagal reactions, electrolyte disturbances, pharmacological side effects or cardiac tamponade were excluded from the study.

We assembled baseline characteristics such as demographic data, cardiovascular history, risk factors (diabetes mellitus, smoking status, hypertension), prior embolic events and family history of cardiac artery disease (Table 1). We classified all patients who had been treated with insulin, oral antihyperglycemic agents or lifestyle modification as diabetic mellitus (DM) patients.

ABG level samples were collected in the emergency room for all patients and measured with an arterial blood gas analyzer or laboratory analyzers routinely used at each hospital. For purposes of this study and adhering to the recommendations of the Polish Diabetes Association [18], patients were divided into three groups depending of ABG: normoglycemic (≤ 7.8 mmol/L), impaired glucose tolerance (IGT) group (7.8–11.1 mmol/L) and acute hyperglycemia group (> 11.1 mmol/L). All patients with previously diagnosed DM and those with hyperglycemia received antihyperglycemic therapy.

All patients were treated with primary PCI of the infarct-related artery which was identified on the basis of ECG and coronary angiography findings. PCI was performed using standard equipment and techniques including stent implantation. The angiographic success of revascularization was
defined as the Thrombolysis In Myocardial Infarction (TIMI) 3 flow.

The study was approved by the local research Ethics Committee.

Statistical analysis

Statistical analysis of the data was carried out using Statistica 10.0 set. Continuous variables were presented as means ± standard deviation. Comparisons between groups were performed using the χ² test, non-parametric Mann-Whitney test, Kruskal-Wallis test for continuous variables. Statistical significance was assumed at a p value of < 0.05.

Results

Forty patients were included in the study. The control group was collected from age-, gender- and infarct location-matched patients with uncomplicated ACS. The mean age in both groups was almost the same 71.5 ± 11.1 vs. 71.6 ± 11.1, respectively. Exactly half of patients were male in the groups. There were no statistically significant differences in risk factors between patients with or without CS (Table 1). Only previous stroke was presented more often in CS (+) group (respectively 15% vs. 3%, p < 0.05). STEMI patients were in the majority in both groups (90% vs. 88%). None of uncomplicated ACS patients died when mortality rate in CS (+) group reached 22 (55%) patients.

In comparison with the control group, patients who developed CS during hospitalization had significantly higher BG levels on admission, respectively 15.4 ± 6.26 vs. 7.97 ± 2.28 mmol/L, p < 0.01 (Fig. 1). This difference was strongly expressed in both DM and non-DM. Average ABG level in patients without DM history in CS (+) and CS (–) group was, respectively, 14.8 ± 6.03 vs. 8.00 ± 2.35 mmol/L (p < 0.001). Statistically signi-
significant difference in BG level between the study and control group are also present in diabetics, respectively 18.1 ± 7.09 vs. 7.73 ± 1.72 mmol/L (p < 0.05). In the study group, a huge majority of patients — 31 (78%) were those with acute hyperglycemia (ABG > 11.1 mmol/L). The opposite trend was observed in the control group where 21 (53%) patients were normoglycemic (ABG < 7.8 mmol/L), 17 (42%) patients had IGT (ABG 7.8–11.1 mmol/L) and only 2 (5%) patients were hyperglycemic (Table 2). The difference was statistically significant — p < 0.001.

Evaluation of the relationship between the level of BG on admission and sex in CS [+] group showed that distribution of hyperglycemia in a group of men and women was almost the same. In both sexes, the vast majority of respondents characterized the glucose level > 11.1 mmol/L (respectively 15 [75%] men and 16 [80%] women). Only 1 in 10 women and 1 in 10 men had a BG concentration of 7.8–11.1 mmol/L. Similarly, 15% of women and 10% of men were normoglycemic (ABG < 7.8 mmol/L). Due to the reports of other research [19], we evaluated the relationship between sex and death in patients with acute hyperglycemia (ABG > 11.1 mmol/L). In this study, gender did not affect mortality rates in patients with the highest levels of ABG — respectively 9 (60%) women vs. 7 (44%) men died (p > 0.05).

Also the presence of chest pain was not related to glucose levels on admission in CS [+] group. Mean ABG level in patients with or without stenocardia was, respectively, 17.4 ± 8.20 vs. 15.0 ± 5.84 mmol/L (p = NS). Although the CS [–] group demonstrated a statistically significant relationship between the level of BG and the presence of chest pain, the pain-free patients presented higher levels of ABG, respectively 7.61 ± 1.69 vs. 12.5 ± 4.07 mmol/L (p < 0.051).

There was no statistically significant correlation between the level of glucose on admission and in-hospital mortality (Fig. 2). Average ABG in patients who survived and in those who died were, respectively, 15.42 ± 5.61 vs. 15.40 ± 6.87 mmol/L (p > 0.05). Comparison in groups depending on ABG level, did not confirm that hyperglycemia is a predictor of death in ACS complicated by CS.

Discussion

Despite the continuous improvement of procedures for the treatment from first medical contact, early revascularization techniques and intensive care, the mortality rate in patients with ACS complicated by CS has not reduced for many years. This study tried to answer if hyperglycemia diagnosed on admission is associated with increased risk of in-hospital death in CS patients.

Our study confirmed the presence of hyperglycemia in almost all patients with CS. We clearly showed that regardless of DM status and sex, hyperglycemia was a part of the clinical characteristics of patients with ACS complicated by CS. What is more, levels of ABG were significantly higher in patients with CS than in those who did not develop this deadly complication.

Mechanisms for this hyperglycemia in patients with CS remain not fully explained. Some research connect high BG levels with the degree of biological stress which leads to secretion of stress hormones, including catecholamines, cortisol, various inflammatory cytokines and a promotion of

<table>
<thead>
<tr>
<th>ABG [mmol/L]</th>
<th>CS (+), n = 40</th>
<th>CS (–), n = 40</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7.8</td>
<td>5 (12%)</td>
<td>21 (53%)</td>
<td>&lt; 0.001</td>
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<tr>
<td>7.8–11.1</td>
<td>4 (10%)</td>
<td>17 (42%)</td>
<td>&lt; 0.001</td>
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<tr>
<td>&gt; 11.1</td>
<td>31 (78%)</td>
<td>2 (5%)</td>
<td>&lt; 0.001</td>
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Figure 2. Correlation between admission blood glucose level and fatal outcome in patients with cardiogenic shock; CI — confidence interval; AUC — area under the curve.
glycogenolysis and gluconeogenesis [20]. Insulin resistance is also induced by growth hormone and free fatty acids [6]. Stress hyperglycemia has been reported to promote platelet activation which is responsible for impaired microcirculation and cell damage exacerbation [21].

The phenomenon of hyperglycemia in serious, acute illnesses has been more widely studied in recent years. Braeley et al. [6] showed that increased BG level causes harm through a variety of ways in critically ill. Recent study of Mansour et al. [7] confirmed that increased BG level (≥ 7.8 mmol/L) is an unfavorable prognostic factor also in patients with ACS. Hyperglycemia in these patients leads to higher levels of cardiac necrosis markers and lower left ventricular ejection fraction [9, 22]. It also leads to increased endothelial dysfunction, hypercoagulability and impaired fibrinolysis [23, 24]. ABG ≥ 8.9 mmol/L was found to be an independent prognostic factor of no-reflow phenomenon in the study by Iwakura et al. [21]. A similar correlation was reported by Ishihara et al. [25] for patients with ABG > 11.1 mmol/L.

In Gąsior et al. [11] study, higher incidence of CS complicating ACS was observed among patients with high BG levels (≥ 7.8 mmol/L). Also Worthley et al. [26] showed that CS development is a prognostic implication of hyperglycemia in AMI. Zeller et al. [13] reported abnormal fasting glycemia as a predictor of CS.

Some studies have also confirmed the effect of hyperglycemia on increased mortality in patients with CS. In Pres et al. [14] research, evaluated BG level on admission (≥ 7.8 mmol/L), resulted in higher in-hospital and long-term mortality in patients with STEMI complicated by CS. Also Valente et al. [15] in an univariate analysis showed that hyperglycemia (> 11.1 mmol/L) was an independent predictor of in-hospital mortality. However, multivariate analysis did not confirm this association. In Tada et al. [27] study, a group of 81 patients transported by ambulance with CS complicating ACS, demonstrated ABG level of 9.2 mmol/L as a strongest prognostic indicator of death. It should be noted that in quoted study ACS was not the only cause of CS and the rate of in hospital death was only 12.3%.

In our study, there was no statistically significant correlation between the level of glucose on admission to hospital and in-hospital mortality. Average ABG in patients who survived and in those who died did not differ significantly. Also comparison in groups depending on ABG level and calculations with use of receiver-operating characteristics curves showed no relationship between the level of glucose on admission and patients in-hospital death. Some other authors also did not confirm the prognostic value of ABG. Foo et al. [28] in a prospective cohort study of 2,127 patients with ACS, demonstrated that admission serum glucose concentration was not independently associated with fatal outcome. In the univariate analysis, de Faria Modenesi et al. [29] reported that in 361 patients with ACS, the presence of stress hyperglycemia was associated with death but multivariate analysis did not confirm this finding. The report from the DIGAMI 2 trial [30] proved no relationship between 1-year risk of death, re-infarction or stroke and glycemic variability in DM patients with AMI who have been treated with insulin infusion during hospitalization.

Other studies report that hyperglycemia is a poor prognostic factor, but only in patients without a prior history of DM. Vis et al. [31] investigated 208 consecutive non-DM patients with STEMI and CS on admission. ABG level was a strong independent predictor of 1-year mortality which was respectively 21%, 27% and 60% in groups selected depending on admission glycemia (≤ 7.8 mmol/L, 7.8–11.1 mmol/L and > 11.1 mmol/L; p < 0.001, respectively). It should be noted that all patients enrolled in this study had CS on admission. The latest study of Yang et al. [32] confirmed that in patients with STEMI complicated by CS, the ABG level was independently associated with increased risk of 30-day mortality and had an additional predictive value for established risk score models in nondiabetic patients but not in diabetics. Unfortunately, the authors of this study could not identify the impact of BG lowering therapy on mortality because data on BG levels during the course of hospitalization and therapeutic BG targets were not available in their registries.

Given such divergent results, prognostic value of hyperglycemia in patients with ACS still requires further studies. Specific group which includes CS patients needs extremely careful analysis. Despite few reports finding ABG as an independent risk factor of shock appearance [11, 13, 26] it is still not clear whether admission hyperglycemia is not just simply a manifestation of ongoing critical illness [6]. It is surely a characteristic feature of the already present CS. Therefore, the key issue is the time between collecting blood samples and the onset of the first CS symptoms. Further studies should reconsider whether admission hyperglycemia or CS itself, as the most severe complication, determines death in ACS patients.
Limitations of the study

This is a single center registry. The primary limitation of this study was the small number of patients. The relatively low incidence of CS as a complication of ACS and the exclusion of patients transported from other hospitals, resulted in a significant reduction of the study group size. Other major limitation is the inability to evaluate the time window between collection of blood samples and occurrence of first CS symptoms.

Also because of the widely different clinical condition of patients before admission to the clinic, information about the time of the last meal was often impossible to obtain. Therapeutic interventions and medications administered by ambulance personnel were significantly different in individual cases. In this study, we were unable to determine how these actions impacted the BG level on admission.

Conclusions

Hyperglycemia on admission is a clinical feature for patients with ACS who develop CS, however its prognostic value requires further studies.

Conflict of interest: None declared

References