Diabetes and Coronary Surgery

*Metabolic and clinical studies on diabetic patients after coronary surgery with special reference to cardiac metabolism and high-dose GIK*

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Krebs once quoted Noël Coward: “Work is fun, and there is no fun like work”

To Márta, Marci and Zsófi, the memory of my parents

and my old high-school “Bolyai-Kollégium” in Marosvásárhely
ABSTRACT

Introduction An increasing proportion of the patients undergoing cardiac surgery have diabetes mellitus, in particular type II diabetics. In spite of this, diabetic patients have received limited attention in this setting. Although diabetes is a metabolic disease cardiac metabolism in association with surgery has previously not been explored in diabetics. This investigation was carried out to describe the metabolic state of the heart in diabetics after cardiac surgery and to study if it is accessible to metabolic intervention with high-dose GIK. Also, the potential hazards associated with such a regime in clinical practice were evaluated. Furthermore, a comparison of the outcome in diabetic and non-diabetic patients after coronary surgery was done.

Methods Myocardial metabolism and how it was influenced by high-dose GIK was assessed with coronary sinus catheter technique in a prospective randomized study on 20 type II diabetic patients undergoing CABG (paper I, II). Safety issues concerning high-dose GIK were assessed in two retrospective studies. The potential role of metabolic interventions for neurological injury was assessed in a cohort of 775 consecutive patients undergoing CABG or combined CABG + valve surgery, in whom metabolic interventions gradually replaced traditional treatment for postoperative heart failure (paper III). A detailed analysis of blood glucose and electrolyte control was done in all cases (n=89) receiving high-dose GIK during one year (paper IV). The hemodynamic impact of high-dose GIK was assessed with standard postoperative monitoring including Swan-Ganz catheters (paper II, IV). Outcome and prognosis after CABG in diabetic patients (n=540) were compared with non-diabetics (n=2239) with the aid of the institutional database comprising all isolated CABG procedures from 1995-1999 (paper V).

Results The metabolism of the diabetic heart after CABG was characterized by predominant uptake of FFA and restricted uptake of carbohydrate substrates. A high extraction rate of beta-hydroxybutyric acid and glutamate was also found. Alanine was released from the heart (paper I). High-dose GIK induced a shift towards uptake of carbohydrates, in particular lactate, at the expense of FFA and beta-hydroxybutyric acid (paper II). A substantial systemic glucose uptake was found during high-dose GIK treatment but the uptake tended to be lower and blood glucose higher if adrenergic drugs were used or/and if the patient was a diabetic (paper IV). High-dose GIK was associated with beneficial effects on cardiac output both in the prospective and retrospective analyses (paper II, IV). No evidence for untoward neurological effects associated with GIK treatment was found. History of cerebrovascular disease was the most important risk factor for postoperative cerebral complications and in general markers for advanced atherosclerotic disease were found to be of importance (paper III). High-dose GIK in clinical practice was associated with acceptable blood glucose and electrolyte control and no serious adverse events were recorded (paper IV). Patients with diabetes undergoing CABG had an acceptable short-term mortality that did not differ significantly from non-diabetic patients. However, diabetic patients had a higher early postoperative morbidity particularly with regard to stroke, renal- and infectious complications. Also, long-term survival was markedly reduced in diabetic patients, particularly in insulin treated patients (paper V).

Comments FFA were the main source of energy for the heart in type II diabetics after CABG whereas the uptake of carbohydrates was restricted. The high extraction rates of beta-hydroxybutyric acid and glutamate may represent an adaptation to the unfavorable metabolic situation of the post-ischemic diabetic heart. High-dose GIK can be used in type II diabetic patients after cardiac surgery to promote carbohydrate uptake at the expense of FFA and beta-hydroxybutyric acid. The magnitude of this shift was sufficient to account for the entire myocardial oxygen consumption assuming that the substrates extracted were oxidized. This could have implications for the treatment of the diabetic heart in association with surgery and ischemia. Provided careful monitoring high-dose GIK can be safely used in clinical practice and this treatment deserves further evaluation in the treatment of postoperative heart failure. High-dose GIK also provides a means for strict blood glucose control and as substantial amounts of glucose can be infused even in critically ill patients, it may prove useful for nutrition in critical care. Several of the risk factors for neurological injury identified constitute markers for advanced atherosclerotic disease, thus, also providing an explanation for the increased risk of neurological injury in diabetics after cardiac surgery. Short-term mortality was acceptable in diabetics after CABG. However, further efforts are warranted to address postoperative morbidity and late outcome. This represents a challenge as diabetic patients are accounting for an increasing proportion of the patients undergoing CABG.

Key words: diabetes, heart, coronary surgery, cardiac surgery, myocardial metabolism, free fatty acids, beta-hydroxybutyric acid, glutamate, glucose, insulin, potassium, high-dose GIK, neurological injury, complications, risk factors, morbidity, mortality.
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### ABBREVIATIONS

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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BW</td>
<td>Body Weight</td>
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<tr>
<td>BSA</td>
<td>Body Surface Area</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft surgery</td>
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<td>CI</td>
<td>Cardiac Index</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary Bypass</td>
</tr>
<tr>
<td>FFA</td>
<td>Free Fatty Acids</td>
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<tr>
<td>GIK</td>
<td>Glucose-Insulin-Potassium</td>
</tr>
<tr>
<td>IABP</td>
<td>Intra-aortic Balloon Pump</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>LITA</td>
<td>Left Internal Thoracic Artery</td>
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<tr>
<td>LVSWI</td>
<td>Left Ventricular Stroke Work Index</td>
</tr>
<tr>
<td>MOF</td>
<td>Multi-organ Failure</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PDE III</td>
<td>Phospho-diesterase III</td>
</tr>
<tr>
<td>PDH</td>
<td>Pyruvate Dehydrogenase</td>
</tr>
<tr>
<td>PTCA</td>
<td>Percutaneous Transluminal Coronary Angioplasty</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SVRI</td>
<td>Systemic Vascular Resistance Index</td>
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INTRODUCTION

Diabetes mellitus

Diabetes has been recognized since ancient times and Arataeus (ca AD 70) referring to the polyuria gave it its name [1]. The scientific, experimental studies of diabetes began with Claude Bernard who recognized that hyperglycemia (1855) is the cardinal sign of the disease. In 1921 Banting and Best discovered insulin but more than three decades elapsed before the chemical structure was established [1,2]. The introduction of effective metabolic treatment has improved the prognosis in diabetics and subsequently the long-term consequences of diabetes on the cardiovascular system have become evident. The prevalence of diabetes in Sweden is approximately 3% and 90% of the diabetic patients are type II diabetics [3,4]. Diabetic patients are overrepresented in populations needing coronary interventions. A recent survey demonstrated that the proportions of diabetics ranged from 11.8 – 27.7% out of those undergoing CABG within the European community [5]. However, PTCA is accounting for an increasing proportion of coronary interventions [6] and, hence, the patients admitted for surgery have more extensive coronary disease [7-9]. This fact, and data suggesting that diabetics benefit more from CABG than PTCA contributes to a development implying that the proportion of diabetic patients accepted for coronary surgery is increasing [10,11].

Neuroendocrine stress and cardiac metabolism

In 1932 Cuthbertson reported that trauma is characterized by increased metabolic rate and negative nitrogen balance [12]. Wilmore described the role of stress hormones for the metabolic response to trauma and insulin resistance. Posttraumatic metabolism is characterized by hyperglycemia, increased lipolysis and protein catabolism [13]. The magnitude of this reaction is proportional to the severity of the trauma [14].

Knowledge about the fuels of the human heart started with the introduction of coronary sinus catheterization by Bing in 1947 [15]. However, half a century later the numbers of available studies on the human heart in association with disease are few. The consequences of neuroendocrine stress on cardiac metabolism in association with cardiac surgery were described by Svensson and Svedjeholm [16,17]. Glucose-insulin-potassium (GIK) was introduced by Sodi-Pallares in 1962 as a polarizing agent to promote electrical stability in myocardial infarction [18]. Later as the potential detrimental effects of neuroendocrine stress and its metabolic consequences for the heart in association with ischemia were recognized GIK was used as means to promote carbohydrate metabolism at the expense of FFA. Despite
early encouraging results for treatment of myocardial infarction GIK was abandoned due to inconclusive trials [19]. In retrospect this was done without sufficient statistical power [19] [20] and furthermore some of the early inconclusive results may have been due to use of inappropriate GIK regimes.

Increasing awareness of the role of insulin resistance in association with trauma and critical illness contributed to further research on GIK in the setting of cardiac surgery. In humans undergoing CABG the effects of GIK regimes employing supraphysiological insulin doses on systemic- and myocardial metabolism were studied by Ekroth, Nilsson, Svensson and Svedjeholm. It was found that insulin doses of 1 IU/kg BW and hour caused a shift from myocardial FFA uptake to carbohydrate uptake and induced maximal systemic glucose uptake, albeit reduced compared with preoperative state [17,21-23]. Higher doses of insulin were found to have pronounced vasodilative properties but did not further enhance the metabolic effect [17,23,24].

**Diabetes and coronary surgery**

An increasing proportion of patients undergoing cardiac surgery have diabetes mellitus, in particular type II diabetes. The shift towards more diabetic patients being operated represents a challenge in coronary surgery. Due to its associated complications diabetes remains one of the main risk factors for postoperative morbidity, early- and late mortality in cardiac surgery [25-27]. Diabetes accelerates the coronary atherosclerotic process [28,29], thus producing less favorable conditions for surgical revascularization. A preoperatively reduced left ventricular systolic function has been claimed to carry more unfavorable prognostic implications in diabetics compared with non-diabetics [8,9]. Furthermore, diastolic left ventricular dysfunction is a common finding in diabetic hearts before surgery [30].

In spite of this, diabetic patients have received limited attention in cardiac surgery, and although diabetes is a metabolic disease cardiac metabolism in association with surgery has previously not been explored in diabetics. Previous studies in non-diabetic patients have demonstrated various degrees of metabolic derangement and insulin resistance after cardiac surgery, which may contribute to development of postoperative heart failure [16,17]. There is reason to suspect that diabetics could be more susceptible to metabolic derangement in this setting. Due to neuroendocrine stress high-doses of insulin are required to achieve maximal metabolic effects after cardiac surgery in non-diabetic patients [24,31]. Although diabetic
patients in particular can be expected to benefit from such treatment, the impact of GIK on cardiac metabolism in diabetics remains unexplored. It is not known if the supraphysiological doses of insulin used in non-diabetic patients are sufficient to achieve similar effects in diabetic patients.

This investigation was carried out to describe the metabolic state of the heart in type II diabetics after cardiac surgery (paper I) and to study if it is accessible to metabolic intervention with high-dose GIK (paper II). Also, the clinical experience and the potential hazards and associated with such a regime in clinical practice were evaluated (paper III-IV). Furthermore, a description of patient characteristics and a comparison of the clinical outcome in all diabetic and non-diabetic patients undergoing CABG in the southeast health region of Sweden during 1995-1999 were done (paper V).
AIMS OF THE STUDY

- to describe myocardial uptake and release of substrates in diabetic patients early after elective coronary surgery
- to evaluate the effects of high-dose GIK on myocardial uptake and release of substrates in diabetic patients early after elective coronary surgery
- to evaluate the effects of high-dose GIK on the hemodynamic state in diabetic patients after elective coronary surgery
- to evaluate clinical safety of high-dose GIK in clinical practice with respect to hemodynamic recovery
- to evaluate clinical safety of high-dose GIK in clinical practice with respect to blood glucose and electrolyte control
- to evaluate the role of diabetes and metabolic interventions including high-dose GIK with respect to postoperative neurological injury
- to describe the diabetic population undergoing CABG in the southeast health region of Sweden
- to compare outcome in diabetic and non-diabetic patients undergoing coronary surgery in the southeast health region of Sweden with respect to postoperative morbidity, early mortality and long-term survival
MATERIAL AND METHODS

PATIENTS
In paper I 10 and in paper II 20 patients with type II diabetes undergoing elective CABG for stable angina pectoris between September 1995 and October 1999 were studied. Exclusion criteria were poor left ventricular function (left ventricular ejection fraction <0.40), age > 80 years, clinical signs of serious late complications of diabetes, liver disease or metabolic disturbance other than diabetes. Demographic data are given in table 1.

In paper III a cohort of 775 consecutive cases operated by two surgeons with CABG or combined CABG + valve procedures from January 1991-July 1995 were studied. In this cohort inotropic therapy for treatment of intraoperative heart failure was gradually replaced by metabolic treatment during the study period (figure 1 of paper III). Demographic data are presented in table 1 and further details are given in table 1 of paper III.

In paper IV all patients receiving high-dose GIK during 1994 were studied. 88 patients undergoing 89 procedures from a total of 854 cardiac surgical procedures were treated with high-dose GIK. Sixteen of these high-dose GIK treated cases were diabetics. An additional group of sixteen randomly chosen diabetic patients with routine blood glucose control undergoing uncomplicated elective CABG during 1994 was also included as a reference to assess the quality of blood glucose control in the high-dose GIK treated diabetics. Demographic data are presented in table 1 and further details are given in table 1 of paper IV.

In paper V 2779 consecutive cases undergoing isolated CABG from January 1995 to 31 December 1999 at the University Hospital in Linköping were studied. Five hundred and forty of these cases had a history of diabetes mellitus on admission. Demographic data are presented in table 1 and further details are given in table 1 of paper V.
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<th>Preoperative data</th>
<th>Paper I-II contr n=10 GIK n=10</th>
<th>Paper III n=775</th>
<th>Paper IV GIK n= 89 DM contr n=16</th>
<th>Paper V DM n=540 no DM n=2239</th>
</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>56 ± 9 58 ± 8</td>
<td>65 ± 9 69 ± 9</td>
<td>64 ± 7 64 ± 9</td>
<td>66 ± 9 66 ± 9</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>30 10</td>
<td>20.4 33.7</td>
<td>37.8 28.3 20.3</td>
<td></td>
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<tr>
<td>Hypertension (%)</td>
<td>30 60</td>
<td>31.5 33.7</td>
<td>25 49.3 38.2</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>100 100</td>
<td>11.3 18.0</td>
<td>100 100 0</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92 ± 18 87 ± 12</td>
<td>80 ± 12 75 ± 12</td>
<td>78 ± 14 82 ± 14</td>
<td>79 ± 13 72 ± 8</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>173 ± 8 174 ± 8</td>
<td>172 ± 8 171 ± 8</td>
<td>169 ± 10 171 ± 8</td>
<td>172 ± 8 172 ± 8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3 ± 3.4 28.7 ± 3.2</td>
<td>26.8 ± 3.5</td>
<td>25.8 ± 3.7 27.4 ± 4.2</td>
<td>28.0 ± 4.1 26.4 ± 3.5</td>
</tr>
<tr>
<td>Preoperative long-term insulin treatment (%)</td>
<td>60 60</td>
<td>6.1 11</td>
<td>75 44</td>
<td>44 0</td>
</tr>
<tr>
<td>Preoperative HbA1c (%)</td>
<td>6.7 ± 1.1 7.2 ± 0.8</td>
<td>------ ------</td>
<td>------ ------</td>
<td>------ ------</td>
</tr>
<tr>
<td>EF &lt;0.35 (%)</td>
<td>0 0</td>
<td>13.5 31.4</td>
<td>0 6.8</td>
<td>5.0 17.4</td>
</tr>
<tr>
<td>Recent MI (&lt;4 weeks) (%)</td>
<td>0 0</td>
<td>17.7 11.2</td>
<td>6.2 21.5</td>
<td>17.4 53.0</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>0 0</td>
<td>29.0 29.2</td>
<td>12.5 53.0</td>
<td>47.6 75.3</td>
</tr>
<tr>
<td>Higgins score</td>
<td>1.6 ± 1.5 1.2 ± 0.4</td>
<td>2.3 ± 2.6§ 5.3 ± 3.4</td>
<td>2.3 ± 1.5 3.0 ± 2.6</td>
<td>2.1 ± 2.5</td>
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<tr>
<td>Intraoperative data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of distal anastomoses</td>
<td>3.5 ± 0.8 3.7 ± 1.1</td>
<td>3.4 ± 1.3* 3.4 ± 1.3* 3.3 ± 0.9</td>
<td>3.7 ± 1.1 3.6 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Arterial grafts used (%)</td>
<td>90 90 91.6* 87.0* 100 95.4 94.0</td>
<td>0 0 4.8 18.0 0 0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG + valve (%)</td>
<td>0 0 0.4* 18.0 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedures other than CABG / CABG + valve (%)</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic cross clamp time (minutes)</td>
<td>46 ± 15 45 ± 21 42 ± 22 76 ± 41 42 ± 10 47 ± 17 44 ± 18</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CPB time (minutes)</td>
<td>84 ± 21 77 ± 24 87 ± 42 144 ± 64 81 ± 18 87 ± 29 81 ± 31</td>
<td></td>
<td></td>
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<tr>
<td>Outcome</td>
<td>30-day mortality (%)</td>
<td>0 0 0.9 5.6 0 2.6 1.6</td>
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</table>

**Table 1.** Preoperative demographic data and intraoperative data for all patients included in the thesis (mean±SD). DM = insulin or oral antidiabetic treated diabetics, except for paper V where diet treated diabetics also were included. EF<0.35 = left ventricular ejection fraction below 0.35. Recent MI = recent myocardial infarction (<4 weeks). Arterial grafts = % of patients receiving arterial grafts. BMI = body mass index. HbA1c = glycosylated hemoglobin. § = based on 490 observations; * represents all CABG procedures including combined CABG + valve procedures.

**Comment:** The sample size of the prospective study was chosen with respect to the end points of the study. In the retrospective studies (paper III-IV-V) the cases included were chosen as consecutive cases over given time intervals.

Unless specified or stated otherwise, the term “patients” is used synonymously with “cases” representing a single cardiac surgical procedure. Inevitably some overlap exists between the study cohorts. The 20 diabetic patients in the prospective study (paper I-II) and 108 of the 775 cases in paper III were also registered in the institutional database (paper V). Of the 89 cases
treated with high-dose GIK in paper IV 31 were also registered in the database that served paper III. Thus, in all 3520 cases were studied.

Linköping University Hospital is the referral center for the southeastern health region of Sweden and the sample in paper V, hence, represents all CABG procedures performed in that area.

**CLINICAL MANAGEMENT**

After an overnight's fast drugs were withheld with the exception of betablockers and calcium-antagonists. The patients were premedicated with 4 - 10 mg oxycodone and 0.2 - 0.5 mg scopolamine intramuscularly. Anesthesia was induced with thiopentone at a dose of 2-3 mg/kg body weight (BW) and fentanyl at a dose of 30 µg/kg BW (paper I-II) or thiopentone 1 - 2 mg/kg BW and fentanyl 10 µg/kg BW (paper III-V). Pancuronium bromide was used for neuromuscular blockade. Anesthesia was maintained with fentanyl and isoflurane.

The majority of patients underwent CABG using standard techniques with cardiopulmonary bypass (CPB) and aortic cross clamping. Ringer's acetate and mannitol was used for priming the extracorporeal circuit. Moderate hemodilution (hematocrit 20 - 25%) and light to moderate hypothermia (32-36 °C) were usually employed. Antegrade or combined ante- and retrograde delivery of modified St. Thomas' cold crystalloid cardioplegic solution (Plegisol, Abbot, IL, US) was used for myocardial protection. Weaning from CPB was started at a rectal temperature of 35-36 °C (paper III-V) or 36 °C (paper I-II). Heparin was neutralized with protamine chloride. Ringer's acetate was used for volume substitution postoperatively. Shed mediastinal blood was routinely retransfused in the ICU. Postoperative rewarming was facilitated by radiant heat provided by a thermal ceiling.

**Comment:** In papers I and II, all patients were operated before noon and the patients were sedated postoperatively during the study period. Immediately before closure of the sternum 4 mg of pancuronium was given intravenously and repeated during the study period to prevent shivering. To minimize influence of postoperative events such as extubation, pain, shivering and emotional stress during the study period the patients were sedated with a continuous infusion of midazolam (2-6 mg/hour) and analgesia was provided during the study period with intravenous ketobemidone infusion 1-4 mg/hour supplemented if necessary with intermittent doses of intravenous fentanyl (100-200 µg).

In paper III prevention and treatment of postoperative heart failure differed from traditional treatment by frequent use of metabolic interventions, which gradually replaced the use of inotropic drugs for weaning from CPB (figure 1 paper III).

In the paper V 4.3% of the CABG procedures were done without CPB.
HIGH-DOSE GIK

Fast-acting insulin (Actrapid Novo®) was infused in a central vein at a rate of 1 IU/kg BW and hour for six hours. A bolus of 25 IU was injected five minutes after starting the glucose infusion. A 30% glucose solution supplemented with 10 mmol magnesium and 40 mmol phosphate per liter was infused with the aim to keep blood glucose between 7 - 10 mmol/L (paper II) or 7 - 12 mmol/L (paper III-V). After stopping insulin the glucose infusion was gradually decreased. Potassium was infused separately by guidance of serum potassium level, which was allowed to decrease to approximately 3.5 mmol/L.

Comment: The high-dose GIK is a clinical application of a hyperinsulinemic glucose clamp, therefore blood glucose level in the short perspective is influenced only by the rate of glucose infusion. The high-dose GIK regime was modified in terms of desired blood glucose level from 7 - 12 mmol/L at the time of retrospective studies to 7 - 10 mmol/L at the time of the prospective study (paper II). This was done because initial concerns regarding the risk for hypoglycemic episodes had diminished, and the value of strict blood glucose control to reduce the incidence of postoperative infections had been recognized [32]. For future clinical application a modification of target blood glucose to 6 – 8 mmol/L is under consideration.

STUDY PROTOCOL

Myocardial Uptake and Release of Substrates in Type II Diabetics Undergoing Coronary Surgery (paper I)

Myocardial uptake and release of substrates was investigated in ten type II diabetic patients undergoing elective CABG. The coronary sinus was catheterized postoperatively and the patients were thereafter transferred to the ICU. The study was commenced on average 3 hours after release of the aortic cross clamp. Simultaneous blood sampling from the coronary sinus and radial artery were done in the basal state (0), after 30 minutes and 1- 2 - 4 hours and coronary sinus blood flow was measured at the same intervals. Samples were analyzed for free fatty acids (FFA), glucose, lactate, glycerol, beta-hydroxybutyric acid, glutamate and alanine. All substrates were analyzed in whole blood except FFA. Glutamate and alanine were analyzed both in whole blood and plasma.

Comment: A consequence of the study design was the lack of preoperative measurements. This limitation was accepted because of reasons such as the use of retrograde cardioplegia and risk of coronary sinus catheter dislocation.
Effects of high-dose glucose-insulin-potassium on myocardial metabolism in type II diabetic patients after coronary surgery (paper II)

The influence of high-dose GIK on myocardial uptake and release of substrates was investigated in type II diabetic patients undergoing elective CABG. Twenty type II diabetic patients were randomly allocated to postoperative high-dose GIK (glucose-insulin-potassium) treatment (n=10) or a control group receiving standard postoperative glucose control (n=10). The coronary sinus was catheterized postoperatively and the patients were thereafter transferred to the ICU. The study was commenced on average 3 hours after release of the aortic cross clamp. Simultaneous blood sampling from the coronary sinus and radial artery were done in the basal state (before starting GIK), after 30 minutes and 1 - 2 - 4 hours and coronary sinus blood flow was measured at the same intervals. Hemodynamic state and coronary sinus blood flow was measured at the same intervals.

Samples for glucose, lactate, glycerol, and beta-hydroxybutyric acid were analyzed in whole blood. Samples for free fatty acids (FFA) were analyzed in plasma. Glutamate and alanine were analyzed both in plasma and whole blood.

Comment: The study was not blinded because of ethical concerns associated with the use of supraphysiological insulin doses and the need for appropriate blood glucose control. The control group was treated according to clinical routine with regard to blood glucose control, which implied that insulin (Actrapid®) infusion was started if blood glucose level exceeded 10 mmol/L. During the study period three of the control patients required insulin infusion ranging from 1 – 10 IU/hour.

Originally three arms of the study were considered with one arm investigating the effect of a GIK regime employing insulin doses of 0.08 IU/kg BW and hour [33]. However, this arm had to be abandoned with the first patient included because of unacceptable blood glucose control.

Neurological injury after surgery for ischemic heart disease: risk factors, outcome and role of metabolic interventions (paper III)

Risk factors for neurological injury were investigated with multivariable statistics in a cohort of 775 consecutive patients operated by two surgeons with CABG or combined CABG + valve procedures. In this cohort traditional treatment with inotropic drugs for postoperative heart failure had been gradually replaced by metabolic interventions (figure 1 of paper III). Data were retrospectively collected from the records and stored in a database. Post-discharge mortality data were retrieved from the Swedish Civil Registry and outcome in patients with neurological injury records was investigated by retrieving records from referring hospitals.
Comment: A comparatively broad and complete set of data (appendix A paper III) was available and thus multivariate analysis was considered appropriate to identify independent risk factors for neurological injury. However, although the material comprised 775 procedures the limited number of events rendered multivariate analysis susceptible to misclassification and as false positive diagnosis could be expected to have a more pronounced influence only patients with certain neurological injury were included. The following cerebral complications were classified as neurological injury: 1) stroke 2) depression of consciousness or confusion if associated with signs of cerebral injury on CT-scan or focal neurological deficit 3) transient ischemic attacks with focal neurological deficit.

High-dose GIK in cardiac surgery - clinical safety issues and lessons learned (paper IV)

To assess safety issues associated with high-dose GIK in clinical practice the records of all patients receiving high-dose GIK during one year (1994) were investigated in detail for analysis of clinical outcome, adverse effects, blood glucose and electrolyte control. Hemodynamic recovery was assessed in the patients that had a Swan-Ganz catheter and complete hemodynamic data sets available for analysis (n=25).

Sixteen of the 89 high-dose GIK treated cases were tablet or insulin treated diabetics. These patients were compared regarding blood glucose control not only with the non-diabetics receiving high-dose GIK but also with a group of sixteen randomly chosen diabetics undergoing elective uncomplicated CABG in 1994. The latter group was treated according to clinical routine with low dose insulin infusion if blood glucose exceeded 10 mmol/L.

Early postoperative outcome and long-term survival in 540 diabetic and 2239 non-diabetic patients undergoing coronary surgery (paper V)

To describe patient characteristics and to compare early postoperative outcome and long-term survival in diabetic and non-diabetic patients after CABG data from the institutional computerized database were retrieved (Summit Vista for Windows; Summit Medical Systems Inc. Version 1.98.1). Demographic and peri-procedural data including complications had been registered prospectively and all fields were defined in a data dictionary. Data from 2779 consecutive patients undergoing isolated CABG at Linköping Heart Center from January 1995 to 31 December 1999 were studied. Five hundred and forty (19.4%) of these patients had a history of diabetes mellitus on admission that had necessitated active therapy with diet or medication. Long-term survival was assessed with data retrieved from the Swedish Civil Registry and included follow up to March 2000.
Comment: The major strengths of the study were the completeness of survival data, prospective data collection and that the material represents all diabetic patients undergoing CABG in the southeast health region of Sweden. The limitations of the study included aspects inherent to large data registries with various degrees of incomplete data and hazards associated with definitions of data entries and possible misclassification of some individual data. To attenuate these limitations only reasonably complete data were assessed, apparently deviant data were double-checked with the original records and missing data entries for mortality and cause of death were retrieved from the original records.

METHODS

Biochemical analyses

Glutamate, alanine, lactate and glucose were analyzed in whole blood. Whole blood samples were immediately deproteinized with ice-cold perchloric acid. After centrifugation the protein-free extracts were deep-frozen to -70 °C. Beta-hydroxybutyric acid (3-hydroxybutyrate) was measured according to Basso [34]. Glutamate concentration was determined fluorometrically by an adapted glutamate dehydrogenase method [35]. D-glucose [36,37], lactate [38] and alanine [39] were also determined fluorometrically. FFA were analyzed in plasma according to Ho [40]. Plasma samples were stored at −70 °C until analysis. Both whole blood and plasma analyses were done batch wise, care being taken that corresponding arterial and venous samples were analyzed simultaneously.

Alanine and glutamate were also analyzed in plasma with a conventional amino acid analyzer (Beckman system 6300, Beckman Instruments, Inc., Palo Alto, CA).

Free insulin was determined after polyethylene glycol precipitation as described by Arnqvist [41]. Insulin was measured by Mercodia Iso-Insulin ELISA (Mercodia AB, Uppsala, Sweden), a two-site enzyme immunoassay containing two monoclonal antibodies against insulin.

Oxygen saturation and hemoglobin concentrations were measured with an OSM3 oximeter (Radiometer AS, Copenhagen, Denmark).

Comment: All whole blood determinations were carried out in duplicate with an error of the methods expressed as coefficient of variation of a single determination as follows: glucose 2.4%, lactate 2.0%, glycerol 1.9%, beta-hydroxybutyric acid 3.8%, alanine 6.0%, glutamate 5.5%, FFA 5.0%. The coefficient of variation for amino acid analyses in plasma was 5.6% for glutamate and 2.8% for alanine. The interassay coefficient of variation for analyses of free insulin was 3%.
Hemodynamic measurements

Cardiac output A Swan-Ganz catheter (Arrow Hands Off® Infusion Port Thermodilution Catheter Arrow International Inc. Reading, PA, USA) was usually inserted through the right internal jugular vein into the pulmonary artery. Cardiac output was measured with thermodilution technique. In paper II it was calculated from the mean value of three observations. Derived hemodynamic variables were calculated from standard formulae.

Pressure measurements The systemic blood pressure was measured in the radial artery. For the measurement of central venous-, pulmonary artery- and pulmonary capillary wedge pressure the 7.5 F Swan Ganz (Arrow Hands Off® Infusion Port Thermodilution Catheter Arrow International Inc. Reading, PA, USA) catheter was used.

Coronary sinus flow A coronary sinus catheter (Wilton Webster Labs Inc., Altadena, Calif.) was inserted through the right internal jugular vein. The final mid-coronary sinus position was confirmed with fluoroscopy and measurement of oxygen saturation. Coronary sinus blood flow (CF 300A flowmeter; Webster Labs Inc.) was measured with retrograde thermodilution technique [42]. The mean of three measurements was used.

Comment: A coronary sinus catheter provides information about the flow at the tip of the catheter and is dependent on the anatomy of the coronary sinus and the exact position of the catheter tip. In agreement with previous studies the sample size used in paper II seemed sufficient to neutralize individual differences in the position of the catheter, as suggested by the finding that there was no inter-group difference in coronary sinus flow measured in the basal state.

Statistical analyses
Data are presented as mean ± standard error of the mean (SEM) (paper I-II, IV) or mean ± standard deviation (SD) (paper III, V). Statistical significance was defined as a probability value less than 0.05.

Mann-Whitney U-test was used to determine statistical difference from zero in paper I-II and for comparison of continuous variables in paper III and V. For comparison of categorical variables in paper III and V Fisher’s exact test was used. Repeated measures analysis of variance (ANOVA) was employed for assessment of changes occurring over time (paper I) and inter-group differences of continuous variables (paper II and
IV) as appropriate. Post-hoc analysis was performed with the Tukey honest significant difference test.

In paper III independent risk factors for postoperative cerebral complication was assessed by a stepwise forward multivariate logistic regression model.

In paper V cumulative long-term survival was assessed with Kaplan-Meier analysis. A statistical package was used to perform the analyses (Statistica 5.5 and 5.1, StatSoft, Inc., Tulsa, OK). In the paper V the Statview for Windows 5.0.1 (SAS Institute Inc) was also used.

**Comment:** The Mann Whitney U-test was used in paper I-II because of small sample sizes and in paper III and V because of the distribution of data [43]. Fisher’s exact test was used for comparison of categorical data as expected values for some variables fell below five (paper III, V).

To account for multiple comparisons and to assess changes occurring over time repeated measures ANOVA with appropriate post hoc test was used, except for analyses of repeated measurements to determine statistical difference from zero. For the latter purpose the Mann-Whitney U-test with the Bonferroni correction was used (paper I-II). However, the Bonferroni correction amplifies the risk of a type II error already present because of the generally small arterio-venous concentration differences of highly perfused tissues. As the risk for type II error outweighs the risk for type I error in a descriptive study, the results in paper I were given with both non-adjusted and Bonferroni adjusted significance levels to facilitate comparisons with previous studies and to aid in the interpretation of data.

For analysis of independent predictors of neurological injury (paper III) univariate logistic regression was first employed (variables tested are presented in the appendix of paper III). Variables were tested in a stepwise forward multivariate logistic regression model if the univariate p value was less than 0.25. Due to the limited number of events cross-validation of the final model was undertaken.
CALCULATIONS AND DEFINITIONS

Myocardial fluxes of substrates were calculated as the product of arterial-coronary sinus blood or plasma concentration differences and coronary sinus blood or plasma flow as appropriate.

A release of substrates was defined as a myocardial flux value significantly less than zero (p<0.05), whereas uptake of substrates was defined as a myocardial flux significantly greater than zero (p<0.05).

Oxygen consumption of the heart was estimated as the product of arterial-coronary sinus blood oxygen content difference and the coronary sinus blood flow. Oxygen content = [B-Hb* HbSO₂ * (6.2 * 10^{-4})] + (PO₂ * 0.01), where B-Hb represents blood hemoglobin (in grams per liter); HbSO₂ is oxygen saturation expressed as percentage, and PO₂ is oxygen tension (in kilopascals) [44].

ETHICAL ASPECTS

The prospective studies were performed according to the principles of the Helsinki Declaration of Human Rights, and were approved by the Ethics committee for medical research at the University Hospital of Linköping (Dnr: 96088). Signed informed consent was obtained from each patient in the prospective studies.
RESULTS

METABOLISM OF THE DIABETIC HEART AFTER CORONARY SURGERY (PAPER I)

FFA
The arterial level of plasma FFA was 0.67 ± 0.05 mmol/L in the basal state and did not change significantly during the study period (table 2 of paper I). The diabetic heart extracted FFA throughout the study period (table 3 of paper I). Myocardial uptake of FFA was 11.9 ± 3.7 µmol/min in the basal state and did not change significantly during the study period (table 3 of paper I). No significant correlation between arterial levels and arterial-coronary sinus differences of FFA was found. Fractional extraction of FFA is showed in figure 1.

Beta-hydroxybutyric acid
The arterial level of beta-hydroxybutyric acid was 149 ± 58 µmol/L in the basal state and tended to increase during the study period with a peak at 2 hours (450 ± 84 µmol/L; table 2 of paper I). A significant myocardial uptake was observed from thirty minutes and onwards with a peak at 2 hours (14 ± 5.8 µmol/min; table 3 of paper I). The fractional extraction of beta-hydroxybutyric acid was 31% on average with a peak of 42% (figure 1). A significant correlation between arterial levels and arterial-coronary sinus difference of beta-hydroxybutyric acid was found during the study period for (r=0.90; p<0.001, figure 12 page 41).

Glucose
Arterial level of glucose was 7.2 ± 0.4 mmol/L in the basal state and did not change significantly during the study period (table 2 of paper I). No significant uptake of glucose was observed during the study period (table 3 of paper I).

Lactate
Arterial level of lactate was 1.15 ± 0.12 mmol/L in the basal state and did not change significantly during the study period. No significant uptake or release of lactate was observed during the study period (table 3 of paper I).
Figure 1. Fractional extraction of FFA, beta-hydroxybutyric acid and glutamate by the heart in type II diabetic patients after elective CABG. 0 denotes the basal state when the study commenced (approximately 3 hours after release of the aortic cross clamp).

Glutamate

Arterial level of glutamate in plasma was 100 ± 13 µmol/L and did not change significantly during the study period (table 2 of paper I). A significant uptake of glutamate from plasma was found in the basal state (4.8 ± 2.2 µmol/min) and throughout the study period (table 3 of paper I). A fractional extraction of glutamate comparable with that of beta-hydroxybutyric acid was found (figure 1). A significant correlation between arterial levels and arterial-coronary sinus differences of plasma glutamate was found during the study period (r=0.74; p<0.001; figure 13 page 42).

Alanine

Arterial level of alanine in plasma was 254 ± 32 µmol/L in the basal state and did not change significantly during the study period (table 2 of paper I). Alanine was released from the diabetic heart in the basal state (-5.8 ± 2.8 µmol/min) and onwards after CABG (table 3 of paper I).
EFFECTS OF HIGH-DOSE GIK ON ARTERIAL LEVELS AND MYOCARDIAL UPTAKE OF SUBSTRATES (PAPER II)

During high-dose GIK treatment plasma insulin increased from 84 ± 28 pmol/L to 14 007 ± 1509 pmol/L after 4 hours (table 3 of paper II).

FFA
High-dose GIK induced a reduction in arterial FFA levels and a reduction in myocardial uptake of FFA. Arterial levels of FFA decreased from 0.63 ± 0.84 mmol/L in the basal state to 0.27 ± 0.70 mmol/L at the end of the study period (p=0.0007; table 3 of paper II). In the high-dose GIK group uptake of FFA by the diabetic heart was only detected in the basal state (table 4 of paper II). Myocardial FFA uptake decreased from 8.5 ± 1.7 µmol/min in the basal state to 2.0 ± 1.2 µmol/min at the end of the study period (p<0.05).

Beta-hydroxybutyric acid
Arterial levels of beta-hydroxybutyric acid tended to decrease during high-dose GIK treatment and no uptake of beta-hydroxybutyric acid was found after one hour and onwards during the study period (table 3-4 of paper II). Significant inter-group differences in both arterial levels and myocardial uptake of beta-hydroxybutyric acid were observed after the basal state (table 3-4 of paper II).

Glucose
Arterial level of glucose transiently increased during the early part of the study from 6.1 ± 0.5 mmol/L in the basal state to a peak of 8.5 ± 0.5 at 30 minutes (p<0.01) but thereafter gradually decreased so that no significant difference compared with the basal state was found after 1 hour of high-dose GIK treatment (table 3 of paper II). At the end of the study period blood glucose was 7.0 ± 0.4 and for the first time a statistically significant uptake of glucose was recorded (62 ± 18 µmol/min; figure 2). However, inter-group differences after the basal state and changes occurring over time did not reach statistical significance.
Figure 2. Myocardial flux of glucose in high-dose GIK treated and control patients after elective CABG (paper II). 0 denotes the basal state before starting high-dose GIK. * indicates myocardial uptake (p<0.05).

Lactate
Arterial level of lactate transiently increased from 1.22 ± 0.22 mmol/L in the basal state to 1.65 ± 0.11 mmol/L after 1 hour of high-dose GIK treatment (p<0.01) but thereafter decreased to levels comparable with the basal state (table 3 of paper II). A myocardial uptake of lactate was found throughout the study period in the high-dose GIK group but it increased from 23.4 ± 7.2 µmol/min in the basal state to 74.0 ± 12 µmol/min after 1 hour of high-dose GIK treatment (p<0.01) and furthermore inter-group difference was statistically significant after the basal state (figure 3).
Figure 3. Myocardial flux of lactate in high-dose GIK and control patients after elective CABG (paper II). 0 denotes the basal state before starting high-dose GIK. * indicates myocardial uptake (p<0.05). # indicates significant inter group difference after the basal state (p<0.01); ‡ indicates significant change compared with the basal state (p<0.01).

The difference in myocardial lactate uptake between the control group and high-dose GIK group was explained by a higher fractional extraction in high-dose GIK treated patients (p=0.008). In the high-dose GIK group the average fractional extraction of lactate increased from 15.9% in the basal state to 33.8% at 1 hour (p<0.05) and thereafter ranged between 25 - 32%.

Comment: The uptake of glucose and lactate at the end of the study period would have sufficed to explain the entire oxygen consumption assuming that all substrates taken up by the heart were oxidized.

Glutamate
Arterial level of glutamate was 154 ± 11 µmol/L (whole blood) in the basal state and did not change significantly during high-dose GIK (table 3 of paper II). A significant uptake of glutamate ranging from 1.4 ± 1.0 µmol/min to 4.3 ± 2.4 µmol/min was found during high-
dose GIK but did not differ statistically from the basal state or the control group (table 4 of paper II).

Alanine
No differences in arterial levels or myocardial release of alanine compared with the control group or the basal state were observed during high-dose GIK. However, in contrast to the control group release of alanine (whole blood measurements) was not statistically significant in the high-dose GIK group (table 4 of paper II).

Comment: Myocardial release of alanine is a characteristic finding after coronary surgery in non-diabetic patients [45]. Conservative statistical methods may account for the failure to demonstrate a release of alanine in paper II (possible type II error).

Figure 4. The average rate of glucose infusion during high-dose insulin infusion in diabetic patients after elective CABG (paper II) and in different subsets of patients treated with high-dose GIK because of clinical indication (paper IV). Diab = diabetic patients, Ino= patients receiving inotropic drugs, Diab + Ino = diabetic patients receiving inotropic drugs, Neither = patients without diabetes or treatment with inotropic drugs.
EFFECTS OF HIGH-DOSE GIK ON SYSTEMIC GLUCOSE UPTAKE (PAPERS II, IV)

In diabetic patients undergoing elective CABG the average glucose infusion rate in the high-dose GIK group ranged between $4.7 \pm 0.2 \text{ mg/kg BW and minute}$ to $5.1 \pm 0.6 \text{ mg/kg BW and minute}$ during insulin infusion (paper II). The average blood glucose and glucose infusion rate for these patients compared with those who received high-dose GIK because of postoperative heart failure or other clinical indications (paper IV) are given in figures 4 and 5. The average rate of glucose infusion during the first six hours was lower in critically ill diabetic patients ($4.22 \pm 0.15 \text{ mg/kg BW * minute}$) compared with critically ill non-diabetic patients ($4.91 \pm 0.14 \text{ mg/kg BW * minute}$; $p=0.023$). The need for glucose infusion tended to be lower in patients receiving simultaneous treatment with inotropes compared with those receiving only metabolic treatment ($4.69 \pm 0.14$ vs $4.99 \pm 0.23 \text{ mg/kg BW * minute}$; $p=0.23$).

![Figure 5. The average blood glucose during high-dose insulin infusion in diabetic patients after elective CABG (paper II) and in different subsets of patients treated with high-dose GIK because of clinical indication (paper IV). Diab = diabetic patients, Ino= patients receiving inotropic drugs, Diab + Ino = diabetic patients receiving inotropic drugs, Neither = patients without diabetes or treatment with inotropic drugs.](image-url)
HEMODYNAMIC EFFECTS OF HIGH-DOSE GIK IN DIABETICS AFTER ELECTIVE CABG (PAPER II)

In the high-dose GIK group cardiac index increased from 2.1± 0.1 L/min*m² BSA in the basal state to 2.9 ± 0.2 L/min*m² BSA after 4 hours (p<0.05; figure 6). Stroke volume index increased from 28.4 ± 2.0 in the basal state to 36.6 ± 2.1 ml/beat *m² BSA in the high-dose GIK group and a reduction in systemic vascular resistance during the study period was observed in both groups (figure 7). No significant change in left ventricular stroke work index occurred in either group. Inter-group differences reached statistical significance only for cardiac index but a borderline p-value was found for stroke volume index (p=0.06). Further details are given in table 2 of paper II.

**Coronary sinus flow** In the basal state coronary sinus flow was 141 ± 38 and 122 ± 19 ml/min in the control group and high-dose GIK group respectively. No significant change in coronary sinus flow occurred over time in either group and no inter-group difference was found during the study period (table 4 of paper II).

![Graph showing cardiac index changes over time](image)

**Figure 6.** Cardiac index in controls and high-dose GIK treated diabetic patients after elective CABG (paper II). 0 denotes basal state before starting high-dose GIK. * indicates significant change compared with basal state (p<0.01). # indicates inter group difference after the basal state (p=0.017).
HEMODYNAMIC RECOVERY IN PATIENTS TREATED WITH HIGH-DOSE GIK BECAUSE OF POSTOPERATIVE HEART FAILURE (PAPER IV)

The hemodynamic recovery in the 25 patients who had complete Swan-Ganz data and were treated with high-dose GIK because of postoperative heart failure is given in table 2. The results are given in relation to the use of additional inotropic treatment. Details of additional circulatory and metabolic support are presented in table 2 and table 3 of paper IV. An increase of CI and a decrease of SVRI were found regardless of simultaneous treatment with inotropic drugs. The requirement of vasoconstrictors to account for vasodilatation caused by high-dose GIK is shown in table 2 and figures 6 - 7 of paper IV. A significant increase of both CI and LVSWI was found only in patients who received no additional inotropic support.

Figure 7. The systemic vascular resistance index in controls and high-dose GIK treated diabetic patients after elective CABG (paper II). 0 denotes basal state before starting high-dose GIK. * indicates significant change compared with basal state (**p<0.01; ***p<0.001).
<table>
<thead>
<tr>
<th>Hemodynamic state (n=25)</th>
<th>Pre-GIK</th>
<th>8 hours</th>
<th>16 hours</th>
</tr>
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<tbody>
<tr>
<td>CI</td>
<td>1.8±0.1</td>
<td>2.6±0.1***</td>
<td>2.7±0.1***</td>
</tr>
<tr>
<td>LVSWI</td>
<td>25.6±1.3</td>
<td>29.2±1.5</td>
<td>29.9±1.4*</td>
</tr>
<tr>
<td>SVRI</td>
<td>2954±166</td>
<td>1814±89***</td>
<td>1873±68***</td>
</tr>
</tbody>
</table>

Hemodynamic state GIK + Inotropes (n=18)

| CI                      | 1.9±0.1 | 2.6±0.1*** | 2.6±0.1*** |
| LVSWI                   | 25.8±1.6 | 28.4±1.9 | 28.7±1.7 |
| SVRI                    | 2841±208 | 1786±88** | 1816±82** |

Hemodynamic state without inotropes (n=7)

| CI                      | 1.7±0.1 | 3.0±0.2*** | 3.1±0.2***# |
| LVSWI                   | 25.1±2.5 | 31.4±2.3 | 33.2±2.1* |
| SVRI                    | 3243±247 | 1883±235** | 2019±115* |

Table 2. The general hemodynamic recovery in all high-dose GIK treated patients from paper IV with complete Swan-Ganz data (n=25) and related to if they received or did not receive additional inotropic treatment. CI = cardiac index, L/(min*m² BSA); LVSWI = left ventricular stroke work index, gram / (beat*m² BSA); SVRI = systemic vascular resistance index, dynesec / (cm³*m² BSA). *Indicate significant change compared with the state before treatment. * p<0.05, **p<0.01, ***p<0.001. # Indicates statistically significant difference between the groups (p<0.05).

CLINICAL SAFETY ISSUES ASSOCIATED WITH HIGH-DOSE GIK (PAPERS III, IV)

Neurological injury – role of high-dose GIK (paper III)

No evidence or tendencies suggesting an increased risk for neurological complications associated with the use of high-dose GIK or intravenous glutamate were found in the cohort of 775 patients undergoing CABG or combined CABG + valve procedures in whom metabolic interventions over a five-year period gradually replaced inotropic drugs as the first line for treatment of postoperative heart failure (figure 1 of paper III).

Cerebral complications occurred in 5.5% of all patients with signs of postoperative heart failure, in 12.5% of patients treated with inotropes for weaning from CPB, in 10% of patients treated with mechanical circulatory support, in 3.7% of patients treated with high-dose GIK and in 2.6% of patients treated with intravenous glutamate. To address the potential role of postoperative heart failure as a risk factor for neurological injury a model recalculation was
undertaken by entering this variable to the final multivariate model. This yielded a risk model with an OR of 2.7 (95% CI 0.9-8.6; p=0.08) for postoperative heart failure. Repeated recalculations of this model (including postoperative heart failure) by separately entering each of the measures to treat or prevent postoperative heart failure resulted in the following odds ratios with respect to neurological injury: Use of high-dose GIK OR 0.3 (95% CI 0.1-1.7; p=0.16), use of intravenous glutamate OR 0.3 (95% CI 0.1-2.0; p=0.23), inotropes for weaning from CPB OR 1.8 (95% CI 0.3-11.6; p=0.51) and use of mechanical circulatory support OR 2.1 (95% CI 0.2-25.3; p=0.56).

**Figure 8.** The average blood glucose level (solid line; left axis; mmol/L) and the average infusion rate of 30% glucose (dashed line; right axis; mL/hour) in all high-dose GIK treated cases during 1994 (n=89; mean ± SEM). The transverse bar indicates the duration of insulin infusion.

**Blood glucose control with high-dose GIK treatment in clinical practice (paper IV)**

Average blood glucose and glucose infusion rate in the 89 cases treated with high-dose GIK after cardiac surgery because of clinical indication is shown in figure 8. Hypoglycemia (blood glucose < 4 mmol/l) was found in 1.4% of the readings (n=1047). Hypoglycemia occurred at some stage in 11.2% of the patients. The lowest value recorded was 3.1 mmol/L. Moderate hyperglycemia was aimed at in all cases but more pronounced hyperglycemia with blood
glucose > 14.0 mmol/L was found in 2.8% of the readings and was recorded at some stage within the first 16 hours of treatment in 14.6% of cases. The diabetics comprised 18% of the study population but they accounted for 46.2% of the patients with blood glucose > 14.0 mmol/L. Blood glucose control in the high-dose GIK treated diabetic patients compared with 16 routinely managed diabetics undergoing elective CABG with uncomplicated postoperative course is displayed in figure 9.

**Comment:** Blood glucose was recorded 2-3 times during the first hour and thereafter approximately once every hour.

**Figure 9.** Average blood glucose ± SEM during the first 16 postoperative hours in critically ill diabetic patients (n=16) treated with high-dose GIK and diabetic controls consisting of diabetic patients with routine blood glucose control undergoing elective CABG with uncomplicated postoperative course (n=16).

**Potassium control with high-dose GIK treatment in clinical practice (paper IV)**

Average serum-potassium and potassium infusion rate in the 89 cases treated with high-dose GIK after cardiac surgery because of clinical indication in 1994 is presented in figure 10. A s-potassium <3.5 mmol/L was found in 14.9% of the readings (n=987) and at least one episode
of s-potassium <3.5 mmol/L within the first 16 hours of treatment was observed in 67.4% of the patients. The lowest value recorded was 2.6 mmol/L. Hyperkalemia (s-K > 5.0 mmol/L) appeared 2.7% of the readings and was found in 7.9% of the cases at some stage. The highest value recorded was 5.9 mmol/L and usually occurred after stopping the insulin infusion.

Comment: Serum potassium was recorded approximately once every hour. Hypokalemia was frequent, as the target s-potassium during treatment was down towards 3.5 mmol/L to avoid hyperkalemia when the insulin infusion was stopped. The incidence of ventricular tachycardia did not differ significantly between patients with s-potassium recording below 3.5 mmol/L and those without such episodes. No case of ventricular fibrillation was observed. No patient required electrical cardioversion (paper IV).

Figure 10. The average serum potassium level (solid line; left axis; mmol/L; mean ± SEM) and the average infusion rate of potassium (dashed line; right axis; mmol/hour; mean) in all high-dose GIK treated patients from paper IV (n=89). The transverse bar indicates the duration of insulin infusion.

Vasodilatation associated with high-dose GIK treatment in clinical practice (paper IV)
Vasodilatation was common in the patients treated with high-dose GIK after cardiac surgery because of clinical indication in 1994. In 58.4% of the patients noradrenaline or / and angiotensin II was added to the treatment at some stage to counteract vasodilatation (table 2 of paper IV). The use of noradrenaline and angiotensin II in high-dose GIK patients with and without simultaneous PDE III treatment are presented in figures 6 and 7 of paper IV.
In the 25 patients with complete hemodynamic data SVRI had decreased from 2954 ± 166 to 1814 ± 89 dynesec / (cm$^5$*m$^2$ BSA) after 8 hours of high-dose GIK treatment (table 2).

NEUROLOGICAL INJURY AFTER SURGERY FOR ISCHEMIC HEART DISEASE: RISK FACTORS (PAPER III)

Incidence of neurological injury after CABG and CABG + valve procedures
In the cohort of 775 patients (paper III) undergoing CABG or combined CABG + valve procedures in whom metabolic interventions over a five-year period gradually replaced inotropic drugs as the first line for treatment of postoperative heart failure the incidence of neurological injury was 1.8% after isolated CABG and 5.4% after combined CABG + valve procedures.

Comment Retrospective studies generally yield a lower incidence of neurological injuries as compared to prospective studies [46,47]. Furthermore, the reported complications refer to events during hospitalization at our hospital and events after discharge may have been missed [47,48].

Risk factors for neurological injury after CABG and CABG + valve procedures
The patients with neurological injury were on average four years older (69 ± 11 years) compared with those without postoperative cerebral complications. Previous history of cerebrovascular disease was found in one third (table 1 paper III) and signs of advanced peripheral vascular disease or calcification of the ascending aorta on palpation were found in another third of the patients with cerebral complications (table 2 paper III). The patients with neurological injury also had more extensive coronary artery disease as indicated by a higher number of bypasses performed. Furthermore, the patients with neurological injuries had longer aortic cross clamp time and CPB time. Postoperative heart failure and atrial fibrillation were more frequently encountered (table 1 of paper III).

Forward stepwise multiple logistic regression analysis indicated that history of cerebrovascular disease was the most important risk factor for postoperative neurological injury. Advanced age, aortic cross clamp time, the number of bypasses and history of chronic obstructive pulmonary disease also emerged as independent risk factors. Odds ratios and confidence intervals are given in table 3.
OR 95% CI p-value final model Improvement of $\chi^2$

<p>| | | | | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>History of cerebrovascular</td>
<td>11.5</td>
<td>3.2-41.7</td>
<td>0.0002</td>
<td>8.23</td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Aortic cross-clamp time</td>
<td>1.03</td>
<td>1.01-1.06</td>
<td>0.002</td>
<td>10.43</td>
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<td>Age ≥ 70 years</td>
<td>4.6</td>
<td>1.4-15.2</td>
<td>0.011</td>
<td>6.17</td>
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<tr>
<td>History of COPD</td>
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<td>1.5-28.4</td>
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<td>4.31</td>
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</tr>
<tr>
<td>Number of bypasses</td>
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<td>1.1-2.4</td>
<td>0.021</td>
<td>5.52</td>
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<td>Model</td>
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<td></td>
<td>0.0000018</td>
<td>34.66</td>
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</tr>
</tbody>
</table>

**Table 3.** Multivariate forward stepwise logistic regression analysis of risk factors for neurological injury after CABG and CABG + valve procedures. OR = odds ratio. CI = confidence interval. Number of bypasses indicates number of distal coronary anastomoses.

**Comment:** The limited number of events explain the wide confidence intervals obtained and, hence, odds ratios should be interpreted cautiously. Because of these circumstances cross-validation of the final model was undertaken. Of the variables in the final model chronic obstructive pulmonary disease and the number of bypasses did not resist cross-validation.

**DIABETES AND NEUROLOGICAL OUTCOME AFTER CARDIAC SURGERY (PAPERS III, V)**

In paper III comprising both CABG and combined valve + CABG procedures the incidence of neurological injury was 3.5% in diabetic patients and 1.8% in non-diabetic patients (p=0.23). However, diabetes did not emerge as an independent risk factor in the multivariate analysis (table 3). In paper V comprising the institutional database of isolated CABG procedures from 1995-1999 (n=2779) the incidence of stroke was 4.3% in diabetic patients and 1.7% in non-diabetic patients (p<0.001).

**Comment:** In paper III only patients with oral anti-diabetic agents or insulin were registered as diabetics whereas in paper V all patients with known diabetes, including those with dietary treatment, were registered as diabetics. In paper III patients with both permanent and transient neurological injuries were classified as neurological injury and in and paper V similar criteria were used to register cases in the database as stroke.
EARLY POSTOPERATIVE OUTCOME AND LONG-TERM SURVIVAL IN DIABETICS AND NON-DIABETICS AFTER ISOLATED CABG (PAPER V)

Patient characteristics
The diabetic group was characterized by lower mean age (64 ± 9 vs 66 ± 9 years; p<0.001), higher BMI (28 ± 4 vs 26 ± 4 kg/m²; p<0.001), higher Higgins score (3.0 ± 2.6 vs 2.1 ± 2.5; p<0.001) and a higher proportion of patients with female gender (28% vs 20%; p<0.001), hypertension (49% vs 38%; p<0.001), triple-vessel disease (78% vs. 69%; p<0.001) and unstable angina (53% vs 48%; p=0.03). Among diabetics there was also a higher need for intravenous nitrates (27.5 % vs 21.6%; p= 0.004) and recently sustained myocardial infarct (<3 weeks) was more common (21.5% vs 17.4%; p=0.04). Left-main stenosis was less frequently encountered in the diabetic patients (16.4% vs 21.1%; p=0.02). Further details are given in table 1 of paper V.

Intraoperative characteristics
The diabetic group was characterized by a higher number of distal anastomoses (3.7 ± 1.1 vs 3.6 ± 1.2; p=0.004), longer aortic cross clamp time (47.1 ± 17.3 vs 43.7 ± 17.6 minutes; p<0.001) and CPB time (86.7 ± 28.4 vs. 81.0 ± 30.6 minutes; p<0.001). No significant difference was found in the use of inotropes but high-dose GIK was more frequently used in diabetic patients (15.4% vs. 9.2%; p<0.001). Further details are given in table 2 of paper V.

Postoperative outcome
The diabetic group had a longer ICU- and hospital stays. Hemotransfusions were more frequently used in the diabetic group. Stroke, renal failure, use of dialysis, wound infections and reoperations for mediastinitis were more often observed in the diabetic patients. Details are given in table 4.

Univariate analysis of diabetes as a risk factor for major complications is given in table 5. Inter-group differences regarding mortality and major complications depending on the type of the diabetic treatment on admission is given in figure 14 page 48.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetics N=540</th>
<th>Non-Diabetics N=2239</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay (days)</td>
<td>1.8 ± 2.9</td>
<td>1.6 ± 2.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Mechanical ventilation time (hours)</td>
<td>18.6 ± 60.2</td>
<td>14.4 ± 41.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Mechanical ventilation&gt;5 days (%)</td>
<td>2.6</td>
<td>1.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Use of inotropes in the ICU (%)</td>
<td>13.9</td>
<td>9.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Use of high-dose GIK in the ICU</td>
<td>17.2</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of iv glutamate in the ICU (%)</td>
<td>3.9</td>
<td>3.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Perioperative myocardial infarct (%)</td>
<td>0.9</td>
<td>1.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>3.9</td>
<td>2.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Dialysis (%)</td>
<td>0.9</td>
<td>0.2</td>
<td>0.03</td>
</tr>
<tr>
<td>MOF (%)</td>
<td>0.7</td>
<td>0.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Postoperative stroke (%)</td>
<td>4.3</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reoperation for bleeding (%)</td>
<td>3.0</td>
<td>3.0</td>
<td>0.99</td>
</tr>
<tr>
<td>Hemotransfusion (%)</td>
<td>46.0</td>
<td>37.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Units of erythrocytes/patient</td>
<td>1.6 ± 2.8</td>
<td>1.5 ± 3.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Reoperation for mediastinitis (%)</td>
<td>1.3</td>
<td>0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superficial or deep sternal wound infection (%)</td>
<td>4.3</td>
<td>1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>7.9 ± 4.3</td>
<td>7.3 ± 3.1</td>
<td>0.002</td>
</tr>
<tr>
<td>30-day mortality (%)</td>
<td>2.6</td>
<td>1.6</td>
<td>0.15</td>
</tr>
<tr>
<td>6-month mortality (%)</td>
<td>4.1</td>
<td>2.8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**Table 4.** Postoperative outcome. ICU = intensive care unit. GIK = glucose-insulin-potassium. Renal failure = postoperative s-creatinine > 170 µmol/L regardless of preoperative value. Dialysis = postoperative need for dialysis that was not present on admission. Hemotransfusion = transfusion of erythrocytes, MOF = multi-organ failure.

**Infectious complications**

The diabetic patients had a higher incidence of reoperations for mediastinitis (1.3% vs. 0.2%; p<0.001). The incidence of deep and superficial sternal wound infections was also higher in the diabetic group (4.3% vs. 1.5%; p<0.001).

**Renal complications**

Preoperative dialysis was observed in 0.6% of the diabetics and 0.4% of the non-diabetics. Need for postoperative dialysis not present preoperatively was higher in the diabetic group (0.9% vs. 0.2%; p=0.03). A postoperative s-creatinine exceeding 170 µmol/L was observed in 3.9% of the diabetics compared with 2.2% of the non-diabetics (p=0.03).
<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>1.6</td>
<td>0.9 - 3.0</td>
<td>0.13</td>
<td>2779</td>
</tr>
<tr>
<td>Crude mortality during follow-up</td>
<td>1.9</td>
<td>1.4 - 2.6</td>
<td>0.0002</td>
<td>2779</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.6</td>
<td>1.6 - 4.5</td>
<td>0.0003</td>
<td>2773</td>
</tr>
<tr>
<td>Dialysis</td>
<td>4.2</td>
<td>1.2 - 14.4</td>
<td>0.03</td>
<td>2769</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.8</td>
<td>1.1 - 3.0</td>
<td>0.03</td>
<td>2771</td>
</tr>
<tr>
<td>Sternal wound infection</td>
<td>2.9</td>
<td>1.7 - 4.9</td>
<td>0.00012</td>
<td>2773</td>
</tr>
<tr>
<td>Perioperative myocardial infarct</td>
<td>0.6</td>
<td>0.2 - 1.5</td>
<td>0.26</td>
<td>2743</td>
</tr>
<tr>
<td>Hemotransfusion</td>
<td>1.4</td>
<td>1.1 - 1.8</td>
<td>0.005</td>
<td>1826</td>
</tr>
<tr>
<td>Use of inotropes in the ICU</td>
<td>1.5</td>
<td>1.1 - 2.0</td>
<td>0.0005</td>
<td>2765</td>
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<tr>
<td>Sepsis</td>
<td>0.7</td>
<td>0.2 - 2.4</td>
<td>0.55</td>
<td>2773</td>
</tr>
</tbody>
</table>

Table 5. Univariate analysis of diabetes as a risk factor for postoperative events. OR = odds ratio. CI = confidence interval. Dialysis = need for dialysis not present before surgery. Renal failure = postoperative s-creatinine > 170 μmol/L. Perioperative myocardial infarct = fulfilling both Q wave and enzyme criteria as given in paper V. Hemotransfusion = transfusion of erythrocytes. n= number of observations.

Neurological outcome

In paper V the total incidence of stroke was 4.3% in the diabetic group and 1.7% in the non-diabetic group (p<0.001). For further details about postoperative neurological injury in diabetics see page 35.

Comment: As the complications presented only refer to in-hospital events the incidence of some complications, such as neurological injury, and in particular wound infections may have been underestimated [49]. A sufficiently broad set of validated and complete data was not available to reliably address the role of diabetes as an independent risk factor for morbidity and mortality.

Mortality

Thirty-day mortality was 2.6% in the diabetic group and did not differ significantly from the 1.6% mortality observed in non-diabetics. The primary cause of early mortality was cardiac in 41.7% in the diabetic patients and 67.6% of the non-diabetic patients. Neurological injury was the cause of the early death in 33.3% of the diabetic patients compared with 14.7% in the non-diabetic patients. Median follow-up was 32 months and ranged from 3 - 63 months. The crude mortality during this period was 10.2% in the diabetic group compared with 5.6% in the non-diabetic group (p<0.001). Cumulative five-year survival (Kaplan-Meier) was 84.4% in diabetics and 91.3% in non-diabetics (p<0.001; figure 11). The cumulative 5-year-survival depending on type of diabetes treatment on admission is shown in figure 15 on page 50.
Patients with insulin treated diabetes had a poorer long-term survival than those on oral anti-diabetic agents or diet.

In the diabetic population the use of LITA was associated with a 2.3% 30-day mortality compared with 8.0% mortality if LITA was not used (p=0.13). At six months the mortality associated with LITA use in diabetics was 3.9% vs. 12.0% if LITA was not used (p=0.07).

Comment: In the 775 patients from paper III in whom traditional treatment of postoperative heart failure was replaced by metabolic interventions 30-day mortality was 1.1% in diabetic patients (n=85) and 0.9% in non-diabetic patients (n=690). The results on the use of LITA have to be interpreted with regard to the limited number of diabetics (n=25) that did not receive a LITA graft.

Figure 11. Cumulative 5-year survival (Kaplan-Meier) in diabetic and non-diabetic patients after CABG.
GENERAL DISCUSSION

Different aspects concerning diabetics undergoing CABG and treatment of both diabetics and non-diabetics with high-dose GIK have been studied. Methodological issues have been commented in the methods section. The purpose of the general discussion is to shed further light on clinical issues associated with diabetics undergoing coronary surgery with special reference to cardiac metabolism and experience of high-dose GIK.

The metabolic state of the heart in type II diabetics patients after elective coronary surgery

The knowledge about myocardial metabolism in human diabetic hearts is limited [50,51] and to our knowledge this is the first study on myocardial uptake and release of key metabolic substrates in diabetics undergoing cardiac surgery.

Type II diabetic patients were studied as this group of patients accounts for an increasing proportion of patients undergoing CABG. Perioperatively the patients were managed according to a clinical protocol employing insulin infusion if necessary to achieve stable blood glucose below 10 mmol/L. To achieve stable study conditions the patients were provided a deeper level of sedation, analgesia and relaxation than is routinely used in our clinical practice postoperatively. In spite of these factors, which may have attenuated neuroendocrine stress response and contributed to satisfactory blood glucose control, FFA accounted for the major energy supply whereas uptake of carbohydrates was restricted. These observations are in agreement with those found in non-diabetic patients studied under similar conditions [16,45,52] with the exception that a myocardial uptake of lactate seems to be more restricted in diabetics. No uptake of lactate was detected at any time during the study period. However, in paper II the diabetic patients in the high-dose GIK group had a significant uptake of lactate already in the basal state.

To explain these discrepancies - apart from methodological aspects discussed in the methods section - one has to consider that myocardial uptake or release of lactate is dependent on several factors such as arterial lactate levels, influence of ischemia and factors that are known to affect pyruvate dehydrogenase (PDH) activity [53-55]. The reliance on FFA and beta-hydroxybutyric acid, which are known to inhibit PDH at the acetyl-CoA level, could partly explain the findings in paper I [56]. The diabetic patients in the high-dose GIK group (paper
II) were probably metabolically better controlled in the basal state as suggested by somewhat lower BMI (associated with less insulin resistance), lower levels of FFA and blood glucose. Conversely, in studies performed more than a decade ago in non-diabetic patients sustaining more pronounced influence of neuroendocrine stress as suggested by higher levels of FFA and blood glucose we failed to detect myocardial uptake of lactate several hours after CABG [17]. Thus, various degrees of neuroendocrine stress and insulin resistance seems to play a role for the degree of metabolic derangement observed.

**Figure 12.** The relationship between arterial levels of beta-hydroxybutyric acid and arterial-coronary sinus differences of beta-hydroxybutyric acid obtained during the whole study period in type II diabetics after elective CABG (paper I). $r =$ Spearman rank correlation coefficient

In diabetic patients after CABG the relationship between arterial levels of FFA and myocardial uptake normally found was not identified during the study period [17]. Furthermore, in contrast to what has been found in non-diabetic patients [17,52] beta-hydroxybutyric acid contributed significantly to myocardial energy uptake in spite of only low to moderately elevated levels. The high fractional extraction rates observed suggest that the diabetic heart has an enhanced capacity or need to utilize beta-hydroxybutyric acid. Potentially the beta-hydroxybutyric acid taken up could have accounted for approximately 10-
15% of myocardial oxygen consumption during the study period. Certainly, the true role of ketone bodies for myocardial energy production would have been better estimated if we would have had aceto-acetate analyses available.

In agreement with previous data from non-diabetic patients after coronary surgery a high extraction rate of glutamate was also observed [17,57]. Glutamate is important for the intermediary metabolism of the cardiomyocytes and it has been claimed that this role is enhanced in association with ischemia and neuro-endocrine stress [53]. In diabetic patients (figure 1) the myocardial extraction rate of glutamate from plasma was comparable with that of beta-hydroxybutyric acid. Beta-hydroxybutyric acid is known to be an effective substrate for mitochondrial respiration in the heart [58] and considering the suggested role of glutamate for intermediary metabolism, it is conceivable that uptake of these substrates represents adaptive mechanisms to an unfavorable metabolic state for the post-ischemic heart.

**Figure 13.** The relationship between arterial levels and arterial-coronary sinus differences of plasma glutamate obtained during the whole study period in type II diabetics after elective CABG (paper I); r= Spearman rank correlation coefficient.
High-dose GIK can modulate cardiac metabolism in type II diabetic patients after CABG

In non-diabetic patients it has been demonstrated that GIK can enhance myocardial uptake of carbohydrate substrates but due to neuroendocrine stress high-doses of insulin are required. Available data suggests that insulin doses up to 1 IU/kg body weight and hour may be required to achieve maximal systemic glucose uptake and only such doses have been documented to cause a shift in myocardial substrate uptake from FFA to carbohydrate substrates [16,24,52,53]. This dosage was used in the current study and resulted in a 150-fold increase of plasma insulin to approximately 14 000 pmol/L.

High-dose GIK enhanced myocardial uptake of carbohydrate substrates at the expense of FFA and beta-hydroxybutyric acid. The effect on myocardial glucose uptake was less evident as that on myocardial lactate uptake. Apart from methodological aspects, an attenuated effect of GIK on myocardial glucose uptake in diabetic patients or a predominant direct or indirect activation of PDH behind the action of insulin (discussed below) during these circumstances could explain this discrepancy. However, despite conservative statistical assessment a significant uptake of glucose was observed at the end of the study period in the high-dose GIK group. At this stage the uptake of glucose and lactate would have sufficed to explain the entire oxygen consumption if all substrates taken up by the heart were metabolized.

The methods employed do not give direct insight into mechanisms behind the action of high-dose GIK on myocardial substrate uptake. Thus, the interpretations are dependent on available knowledge about metabolic pathways and interactions.

Normally myocardial uptake of carbohydrate substrates is not insulin dependent albeit facilitated by insulin [59]. In our study high-dose GIK caused a marked reduction in arterial FFA and beta-hydroxybutyric acid, which indirectly may have enhanced uptake of carbohydrates and the activity of pyruvate dehydrogenase [53,54]. The interpretation of lactate exchange is aided by the restricted metabolic fate of lactate and the fact that myocardial lactate uptake normally is closely related to arterial levels in the non-ischemic myocardium [60]. After uptake by the cardiomyocytes lactate is converted to pyruvate and, thereafter, either oxidized in the mitochondria or transaminated to alanine [60]. Therefore, the observed impact on myocardial lactate uptake without a concomitant increase of alanine release is compatible with enhanced pyruvate dehydrogenase activity. Furthermore, insulin
can directly enhance uptake of carbohydrates by stimulating glucose transporters and possibly by intracellular stimulation of pyruvate dehydrogenase [54,55].

These results could have clinical implications as they show that myocardial substrate uptake can be modified in the desired direction even in diabetic patients after cardiac surgery. Energy derived from carbohydrates with a simultaneous reduction of FFA levels not only provides a better oxygen economy but has also been claimed to be important for the preservation of mechanical function, structure, and ionic balance in association with myocardial ischemia [53,54,61].

**Systemic glucose uptake induced by high-dose GIK**

Previous studies in non-diabetic patients after elective CABG have demonstrated a severe state of insulin resistance [62,63]. To some extent the consequences of insulin resistance on systemic glucose uptake can be overcome with the aid of supraphysiological insulin doses but compared with preoperative state systemic glucose uptake is markedly reduced [16,24]. The high-dose GIK used in the present investigation is a clinical application of hyperinsulinemic glucose clamps used for studies on systemic glucose uptake. As the results of the present investigation are unique and blood glucose control was reasonably acceptable we believe that the data on systemic glucose uptake deserve comment. In general glucose infusion rates tended to be lower and blood glucose levels higher in patients with diabetes and those treated with inotropic drugs (figures 4-5; page 26-27). However, in critically ill patients only minor, albeit statistically significant, differences in the amount of glucose that could be provided were found between diabetic and non-diabetic patients. This illustrates the pseudo-diabetic state associated with stress metabolism.

These observations from paper II and IV could have clinical implications also for general intensive care as they show that substantial amounts of energy in the form of glucose can be provided to diabetic and critically ill patients with maintenance of acceptable blood glucose control. The need for large doses of insulin to achieve this effect, at least in diabetics, was illustrated by the fact that one arm of the study in paper II originally designed to investigate the impact of a GIK regime employing insulin doses of 0.08 IU/kg BW and hour [33] had to be abandoned with the first patient because of unacceptable blood glucose control.
Beneficial hemodynamic impact of high-dose GIK

The beneficial hemodynamic impact of GIK is well documented after cardiac surgery. Although the present study was not designed to primarily investigate hemodynamic effects it is evident that high-dose GIK was associated with beneficial effects on cardiac output both in the prospective and retrospective analyses (paper II, IV). In agreement with previous studies using supraphysiological insulin doses this was mainly related to vasodilation and reduction of SVRI (paper II). Recent data from non-diabetic patients suggest that vasodilation alone does not explain the improvement in cardiac output [64].

Obviously, the state of the myocardium when treatment is instituted is of importance for the impact of GIK. In critically ill patients in whom myocardial recovery is an important issue also an increase of LVSWI was observed (paper IV). The interpretations have to be made cautiously due to the limited number of patients, the retrospective character of the study and that hemodynamic measurements and calculations were made in the clinical setting. Simultaneous treatment with inotropes and additional metabolic treatment with glutamate was given to a substantial proportion of the patients. However, the improvement of hemodynamic state was apparently not dependent on additional inotropic treatment. The patients treated with inotropes had a poorer hemodynamic recovery and an increase of LVSWI was recorded only in patients not receiving additional inotropic drugs (table 2). Also, these results are consistent with a randomized trial demonstrating a substantially lower need for inotropic drugs and a markedly better hemodynamic recovery in GIK treated patients requiring IABP support after cardiac surgery compared with conventionally treated controls [33].

High-dose GIK can be safely used in clinical practice

Extremely high-doses of insulin have been used in animal experimental models with promising results regarding preservation of myocardial viability and recovery of hemodynamic performance after severe ischemia [65,66]. However, such regimes have to our knowledge not been implemented in clinical practice, presumably due to fear of pronounced vasodilatation and electrolyte shifts. In light of this, we have developed a high-dose GIK regime that should provide maximal metabolic effects in most patients, without having the pronounced vasodilative properties of the "hemodynamic doses" of insulin described in previous studies [24,52,67]. Due to encouraging early experience with metabolic support for treatment of postoperative heart failure [67] this regime has been incorporated into the therapeutic arsenal of most anesthesiologists and surgeons at our institution.
In the one-year series presented in paper IV high-dose GIK was used in just over 10% of the cases, mainly to treat or prevent cardiac failure on weaning from CPB and in the early postoperative setting. The decisions to use high-dose GIK were taken by the individual anesthetists and surgeons responsible for respective patient. In the ICU the high-dose GIK treatment was managed and supervised by a nurse. A detailed review of high-dose GIK utilization under these circumstances has not been performed previously.

Apart from blood glucose control, vasodilatation and s-potassium control are central issues when using high-dose GIK. Vasodilatation was common but did not present major problems. In fact, nitroprusside was used for afterload reduction in half of the patients at the early stage of treatment. As the treatment proceeded, some degree of vasodilation developed in most patients and nitroprusside was discontinued. A vasoconstrictor (angiotensin II or noradrenaline) was instituted in just over half of the GIK treated patients at some stage to prevent hypotension. The need for vasoconstrictors was higher in patients treated with PDE III inhibitors (figures 6-7 of paper IV). However, no case of refractory vasodilatation was encountered.

Blood glucose management in general was satisfactory, stable blood glucose levels were routine and we found no case where glucose infusion was prematurely stopped before the effect of insulin had subsided. Episodes of hypoglycemia were infrequent and mild. Hyperglycemia was common mainly due to the target values set by the protocol, but also due to human factors. Thus, the results from paper IV provided room for adjustment of the target blood glucose and information of value for educational purposes. With the insulin doses employed blood glucose level in the short perspective is influenced only by the rate of glucose infusion. Hence, high-dose GIK provides a means for strict blood glucose control, which could have clinical implications with regard to efforts to reduce the incidence of wound infection and the extent of cerebral injury in stroke [32,68].

Potassium was infused separately but s-potassium was allowed to decrease to 3.5 mmol/L to avoid rebound hyperkalemia when insulin infusion was stopped (figure 10; page 33). As a consequence hypokalemia was common but no episode of clinically significant hyperkalemia was encountered. As hyperkalemia did not pose any problems there seems to be room for minor modification of the protocol also with respect to s-potassium control.
Over the last decade this regime has been used in approximately 700 patients at our institution without any serious adverse effects. However, detailed review of therapies like the one employed here can contribute to improve protocols and be used for educational purposes. Overall paper IV demonstrated that GIK regimes employing doses of insulin sufficient to achieve maximal systemic glucose uptake after cardiac surgery could be safely employed in clinical practice.

**High-dose GIK did not increase the risk for neurological injury**

In the practice of our research group metabolic interventions with high-dose GIK and intravenous glutamate over a five-year period gradually replaced inotropic drugs as the first line for treatment of postoperative heart failure (figure 1 of paper III) [69]. Both glutamate and glucose have been claimed to play a role in the development of neurological injury [70-72]. Hence, surveillance of this treatment with regard to neurological outcome was considered mandatory. The initial experience was registered in a database, which provided us with the opportunity to analyze a comparatively broad set of data (appendix paper III), including traditional and alternative measures for treatment and prevention of postoperative heart failure, as risk factors for cerebral complications. No evidence or tendencies suggesting an increased risk for neurological complications associated with the use of high-dose GIK or intravenous glutamate were found. Further surveillance of these new treatments is warranted but currently it seems that GIK can be safely used in cardiac surgery with regard to neurological outcome provided that blood glucose management is adequate.

**Neurological injury after surgery for ischemic heart disease – risk factors and role of diabetes**

Due to shifts in the population undergoing cardiac surgery neurological complication has become one of the most important issues to address in cardiac surgery [69,73]. Diabetic patients have a markedly increased risk of sustaining neurological complications in association with cardiac surgery [9,25,27]. However, the role of diabetes per se is under debate. Of the risk factors that have been identified advanced age, history of cerebrovascular disease and combined coronary and valve operations are those most consistently associated with stroke [47,74]. Although neurological injury was encountered more frequently in diabetic patients diabetes did not emerge as an independent risk factor in the multivariate analysis of paper III. In
agreement with previous studies history of cerebrovascular disease emerged as the most important independent risk factor for postoperative neurological injury [48,73-76]. Furthermore, advanced age, prolonged aortic cross clamp time, chronic obstructive pulmonary disease (COPD) and number of bypasses emerged as independent risk factors in the multivariable analysis. Cross-validation of the model supported the validity of these risk factors with the exception of COPD and the number of bypasses. The overall incidence of neurological complications did not differ markedly from the previous studies [25,26,77,78].

It is conceivable that history of cerebrovascular disease, advanced age, aortic cross clamp time and extent of coronary disease all to some extent constitute markers for advanced atherosclerotic disease. As the atherosclerotic process is known to be accelerated in diabetics an explanation for the increased risk of neurological injury in diabetics after cardiac surgery is given [28,29].

![Figure 14.](image)

**Figure 14.** 30-day mortality and the incidence of stroke, renal failure and sternal wound infections after CABG in non-diabetics (control n=2239) and diabetic patients depending on diabetic therapy (diet n=97; tablet n=205; insulin n=238). * indicate statistically significant difference within the diabetic cohort of patients depending on anti-diabetic therapy on admission.
Although the true impact of diabetes per se on the incidence of stroke remains to be clarified it is well known that hyperglycemia in general is associated with a poorer prognosis in association with stroke [71,72]. However, it has not been established if this represents a consequence of a more severe clinical condition or if hyperglycemia per se contributes to the poorer outcome by aggravating neurological injury [72].

**Acceptable short-term mortality but increased postoperative morbidity and poorer long-term survival in diabetic patients after CABG**

Diabetics account for an increasing proportion of the patients undergoing CABG [11]. In paper V 19.4% of the patients were diabetics when all patients with an established diagnosis and active treatment ranging from diet to insulin were included. The patient characteristics in general agree with previous studies showing a lower mean age and a higher proportion of patients with female gender, hypertension and triple-vessel disease [8,9]. The age distribution and the prevalence of triple-vessel is consistent with studies demonstrating a more rapidly evolving atherosclerotic progress in diabetics [28,29].

It is well known that diabetic patients have a higher mortality and morbidity in association with CABG but the role of diabetes per se is controversial. Some investigators have claimed associated risk factors to explain the differences in postoperative mortality [27] whereas others have found diabetes to be an independent risk factor for mortality even after adjustment for confounding factors [9,25,26]. Apart from studies that have either included a limited number of patients [79] or matched surgical populations [77,80] an increased early postoperative mortality has been reported in diabetic patients [9,25-27].

In contrast to most studies we found no significant difference in postoperative 30-day mortality between diabetic and non-diabetic patients. However, in agreement with previous studies we found a less favorable late outcome in diabetic patients with a 1.9 fold increased risk of late mortality during the follow up compared with non-diabetics (table 5 and figure 11; pages 38 - 39). Patients with insulin-treated diabetes in particular seemed to account for the difference in long-term outcome between diabetics and non-diabetics (figure 15). Also, consistent with previous studies an increased risk of postoperative morbidity particularly with regard to renal failure, neurological injury and wound infections was observed [25]. The risk for postoperative renal failure and wound infections was influenced by the type of diabetic treatment required on admission (figure 14) [26,77,78,81].
In general the incidence of complications was on level with that reported in the literature but the short-term mortality compares favorably with most previous studies (table 6; page 55) [9,25,26,79,80,82-85]. This difference does not seem to be explained by the case mix. The mean age and also the proportion of patients with unstable angina was higher than in most previous studies [9,25,26,82,85,86]. However, the results regarding unstable angina have to be interpreted with regard to a shift towards a larger proportion of Braunwald Class II C patients being operated during recent years, particularly after the FRISC II trial [87]. In a similar large scale Swedish study the thirty-day mortality rate was more than two-fold higher [25]. Our results do not provide any clear explanations to this discrepancy but the latter study was done approximately five years earlier, included a higher proportion of redo-procedures and patients with previous history of cerebrovascular disease. Also, differences in perioperative management deserve consideration.
The use of arterial grafts in diabetics was comparatively high in our study [25,26]. The use of LITA is associated with reduced long-term mortality and possibly a reduced operative mortality [88,89]. In our study non-use of LITA was associated with a trend suggesting that these premises also apply to diabetic patients but the number of patients were too few to provide a clear cut answer. However, available data in the literature suggest that the impact of LITA for long-term survival is similar in diabetics and non-diabetics although the use of LITA does not negate the adverse effect of diabetes on long-term survival [90].

The perioperative management of the patients in paper V differed from traditional care by the use of metabolic interventions with high-dose GIK and glutamate for treatment and prevention of postoperative heart failure [67,91]. This provides an explanation to the comparatively low use of inotropic agents intraoperatively. To what extent these characteristics of perioperative care contributed to the overall results remains to be established. The low 30-day mortality rate in diabetics (1.1%) in the cohort of patients (paper III) in whom traditional treatment with inotropic drugs was replaced by metabolic interventions add further incentive to explore the potential benefits of metabolic strategies in diabetic patients undergoing cardiac surgery (table 6).

Although the role of metabolic interventions remains to be established it is noteworthy that other investigators who have used insulin or GIK for metabolic control in diabetics undergoing CABG have also presented favorable results [77,92]. Furthermore, in diabetics with acute myocardial infarction insulin infusions have been shown to reduce late mortality [93]. The latter study is particularly interesting as it suggests that optimization of metabolic control in the acute phase and during follow up can enhance long-term survival in diabetic patients. Considering the impaired long-term survival in diabetics after CABG similar approaches deserve evaluation after cardiac surgery.

**Concluding remarks**

This investigation has been carried out to identify metabolic states accessible to intervention and to update the current results on outcome in diabetics after coronary surgery.

There is evidence suggesting that diabetic patients have been a neglected group in cardiovascular medicine. Advances in the treatment of coronary artery disease such as the
<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetics</th>
<th>Non-diabetics</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verska, 1975</td>
<td>9% (n=35)</td>
<td>4% (n=77)</td>
<td></td>
</tr>
<tr>
<td>Johnson, 1982</td>
<td>7.7% (n=261)</td>
<td>3.1% (n=1931)</td>
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</tr>
<tr>
<td>Salomon, 1983</td>
<td>5.1% (n=250)*</td>
<td>2.5% (n=3295)</td>
<td>*diet-oral</td>
</tr>
<tr>
<td></td>
<td>4.5% (n=162)#</td>
<td></td>
<td>#insulin</td>
</tr>
<tr>
<td>Lawrie, 1986</td>
<td>7.1% (n=212)</td>
<td>4.5% (n=1222)</td>
<td></td>
</tr>
<tr>
<td>Clement, 1988</td>
<td>1.8% (n=396)</td>
<td>2.5% (n=396)</td>
<td>matched controls</td>
</tr>
<tr>
<td>Herlitz, 1996</td>
<td>6.7% (n=268)</td>
<td>3.0% (n=1859)</td>
<td>All diabetic patients undergoing CABG from western Sweden 1988-91</td>
</tr>
<tr>
<td>Risum, 1996</td>
<td>2.2% (n=45)</td>
<td>3.1% (n=990)</td>
<td>small diabetic sample</td>
</tr>
<tr>
<td>Cohen, 1998</td>
<td>5.0% (n=1034)</td>
<td>2.5% (n=3350)</td>
<td></td>
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<tr>
<td>Weintraub, 1999</td>
<td>4.6% (n=2088)</td>
<td></td>
<td>first CABG Hospital death</td>
</tr>
<tr>
<td>Corbineau, 1999</td>
<td>6.9% (n=188)</td>
<td>4.0% (n=2273)</td>
<td></td>
</tr>
<tr>
<td>Thourani, 1999</td>
<td>3.9% (n=2278)</td>
<td>1.6% (n=9920)</td>
<td></td>
</tr>
<tr>
<td>Svedjeholm, 2001§</td>
<td>1.1% (n=85)</td>
<td>0.9% (n=690)</td>
<td>metabolic strategy small diabetic sample</td>
</tr>
<tr>
<td>Szabó, 2001</td>
<td>2.6% (n=540)</td>
<td>1.6% (n=2239)</td>
<td>All diabetic patients undergoing CABG from southeast Sweden 1995-99</td>
</tr>
</tbody>
</table>

Table 6. Summary of comparative studies on diabetic and non-diabetic populations undergoing coronary surgery. §= CABG including valve procedures. Postoperative 30-day mortality is given if not denoted otherwise. The numbers of patients included are given within brackets.

Introduction beta-blockers, ACE-inhibitors and platelet inhibitors have not been fully utilized in the diabetic population due to concerns that they might deteriorate glucose control and mask hypoglycemia or that diabetic patients would not benefit from them. On the contrary, subsequent experience have showed that not only do diabetic patients benefit from these approaches but that they, in fact, may benefit more than non-diabetic patients [94-97]. There is reason to believe that there is potential for similar advances in the management of diabetic patients in association with and after coronary surgery.

The results of our study have demonstrated that there is scope for modulation of cardiac metabolism and that GIK regimes employing supraphysiological doses of insulin can achieve
these objectives. In cardiological practice recent studies have showed a survival benefit associated with GIK in acute myocardial infarction and several indices of improved outcome with GIK after cardiac surgery have also been reported [19,20,33,67,92,98-101]. Strict postoperative blood glucose control reduces the incidence of postoperative infections [32] and could potentially alleviate the consequences of neurological injury [68]. Also, the role of preoperative blood glucose control and potential benefits of improved preoperative metabolic control with insulin may deserve exploration.

Efforts to reduce the incidence and consequences of neurological injury after cardiac surgery are of paramount importance not only in diabetic patients [73]. The more extensive coronary artery disease usually found in diabetics may require a more aggressive approach to achieve complete revascularization and more aggressive anti-platelet treatment to prevent graft failure. Furthermore, investigations are warranted to identify optimal treatment to slow down the atherosclerotic process in diabetics. With regard to long-term outcome, it has been found that extended metabolic control with intense insulin treatment after myocardial infarction has beneficial effects on long-term survival in diabetics [93]. A similar approach in cardiac surgery deserves evaluation. Pharmacological modulation of metabolism besides insulin could also play a role for such efforts.

To conclude, this study demonstrates a potential rationale for modulation of cardiac metabolism in type II diabetics after CABG and that this can be achieved with high-dose GIK. It was found that diabetic patients can undergo CABG with an acceptable mortality risk comparable to that found in non-diabetic patients. The role of the employed metabolic strategies deserves evaluation. Also, further efforts are warranted to address early postoperative morbidity and late-outcome and they should have high priority as diabetic patients are accounting for an increasing proportion of the patients undergoing CABG. Such endeavors may require increased cooperation with diabetologists and cardiologists. The present investigation has been carried out as an attempt to contribute to advances in that direction.
SUMMARY

- The diabetic heart was characterized by predominant extraction of FFA and no uptake of carbohydrates early after CABG
- A high fractional extraction rate of beta-hydroxybutyric acid and glutamate was observed in the diabetic heart early after CABG
- The employed dose of insulin (1 IU / kg BW and hour) was sufficient to modulate cardiac substrate uptake in the desired direction
- High-dose GIK induced a marked reduction in the levels of FFA and beta-hydroxybutyric acid
- High-dose GIK induced a shift towards myocardial uptake of carbohydrates, mainly lactate, at the expense of FFA and beta-hydroxybutyric acid
- High-dose GIK induced a substantial systemic glucose uptake even in critically ill patients but the need for glucose tended to be lower in diabetics and in patients treated with inotropes
- In diabetics undergoing elective CABG high-dose GIK was associated with an increase of CI mainly related to a decrease of SVRI
- In patients treated with high-dose GIK because of postoperative heart failure hemodynamic improvement was not dependent on additional use of inotropic drugs.
- Provided careful monitoring the high-dose GIK regime employed can be safely used in clinical practice and deserves further evaluation in the treatment of postoperative heart failure
- High-dose GIK was associated with acceptable blood glucose and electrolyte control in the clinical practice
- No evidence were found suggesting an increased risk for neurological injury associated with the use of high-dose GIK or glutamate
- History of cerebrovascular disease emerged as the most important independent risk factor for neurological injury after CABG and in general markers of atherosclerotic disease seemed to be of importance
- Patients with diabetes mellitus undergoing CABG were characterized by a lower mean age and a higher prevalence of female gender, hypertension, triple-vessel disease and unstable angina compared with non-diabetic patients.
• Patients with diabetes mellitus undergoing CABG more often presented with renal failure, stroke and wound infections postoperatively

• Patients with diabetes mellitus undergoing CABG had a higher need for inotropes, hemotransfusions and dialysis postoperatively

• Patients with diabetes mellitus undergoing CABG had an acceptable 30-day mortality (2.6%) that was not statistically different from non-diabetics (1.6%) but cumulative 5-year survival (84.4% vs 91.3%) was impaired, mainly due to the poor long-term outcome in insulin-treated patients.
Acknowledgements

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