Computer assisted decision support in acutely ill patients. Application in glucose management and quantification of myocardial reperfusion
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Chapter 5a

Refractory hyperglycemia induced by glucose-insulin-potassium infusion in acute myocardial infarction

Mathijs Vogelzang, Tone Svilaas, Iwan C. C. van der Horst, Maarten W. N. Nijsten, Felix Zijlstra

Neth Heart J 2006, 14:46–48
Abstract

Background Recent randomized clinical trials have not confirmed the beneficial effects of glucose-insulin-potassium (GIK) infusion observed in experimental models of myocardial ischemia and infarction.

Methods and results We investigated glucose levels and insulin dose in 107 patients treated with reperfusion therapy and GIK for acute myocardial infarction. Despite high insulin infusion rates, persistent hyperglycemia occurred in 37% of the patients. These patients had significantly larger infarct sizes, as measured by enzyme release (P=0.006). In a multivariate model predicting high troponin levels, refractory hyperglycemia remained a significant parameter (P=0.02).

Conclusions These findings suggest that refractory hyperglycemia caused by high-dose glucose infusion may, at least in part, explain the discrepancy between the experimental and clinical data.

Background

Although mechanical reperfusion therapy has significantly improved outcome after acute ST-segment elevation myocardial infarction (STEMI), heart failure due to impaired pump function remains an important problem. Metabolic intervention has been suggested as a next step to improve outcome by protection of ischemic myocardial cells. In animal experiments glucose-insulin-potassium (GIK) infusion has been shown to improve outcome after myocardial infarction.\textsuperscript{1,2} Recently, several randomized controlled trials have shown no significant benefit of GIK infusion.\textsuperscript{3,4} The reasons for these failures remain unclear. One of the potential explanations could be that hyperglycemia induced by GIK may have offset intrinsic benefits of GIK in these clinical trials. We analyzed the magnitude of hyperglycemia and its relation with enzymatic infarct size in GIK-treated patients in the GIPS-II trial.

Methods

The GIPS-II trial was a randomized controlled trial comparing GIK infusion with conventional treatment in STEMI patients.\textsuperscript{5} Primary percutaneous coronary intervention was aimed for in all patients. We examined the glucose levels and insulin doses of the subgroup treated with GIK at our center. Patients received an infusion of 2.0 ml/kg/hour of 20% glucose (equivalent to 400 mg/kg/hour) with 80 mmol/L potassium for 12 hours. Insulin was administered at a variable rate through a perfusor.
Blood glucose was checked hourly and the insulin pump rate was adjusted according to a previously published algorithm. Maximum pump rate was set to 38 IU/hour. Ischemic time was defined as time from onset of symptoms to first balloon inflation. Infarct size was measured as the area under the linearly interpolated curve of serial measurements of lactate dehydrogenase (LDH), Troponin I, creatine phosphokinase (CK), and the myocardial band of CK (CK-MB) for the first 48 hours after admission. Patients were considered as suffering from ‘refractory hyperglycemia’ if they had a period of at least three consecutive hours with a glucose level above 10 mmol/L despite insulin infusion of more than 10 units per hour. To compare groups, we used student’s t test, the Mann-Whitney U test or Fisher’s exact test when appropriate. The association of variables with infarct size was assessed by means of a binary logistic regression predicting whether patients fell within the highest tertile of the area under the curve of Troponin I.

Results

We included 107 consecutive GIK-treated patients in our analysis. The number of glucose measurements per patient in the first 12 hours was $10 \pm 2$ (mean $\pm$ SD). Glucose at admission was $7.6 \pm 2.0$ mmol/L. Two hours after starting the GIK infusion, glucose was $11.7 \pm 3.7$ mmol/L, an increase of $4.1$ mmol/L (95% confidence interval 3.3 to 4.9 mmol/L, $P < 0.001$). The mean maximum glucose value during the first 12 hours was $13.7 \pm 3.2$ mmol/L. Only 19 patients (18%) had no single value above 11.1 mmol/L. At the start of GIK infusion, median (interquartile range, IQR) insulin infusion rate was 5 (3-9) IU/hour. Median total units of insulin administered over 12 hours was 94 (44-180). Insulin infusion rate exceeded 10 IU/hour at any moment in 65 patients (61%). The maximum rate allowed by the protocol, 38 IU/hour, was reached in 7 patients (7%). Our criteria for ‘refractory hyperglycemia’ were met by 40 patients (37%). Table 1 shows differences in baseline characteristics, glucose and insulin parameters, and cardiac enzyme release between these patients and the patients without refractory hyperglycemia. Figure 1 shows the median and interquartile range of glucose levels and insulin dose for both patient groups over time. In our study group, 3 patients died within 30 days of admission, of whom 2 patients suffered from refractory hyperglycemia and 1 did not. In logistic regression analysis, presence of refractory hyperglycemia and age were significantly associated with the Troponin I area under the curve being within the highest tertile (table 2). In a bivariate model including these two parameters, refractory hyperglycemia remained significantly associated with high enzyme release (odds ratio (95% confidence interval): 2.80 (1.19-6.6), $P=0.02$).
Chapter 5

Table 5.1: Comparison of patients with and without refractory hyperglycemia

<table>
<thead>
<tr>
<th></th>
<th>No refractory hyperglycemia</th>
<th>Refractory hyperglycemia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>67 (63%)</td>
<td>40 (37%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58 ± 12</td>
<td>63 ± 12</td>
<td>0.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>51 (76%)</td>
<td>29 (73%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.7 ± 2.9</td>
<td>27.7 ± 3.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischemic time (minutes)</td>
<td>186 ± 76</td>
<td>234 ± 124</td>
<td>0.03</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0 (0%)</td>
<td>4 (10%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>23 (34%)</td>
<td>23 (58%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Admission glucose (mmol/L)</td>
<td>7.0 ± 1.9</td>
<td>8.7 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose after 2h of GIK</td>
<td>9.9 ± 2.5</td>
<td>14.7 ± 3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>inf (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum insulin rate</td>
<td>9.0 (6.5-12.0)</td>
<td>28 (21.8-37.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total units of insulin</td>
<td>57 (35-89)</td>
<td>223 (159-278)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>administered (IU)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC-48h LDH</td>
<td>227 (160-331)</td>
<td>303 (198-441)</td>
<td>0.01</td>
</tr>
<tr>
<td>AUC-48h Troponin T</td>
<td>100 (50-178)</td>
<td>180 (81-283)</td>
<td>0.006</td>
</tr>
<tr>
<td>AUC-48h CK-MB</td>
<td>18 (11-30)</td>
<td>27 (14-37)</td>
<td>0.03</td>
</tr>
<tr>
<td>AUC-48h CK</td>
<td>195 (114-342)</td>
<td>330 (162-584)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or median (interquartile range). AUC-48h: area under the curve from 0 to 48 hours after admission. CK: creatine phosphokinase. GIK: glucose-insulin-potassium. LDH: lactate dehydrogenase. MB: myocardial band.

Table 5.2: Results of binary logistic regression predicting the Troponin I release to be in the highest tertile.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory hyperglycemia</td>
<td>3.19 (1.38-7.36)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.45 (1.02-2.06)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>6.36 (0.64-63.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Admission glucose (per mmol/L)</td>
<td>1.17 (0.96-1.43)</td>
<td>0.12</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>1.89 (0.84-4.27)</td>
<td>0.13</td>
</tr>
<tr>
<td>Ischemic time (per quartile)</td>
<td>1.27 (0.88-1.84)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.66 (0.27-1.63)</td>
<td>0.37</td>
</tr>
<tr>
<td>Body mass index &gt;27.5</td>
<td>0.76 (0.32-1.80)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Cl: confidence interval.

Discussion

Our findings demonstrate that high-dose glucose infusion can lead to hyperglycemia that is barely responsive to high doses of insulin. In our study group, more than
one third of the patients suffered from refractory hyperglycemia. Furthermore, hyperglycemia was associated with increased infarct sizes as measured by enzyme release. However, as this is an observational study, we cannot distinguish whether GIK-induced hyperglycemia is a marker or a mediator of myocardial ischemia and cell death. Hyperglycemia was associated with a number of possibly unfavorable parameters such as old age, presence of diabetes, anterior infarction site, and longer ischemic time, which may account for part of the association with enzyme release.
Furthermore, myocardial damage induces a stress reaction that can lead to insulin resistance. The observation that hyperglycemia is a marker of disease in myocardial infarction has been thoroughly studied before. However, a large body of evidence supports the detrimental effects of hyperglycemia accompanying acute myocardial infarction, and its mediating role in acutely ill patients. We therefore hypothesize that part of the relation we found between glucose levels and enzymatic infarct size may be explained by hyperglycemia playing an active role by either causing additional myocardial cell injury or by impairing repair mechanisms during reperfusion. It is conceivable that the refractory hyperglycemia has offset any positive effects of GIK, and this might in part explain why recent trials have not confirmed the positive results observed in experimental studies. Our results show that high doses of insulin failed to adequately reduce hyperglycemia induced by GIK, and we therefore suggest that future studies investigating GIK should use lower doses of glucose to avoid hyperglycemia.

References

Chapter 5b

Glucose metabolism and acute myocardial infarction

Mathijs Vogelzang, Felix Zijlstra

_Eur Heart J_ 2006, 27:1264–1265
For over 50 years, efforts have been made to develop beneficial glycometabolic support strategies for patients with myocardial ischemia and infarction.¹ The concept of providing maximal metabolic support to injured myocardial cells is elegant, and has led to relatively simple and low-cost interventions. Glucose-insulin-potassium (GIK) therapy focuses on infusion of high doses of glucose to halt free fatty acid production, and various schemes have been studied over the past decades. Clinical results of GIK infusion have been mixed, with results varying from impressive survival benefits to excess mortality. The CREATE-ECLA study, in which 20 201 patients were randomized to GIK infusion or standard treatment after ST-segment elevation myocardial infarction, showed no benefit of GIK infusion (hazard ratio for 30-day mortality: 1.03, 95% confidence interval, 0.95-1.13).² GIK also showed a neutral effect on secondary endpoints. This result, together with a number of other recent studies,¹ supports the current opinion that GIK does not give a clinically significant benefit in acute myocardial infarction (AMI). The traditional GIK scheme often induces hyperglycemia, as the insulin component is not titrated to maintain normoglycemia.

In this issue of the European Heart Journal, Goyal and colleagues report on elevated glucose levels in patients with AMI and the prognostic value of these levels for adverse outcome (30- and 180-day mortality).³ Goyal and colleagues have analyzed the glucose values collected in the CARDINAL (Complement and ReDuction of INfarct size after Angioplasty or Lytics) studies. In a cohort of 1469 patients, glucose levels were determined at baseline and 24 hours thereafter. More than half of the patients had a baseline glucose level higher than 7.8 mmol/L. Of these patients, a third showed no or only moderate decrease in glucose during the first 24 hours. Moreover, a considerable number of patients who presented with a baseline glucose lower than 7.8 mmol/L had a rising glucose level during the first 24 hours. Although a large number of reports have described the association between hyperglycemia at admission and adverse outcome,⁴ data on glucose levels at later moments after infarction are scarce. The association between hyperglycemia at admission and adverse outcome was confirmed by Goyal et al., but more importantly, the change in glucose in the first 24 hours was shown to be an independent predictor of adverse outcome. There are three straightforward explanations for this association. First, the change in glucose may be a marker of clinical condition. As the multivariate prognostic model only included baseline characteristics, the change in glucose was the only parameter that contained information about the clinical course of a patient during the first 24 hours. Adverse developments during this important initial period, for example unsuccessful reperfusion therapy, may prevent a drop in glucose level. Second, failure of glucose to drop may be a result of pre-existing glycometabolic dysregulation, either sub-clinical or frank previously undiagnosed diabetes, which is known to negatively affect prog-
Glucose metabolism and acute myocardial infarction

The third possibility is most interesting from an intervention-oriented point of view: hyperglycemia might be causally related to adverse outcome, and treatment may therefore improve outcome. Unfortunately, this retrospective study cannot discern the respective contributions of these explanations. Indeed, retrospective studies cannot answer the question whether insulin therapy to treat persistent hyperglycemia will be beneficial in AMI patients.

In critically ill patients admitted to a predominantly cardiosurgical intensive care unit, a large randomized clinical trial has evaluated intensive insulin therapy aiming for normoglycemia. In a cohort of 1548 patients, insulin therapy markedly reduced mortality during the stay on the intensive care unit (8.0 versus 5.8%, \(P<0.04\)).

A number of complications related to critical illness occurred significantly less frequently with intensive insulin therapy. Although the exact mechanisms that have led to these impressive results of intensive insulin therapy still need more study, a number of mechanisms that may play a role have been identified. Some of these mechanisms may also apply to patients with AMI. For instance, hyperglycemia is associated with a pro-inflammatory and pro-thrombotic state, and interferes with normal endothelial function. Insulin not only antagonizes these negative aspects of hyperglycemia, but also may boast intrinsic beneficial effects, such as improved glucose utilization and increased myocardial perfusion.

On the other hand, evident differences between patients with AMI and patients admitted to an intensive care unit exist as well. Most importantly, the hospital stay of patients with AMI is short, whereas intensive care unit stays of up to a week are relatively common. This is particularly relevant to metabolic control, as a post-hoc analysis revealed that patients who stayed longer than five days at the intensive care unit almost completely accounted for the mortality improvement in the previously mentioned study.

At the moment, the DIGAMI and DIGAMI 2 studies are the most important studies that have evaluated glucose control after AMI. These studies have included both known diabetics and unknown diabetics with an admission glucose level higher than 11.0 mmol/L. The treatment arm of the first DIGAMI study received therapy according to a protocol aiming for a glucose level between 7.0 and 10.9 mmol/L during the initial hospital stay, and subcutaneous insulin therapy for at least 3 months after the index infarction. The DIGAMI trial randomized 620 patients, and mortality after one year was 18.6% in the intensive treatment group and 26.1% in the control group (\(P=0.027\)). Albeit being high compared with current standards, the glucose levels in both arms differed considerably; the intensive treatment realized a glucose decrease of 5.8 mmol/L in the first 24 hours (from 15.4 to 9.6 mmol/L), and the control group decreased by 4.0 mmol/L (from 15.7 to 11.7 mmol/L). It was unclear what the relative contributions of acute and long-term control were to the overall benefi-
cial effect. The DIGAMI 2 study randomized patients into three arms to gain further insight in the contributions of both acute and chronic therapy: one arm only received in-hospital control, one arm received both in-hospital and long-term control and one arm received regular care. Unfortunately, the study was stopped prematurely due to a declining inclusion rate, and upon analysis, the achieved level of control was below par. The mean glucose level after 24 hours was only 0.9 mmol/L lower in the treatment arms compared with the control arm (9.1 versus 10.0 mmol/L). This modest difference in glucose levels had no significant effect on all-cause mortality. One conclusion is that glucose control, in particular when aiming for the low levels that are currently considered desirable, is much harder to achieve in patients with AMI than in other critically ill patients admitted to an intensive care unit. Patients with AMI may eat meals, which cause hyperglycemia, and the balance between aggressive treatment that may cause hypoglycemia, or gentle treatment that may lead to suboptimal control is hard to find. Even a constant well-titrated insulin infusion in a fasting patient may cause hypoglycemia when the stress response of acute myocardial ischemia subsides. This may happen much quicker in AMI patients, compared with other critically ill patients, for instance due to successful reperfusion therapy.

In intensive care units, nurses with standardized glucose control protocols achieve safer, tighter glucose control than doctors. At our surgical intensive care unit, we have recently developed a computer program that recommends insulin pump rates and glucose sampling frequency to intensive care nurses. Glucose control was satisfactory, and the number of measurements advised by the computer program was low compared with a number of previously published glucose control protocols. We also believe that a computer program that can make use of more complex algorithms than simple flowchart-based protocols may be able to safely achieve better control in patients with AMI as well. A systematic method to achieve safe, tight glucose control is a prerequisite before we can embark on trials investigating the value of intensive insulin therapy in AMI patients. In conclusion, Goyal et al. have made an important contribution to our knowledge of glucose metabolism during AMI. Glucose levels at admission as well as after 24 hours have strong prognostic implications. The quest for a successful metabolic intervention to further improve prognosis in patients with acute myocardial infarction will continue.

Acknowledgments

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References
