Glucose metabolism and acute myocardial infarction

Mathijs Vogelzang* and Felix Zijlstra

Department of Cardiology, Thoraxcenter, University Medical Center Groningen, University of Groningen, PO Box 30 001, 9700 RB Groningen, The Netherlands

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This editorial refers to 'Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the Cardinal study'† by A. Goyal et al., on page 1289

For over 50 years, efforts have been made to develop beneficial glycometabolic support strategies for patients with myocardial ischaemia 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% CI, 0.95–1.13).2 GIK also showed a neutral effect on secondary endpoints. This result, together with a number of other recent studies,3 supports the current opinion that GIK does not give a clinically significant benefit in acute myocardial infarction (AMI). The traditional GIK scheme often induces hyperglycaemia, as the insulin component is not titrated to maintain normoglycaemia.

In the article, Goyal et al.,3 report on elevated glucose levels in patients with AMI and the prognostic value of these levels for adverse outcome (30- and 180-day mortality). Goyal et al. have analysed 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 h thereafter. More than half of the patients had a baseline glucose level higher than 7.8 mmol/L. Of these patients, one-third showed no or only moderate decrease in glucose during the first 24 h. 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 h. Although a large number of reports have described the association between hyperglycaemia at admission and adverse outcome,4 data on glucose levels at later moments after infarction are scarce. The association between hyperglycaemia at admission and adverse outcome was confirmed by Goyal et al., but more importantly, the change in glucose in the first 24 h 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 h. Adverse developments during this important initial period, for example unsuccessful reperfusion therapy, may prevent a drop in glucose level. Second, the failure of glucose to drop may be a result of pre-existing glycometabolic dysregulation, either subclinical or frank previously undiagnosed diabetes, which is known to negatively affect prognosis. The third possibility is most interesting from an intervention-oriented point of view: hyperglycaemia 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 hyperglycaemia will be beneficial in AMI patients.

In critically ill patients admitted to a predominantly cardiovascular care unit, a large randomized clinical trial has evaluated intensive insulin therapy aiming for normoglycaemia.5 In a cohort of 1548 patients, insulin therapy markedly reduced mortality during the stay on the intensive care unit (8.0 vs. 5.8%, P < 0.04).5 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.6 For instance, hyperglycaemia is associated with a pro-inflammatory and pro-thrombotic state, and interferes with normal endothelial function. Insulin not only antagonizes these negative aspects of hyperglycaemia, but may also boast intrinsic beneficial effects, such as improved glucose utilization and increased myocardial perfusion.6 In contrast, evident differences between patients

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* Corresponding author. Tel: +31 50 361 23 55; fax: +31 50 361 43 91. E-mail address: m.vogelzang@thorax.umcg.nl
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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 5 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 1 year was 18.6% in the intensive treatment group and 26.1% in the control group ($P = 0.027$). Albeit being high when 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 h (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 beneficial effect. The DIGAMI-2 study randomized patients into three arms to gain further insight into 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 because of a declining inclusion rate, and upon analysis, the achieved level of control was below par. The mean glucose level after 24 h was only 0.9 mmol/L lower in the treatment arms when compared with the control arm (9.1 vs. 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 hyperglycaemia, and the balance between aggressive treatment that may cause hypoglycaemia, 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 hypoglycaemia when the stress response of acute myocardial ischaemia 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 when 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 h have strong prognostic implications. The quest for a successful metabolic intervention to further improve prognosis in patients with AMI will continue.

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References