Metabolic interventions in acute myocardial infarction

Horst, Johannes
Chapter 4.1

Prognostic value of admission glucose in non-diabetic patients with myocardial infarction

Jorik R Timmer, Iwan CC van der Horst, Jan Paul Ottervanger, José PS Henriques, Jan CA Hoortje, Felix Zijlstra, on behalf of the Zwolle Myocardial Infarction Study Group

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Abstract

Introduction
Patients with acute myocardial infarction (MI) who have diabetes have an increased risk of mortality. In non-diabetic patients, admission glucose levels may also be a predictor of survival. However, data regarding admission glucose and long-term outcome in non-diabetic patients treated with reperfusion therapy for acute MI are limited.

Methods
We investigated long-term clinical outcome in 356 consecutive non-diabetic patients with ST segment elevation MI, treated with primary percutaneous coronary intervention (PCI) or thrombolysis as reperfusion therapy. Mean follow up was 8±2 years. The patients were divided based on admission glucose level; group I: <7.8 mmol/L, group II: 7.8–11.0 mmol/L and group III: ≥11.1 mmol/L.

Results
Mortality in group I (N=163) was 19.0%, in group II (N=151) 26.5% and in group III (N=42) 35.7% (P<0.05). Higher glucose levels were associated with larger enzymatic infarct sizes (P<0.01) and more reduced residual left ventricular function (P<0.05). Multivariate analysis showed that Killip class >1 at admission, odds ration (OR) 2.9 (95% confidence interval 1.7–5.0, P<0.001), age ≥60 years, OR 2.4 (1.5–4.0, P=0.001), thrombolysis as compared to PCI, OR 1.7 (1.1–2.7, P=0.02), admission glucose category, OR 1.4 (1.0–1.9, P=0.04) and anterior location, OR 1.6 (1.0–2.6, 0.03) were independent predictors of long-term clinical outcome.

Conclusion
Elevated admission glucose levels in non-diabetic patients treated with reperfusion therapy for ST segment elevation MI are independently associated with larger infarct size and higher long-term mortality.
Introduction

Prognosis after ST segment elevation myocardial infarction (MI) has improved markedly, in particular due to reperfusion therapy by either thrombolytic therapy or primary percutaneous coronary intervention (PCI).\textsuperscript{1-3} Despite these advantages in treatment regimen, patients with diabetes mellitus (DM) still have a poor prognosis after ST segment elevation MI.\textsuperscript{4,5} Interestingly, this increased risk is not confined to DM patients only, but non DM patients with impaired glucose tolerance (IGT) may also have an increased incidence of cardiovascular complications.\textsuperscript{6} Moreover, increased admission glucose levels may be related to a higher mortality in patients with acute myocardial infarction (MI), regardless of diabetic status.\textsuperscript{7,8} These elevated glucose levels are thought to reflect pre-existent IGT or increased physical stress. However, data regarding admission glucose and long-term clinical outcome in non-diabetic patients after ST segment elevation MI are limited and mainly based on patient groups in which only part of the patients received reperfusion therapy.\textsuperscript{9,10} Therefore, we investigated the influence of admission glucose levels on long-term clinical outcome in non-diabetic patients, all treated with reperfusion therapy, either with thrombolysis or primary PCI, for acute ST segment elevation MI.

Methods

It concerns a sub-analysis of the so-called ‘Zwolle trial’, a randomized study comparing primary PCI with thrombolysis, as described before.\textsuperscript{9} Baseline characteristics, clinical data, angiographic data and outcomes were recorded prospectively in a dedicated database. Patients were enrolled if they had no contraindications for thrombolytic therapy; had symptoms of acute myocardial infarction lasting longer than 30 minutes, accompanied by an electrocardiogram with ST segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads; and presented within 6 hours, or between 6 to 24 hours if there was evidence for continuing ischemia. After informed consent had been obtained, patients were randomly assigned to undergo PCI or to receive streptokinase (SK) as thrombolytic agent. All patients received heparin and aspirin. Additional revascularisation procedures were performed if indicated for symptoms or signs of myocardial ischemia, medication was according to the guidelines.\textsuperscript{11} Global left ventricular ejection fraction was measured by equilibrium radionuclide ventriculography between days 4 and 10 after treatment.\textsuperscript{12} Enzymatic infarct size was estimated by measurement of serial lactate dehydrogenase (LDH) activity. Cumulative enzyme release from 5 to 7 serial measurements up to 72 hours after symptom onset (LDH Q72) was calculated, without knowledge of the randomization outcome or clinical data. Previous cardiovascular disease (CVD) was defined as a history of acute MI, coronary artery bypass grafting or PCI.
Nonfatal recurrent myocardial infarction was defined as the combination of chest pain, changes in the ST T segment, and a second increase in the serum creatine kinase level to more than two times the upper limit of normal. If the creatine kinase level had not decreased to normal levels, a second increase of more than 200 IU per liter over the previous value was regarded as indicating a recurrent infarction. Patients with DM were defined as patients with documented DM using either oral hypoglycemic agents or insulin treatment at admission.

For the purpose of this sub-analysis, patients with DM were excluded. The remaining patients were divided into 3 groups regarding to admission glucose levels. Group I consisted of patients with no evidence of impaired glucose metabolism (glucose <7.8 mmol/L), group II consisted of patients with possible impaired glucose metabolism (glucose 7.8–11.0 mmol/L) and group III consisted of patients with profound impaired glucose metabolism (glucose ≥11.1 mmol/L). These cut-off values are based on diagnostic criteria for IGT and DM advised by the American Diabetes Association. Follow-up information was obtained in September 2000. All outpatients’ reports were reviewed, and general practitioners were contacted by phone. For patients who had clinical events during follow-up, hospital records were reviewed. All subsequent hospital admissions (for angina, recurrent infarction, additional intervention or heart failure) and medication used during follow-up were recorded.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 10.0. Differences between group means were tested by two-tailed Student's t-test. A chi-square statistic was calculated to test differences between proportions, with calculation of odds ratios (OR) and exact 95% confidence intervals. The Fisher exact test was used when the expected value of cells was smaller than 5. Statistical significance was defined as a P-value <0.05. Cumulative survival curves were constructed according to the Kaplan–Meier method and differences between the curves were tested for significance by the Log-rank statistic. Cox proportional-hazards regression model was used to estimate the independent association between glucose levels and long-term mortality. Correlations between numeric variables were calculated using the bivariate Pearson correlation coefficient.

Results

Baseline characteristics

The Zwolle trial patient cohort consisted of 395 patients. Of these patients, 32 (8%) had known DM and from 7 patients no laboratory data were available. Therefore, the present
sub-analysis included 356 patients. Of the 356 patients, the mean age was 59 ±10 year and there were 293 male patients (82%). Residual ejection fraction of the left ventricle (LVEF) was measured in 337 patients (95%) and enzymatic infarct size in 333 patients (94%). During the total follow up period 86 patients died (24%).

Table 1. Baseline clinical and demographic characteristics of three patient groups

<table>
<thead>
<tr>
<th>Glucose level</th>
<th>Group I (&lt;7.8 mmol/L)</th>
<th>Group II (7.8–11.0 mmol/L)</th>
<th>Group III (≥11.1 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>163 (46)</td>
<td>151 (42)</td>
<td>42 (12)</td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>58±11</td>
<td>60±10*</td>
<td>64±9*</td>
</tr>
<tr>
<td>Men</td>
<td>139 (85)</td>
<td>122 (81)</td>
<td>32 (76)</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>57 (35)</td>
<td>58 (38)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>38 (23)</td>
<td>27 (18)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>92 (58)</td>
<td>74 (49)</td>
<td>26 (62)</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>84 (52)</td>
<td>66 (44)</td>
<td>24 (57)</td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>15 (9)</td>
<td>19 (13)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Time to admission, min (mean±SD)</td>
<td>190±205</td>
<td>171±175</td>
<td>229±239</td>
</tr>
</tbody>
</table>

Outcome

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>31 (19)</td>
<td>40 (27)</td>
<td>15 (36)*</td>
</tr>
<tr>
<td>MACE</td>
<td>53 (33 )</td>
<td>58 (38)</td>
<td>17 (41)</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise indicated. * Denotes statistical difference (P<0.05) compared to group I. MI = myocardial infarction. CVD = cardiovascular disease. MACE = major adverse cardiac event. PCI = percutaneous coronary intervention.

**Admission glucose levels**

The mean admission glucose level was 8.6±3.1 mmol/L (range 5.1 to 34.1 mmol/L). Mean glucose levels were higher in females compared to males (9.3±4.1 versus 8.4±2.9 mmol/L, P=0.048), in patients with age ≥60 year (9.0±3.5 versus 8.2±2.6 mmol/L, P=0.016) and in those who had Killip class >1 at presentation (9.7±4.8 mmol/L versus 8.5±2.8 mmol/L, P=0.019). There was no association between infarct location, reperfusion strategy, previous CVD, multi-vessel disease and glucose levels. In table 1, the baseline characteristics of patients in the 3 glucose categories are compared. Again, elevated glucose was more often observed in females, in patients with a higher age and in those with Killip class >1 at presentation. There were no significant differences with regard to discharge medication between the three glucose categories.
Glucose and infarct size

There was a clear association between glucose levels, enzymatic infarct size and LVEF. Higher admission glucose was strongly correlated with larger enzymatic infarct size (R = 0.2, P<0.01) and lower LVEF (R = 0.1, P<0.05). Subsequently, mean enzymatic infarct size was highest in the patient group with the highest admission glucose (figure 1) and the mean residual LVEF was lowest in this patient group (figure 2).

Table 2. Predictors of Long-term Mortality, multivariate analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip class &gt;1</td>
<td>2.9</td>
<td>1.7–5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥60 year</td>
<td>2.4</td>
<td>1.5–4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Thrombolysis*</td>
<td>1.7</td>
<td>1.1–2.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Glucose category†</td>
<td>1.4</td>
<td>1.0–1.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>1.6</td>
<td>1.0–2.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>1.3</td>
<td>0.8–2.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>1.3</td>
<td>0.8–2.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.2</td>
<td>0.7–2.1</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* As compared to primary percutaneous coronary intervention. † Glucose < 7.8 mmol/L, 7.8 – 11.0 mmol/L and glucose ≥11.1 mmol/L; glucose <7.8 mmol/L was the reference group. MI = myocardial infarction. CVD = cardiovascular disease.

Long-term mortality

Mean glucose level in patients who died during follow-up was 9.5±4.6 mmol/L compared with 8.3±2.5 mmol/L in survivors (P=0.003). There was a gradual increase in mortality between the three glucose categories. Thirty-one patients died in group I (19.0%), 40 patients in group II (26.5%) and 15 patients in group III (35.7%). Mortality was significantly higher in the patient group with highest glucose compared to the group with normal glucose levels (P<0.05). MACE endpoints were reached in 53 patients (32.5%) in group I, in 58 patients (38.4%) in group II and in 17 (40.5%) patients in group III (table 1). Kaplan-Meier curves for cumulative mortality of patients in the 3 categories are shown in figure 3. Log-rank statistics showed significant differences in overall mortality between the patient groups (Log-rank 7.1; P = 0.029).

Reperfusion strategy

In order to investigate whether reperfusion strategy influences the association of admission glucose with long-term outcome, we stratified patients according to their randomization (primary PCI or thrombolysis). Regardless of reperfusion strategy, higher glucose levels were associated with more reduced LVEF and higher mortality. In all three
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P=0.02), admission glucose category, OR 1.4 (1.0–1.9, P=0.04) and anterior location, OR 1.6 (1.0–2.6, P=0.03) were independent predictors of long-term mortality (table 2).

Discussion

Our study demonstrates that in non DM patients with ST segment elevation MI, elevated glucose levels on admission are associated with larger infarct sizes and increased long-term mortality compared to normal glucose levels on admission. Although the pathophysiological mechanism is unknown, this adverse relation of elevated glucose levels on admission with increased mortality is evident, despite the use or method of reperfusion therapy, and adjusting for other predictors of long-term mortality.

Impaired glucose tolerance

Patients with elevated glucose levels on admission may represent individuals who do not meet the diagnostic criteria of DM but have a mild form of dysglycemia. This impairment in glucose metabolism may lead to hyperglycemia during stressful events, such as acute
patient groups treatment with PCI resulted in better preservation of LVEF, a smaller enzymatic infarct size and lower mortality compared to treatment with thrombolysis. In patients treated with primary PCI, no significant difference with regard to TIMI flow (Thrombolysis In Myocardial Infarction) prior and post intervention was present between the glucose categories.

Figure 1. Mean enzymatic infarct size (LDH Q72) in the three patient groups

Multivariate analyses
To study the independent predictive value of admission glucose on long-term survival, multivariate regression analysis was performed including age, reperfusion strategy, gender and all variables that were significant predictors in univariate analysis. Unadjusted predictors of long-term mortality were Killip class >1, increased age, anterior MI, previous CVD and multi-vessel disease. After multivariate analysis, the presence of Killip class >1 at admission odds ratio (OR) 2.9 (95% confidence interval 1.7–5.0, P<0.001), age ≥60 years, OR 2.4 (1.5–4.0, P=0.001), thrombolysis as reperfusion strategy, OR 1.7 (1.1–2.7,
MI. This sub or pre diabetic state, also known as impaired glucose tolerance (IGT), is associated with a higher incidence of cardiovascular events.\textsuperscript{15,16} As these patients also appear to have an increased mortality after acute MI, specific risk reducing interventions should be considered. Exercise training, dietary modifications and medical intervention reduce the risk of subsequent DM in these patients and may be of value.\textsuperscript{17,18}

Figure 3. Kaplan-Meier curve showing overall mortality of the three patient groups. Log-rank $P=0.029$

However, intervention during hospitalization may also be of benefit. Interestingly, a stringent insulin regimen in DM patients with acute MI abolished the increase in mortality associated with elevated admission glucose levels. Whether insulin therapy or intervention through other hypoglycemic agents is also beneficial for IGT patients with acute MI is unknown.

**Stress related hyperglycemia and GIK**

A stress response is accompanied by high levels of catecholamines such as cortisol and adrenaline. These hormones increase glycogenolysis, lipolysis and reduce insulin
sensitivity resulting in elevated glucose levels. Therefore, patients with elevated glucose levels could represent patients with an increased response to stress, for example due to more severe hemodynamic compromise or more extensive myocardial damage. Indeed, in our study, patients with elevated glucose levels did more often have Killip class >1 at admission, had larger enzymatic infarct size and more reduced LVEF. All these variables are known to be predictors of long-term mortality. However, in our sub-analysis, after adjusting for confounding variables (including Killip class), there was still an association between admission glucose and long-term mortality. Furthermore, other evidence also suggests that dysglycemia during acute MI is more than only an epiphenomenon. Stress induced elevation of free fatty acids (FFA) may also compromise myocardial function as they reduce contractility and increase ischemic and reperfusion injury. Moreover, the adverse relation between admission glucose and clinical outcome is also present in patients suffering from acute coronary events without myocardial damage. There is some evidence that improvement of metabolic control through infusion of fluids containing glucose, insulin and potassium (GIK) may reduce mortality in acute MI. The beneficial effect of GIK is thought to result from a shift in primary energy substrate from FFA to glucose during ischemia. Our study confirms the importance of dysglycemia during acute MI, but further investigations regarding glycometabolic control should be initiated and awaited for.

Reperfusion strategy

Patients treated with PCI had better survival and less reduced LVEF than patients treated with thrombolysis, these results are in line with other studies. The impact of glucose levels on outcome however, was independent of reperfusion strategy. Patients with higher glucose levels had higher mortality, larger enzymatic infarct sizes and more reduced LVEF whether treated with PCI or with thrombolysis. So, apart from primary PCI, additional treatment of patients with elevated glucose is needed.

Study limitations

Our study included only a limited number of patients from a single center. We have no data on glycolysated hemoglobin (HbA1C) in our patients, which could have given more insight in the prevalence of IGT in our population. No routine tests were performed to detect undiagnosed DM after admission. However, a significant interaction of diabetic status with the association of hyperglycemia with adverse outcome is unlikely. Although non-fasting admission glucose levels may be influenced by prior meals or diurnal variations, the impact of a concomitant acute MI on glucose levels is probably much more substantial. Furthermore, as admission glucose is readily available, it has the advantage that immediate intervention can be instituted. Metabolic control through GIK infusions as
adjunctive treatment was not used in our patients and, especially in patients with more severe glycometabolic derangement, this may have had influence on outcome. During the study period, intracoronary stenting and treatment with glycoprotein IIb/IIIa receptor blockers or clopidogrel were not available.

**Conclusion**

Elevated admission glucose levels in non-diabetic patients with admission MI are independently associated with larger infarct sizes and a higher long-term mortality when compared to patients with normal glucose levels. These findings warrant further investigation regarding glycometabolic control during acute MI and secondary prevention programs in patients with high admission glucose.

**References**


Metabolic interventions in acute myocardial infarction
Chapter 4.2

Hyperglycemia reduces myocardial reperfusion after primary percutaneous coronary intervention for ST elevation myocardial infarction

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Submitted
Abstract

Background
Patients with hyperglycemia on admission have an adverse prognosis after ST segment elevation myocardial infarction (MI). However, the causal link between disturbances in glucose metabolism and outcome is unclear. We sought to investigate whether hyperglycemia is related to impaired myocardial perfusion in ST segment elevation MI patients.

Methods
A total of 464 patients with ST segment elevation MI treated with primary percutaneous coronary intervention (PCI) were included. To determine myocardial reperfusion we determined ST segment elevation resolution on the electrocardiogram and myocardial blush grade during PCI.

Results
A total of 93 patients (20%) had hyperglycemia (glucose ≥11.0 mmol/L). They had more often a reduced myocardial blush grade (26% versus 15%, P=0.02) and incomplete ST segment elevation resolution (59% versus 39%, P=0.01) compared to patients without hyperglycemia on admission. Patients with hyperglycemia also had more reduced left ventricular function and higher mortality. These observations were demonstrated in patients with and without diabetes mellitus. Multivariate analyses did not change these findings.

Conclusion
Hyperglycemia on admission is associated with reduced myocardial reperfusion after primary PCI. This is associated with an adverse clinical outcome.
Introduction

It has been demonstrated that hyperglycemia on admission is associated with an adverse prognosis after acute myocardial infarction (MI), both in patients with and without diabetes mellitus.\textsuperscript{1,2} However, the causal link between disturbances in glucose metabolism and outcome is not yet clear. Evidence suggests that hyperglycemia could be associated with impaired microvascular myocardial reperfusion.\textsuperscript{3,4} We studied the association between hyperglycemia and myocardial reperfusion in patients treated with primary percutaneous coronary intervention (PCI) for acute ST segment elevation MI (MI). Both electrocardiographic (ST segment elevation resolution) and angiographic (myocardial blush grade) parameters of myocardial reperfusion were used. We also investigated the impact of reduced myocardial reperfusion on clinical outcome.

Methods

Study population
All consecutive patients with symptoms consistent with acute MI of >30 min duration, presenting within 24 hours after the onset of symptoms and with ST segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads on the electrocardiogram were evaluated for inclusion in this study. Patients were excluded when pre-treated with thrombolysis or when an illness associated with a marked restricted life expectancy was present. All patients went to the catheterization laboratory as soon as possible, where both coronary arteries were visualized. PCI was performed with standard techniques if the coronary anatomy was suitable for angioplasty. Additional treatment consisted of intravenous heparin, nitroglycerin and aspirin. After sheath removal, low-molecular-weight heparin was given for 1 to 3 days. Baseline characteristics, clinical data, angiographic data and outcomes were recorded prospectively in a dedicated database.

Measurements and definitions
Core laboratory annalists (Diagram BV, Zwolle, The Netherlands) who were unaware of the clinical history and outcome of the patients assessed ST segment elevation resolution, TIMI (thrombolysis in myocardial infarction) flow and myocardial blush grade. TIMI flow and myocardial blush grade were visually assessed on the angiogram. Myocardial blush grade has been defined previously\textsuperscript{5}: 0, no myocardial blush; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contra or ipsilateral non-infarct related coronary artery; and 3, normal myocardial blush or contrast density, comparable with that obtained during
angiography of a contralateral or ipsilateral non-infarct-related coronary artery. When myocardial blush persisted (“staining”), this phenomenon suggested leakage of contrast medium into the extravascular space and was graded 0. ST segment elevation resolution was analyzed as previously described in detail. In short, ST segment elevation resolution was defined as complete when there was ≥70% ST segment elevation resolution, partial when there was 30-70% resolution and absent if resolution was less than 30% as measured 180 minutes after primary PCI compared to ST elevation on admission. Left ventricular ejection fraction (LVEF) was measured before discharge by radionuclide ventriculography or by echocardiography. Radionuclide ventriculography was performed by using the multiple gated equilibrium method following the labeling of red blood cells of the patient with technetium-99m-pertechnate. A General Electric 300 gamma camera with a low-energy all-purpose parallel-hole collimator was used. Global ejection fraction was calculated by a General Electric Star View computer using the fully automatic PAGE program. Hyperglycemia was defined as whole blood glucose levels (Modular system – Roche/Hitachi, Basel, Switzerland) on admission of ≥11.1 mmol/L (≥200 mg/dL), as stated by the American Diabetes Association.

**Statistical analysis**

Differences between group means at baseline were assessed with the two-tailed Student’s t-test. Chi-square analysis or Fisher’s exact test was used to test differences between proportions. To study independent predictors of reduced myocardial reperfusion, multivariate logistic regression analysis was performed. Statistical significance was considered a two-tailed P-value <0.05. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 10.1 was used for all statistical analysis.

**Results**

**Study population**

A total of 464 patients were included in this analysis. Myocardial blush grade was available in 401 patients (86%) and ST segment elevation resolution data were available in 302 patients (65%). Ejection fraction was measured in 404 patients (87%). Mean age was 61±12 years, 368 patients (79%) were men. At the end of the follow up period (mean 1.6±1.1 years) 38 patients (8%) had died. Baseline characteristics of the patient groups according to the absence or presence of hyperglycemia are shown in table 1.
Table 1. Baseline characteristics of the patient groups according to admission glucose

<table>
<thead>
<tr>
<th></th>
<th>Glucose &lt;11.1 mmol/L</th>
<th>Glucose ≥11.1 mmol/L</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>371</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>60.3±12.0</td>
<td>62.8±11.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Men</td>
<td>307 (83)</td>
<td>61 (66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>39 (11)</td>
<td>14 (15)</td>
<td>0.22</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>20 (5)</td>
<td>4 (4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>8 (2)</td>
<td>4 (4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (3)</td>
<td>38 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>99 (27)</td>
<td>31 (33)</td>
<td>0.20</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>195 (53)</td>
<td>42 (45)</td>
<td>0.20</td>
</tr>
<tr>
<td>Positive family history</td>
<td>145 (39)</td>
<td>34 (37)</td>
<td>0.66</td>
</tr>
<tr>
<td>Ischemic time ≤3 hour</td>
<td>198 (60)</td>
<td>52 (61)</td>
<td>0.94</td>
</tr>
<tr>
<td>Heart rate (beats /minute)</td>
<td>73±18</td>
<td>81±26</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic BP ≤100 mmHg</td>
<td>37 (10)</td>
<td>14 (15)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diastolic BP ≤60 mmHg</td>
<td>71 (19)</td>
<td>23 (25)</td>
<td>0.23</td>
</tr>
<tr>
<td>Killip class ≥2</td>
<td>20 (5)</td>
<td>14 (15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>176 (47)</td>
<td>48 (52)</td>
<td>0.47</td>
</tr>
<tr>
<td>Ischemic time ≤3 hour</td>
<td>198 (60)</td>
<td>52 (61)</td>
<td>0.94</td>
</tr>
<tr>
<td>Heart rate (beats /minute)</td>
<td>73±18</td>
<td>81±26</td>
<td>0.01</td>
</tr>
<tr>
<td>Admission glucose (mmol/L)*</td>
<td>8.1±1.4</td>
<td>14.4±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose at 16 hours (mmol/L)*</td>
<td>7.9±1.9</td>
<td>12.0±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative ST elevation (mm)</td>
<td>9.4±8.7</td>
<td>9.0±6.9</td>
<td>0.77</td>
</tr>
<tr>
<td>IABP</td>
<td>30 (8)</td>
<td>12 (13)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise indicated. * Data are mean ± SD. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass grafting. BP = blood pressure. IABP= intra aortic balloon pumping.

**Hyperglycemia and myocardial reperfusion**

Both complete ST segment elevation resolution (61% versus 42%, P=0.009) and optimal myocardial blush (85% versus 74%, P=0.02) were higher in patients with normal glucose levels compared to those with hyperglycemia. Patients with hyperglycemia had more often a reduced LVEF (LVEF ≤30%) (28% versus 16%, P=0.01) and a higher mortality compared to patients without hyperglycemia (14% versus 7%, P=0.02), table 2.

**Diabetes mellitus and myocardial perfusion**

In diabetic patients, the absence of hyperglycemia was associated with a higher presence of complete ST segment elevation resolution (56% versus 41%, P=0.46) and optimal
myocardial blush grade (91% versus 74%, P=0.23). Also in non-diabetic patients with normal glucose levels, both complete ST segment elevation resolution (61% versus 42%, P=0.04) and optimal myocardial blush grade (85% versus 74%, P=0.07) were higher compared to those without hyperglycemia.

*Table 2. Myocardial reperfusion and outcome of the patient groups according to admission glucose*

<table>
<thead>
<tr>
<th></th>
<th>Glucose &lt;11.1 mmol/L</th>
<th>Glucose ≥11.1 mmol/L</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial reperfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial blush grade (2-3)</td>
<td>272 (85)</td>
<td>59 (74)</td>
<td>0.02</td>
</tr>
<tr>
<td>Complete resolution</td>
<td>152 (61)</td>
<td>22 (42)</td>
<td>0.009</td>
</tr>
<tr>
<td>Myocardial infarct size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF ≤30%</td>
<td>51 (16)</td>
<td>23 (28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality</td>
<td>25 (7)</td>
<td>13 (14)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Data are number (%). LVEF = left ventricular ejection fraction.

**Multivariate analyses - ST segment elevation resolution**

To identify whether hyperglycemia was independently associated with ST segment elevation resolution we performed multivariate analyses and included age and gender and all clinical variables significantly different between patients with and without ST segment elevation resolution (anterior MI P=0.04, hyperglycemia P=0.009 and cumulative ST elevation P=0.002). After multivariate analyses, the variables that were independently associated with incomplete ST segment elevation resolution were the presence of admission hyperglycemia, relative risk (RR) 2.1 (95% confidence interval 1.1–4.0, P=0.02), anterior MI, RR 2.4 (1.4–4.0, P=0.001) and a cumulative ST elevation on admission RR 1.1 per mm elevation (1.0–1.1, P=0.001). Gender (P=0.54) and age (P=0.94) were not significantly associated with ST segment elevation resolution after multivariate analysis. The addition of time to treatment to our analysis did not change these findings.

**Multivariate analyses - myocardial blush grade**

Univariate angiographic characteristics of patients with and without hyperglycemia are shown in table 3. The only variable that was associated with hyperglycemia was a myocardial blush grade 0-1. After multivariate analysis including all angiographic variables (MVD, collaterals, infarct related vessel, TIMI flow and myocardial blush grade) hyperglycemia at admission remained associated with an impaired blush grade of 0-1, RR 2.2 (1.2–4.2, P=0.02). A stratified analysis including only patients with TIMI 3 flow after PCI also showed more often a reduced myocardial blush grade in patients with hyperglycemia.
(20% versus 9%, P=0.01). Furthermore, there was a gradual increase (7%, 9%, 10%, 12% and 19%) in reduced myocardial blush grade with increasing glucose levels (quintiles) in these patients (figure 1).

**Figure 1. Association between glucose at admission and myocardial blush grade**

**Myocardial reperfusion and outcome**

Reduced LVEF was more often present in patients with incomplete ST segment elevation resolution (25% versus 12%, P=0.01) and in those with reduced myocardial blush (33% versus 14%, P<0.001). Mortality was also higher in patients with incomplete ST segment elevation resolution (6% versus 3%, P=0.15) and in those with reduced myocardial blush (16% versus 4%, P<0.001). These associations between reduced myocardial reperfusion and worse outcome were observed in patients with and without hyperglycemia.

**Discussion**

This is the first study to report on the influence of hyperglycemia on myocardial reperfusion as assessed by myocardial blush grade and ST segment elevation resolution. Elevated glucose levels on admission were independently associated with both incomplete ST segment elevation resolution and reduced myocardial blush. These findings suggest microvascular dysfunction in hyperglycemic patients with ST segment elevation MI and might explain their adverse prognosis. Whether meticulous regulation of
Metabolic interventions in acute myocardial infarction

glucose levels, prior or following restoration of epicardial flow, improves myocardial reperfusion is unclear.

Table 3. Angiographic variables of the patient groups with regard to admission glucose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glucose &lt;11.1 mmol/L</th>
<th>Glucose ≥11.1 mmol/L</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-vessel disease</td>
<td>188 (51)</td>
<td>54 (58)</td>
<td>0.20</td>
</tr>
<tr>
<td>Collaterals</td>
<td>39 (12)</td>
<td>7 (8)</td>
<td>0.36</td>
</tr>
<tr>
<td>IRV (LAD)</td>
<td>164 (46)</td>
<td>42 (46)</td>
<td>0.91</td>
</tr>
<tr>
<td>TIMI 0 flow before PCI</td>
<td>222 (63)</td>
<td>58 (64)</td>
<td>0.86</td>
</tr>
<tr>
<td>TIMI 2-3 flow after PCI</td>
<td>232 (96)</td>
<td>82 (94)</td>
<td>0.44</td>
</tr>
<tr>
<td>Myocardial blush grade 0-1</td>
<td>49 (15)</td>
<td>21 (26)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are number (%). IRV = infarct related vessel. LAD = left descending artery. TIMI = thrombolysis in myocardial infarction.

Increased age and diabetes were both more prevalent in hyperglycemic patients and their presence has been associated with reduced myocardial flow after restoration of epicardial flow.\(^4;^8\) However, in our analysis, age was not associated with impaired ST segment elevation resolution and also non-diabetic patients with hyperglycemia appeared to have reduced myocardial reperfusion. There are several mechanisms that could clarify these findings. Hyperglycemia is associated with both plugging of leukocytes in the microvasculature of the myocardium and with increased procoaguable properties of platelets.\(^9;^11\) Furthermore, the ability of platelets to induce vasodilatation is reduced by high levels of glucose.\(^12\) However, there may also be a link between stress, hyperglycemia and reduced myocardial reperfusion. Killip class ≥2 was significantly higher in patients with hyperglycemia (5% versus 15%, P=0.001). Stress, induced by hemodynamic instability, increases both levels of free fatty acids and glucose.\(^13\) These free fatty acids reduce endothelium derived vasodilatation and inhibit the myocardial use of glucose.\(^14;^15\) Furthermore, improvement of myocardial flow by insulin is diminished, as it is dependent on the concomitant use of glucose. Administration of solutions containing glucose – insulin and potassium (GIK) may decrease the level of free fatty acids and promote the use of glucose as myocardial energy substrate. There is some evidence that improvement of metabolic control through infusion of fluids containing GIK may reduce mortality in acute MI.\(^16;^18\) Whether this improved prognosis results from improved myocardial reperfusion is unclear. However, evidence suggests GIK infusion improves myocardial perfusion in segments adjacent to the recently infarcted area.\(^19\) Besides GIK infusion, other specific interventions, such as the use of glycoprotein IIb/IIIa receptor blockers, might be beneficial. Also in our study, patients with incomplete ST segment elevation resolution and reduced myocardial blush grade had significantly more reduced LVEF and higher
Admission glucose and myocardial perfusion

mortality. Therefore, the search for improvement of myocardial flow is pivotal and further investigations are warranted.

**Study limitations**

As glycolysated hemoglobin levels, reflecting long-term glucose metabolism, were not available, it remains unclear whether isolated acute hyperglycemia or more long-standing disturbed glucose metabolism was associated with reduced myocardial reperfusion. No routine tests were performed to diagnose previously unrecognized diabetes in all patients, so some hyperglycemic patients may have had undiagnosed diabetes at discharge.

**Conclusion**

Hyperglycemia on admission is independently associated with impaired myocardial reperfusion. Impaired reperfusion was associated reduced LVEF and a higher mortality. Further investigation with regard to improvement of myocardial reperfusion in hyperglycemia is warranted.

**References**


Chapter 4.3

Hyperglycemia and no reflow phenomenon in acute myocardial infarction

Iwan CC van der Horst, Arnoud WJ van 't Hof, Henk JG Bilo, Felix Zijlstra

Journal of the American College of Cardiology 2003;41:2100

To the editor:
Dr Iwakura and colleagues conclude that hyperglycemia might be associated with impaired microvascular function after acute myocardial infarction (MI), this conclusion was reached by a retrospective analysis of 146 patients.\textsuperscript{1} The authors were the first to find an independent relation between elevated blood glucose levels at admission and no reflow phenomenon. They also stated that this relation was independent of HbA1C level or diabetes mellitus (DM), since there were no difference in HbA1c level or the frequency of DM in the no reflow and reflow group.

We have some considerations about these results. First, the authors defined hyperglycemia by the optimal cutoff to differentiate the patients showing no reflow with a receiver-operating characteristic curve analysis. By using this cutoff in the same cohort they found a relation between hyperglycemic patients and no reflow phenomenon. The authors have generated an interesting hypothesis and new studies have to proof the validity of the cutoff. Second, we are interested in more details on the methods used to determine blood glucose and HbA1c levels. Information was lacking is the blood glucose level was measured either with point of care or whole blood glucose measurement and if the method is validated in critically ill patients. Clinically relevant differences in blood glucose level have been observed with point of care and whole blood measurement in patients with shock\textsuperscript{2}, acidosis\textsuperscript{3}, medication\textsuperscript{4}, and different values due to differences in hematocrit\textsuperscript{5}. Finally, the absolute differences of 0.3\% in HbA1c and 13\% in frequency of DM were indeed not statistically significant related to no reflow. It is our suggestion that these clinically relevant differences were not significant due to the small number of patients. Moreover, the authors found that 45.3\% of the patients with hyperglycemia were diabetic versus 9.9\% in patients without hyperglycemia (P<0.0001).

The hypothesis that acute hyperglycemia (i.e. hyperglycemia at admission) is associated with the no reflow phenomenon is intriguing. We however hypothesize that these relation is not independent of chronic hyperglycemia (i.e. elevated HbA1c and/or DM). Therefore new studies have to determine the effect of hyperglycemia on no reflow and preferentially the effect of metabolic regulation.

References
