Metabolic interventions in acute myocardial infarction
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Summary and future perspectives
This thesis primarily describes the results of high-dose glucose-insulin-potassium (GIK) infusion in ST segment elevation MI patients treated with primary percutaneous coronary intervention (PCI).\textsuperscript{1} In the introduction (\textbf{Chapter 1}) it has already been stated that the experimental and clinical evidence accumulated over the better part of a century underscores the importance of glucose metabolism during ischemia/reperfusion of the heart. In 1912, Goulston suggested that treatment with glucose could be beneficial in several categories of heart disease.\textsuperscript{2} Sodi-Pallares and colleagues were the first to report the use of GIK in patients with acute myocardial infarction and found that it limited electrocardiographic changes.\textsuperscript{3} After the promising results of nine early randomized trials with 1932 patients and publication of the first results in patients treated with both reperfusion therapy and GIK the Glucose-Insulin-Potassium Study (GIPS-1) was set up.\textsuperscript{4,5} GIPS-1 included 940 patients randomized to primary PCI with or without GIK (glucose 20% with 80 mmol potassium in 500 ml sodium chloride 0.9% at a rate of 3 ml/kg per hour and 50 IU insulin in 50 ml water administered according to serum glucose concentrations). Baseline insulin-infusion dose and adjustments of the insulin dose, to obtain blood-glucose levels between 7.0 and 11.0 mmol/L, were based on a modified algorithm. In \textbf{Chapter 2.1} we describe the results of GIPS-1 on 30-day mortality and major adverse cardiac events (MACE).\textsuperscript{6} We observed that the mortality rate was lower in the GIK group (4.8%) compared to the control group (5.8%), albeit not statistically significant. After adjustment for differences at baseline, the relative risk of mortality with GIK became 0.61 (0.34–1.10, P=0.09). In the large predefined subgroup of 856 patients without signs of heart failure (Killip class 1), a significant reduction of mortality was seen (1.2% in the GIK compared to 4.2% in the control group, P=0.01). In 84 patients (8.9%) with signs of heart failure (Killip class \geq 2), the effect of GIK is uncertain since a (non-significant) higher mortality rate was observed.

In \textbf{Chapters 2.2 and 2.3}, we analyzed the effects of GIK on myocardial function and determined enzymatic infarct size and left ventricular function. There was no difference in the time course or magnitude of creatine kinase MB (CK-MB) release between the two groups: peak CK-MB level was 249±228 IU/L in the GIK group versus 240±200 IU/L in the control group (NS). The mean left ventricular ejection fraction (LVEF) was higher in the GIK group (43.7±1.0% versus 42.4±11.7%, P=0.12). Poor left ventricular function (LVEF \leq 30%) was observed in 18% in the controls and in 12% in the GIK group (P=0.01). We observed a relation between enzyme release and left ventricular function; the mean peak CK-MB was 463±318 IU/L in patients with LVEF \leq 30% versus 215±166 IU/L in patients with LVEF >30% (P<0.001). We therefore hypothesized that the effect of GIK on left ventricular function is mediated by factors unrelated to enzymatic infarct size. \textbf{Chapter 2.4} describes the effect of GIK on the resolution of ST segment elevation. The electrocardiograms at admission and after 3 hours were analyzed in 612 patients.
Combined complete (>70%) and partial (30-70%) resolution was more commonly observed in the GIK group (87%) when compared to the control group (78%), relative risk 1.72 (95% confidence interval 1.2-2.46, P<0.001). One-year mortality was lower in patients with combined complete and partial resolution compared to patients without resolution (3.8% versus 10.3%, P=0.011). ST segment elevation resolution after reperfusion therapy reflects myocardial flow rather than epicardial flow and predicts clinical outcome better than epicardial vessel patency alone in patients treated with reperfusion therapy. One of the effects of GIK in reperfused MI patients may be the restoration/preservation of myocardial perfusion.

The goal of the infusion of GIK during acute MI is to modulate the (myocardial) metabolism in such a manner that it is related to the preservation of myocardial function and a favorable clinical outcome. In Chapter 2.5, we describe the effect of GIK infusion on glucose and potassium levels. Mean serum glucose was 9.3±4.5 mmol/L in the GIK group compared to 8.4±2.9 mmol/L in the control group (P<0.001). Hyperglycemia (glucose >11.0 mmol/L) occurred in 337 patients (70.8%) treated with GIK and in 157 controls (33.8%) (P<0.001). A total of 48 hyperglycemic patients (9.4%) died versus 21 patients (4.7%) without hyperglycemia (P=0.004). In patients with hyperglycemia, 1-year mortality was 8.3% in the GIK group versus 12.7% in controls (P=0.14). Hypoglycemia (glucose ≤3.0 mmol/L) occurred in 10 patients of whom 2 patients (20%) died, both treated with GIK. Hyperkalemia (potassium >5.5 mmol/L) was present in 15 patients (5.5%) and in 15 controls (3.2%) (P=0.11); of these patients 9 (34.6%) died in the GIK group and 9 (60%) in the control group (P=0.19). Hypokalemia (potassium ≤3.5 mmol/L) occurred in 112 patients (23.5%) in the GIK group and in 191 patients in the control group (41.2%) (P<0.001). A total of 30 patients (9.9%) with hypokalemia died, 10 GIK patients (8.9%) and 20 controls (10.5%) (P=0.84). The beneficial effect of GIK on mortality may be diminished by these derangements.

The 3-year results are represented in Chapter 2.6. All-cause mortality occurred in 98 (10.4%) out of 940 patients after 3 years. Factors related with long-term mortality were age, previous cardiovascular disease, anterior MI, Killip class ≥2, and multi-vessel disease (all P<0.001). In the GIK group, 46 (9.7%) out of 476 patients died compared to 52 (11.2%) out of 464 patients (P=0.44, using the Log-rank test). In patients with Killip class 1 (N=856) randomization to GIK had an independent relation with 3-year mortality, with an adjusted relative risk of 0.56 (0.34-0.94, P=0.028). Other factors related with long-term mortality in Killip class 1 patients were age (P<0.001), previous cardiovascular disease (P<0.001) and multi-vessel disease (P=0.046). Cardiac protection with GIK infusion and primary PCI in acute MI did not result in a significant reduction in mortality in all patients. During the 3-year follow-up, the beneficial effect observed after 30-days in the predefined subgroup of Killip class 1 patients was sustained.
In Chapter 3 we describe the results of an overview off all studies on glucose-insulin-potassium solution. Of 13 published randomized trials, 12 studies reported mortality reduction after GIK. Most promising effects were observed when GIK was given in a high dose and when it was given as an adjunctive to reperfusion therapy.

In the second part of this thesis we describe our observational studies regarding the relation between hyperglycemia and outcome without controlled interventions on glucose metabolism. In Chapter 4.1, we determined whether admission glucose predicted long-term outcome in MI patients without diabetes mellitus that were treated with streptokinase or primary PCI. We observed that 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.

In Chapter 4.2, we describe the results of an analysis of the effect of admission hyperglycemia on myocardial perfusion in MI patients. A total of 93 patients (20%) out of 464 patients 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. Also, in patients with hyperglycemia there was a greater reduction in left ventricular function and a higher mortality. This was observed in patients with and without diabetes mellitus. Hyperglycemia on admission is associated with reduced myocardial reperfusion after primary PCI, which was associated with adverse clinical outcome.

In Chapter 4.3, we respond to a study that stated that hyperglycemia might be associated with impaired microvascular function after acute myocardial infarction (MI). The authors reached this conclusion by a retrospective analysis of 146 patients. The hypothesis that acute hyperglycemia (i.e., hyperglycemia at admission) is associated with the ‘no reflow’ phenomenon is intriguing. However, we hypothesize that ‘no reflow’ is related to acute hyperglycemia and chronic hyperglycemia (i.e., elevated HbA1c and/or DM). Therefore, new studies will have to determine the effect of hyperglycemia on ‘no reflow’ and preferentially on the effect of metabolic regulation.

Although admission glucose is a predictor of unfavorable outcome in MI patients, the predictive value is not strong. We hypothesized that persistent hyperglycemia (an elevated time-averaged glucose during admission) in critically ill patients could be a better predictor. In Chapter 5.1, we describe the relation between an elevated glucose at admission and an elevated time-averaged glucose with short-term MACE in MI patients treated with primary PCI. We included 417 patients of which 89 patients (21.3%) had had at least one MACE. In 17 patients (4.1%) it had been a fatal event and in 72 patients (17.3%) a non-fatal event. MACE occurred more often in patients who were older, had previous cardiovascular disease, anterior infarction location, and multi-vessel disease. The area under the receiver operator characteristic curve was 0.64 for time-averaged glucose
and 0.59 for admission glucose. Time-averaged glucose emerged as a significant independent predictor after multivariate analysis (P<0.01). We concluded that elevated time-averaged glucose in MI has a stronger relation with short-term MACE than elevated admission glucose.

In Chapter 5.2, the relation between hyperglycemia during admission and outcome was analyzed in a retrospective study of critically ill patients admitted to a surgical Intensive Care Unit. An objective measure of hyperglycemia to assess glucose regulation was defined. The so-called, hyperglycemic index (HGI) denotes the area under the curve as ‘above the upper limit of normal’ (glucose level 6.0 mmol/L) divided by ‘the total length of stay’. In 1779 patients with a median ICU-stay of 10 days, 30-day mortality was 17%. Median HGI was 0.9 (0.3-2.1) in survivors compared to 1.7 (0.7-3.3) mmol/L in non-survivors (p<0.001). Area under the receiver operator characteristic curve was 0.64 for HGI, compared with 0.61 and 0.62 for mean morning glucose and mean glucose. HGI was the only significant glucose measure in binary logistic regression. We concluded that HGI quantifies the impact of hyperglycemia in critically ill patients better than other glucose indices. HGI may thus be a useful measure of glucose regulation. We also determined whether the relation between HGI and outcome was present in patients admitted to a medical Intensive Care Unit (Chapter 5.3).

Finally, in Chapter 6, we describe the protocol of the GIPS-2 study. This chapter is already the implementation of future perspectives based on the results described in this thesis. GIPS-2 is an ongoing multi-center trial on the effect of GIK infusion in ST segment elevation MI patients without signs of heart-failure and eligible for reperfusion therapy.

**Future perspectives**

The definite role for metabolic modulation of the ischemic myocardium with GIK infusion has to be determined yet. Studies with GIK in acute MI were primarily based on the premises that infusion of glucose is beneficial for the ischemic myocardium. Decades ago the glucose hypothesis was proposed: enhanced uptake and metabolism of glucose delays cellular damage. Glucose utilization during ischemia prevents the breakdown of glycogen stores and leads to increased net intramyocardial glycogen synthesis, thereby limiting enzymatic infarct size and contracture. Recently, Opie stated that new concepts (table 1) have updated and outdated this hypothesis although the balance of glucose versus fatty acid oxidation remains crucial in ischemia.

We agree, that the potential positive effects of insulin during stress situations are multifarious and open for investigation in different patient groups. Insulin is involved in the uptake of glucose by several tissues including the myocardium. It is also involved
in gene transcription, expression of various metabolic enzymes, and activation of various pathways with mitogenic activity. Insulin inhibits postischemic apoptosis, energetic failure and damage to cardiac tissue, possibly through reduced oxidative stress mediated by KATP channel activation. Insulin stimulates protein synthesis and inhibits intracellular protein breakdown in cardiac tissue. Insulin potentiates ischemic preconditioning. Insulin has an anti-inflammatory effect. Insulin improves the fibrinolytic profile during myocardial ischemia. Insulin/strict-glucose-control restores the abnormalities in the serum lipid profile. Finally, insulin has vasodilating capacities in the blood vessels of muscle tissue as well as in the myocardium.

Table 1. Key new concepts on the role of insulin and glucose in myocardial ischemia (partly adapted from Opie LH, Jonassen A, Yellon DM. Cardiovasc J S Afr 2004;15:S1)18

- Reset of glycolysis-oxidation mismatch20
- Fatty acid oxidation↓, glucose↑21
- Low flow induces myocardial glucose uptake and is related to ATP↑22;23
- Insulin is related to increased myocardial flow24
- Insulin stimulates Akt/PKB25
- Inhibition of malonyl CoA decarboxylase: fatty acid oxidation↓, glucose↑26
- PPAR & nucleus↑27-29
- Fatty acid-induced genes30
- Prosurvival pathway stimulation31;32
- Activation of KATP channel related to reduced oxidative stress33
- Mitochondrial uncoupling proteins 2 and 3 regulatory role on myocardial metabolism34
- AMP-activated protein kinase mediates ischemic glucose uptake35;36

The results of a landmark study on intensive insulin therapy in critically ill patients in order to maintain blood glucose between 4.4 and 6.1 mmol/L and the results of the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study emphasize the beneficial effect of insulin. Although, these studies focussed on the effects of more strict glucose regulation as an important factor in explaining the positive results, the results may also be interpreted in a different manner. In studies regarding acute MI there is a trend towards a significant beneficial effect of insulin or glucose-insulin-potassium infusion despite the fact that normoglycemia was not obtained. Therefore, insulin could be both a moderator for transmembrane glucose transport to obtain normoglycemia and a moderator of the effects that are mentioned above. It is to be expected that in future studies the role of insulin or GIK, with or without meticulous glucose regulation, will be established in the treatment of various conditions. The GIPS-2
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is designed to investigate the effect of GIK infusion in ST segment elevation MI patients without signs of heart-failure and eligible for reperfusion therapy. For patients with signs of heart failure on admission, a more tailored approach seems warranted, such as the admission of glucose 30% or an infusion of no more than 500 ml, or a period of infusion of 12 to 24 hours.62 A first step is to investigate the effect of GIK infusion on the hemodynamics after admission with acute MI. Already we performed a pilot-study on this subject in approximately 90 MI patients. The results of this study will be used to determine a tailored approach.

Only three small prospective studies, including 12 to 30 patients, have been published on the possible beneficial effect of GIK infusion in stable patients with ischemic cardiac dysfunction.63-65 We designed a prospective study to address whether high-dose low-volume infusion of GIK administered through a central line will lead to improved myocardial function without causing hemodynamic disturbances in stable patients suffering from severe ischemic myocardial dysfunction.

To investigate the potential benefit of strict glucose regulation by insulin in patients admitted to Intensive or Coronary Care Units, a feasible algorithm and reliable glucose monitor are mandatory.66 To obtain strict regulation in critically ill patients, it is necessary to measure glucose levels frequently and then change the rate of insulin infusion accordingly. These frequent measurements also protect against adverse hypoglycemic episodes.67 The infusion of either insulin alone or GIK can be adjusted according to an algorithm.68

Table 2. Characteristics of algorithms with proved effective glucose regulation (the most effective form of administration is mentioned first)

- Continuous versus intermittent infusion
- Intravenous versus subcutaneous administration
- Adjusting the rate of infusion to the last two blood-glucose values prevents hypoglycemic episodes and promotes stricter regulation
- Starting with a bolus expedites reaching target values
- Hourly adjustments lead to stricter regulation
- Starting at lower values reduces the period of infusion
- Combining insulin treatment with a supply of energy (i.e. parenteral or enteral feeding, glucose infusion)

At the moment, an algorithm in which the infusion of insulin has been determined on the basis of the last two measured blood-glucose values seems to be the most effective to obtain strict glucose regulation. Other features of an algorithm which seem more
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favorable are represented in table 2. After an algorithm is implemented, it has to be evaluated and adjusted until satisfying results are achieved.

To prevent delay due to long turnaround times of glucose measurements at the laboratory, bedside glucometry, and an accepted method for estimating blood glucose concentrations among ambulatory and hospital ward patients would be useful. Because the accuracy of this system among the critically ill has not been properly evaluated, although it is used, we performed a prospective audit of bedside glucometry in our ICU setting.\(^{59,60}\) We installed point-of-care bloodgas/glucose analyzers – ABL 715 [Radiometer Medical, Copenhagen, Denmark] – in our Intensive and Coronary Care Units.\(^{59,60}\) In 27 male and 19 female Medical Intensive Care Unit patients, aged 32 years to 88 years, we performed a prospective audit in which the reference laboratory instrument [YSI, Yellow Springs Instruments, Ohio, USA] were compared with the bloodgas analyzer. Pearson’s correlation coefficient was calculated, which was fairly good: 0.95. A tested handheld device [Precision PCx, Abbott Laboratories, Illinois, USA] proofed also to be good with 100% of all paired measures within the set ranges. A continuous display of blood glucose levels in critically ill patients for optimal titration of insulin therapy could be a next step.\(^{69-72}\) The performance of the Continuous Glucose Monitoring System [Medtronic MiniMed, Northridge, USA] was recently found to be clinically acceptable.\(^{73}\) In a pilot-study of 20 patients, we also investigated the reliability and accuracy of the Continuous Glucose Monitoring System which was fairly good, with a Pearson’s correlation coefficient of 0.88. We found that glucometry with the bloodgas analyzer, and the continuous monitoring system provided a reasonable estimate of conventional (reference) laboratory glucose assessment. These systems could play an important role in future investigations in both the effect and potential beneficial mechanisms of metabolic modulation in critically ill patients.

At the moment, clinical studies support the effectiveness of metabolic interventions in several groups of critically ill patients.\(^{5,6,57-61,74,75}\) We will have to wait for new clinical studies that will show that experimentally obtained results, such as the effect of insulin on immune function, inflammation, lipid profile, and apoptosis, can be effectively translated in every day practice. In conclusion to this thesis: substantial experimental evidence underscores the potential benefit of treatment with insulin, glucose and potassium for the heart exposed to ischemia and reperfusion.

References


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