Glutamate for Metabolic Intervention in Coronary Surgery
To
Elisabet and Per

"You don’t have to go fast, you just have to keep moving”
M Lemmel, Race Director Ö till Ö
Glutamate for Metabolic Intervention in Coronary Surgery
with special reference to the GLUTAMICS-trial
Abstract


Myocardial ischemia is a major cause of postoperative heart failure and adverse outcome in coronary artery bypass graft surgery (CABG). Conventional treatment of postoperative heart failure with inotropic drugs may aggravate underlying ischemic injury. Glutamate has been claimed to increase myocardial tolerance to ischemia and promote metabolic and hemodynamic recovery after ischemia. The aim of this work was to investigate if intravenous glutamate infusion given in association with CABG for acute coronary syndrome can reduce mortality and prevent or mitigate myocardial injury and postoperative heart failure. We also wanted to assess neurological safety issues, as a concern with the use of glutamate is that it may act as an excitotoxin under certain conditions.

A metabolic strategy for perioperative care was assessed in an observational study on 104 consecutive patients with severe left ventricular dysfunction undergoing CABG. Based on encouraging clinical results, unsurpassed in the literature, the GLUTAMICS-trial was initiated. 861 patients undergoing CABG for acute coronary syndrome were randomly allocated to blinded intravenous infusion of L-glutamic acid solution or saline. The primary endpoint was a composite of postoperative mortality (≤30 days), perioperative myocardial infarction and left ventricular heart failure in association with weaning from cardiopulmonary bypass. Secondary endpoints included neurological safety issues, degree of myocardial injury, postoperative hemodynamic state, use of circulatory support and cardiac mortality. The event rate was lower than anticipated and the primary endpoint did not differ significantly between the groups. Regarding secondary endpoints there were significant differences compatible with a beneficial effect of glutamate on post-ischemic myocardial recovery. The putative effect of glutamate infusion was seen in more ischemic patients (CCS class IV) and in patients with evident or anticipated LV-failure on weaning from CPB. No evidence for increased incidence of clinical or subclinical neurological injury was found. In conclusion, intravenous glutamate infusion is safe in the dosages employed and could provide a novel and important way of promoting myocardial recovery after ischemic injury.

Keywords: myocardial ischemia, coronary artery bypass, cardiac surgery, acute coronary syndrome, glutamate, metabolic intervention, postoperative heart failure, myocardial recovery.

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Swedish summary


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Background

1.1 Introduction
Ischemia of some degree is unavoidable in association with cardiac surgery. It is conceivable that ischemic myocardial injury and heart failure was common in the early days of cardiac surgery before modern techniques of myocardial protection were developed. However, there is surprisingly little documentation about postoperative heart failure or low cardiac output syndrome. In 1967 J. Kirklin noted that when death occurs early after cardiac surgery it is often related to low cardiac output. In spite of the progress in cardiac surgery and perioperative management postoperative heart failure remains a leading cause of death. O’Connor found postoperative heart failure to account for almost two thirds of all in-hospital deaths in a survey of 8641 patients undergoing CABG.

Although acknowledged as a major problem in cardiac surgery there are no generally accepted criteria for the diagnosis of postoperative heart failure. This in turn could explain why treatment for postoperative heart failure is poorly documented with regard to clinical outcome.

The causes and mechanisms for postoperative heart failure have also received limited attention. From a therapeutic aspect, it appears as if postoperative heart failure is regarded mainly as an issue of myocardial stunning that can be alleviated by inotropic drugs. Given that inotropic drugs increase oxygen expenditure excessively in relation to the increase in cardiac output such an approach may not be ideal for all patients. It has been demonstrated that ischemia and evolving myocardial infarction account for a large proportion of patients with postoperative heart failure after CABG. In animal models inotropic agents not only aggravate ischemia and increase the size of evolving myocardial infarction, but also stimulate apoptotic processes.

1.2 Myocardial ischemia and cardiac surgery
As late as 1965 myocardial necrosis was not recognized as a cause of postoperative complications in cardiac surgery. In 1967 Morales and Taber suggested that patchy areas of myocardial necrosis was the cause of postoperative heart failure in patients dying early after cardiac surgery. In 1985 Slogoff and Keats demonstrated that perioperative ischemia prior to cardiopulmonary bypass (CPB) was the main cause of myocardial infarction after CABG. It was also shown that the incidence of postoperative myocardial infarction was closely related to the perioperative management...
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Although acknowledged as a major problem in cardiac surgery there are no generally accepted criteria for the diagnosis of postoperative heart failure. This in turn could explain why treatment for postoperative heart failure is poorly documented with regard to clinical outcome\(^3-5\).

The causes and mechanisms for postoperative heart failure have also received limited attention. From a therapeutic aspect, it appears as if postoperative heart failure is regarded mainly as an issue of myocardial stunning that can be alleviated by inotropic drugs. Given that inotropic drugs increase oxygen expenditure excessively in relation to the increase in cardiac output such an approach may not be ideal for all patients. It has been demonstrated that ischemia and evolving myocardial infarction account for a large proportion of patients with postoperative heart failure after CABG\(^3, 6, 7\). In animal models inotropic agents not only aggravate ischemia and increase the size of evolving myocardial infarction, but also stimulate apoptotic processes\(^8, 9\).

1.2 Myocardial ischemia and cardiac surgery
As late as 1965 myocardial necrosis was not recognized as a cause of postoperative complications in cardiac surgery\(^10, 11\). In 1967 Morales and Taber suggested that patchy areas of myocardial necrosis was the cause of postoperative heart failure in patients dying early after cardiac surgery\(^12\). In 1985 Slogoff and Keats demonstrated that perioperative ischemia prior to cardiopulmonary bypass (CPB) was the main cause of myocardial infarction after CABG\(^13\). It was also shown that the incidence of postoperative myocardial infarction was closely related to the perioperative management
of ischemia. The role of myocardial ischemia for precipitating postoperative myocardial infarction and postoperative heart failure after CABG has been confirmed by other investigators. Whereas perioperative myocardial ischemia plays a key role for outcome after CABG the role of ischemia for eliciting postoperative heart failure after valve surgery appears to be of secondary importance. Occurrence of perioperative myocardial infarction is less frequent and other factors than ischemia account for the major proportion of cases with postoperative heart failure after valve surgery.

In patients undergoing CABG those with unstable angina are particularly prone to perioperative ischemia and the risk for development of permanent myocardial injury. Patients that arrive to surgery with limited cardiac reserve i.e. preoperatively compromised left ventricular function are particularly likely to require treatment for postoperative heart failure.

1.3 Metabolic strategy in cardiac surgery

Besides using conventional pharmacological treatment, an alternative approach to prevent and treat postoperative heart failure could involve adherence to physiological principles to minimize myocardial and systemic oxygen expenditure, and specific measures such as metabolic interventions with glutamate and high-dose GIK to increase myocardial tolerance to ischemia and facilitate myocardial recovery after ischemia.

Glucose-Insulin-Potassium (GIK)

Over the last few years the debate regarding the salutary effects of insulin in association with cardiac surgery has focused on blood glucose control. However, none of these studies have been designed to identify the mechanisms behind the success of blood glucose control or to discriminate between the effects of insulin per se or the effects of blood glucose control. Beyond blood glucose control insulin has several potentially beneficial effects in the post-traumatic state including direct and indirect influence on systemic and myocardial metabolism, hemodynamic state, inflammatory response, endothelia function, coagulation and apoptosis.

Basic research suggests that glucose is important for the preservation of mechanical function, structure, histology and ionic balance during ischemia. It appears that moderate doses of insulin can suffice to achieve blood glucose control and suppression of plasma FFAs after cardiac surgery. Although it is probable that moderate doses of insulin have a benefi-
ceral effect on myocardial metabolism, direct effects on myocardial metabolism have so far only been documented with high-dose GIK (1 IU/kg bodyweight and hour). Assessed with coronary sinus catheter technique a shift in myocardial uptake of substrates from FFA to glucose has been demonstrated not only in elective CABG patients, but also in patients treated with catecholamines after CABG and in diabetic patients undergoing CABG\textsuperscript{26-28}.

In experimental models insulin has been shown to have both inotropic\textsuperscript{29-31} and vasodilatory properties\textsuperscript{32-35}. Intraoperative assessment has confirmed beneficial effects on hemodynamic state with improved cardiac output\textsuperscript{28, 36-44}, improved LVSWI\textsuperscript{37, 38}, less reduction in left ventricular ejection fraction measured by nuclear angiography\textsuperscript{45}, improved central venous oxygen saturation\textsuperscript{46}, fewer episodes of low cardiac output\textsuperscript{47}, and less need for inotropes\textsuperscript{39, 40, 47-49}.

In contrast to inotropic agents, this improvement has been achieved without excessive increase of myocardial oxygen demand\textsuperscript{38} or myocardial oxygen consumption measured by coronary sinus catheters\textsuperscript{50}. The afterload reducing vasodilatory effect has been pronounced in studies using high-dose GIK\textsuperscript{43, 51, 52} and it appears that this vasodilation is not explained by luxury perfusion of skeletal muscle\textsuperscript{41}. The inotropic effect has been more difficult to discriminate in the clinical setting after cardiac surgery but interestingly echocardiographic studies have shown improvement of regional myocardial function in patients with acute myocardial infarction\textsuperscript{53, 54}.

### 1.4 Glutamate

**Glutamate**, C\textsubscript{5}H\textsubscript{9}NO\textsubscript{4}, is a genetically coded non-essential acidic amino acid. Glutamate is the salt of glutamic acid of which there are two forms, L-glutamic acid and D-glutamic acid. The only form of glutamic acid found in higher organisms and in proteins is L-glutamic acid, whereas D-glutamic acid only is found in the cell walls of certain bacteria.

In humans glutamate is a key molecule in cellular metabolism where it contributes to intermediates in the citric acid cycle\textsuperscript{55-57}. Glutamate also plays an important role in disposal of excess nitrogen and lactate\textsuperscript{50, 58, 59}.

In the central nervous system of vertebrae, glutamate acts as an excitatory neurotransmitter and is involved in cognitive functions like learning and memory\textsuperscript{60}. Under certain conditions it may act as an excitotoxin and participate in events leading to neurological damage\textsuperscript{61}. Glutamate administration has been shown to cause neurological injury in rodents but not in primates due to the blood-brain barrier that prevents passage of exogenous...
glutamate to the brain\textsuperscript{62-64}. Furthermore, concentration of glutamate in the brain is fifty-fold higher than in human plasma\textsuperscript{65}.

Glutamate accounts for 20\% of body protein, which equals around 2 kilograms in a person weighing 70 kilograms. Only 10 grams of this is free and less than 0.1 grams is free in the circulation\textsuperscript{66-69}.

Free glutamic acid is present in a wide variety of foods. The substance was identified in 1866 by the German chemist K Ritthausen. Glutamic acid is responsible for the fifth taste, Umami, termed by the Japanese researcher K Ikeda in 1907\textsuperscript{70}. It has been used as a flavor enhancer since the ancient roman kitchen and professor Ikeda patented a method of mass-production in 1908\textsuperscript{71}. The commercially produced glutamic acid is monosodium glutamate, MSG. The global demand of MSG is roughly 1.7 million tons per year\textsuperscript{72}. Extensive use of MSG as a food additive has been claimed to cause the “chinese restaurant syndrome” supposed to be a hypersensitive allergic reaction to MSG, however, several blinded studies could not link MSG to symptoms associated with the “chinese restaurant syndrome”\textsuperscript{73-75}.
1.5 Glutamate for metabolic intervention in coronary surgery

In 1979 Rau observed that certain amino acids protected isolated rabbit myocardium from hypoxia. The amino acids were glutamate, aspartate, ornithine and arginine. They are all active in the malate-aspartate shuttle which links metabolism in the cytosol with mitochondria. Of these amino acids, aspartate and in particular glutamate have been subject to further investigation regarding their metabolic role in association with ischemia. In animal in vitro and in vivo models numerous studies have shown that they protect the myocardium from ischemia and promote recovery of oxidative metabolism after ischemia.

In 1976 Mudge demonstrated that specific alterations of myocardial amino acid metabolism characterized patients with coronary artery disease. These patients exhibited an increased myocardial uptake of glutamate and an increased release of alanine. Thomassen and Pisarenko later confirmed these observations. Thomassen subsequently demonstrated that glutamate administration was associated with delayed onset of angina and ECG-changes in patients subject to exercise testing and pacing.

In 1985 Pisarenko reported beneficial hemodynamic and metabolic effects of intravenous glutamate infusion to patients treated with dopamine because of heart failure after cardiac surgery. Later it was demonstrated that myocardial uptake of amino acids and in particular glutamate preceded normalization of myocardial substrate utilization after CABG. Infusion of intravenous glutamate after CABG was associated with increased myocardial uptake of glutamate, improved lactate utilization and improved hemodynamic state.

Other investigators reported improved cardiac output due to peripheral vasodilatation after intravenous glutamate infusion in routine CABG but failed to demonstrate any metabolic changes as the metabolic state was normal at baseline.

Furthermore a positive effect on ATP preservation in human myocardium during cardioplegic arrest has been shown with glutamate enhancement of cardioplegic solutions.

Intravenous infusion provides the opportunity to supply the heart with substrate during the preoperative and postoperative phase. With this approach encouraging results have been achieved in CABG on high-risk patients, both in study populations and in clinical practice. Based on this experience we wanted to pursue the role of intravenous glutamate as metabolic intervention in coronary surgery in a randomized clinical trial and thus the GLUTAMICS-trial was initiated.
Aims of the thesis

- to report the short term and long term clinical experience of a metabolic strategy in patients with left ventricular dysfunction undergoing CABG
- to review the literature on clinical outcome in patients with left ventricular dysfunction undergoing CABG
- to investigate safety aspects of intravenous glutamate infusion with particular reference to neurological injury in patients undergoing CABG
- to investigate if intravenous glutamate infusion prevents perioperative myocardial infarction in patients undergoing CABG for acute coronary syndrome
- to investigate if intravenous glutamate infusion prevents postoperative heart failure in patients undergoing CABG for acute coronary syndrome
- to investigate if intravenous glutamate infusion prevents postoperative mortality in patients undergoing CABG for acute coronary syndrome
- to investigate if intravenous glutamate infusion promotes postoperative hemodynamic recovery in patients undergoing CABG for acute coronary syndrome
- to investigate if intravenous glutamate infusion reduces need for hemodynamic support and intensive care in patients undergoing CABG for acute coronary syndrome
- to investigate if preemptive use of inotropic drugs influenced the primary endpoint of the GLUTAMICS-trial
- to investigate the influence of intravenous glutamate infusion on the outcome in patients receiving inotropic drugs intraoperatively
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3 Patients and methods

3.1 Patients

This thesis is based on patients from an observational study leading to a prospective randomized clinical trial, the GLUTAMICS-trial. Patients in Paper I consist of 104 consecutive patients with severe left ventricular dysfunction (LVEF <0.40) undergoing CABG at the University Hospital of Linköping between 1991-1995.

Patients in Paper II-IV are all from the GLUTAMICS-trial. The 861 patients in the GLUTAMICS-trial were operated with CABG for acute coronary syndrome between October 4, 2005 and November 12, 2009 at three Swedish Cardiac Surgery Centers (Örebro University Hospital, University Hospital of Linköping and Blekinge County Hospital, Karlskrona). During the study period 2087 patients underwent coronary surgery for acute coronary syndrome, 1064 patients were assessed for eligibility, 865 underwent randomization, 4 patients were excluded due to intraoperative exclusion criteria and 861 completed the study (Figure 1).

Paper II is based on a prespecified subgroup (n=69) in the GLUTAMICS-trial (Figure 2).

Paper III is based on the whole study population in the GLUTAMICS-trial (n=861).

Paper IV is a post hoc analysis of patients from two of the participating centers in the GLUTAMICS-trial (n=788) and of all patients in the GLUTAMICS-trial receiving inotropic drugs intraoperatively (n=166).
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Figure 1.

2087 patients underwent coronary surgery for acute coronary syndrome between October 4, 2005 and November 12, 2009.

1064 patients were assessed for eligibility.

- 865 underwent randomization.
- 58 met exclusion criteria.
- 98 declined participation.
- 30 participated in other trial.
- 13 other reason.

Allocated to glutamate infusion n=430
Allocated to saline infusion n=435

Excluded due to intraoperative exclusion criteria n=2

Received allocated intervention n=428
Received allocated intervention n=433

Follow-up n=428
Follow-up n=433
Lost to follow-up n=0
Lost to follow-up n=0

Analyzed n=428
Analyzed n=433
Excluded from analysis n=0
Excluded from analysis n=0

Figure 2.

Assessed for eligibility n=70
Excluded n=1
Met exclusion criteria n=0
Declined participation n=0
Other reason n=1

Randomized n=69
Allocated to glutamate infusion n=35
Allocated to saline infusion n=34

Received allocated intervention n=35
Received allocated intervention n=34

Lost to follow-up n=0
Lost to follow-up n=0

Analyzed n=35
Analyzed n=34
**Figure 2.**

Assessed for eligibility n=70
- Excluded n=1
  - Met exclusion criteria n=0
  - Declined participation n=0
  - Other reason n=1
- Randomized n=69
  - Allocated to glutamate infusion n=35
    - Received allocated intervention n=35
    - Lost to follow-up n=0
    - Analyzed n=35
  - Allocated to saline infusion n=34
    - Received allocated intervention n=34
    - Lost to follow-up n=0
    - Analyzed n=34
3.2 GLUTAMICS-trial

**GLUTAMICS: GLUTAmate for Metabolic Intervention in Coronary Surgery**

ClinicalTrials.gov Identifier: NCT00489827

The GLUTAMICS-trial was an investigator initiated clinical phase III trial with parallel assignment to intravenous infusion of glutamate or placebo (saline) on patients undergoing CABG for acute coronary syndrome. The trial was first registered at the Swedish medical Product Agency 151/2003/70403 in December 2003. Later as the role of Clinical Trials Gov became increasingly acknowledged a secondary registration was made there: NCT00489827. External monitoring and reporting of adverse events was done according to Good Clinical Practice standard.

Power analysis (80% power; p<0.05) suggested that 2214 patients would be required with regard to primary endpoint assuming 30% reduction of events occurring in 12% of untreated patients. Interim analysis was planned to occur after inclusion of 800 patients. The trial was terminated after interim analysis as prespecified stopping criteria per protocol were fulfilled.

**Intervention**

Intravenous infusion of 0.125M glutamate solution or saline at a rate of 1.65ml/kg body weight and hour commencing at the induction of anesthesia and discontinued 2.5 hours after declamping the aorta or when a total of 500 ml had been infused.

**Glutamate solution**

500 ml 0.125M solution of L-glutamic acid with pH 6.0 and 280 mosmol/kg containing L-glutamic acid 9.2 g, NaCl 0.8g, H₂O ad 500 ml and NaOH quantum satis. Production of glutamate solution and quality control was done by Apoteket AB, Produktion & Laboratorier (APL), Box 6124, SE 90604 Umeå, Sweden.

**Inclusion criteria**

Inclusion criteria were coronary artery bypass surgery for acute coronary syndrome. Patients were eligible for inclusion regardless if the procedure was done on-pump or off-pump or if the patient had a simultaneous valve procedure.
**Exclusion criteria**
Exclusion criteria were, informed consent not possible because of critical condition or other reason, preoperative use of inotropic drugs or mechanical circulatory assist, preoperative dialysis, redo-procedure, unexpected intraoperative finding or event that increased the dignity of the procedure to overshadow the originally planned operation, age > 85 years, body weight > 125 kg and food allergy known to have caused flush, rash or asthma.

**Study design**
Prospective, randomized, placebo controlled, double-blind clinical trial.

**Primary endpoint**
The primary endpoint was a composite of postoperative mortality (≤ 30-days), perioperative myocardial infarction and left ventricular heart failure in association with weaning from CPB.

**Secondary endpoints**
The secondary endpoints included neurological safety issues, degree of myocardial injury, postoperative hemodynamic state, use of inotropic drugs and mechanical circulatory support, severe circulatory failure, atrial fibrillation, renal function, ICU-treatment, cardiac mortality and late mortality.

**Subgroup analysis**
Patients with CCS class IV angina were planned for a subgroup analysis.

**S-100B substudy**
As an early safety measure in the GLUTAMICS-trial a prespecified subgroup of patients (n=69) were analyzed with regard to postoperative S-100B levels to detect potential subclinical neurological injury related to glutamate infusion. Furthermore, we wanted to assess the relationship between S-100B and clinical signs of neurological injury and established risk factors for stroke (Paper II).
3.3 Post-hoc analysis
In the GLUTAMICS-trial two of the participating centers (A and B) exhibited markedly different policies regarding preemptive use of inotropic drugs to facilitate weaning from CPB. Paper IV consists of a post-hoc analysis regarding the influence of inotropic drugs on the GLUTAMICS-trial. This analysis compares the two centers with different policies regarding preemptive use of inotropic drugs and also analyzes the influence of intravenous glutamate infusion on primary and secondary outcome variables in all patients receiving inotropic drugs intraoperatively.

3.4 Clinical management
Paper I
A metabolic strategy was implied which included adherence to physiological principles to minimize myocardial and systemic oxygen expenditure and specific measures such as extended CPB and metabolic support to facilitate myocardial recovery in patients with inadequate hemodynamic state. Volume work by the heart rather than pressure work was promoted by after-load reduction when feasible. The adequacy of hemodynamic state was primarily assessed by measurement of SvO2 and urinary output. Inotropic drugs were used only if SvO2 or urinary output suggested that cardiac output was inadequate despite correction of volume and treatment of other causes. A mechanical assist device was preferred in favor of increasing the dose of inotropic drugs such as dobutamine above 5 μ/kg/min.

On the day of surgery all patients were given their individual doses of beta-blockers and calcium-antagonists. After premedication with morphine hydrochloride and scopolamine, anesthesia was induced with thiopentone and fentanyl, and maintained with fentanyl and isoflurane. Pancuronium bromide was used for neuromuscular blockade. CPB was conducted with a membrane oxygenator and a roller pump generating non-pulsatile flow. Ringer’s acetate and mannitol were used for priming the extracorporeal circuit. Moderate hemodilution (hematocrit 20–25%) and mild to moderate hypothermia (32–35°C) were employed. Antegrade or combined antegrade and retrograde delivery of St.Thomas’ cold crystalloid cardioplegic solution was used for myocardial protection. CPB was prolonged until recovery of left ventricular function was evident. Heparin was neutralized with protamine chloride. In the postoperative period rewarming was facilitated by radiant heat provided by thermal ceiling. Shed mediastinal blood was routinely retransfused after surgery. Ringer’s acetate was used for volume substitution.
Paper II-IV
Clinical management was standardized and similar at the three participating centers with minor differences concerning choice of anesthetic drugs. After an overnight fast, patients received beta-blockers and calcium-antagonists orally, whereas antihypertensive and antidiabetic agents were withheld. Standard premedication consisted of orally administered flunitrazepam (0,5-1,0 mg) or diazepam (5-10 mg) and ketobemidone (0,1-0,2 mg/kg body weight) or morphine (0.1-0.2 mg/kg body weight). Anesthesia was induced with thiopentone (2-3 mg/kg body weight) or propofol (2 mg/kg body weight) supplemented by a bolus dose of fentanyl (3-5 μg/kg body weight). Muscle relaxation was achieved with pancuronium (0.1 mg/kg body weight) or rocuronium (0.6 mg/kg body weight). Anesthesia was maintained with isoflurane, sevoflurane or propofol supplemented with intermittent doses of fentanyl.

Standard monitoring was used consisting of 5-lead echocardiogram, pulse oximetry, continuous arterial blood pressure monitoring using a cannula in the radial artery, central venous pressure and transesophageal echocardiography. A surgical pulmonary artery catheter was introduced in all patients.

Standard surgical techniques were employed. A median sternotomy was performed in all patients. CPB was achieved with an extracorporeal circuit consisting of a heart-lung machine (Stöckert SIII, Sorin Group, Munich, Germany or HL 30, MAQUET Cardiopulmonary AG, Hirrlingen, Germany), an open venous reservoir primed with 2,000 mL Ringer’s acetate, a roller pump with non-pulsatile flow, a hollow-fibre oxygenator with integrated heat exchanger, and a polyvinyl tubingsystem (Sorin Group, Mirandola, Italy). Systemic heparinization was used to keep the activated clotting time >480 seconds. Myocardial protection was achieved with either cold blood cardioplegia or cold crystalloid cardioplegia.

Propofol was used for postoperative sedation. Postoperative analgesia regimen consisted of ketobemidone 7-15 μg/kg body weight administered intermittently intravenously and acetaminophen 1 g every 6th hour.

Extubation was performed when body temperature reached a level above 37°C, hemodynamic values were stable including a mixed venous saturation exceeding 55 %, pO2 was above 10 kPa with FiO2 0,4 and pCO2 was below 6,5 kPa with a respiratory rate less than 30 and drainage loss was less than 100 ml per hour and declining.
3.5 Metabolic intervention

Paper I

In study I a metabolic strategy was implied which included adherence to physiological principles to minimize myocardial and systemic oxygen expenditure and specific measures such as extended CPB and metabolic support with glutamate and/or high-dose GIK to facilitate myocardial recovery in patients with inadequate hemodynamic state.

During the time frame of the study availability of glutamate solutions was restricted due to limited capacity of the local pharmacy to produce solutions. Hence, prophylactic glutamate infusion was reserved for patients with signs of severe myocardial ischemia or heart failure in the operating room before surgery. In these patients glutamate was infused intravenously preoperatively and after release of cross clamp to prevent heart failure at weaning from CPB. Intravenous glutamate was also instituted as treatment in patients with failure to wean from CPB at the first attempt.

High dose glucose-insulin-potassium (GIK) was added to intravenous glutamate infusion in patients with failure to wean from CPB at the first attempt. Details of treatment with intravenous glutamate and high-dose GIK have been reported previously99.

Paper II-IV

In Paper II-IV patients were randomly allocated to blinded intravenous infusion of 0.125M L-glutamic acid solution or saline at a rate of 1.65 ml/kg body weight and hour commencing at the induction of anesthesia. As the by cardioplegia arrested heart is reported to leak glutamate rather than extract exogenous glutamate, the infusions were temporarily stopped during aortic cross-clamping101. Infusions were resumed after declamping of the aorta and continued for a further 2 hours at this rate after which the infusion rate was halved and an additional 50 ml infused. The maximum volume infused to any patient was 500 ml of study solution. The dosage of glutamate was based on studies demonstrating that an infusion rate of 30-40 mg glutamate/kg body weight and hour increased arterial whole blood levels by two-three fold, which was sufficient to meet the myocardial demands or to saturate myocardial capacity to extract glutamate from the circulation102.
3.6 Data collection

Paper I
During a five-year period (1991-1995) when the metabolic strategy was introduced 775 consecutive patients operated for ischemic heart disease by two surgeons were registered in a database. Left ventricular function was assessed by angiography or echocardiography. 104 patients presented with compromised left ventricular function (LVEF<0.40) before surgery. The records of the patients were investigated in detail according to a protocol and data retrieved and stored in a database. Data on late mortality were retrieved from the Swedish Civil Registry.

Paper II-IV
Basic demographic, intraoperative and postoperative data were recorded prospectively in an institutional database, Carath, used at all participating centers.

Key study data were prospectively recorded in a CRF. Preoperatively the patients were classified with regard to CCS class and Braunwald class. Occurrence of angina at rest within 48 hours prior to surgery and occurrence of ST-segment depression ≥ 1 mm or ST-segment elevation ≥ 2 mm from admission to the operating room to the onset of CPB were recorded. Use of inotropic drugs or mechanical circulatory assist was recorded. CT-scan was performed in cases with suspected permanent neurological injury.

In the S-100B substudy, epiaortic scanning of the ascending aorta with ultrasound (Vivid 7 Dimension GE ultrasound scanner and a GE Ultrasound transducer 5.5–9.0 MHz, GE Parallel Design, Tempe, AZ, USA), was done intraoperatively before cannulation for CPB in all patients. Results were recorded according to a protocol. Aortic calcification was classified by the operating surgeon as none, mild, moderate, severe or completely calcified.
3.7 Biochemical analyses

Creatine kinase (CK-MB)
Creatine kinase (CK-MB) in plasma was sampled on the first postoperative day and analyzed using an electrochemiluminescence immunoassay on a Roche Elecsys 2010 instrument (Roche Diagnostics, Basel, Switzerland).

Troponin-T
Troponin-T in plasma was sampled immediately before surgery and on the third postoperative day. Analyses were performed using an electrochemiluminescence immunoassay on a Roche Elecsys 2010 instrument (Roche Diagnostics, Basel, Switzerland).

NT proBNP
NT-proBNP in plasma was sampled in the operating room immediately before induction of anesthesia, postoperatively 24 hours after declamping the aorta and on the third postoperative day. Analyses were performed using an electrochemiluminescence immunoassay on a Roche Elecsys 2010 instrument (Roche Diagnostics, Basel, Switzerland). The between-run coefficient variation at 150 ng/L was 5.0% and at 1400 ng/L it was 6.2%.

S-100B
S-100B in plasma was sampled on the third postoperative day. Analyses were performed using an electrochemiluminescence immunoassay on a Roche Elecsys 2010 instrument (Roche Diagnostics, Basel, Switzerland).

Cystatin-C
Cystatin-C in plasma was sampled on the third postoperative day. Analyses were performed with the Gentian Cystatin-C Immunoassay on a Vitros 5.1 instrument (Ortho Clinical Diagnostics Johnson & Johnson, Raritan, NJ, USA)

Creatinine
Creatinine in plasma was sampled on the third postoperative day. The highest postoperative plasma Creatinine was also registered. Analyses were performed using enzymatic dry chemistry methods on a Vitros 5.1 instrument (Ortho Clinical Diagnostics Johnson & Johnson, Raritan, NJ, USA).
Lactate
Arterial plasma lactate was measured five minutes after administration of protamine sulphate. Lactate was analyzed by a calorimetric method on an ABL 500 (Radiometer Medical ApS, Brønshøj, Denmark) or a Vitros 5.1 instrument (Ortho Clinical Diagnostics Johnson & Johnson, Raritan, NJ, USA).

3.8 Hemodynamic measurements
Left ventricular function was assessed with transesophageal echocardiography prior to surgical incision and in association with weaning from CPB (Agilent Sonos 4500, Philips Electronics, Amsterdam, The Netherlands and Acuson 128XP/10C, Siemens AG, Erlangen, Germany).

Hemodynamic variables (mixed venous oxygen saturation, arterial saturation, heart rate, systolic and diastolic arterial pressure, diastolic pulmonary artery pressure, central venous pressure) were recorded on weaning from CPB or after termination of the last graft in off-pump surgery, five minutes after administration of protamine sulphate and on admission to ICU.

Arterial pressure was measured in the radial artery. Pulmonary artery pressure and intermittent blood sampling for analysis of mixed venous oxygen saturation, SvO2, was retrieved by either a Swan-Ganz catheter or an epidural catheter introduced during surgery through the right ventricular outflow tract into the pulmonary artery. Analyses were performed on an ABL 500 (Radiometer Medical ApS, Brønshøj, Denmark).

3.9 Definitions
Paper I
Use of inotropes was defined as a continuous infusion of beta-receptor stimulants or a bolus or continuous infusion of phosphodiesterase inhibitors regardless of dose. Complications presented refer to in-hospital events. Intraoperative myocardial infarction was diagnosed by biochemical markers or by findings at autopsy as reported previously. Postoperative renal failure is presented according to STS data base definition and furthermore the proportion of patients having an increase of s-creatinine of 50% or more compared to preoperative value is given. Neurological injury included the following cerebral complications: 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. The majority of patients with suspected neuro-
logical injury were examined by a neurologist and by CT-scan. Cognitive dysfunction was not assessed.

**Paper II-III**

Primary and secondary endpoints in the GLUTAMICS-trial were based on a number of prespecified definitions. The most central were 30-day mortality, perioperative myocardial infarction, LV-failure at weaning from CPB, hemodynamic instability at completion of surgery, severe circulatory failure and cardiac mortality. Details of all definitions are presented in the Appendix.

Due to the lack of generally accepted criteria for postoperative heart failure in association with cardiac surgery a clinical endpoints committee was considered necessary. The clinical endpoints committee consisted of consultants in cardiothoracic surgery and cardiothoracic anesthesiology from each of the participating centers. The members of the committee were blinded to the treatment assignment and prespecified criteria were used to reach a consensus decision.

Stroke was defined as appearance of a focal neurological deficit persisting for more than 24 h or depression of consciousness or confusion if associated with signs of cerebral injury on CT scan. Postoperative confusion was registered in the clinical database when there was a state of confusion verified by both nurse and physician that prevented normal mobilization of the patient. Patients with clinical suspicion of neurological injury underwent CT scan of the brain.

**Paper IV**

Intraoperative use of inotropic drugs was defined as infusion of inotropic drugs for at least 30 minutes or a bolus dose of milrinone.

Preemptive use of inotropic drugs to facilitate weaning from CPB was defined as use of inotropic drugs in patients that according to prespecified criteria were deemed, by the clinical endpoints committee, not to have had heart failure at weaning.

**3.10 Statistics**

The data are presented as percentages, means ± standard deviation or medians with range or inter-quartile range. Two-sided Fisher’s exact test was used for comparison of categorical data. Student’s t-test or Mann-Whitney U-test was used as appropriate for comparison of continuous variables. Long-term survival is given as crude 5-year survival and cumulative 10-year survival according to Kaplan-Meier analysis. Forward stepwise multivariable logistic regression analysis was used for identification of inde-
dependent risk factors for severe circulatory failure. Hosmer-Lemeshow goodness-of-fit statistics was calculated for the final model. For all tests statistical significance was defined as $p<0.05$. Adjustment for multiple testing was not performed.

In Paper II statistical analysis was performed by an external professional statistician and blinded to the investigators, as this was a substudy in the still ongoing GLUTAMICS-trial.

All statistical analyses were performed with computerized statistical packages (Statistica 9.1, StatSoft Inc., Tulsa, OK, USA, and SPSS Statistics 18, SPSS Inc., Chicago, IL, USA).

### 3.11 Ethics

All studies were performed according to the Helsinki Declaration of Human Rights and the Regional Ethical Review Board in Linköping (Paper I: Dnr 03-597; 2003-12-16 Papers II-IV: M76-05; 2005-05-09). The GLUTAMICS-trial (Paper II-IV) was approved by the Swedish Medical Products Agency (151:2003/70403) and registered on ClinicalTrials.gov (Identifier: NCT00489827). After written informed consent the patients were enrolled in the study.

The Swedish Medical Products Agency requested surveillance and unblinding in cases of CT-verified stroke within 24 hours of surgery, mortality and suspected unexpected serious adverse reactions (SUSAR). An independent professional monitoring team did external monitoring of all key data and unblinding procedures.
4.1 Observational study on a metabolic strategy (Paper I)

Major demographic and intraoperative data for the study cohort of 104 patients are given in Table 1. The mean age was 65±9 years, 29.8% had unstable angina and the logistic EuroSCORE was 8.3 (95% CI 5.8–10.8). The mean left ventricular ejection fraction was 0.30±0.05 (range 0.20–0.37).

<table>
<thead>
<tr>
<th>Table 1. Demographic and intraoperative data (mean±SD or count n %).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=104</strong></td>
</tr>
<tr>
<td>Age (years) 65±9</td>
</tr>
<tr>
<td>Female gender 19.2% (20/104)</td>
</tr>
<tr>
<td>Diabetes mellitus 20.2% (21/104)</td>
</tr>
<tr>
<td>Logistic EuroSCORE 8.3 (95% CI 5.8–10.8)</td>
</tr>
<tr>
<td>LVEF 0.30±0.05</td>
</tr>
<tr>
<td>s-Creatinine (μmol/L) 106±21</td>
</tr>
<tr>
<td>Unstable angina 29.8% (31/104)</td>
</tr>
<tr>
<td>Urgent/Emergent procedure 27.9% (29/104)</td>
</tr>
<tr>
<td>Number of bypassed vessels 3.5±1.3</td>
</tr>
<tr>
<td>Cross clamp time (minutes) 41±22</td>
</tr>
<tr>
<td>CPB time (minutes) 95±46</td>
</tr>
</tbody>
</table>

Outcome

The overall thirty-day mortality was 1.0% compared to expected mortality of 8.3% according to logistic EuroSCORE. Crude five-year survival overall was 89.4%. Ten-year survival according to Kaplan–Meier is shown in Figure 3.

SvO₂ on arrival to ICU averaged 65.8±7.4%. Mean stay in the ICU was 1.9±2.3 days. Postoperatively 10.6% of the patients had signs of myocardial infarction. Postoperative increase of s-Creatinine by ≥50% of the pre-operative level was found in 2.9% of the patients and the incidence of postoperative renal failure according to the STS definition was 1.0%.
4 Results

4.1 Observational study on a metabolic strategy (Paper I)
Major demographic and intraoperative data for the study cohort of 104 patients are given in Table 1. The mean age was 65±9 years, 29.8% had unstable angina and the logistic EuroSCORE was 8.3 (95% CI 5.8–10.8). The mean left ventricular ejection fraction was 0.30±0.05 (range 0.20–0.37).

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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>s-Creatinine (μmol/L)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Urgent/Emergent procedure</td>
<td>27.9% (29/104)</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>3.5±1.3</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>41±22</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>95±46</td>
</tr>
</tbody>
</table>

Outcome
The overall thirty-day mortality was 1.0% compared to expected mortality of 8.3% according to logistic EuroSCORE. Crude five-year survival overall was 89.4%. Ten-year survival according to Kaplan-Meier is shown in Figure 3.

SvO2 on arrival to ICU averaged 65.8±7.4%. Mean stay in the ICU was 1.9±2.3 days. Postoperatively 10.6% of the patients had signs of myocardial infarction. Postoperative increase of s-Creatinine by ≥50% of the preoperative level was found in 2.9% of the patients and the incidence of postoperative renal failure according to the STS definition was 1.0%.
Figure 3. Cumulative 10-year survival after CABG in patients (n=104) with LVEF<0.40 managed according to the metabolic strategy.

Metabolic support with glutamate increased from 28.6% during the first half to 43.4% during the second half of the period studied (p=0.18). Corresponding figures for high-dose GIK was 10.7% v 34.7% (p=0.025). Overall intravenous metabolic support was given to 41.3% of the patients. Pharmacological circulatory support with inotropes for weaning from CPB decreased from 17.9% during the first half to 2.6% during the second half of the period studied. Mechanical circulatory support was used in 1.9% of the cases. Overall nitroprusside was used in 53.8% of the patients and vasoconstrictors in 21.4%. Of the patients that received high-dose GIK 51.7% required angiotensin or norepinephrine to counteract vasodilatation.
In the ICU low dose inotropes or phosphodiesterase inhibitors were used to enhance urinary output in a total of 37.3% of the patients. The average doses when used were for dobutamine $2.2 \pm 1.1 \mu g/kg$ and min (n=30), dopamine $1.6 \pm 1.1 \mu g/kg$ and min (n=6) and for epinephrine $28 \pm 27 ng/kg$ and min (n=5).

Thirty-day mortality and five-year survival in relationship to type of metabolic treatment is shown in Table 2-3.

**Table 2. Patients treated with intravenous glutamate (mean±SD or count n %).**

| Intravenous glutamate overall | 39.4% (41/104) |
| Intravenous glutamate to prevent heart failure at weaning from CPB | 24.0% (25/104) |
| Intravenous glutamate as treatment of heart failure at weaning from CPB | 15.4% (16/104) |
| Addition of high-dose GIK | 67% (27/41) |
| Inotropes for weaning from CPB | 14.6% (6/41) |
| LVEF | $0.27 \pm 0.05$ |
| Logistic EuroSCORE | 15.1% |
| 30-day mortality | 2.4% |
| 5-year survival | 82.9% |

**Table 3. Patients treated with high-dose GIK (mean±SD or count n %).**

| High-dose GIK as treatment of heart failure at weaning from CPB | 27.9% (29/104) |
| Addition of intravenous glutamate | 93% (27/29) |
| Inotropes for weaning from CPB | 17% (5/29) |
| LVEF | $0.26 \pm 0.05$ |
| Logistic EuroSCORE | 17.4% |
| 30-day mortality | 3.4% |
| 5-year survival | 82.8% |
A key issue in the metabolic strategy was extended reperfusion time on CPB, to allow the heart to recover from ischemia. In patients that could be weaned at the first attempt, CPB time and aortic cross clamp time were 81±27 minutes and 40±19 minutes respectively. In patients with difficulty to wean at the first attempt (n=32) CPB time averaged 127±62 minutes while cross clamp time was 45±28 minutes. Of the patients with initial weaning difficulties 94% were treated with metabolic support and 78% could be weaned from CPB without inotropes. Mechanical circulatory support was used in 1.9% of the cases.

Outcome related to mixed venous oxygen saturation showed that of patients who arrived to the ICU with SvO\textsubscript{2}≥55% and without history of weaning problems no one developed renal failure, 30-day mortality was zero and five-year survival was 95.6%.

**Comment**

This observational study on a metabolic strategy showed lower 30-day mortality (1.0%) than previously reported in patients with severe LV-dysfunction undergoing CABG. 30-day mortality was also substantially lower than the expected risk adjusted mortality of 8.3% according to logistic EuroSCORE. Long-term survival was encouraging with a crude 5-year survival of 89.4%.
4.2 S-100B substudy of the GLUTAMICS-trial (Paper II)

Of the 69 patients included in this prespecified substudy, 35 patients received intravenous glutamate infusion and 34 patients received placebo (intravenous saline infusion). No patients were lost to follow-up (Figure 2). Major pre-, intra-, and postoperative data are given in Table 4.

Table 4. Pre-, intra-, and postoperative data for the S-100B substudy (mean±SD or count n %.)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=34</th>
<th>Glutamate n=35</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±11</td>
<td>68±9</td>
<td>0.40</td>
</tr>
<tr>
<td>Female gender</td>
<td>9.0%(3)</td>
<td>20.0%(7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29.4%(10)</td>
<td>40.0%(14)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2.9%(1)</td>
<td>11.4%(4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Moderate-severe LV-dysfunction</td>
<td>26.5%(9)</td>
<td>20.0%(7)</td>
<td>0.58</td>
</tr>
<tr>
<td>CCS class IV angina</td>
<td>84.0%(29)</td>
<td>80.6%(28)</td>
<td>1.00</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>4.8±3.1</td>
<td>5.6±3.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Calcification of ascending aorta</td>
<td>34.2%(12)</td>
<td>29.4%(10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>0</td>
<td>8.6%(3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>4.1±1.4</td>
<td>3.8±1.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Other operation than isolated CABG</td>
<td>5.9%(2)</td>
<td>8.6%(3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>59±22</td>
<td>64±23</td>
<td>0.34</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>84±29</td>
<td>91±30</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Confusion</td>
<td>8.8%(3)</td>
<td>5.7%(2)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

There was no statistically significant difference in S-100B levels between the glutamate group and the control group (0.07±0.034 µg/L v 0.090±0.042 µg/L; p=0.25). No patient suffered from stroke and there was no mortality.

Overall 21 patients had S-100B above reference level (0.10 µg/L). Major pre-, intra-, and postoperative data for this group versus the group with normal level of S-100B are given in Table 5.
Table 5. Normal versus elevated S-100B (mean±SD or count n %).

<table>
<thead>
<tr>
<th></th>
<th>Normal S-100B</th>
<th>Elevated S-100B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65±9</td>
<td>70±10</td>
<td>0.10</td>
</tr>
<tr>
<td>Female gender</td>
<td>8.3%(4)</td>
<td>28.6%(6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31.3%(15)</td>
<td>42.9%(9)</td>
<td>0.42</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6.3%(3)</td>
<td>9.5%(2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Moderate-severe LV-dysfunction</td>
<td>25.0%(12)</td>
<td>19.0%(4)</td>
<td>0.76</td>
</tr>
<tr>
<td>CCS class IV angina</td>
<td>80.0%(38)</td>
<td>87.5%(18)</td>
<td>0.71</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>4.5±3.1</td>
<td>7.0±3.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Calcification of ascending aorta</td>
<td>21.3%(10)</td>
<td>52.4%(11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>4.2%(2)</td>
<td>4.8%(1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>4.0±1.3</td>
<td>3.8±1.3</td>
<td>0.58</td>
</tr>
<tr>
<td>Other operation than isolated CABG</td>
<td>4.2%(2)</td>
<td>14.3%(3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>59±21</td>
<td>67±26</td>
<td>0.21</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>85±29</td>
<td>93±30</td>
<td>0.35</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Confusion</td>
<td>2.1%(1)</td>
<td>19.0%(4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

In the group with elevated S-100B there was significantly higher EuroSCORE, significantly more calcification of the ascending aorta and significantly higher occurrence of postoperative confusion.

The patients with postoperative confusion also showed significantly elevated S-100B compared with those without confusion (0.132±0.047 µg/L v 0.081±0.036 µg/L; p=0.003).

The levels of S-100B on the third postoperative day depending on study group, occurrence of postoperative confusion and prevalence of aortic calcification on intraoperative epiaortic scanning are shown in Figure 4.
Table 5. Normal versus elevated S-100B (mean±SD or count n %).

In the group with elevated S-100B there was significantly higher Euro-SCORE, significantly more calcification of the ascending aorta and significantly higher occurrence of postoperative confusion.

The patients with postoperative confusion also showed significantly elevated S-100B compared with those without confusion (0.132±0.047 µg/L v 0.081±0.036 µg/L; p=0.003).

The levels of S-100B on the third postoperative day depending on study group, occurrence of postoperative confusion and prevalence of aortic calcification are shown in Figure 4.

Comment
This substudy of the GLUTAMICS-trial regarding neurological safety issues showed that intravenous glutamate infusion during surgery for acute coronary syndrome did not initiate a sustained elevation of plasma S-100B postoperatively. Thus, no evidence for subclinical neurological injury related to glutamate infusion was found. In contrast, postoperative elevation of plasma S-100B was linked to calcification of the ascending aorta and postoperative confusion.
4.3 Results of the GLUTAMICS-trial (Paper III)

The GLUTAMICS-trial was conducted between October 4, 2005 and November 12, 2009. A total of 865 patients were randomized and 4 patients, 2 in the glutamate group and 2 in the placebo group were excluded due to intraoperative exclusion criteria. The total study cohort consists of 861 patients. No patients were lost to follow-up (Figure 1). Patients included in the study were analyzed according to intention to treat.

A summary of the patient characteristics is given in Table 6. The groups were evenly distributed with the exception of significantly more patients with extra-cardiac arterial disease (p=0.04) and left main stenosis (p=0.03) in the glutamate group. There was a trend towards higher EuroSCORE in the glutamate group (p=0.13).

Table 6. Demographic and intraoperative data for the GLUTAMICS-trial (mean±SD or count n %).

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=433</th>
<th>Glutamate n=428</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±9</td>
<td>68±9</td>
</tr>
<tr>
<td>Female gender</td>
<td>18.9%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25.4%</td>
<td>23.9%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8.1%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Extra-cardiac arterial disease</td>
<td>9.3%</td>
<td>13.9%</td>
</tr>
<tr>
<td>COPD</td>
<td>5.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Moderate-severe LV-dysfunction</td>
<td>19.2%</td>
<td>18.5%</td>
</tr>
<tr>
<td>CCS class IV angina</td>
<td>55.9%</td>
<td>54.4%</td>
</tr>
<tr>
<td>Angina at rest &lt;48h preop</td>
<td>23.6%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Intravenous nitroglycerine preop</td>
<td>8.5%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>35.2%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>5.0±2.8</td>
<td>5.3±2.8</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>5.5%</td>
<td>4.2%</td>
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<tr>
<td>Cross clamp time (minutes)</td>
<td>54±22</td>
<td>53±21</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>83±30</td>
<td>84±31</td>
</tr>
</tbody>
</table>
**Outcome for the whole study population in the GLUTAMICS-trial**

There was no significant difference in the incidence of the primary composite endpoint between the groups. Secondary endpoints showed a trend towards fewer patients in the glutamate group who were hemodynamically unstable at completion of surgery (0.3% vs 1.8%; p=0.07) and fewer patients in the glutamate group requiring IABP on admission to ICU (0% vs 1.2%; p=0.06).

Primary and major secondary endpoints for the GLUTAMICS-trial are shown in Table 7.

*Table 7. Outcome GLUTAMICS-trial (mean±SD or count n %).*

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Placebo n=433</th>
<th>Glutamate n=428</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-failure at weaning from CPB</td>
<td>5.8%</td>
<td>7.3%</td>
<td>0.41</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>4.2%</td>
<td>4.7%</td>
<td>0.74</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.2%</td>
<td>0.9%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Placebo n=433</th>
<th>Glutamate n=428</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropes at weaning from CPB</td>
<td>12.3%</td>
<td>13.8%</td>
<td>0.54</td>
</tr>
<tr>
<td>SVo2 at weaning from CPB</td>
<td>72.2±7.3</td>
<td>72.0±7.6</td>
<td>0.69</td>
</tr>
<tr>
<td>a-Lactate mmol/L 5 minutes after protamine</td>
<td>1.7±0.6</td>
<td>1.6±0.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Hemodynamic state at completion of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stable without inotropes</td>
<td>77.4%</td>
<td>78.5%</td>
<td>0.73</td>
</tr>
<tr>
<td>- Stable with inotropes</td>
<td>19.8%</td>
<td>22.3%</td>
<td>0.38</td>
</tr>
<tr>
<td>- Unstable with inotropes / IABP</td>
<td>1.8%</td>
<td>0.3%</td>
<td>0.07</td>
</tr>
<tr>
<td>IABP on admission to ICU</td>
<td>1.2%</td>
<td>0%</td>
<td>0.06</td>
</tr>
<tr>
<td>Severe circulatory failure</td>
<td>4.2%</td>
<td>2.3%</td>
<td>0.18</td>
</tr>
<tr>
<td>Stroke within 24h post op</td>
<td>1.4%</td>
<td>0.9%</td>
<td>0.75</td>
</tr>
<tr>
<td>Dialysis post op</td>
<td>1.4%</td>
<td>0.5%</td>
<td>0.29</td>
</tr>
<tr>
<td>Cardiac mortality (in hospital or 30-day)</td>
<td>0.9%</td>
<td>0.2%</td>
<td>0.37</td>
</tr>
</tbody>
</table>
ICU-stay or time on ventilator did not differ between the groups overall. However, patients with LV-failure at weaning from CPB had significantly shorter median ICU stay (25 [18-57] hours v 92 [41-139] hours; p=0.02) and ventilator treatment (5.0 [3.3-8.0] hours v 7.4 [5.8-49] hours; p=0.02) if they received glutamate infusion (Figure 5).

Cardiac mortality (in-hospital or 30-day) was 0.2% in the glutamate group and 0.9% the control group (p=0.37). There were no significant differences regarding the incidence of postoperative stroke.

Figure 5. Duration of ICU stay and ventilator treatment in patients with LV-failure at weaning from CPB (median+ interquartile range).
Adverse events
There were no significant differences in the incidence of serious or non-serious adverse events between the glutamate group and the placebo group in the GLUTAMICS-trial. A table with all adverse events is presented in the Appendix.
Patients with CCS class IV angina
In the GLUTAMICS-trial patients with CCS class IV angina undergoing isolated CABG were analyzed separately to address the population with unstable angina.

A summary of the patient characteristics for this study cohort (n=458) is given in Table 8. The groups were evenly distributed with the exception of significantly more patients with left main stenosis (p=0.03) in the glutamate group.

Table 8. Demographic and intraoperative data for patients with CCS class IV angina undergoing isolated CABG (mean±SD or count n %).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glutamate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=233</td>
<td>n=225</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68±9</td>
<td>68±9</td>
</tr>
<tr>
<td>Female gender</td>
<td>19.7%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.0%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Extra-cardiac arterial disease</td>
<td>10.7%</td>
<td>14.5%</td>
</tr>
<tr>
<td>COPD</td>
<td>5.6%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Moderate-severe LV-dysfunction</td>
<td>21.0%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Angina at rest &lt;48h preop</td>
<td>38.2%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Intravenous nitroglycerine preop</td>
<td>13.7%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>34.3%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>5.2±3.0</td>
<td>5.4±2.9</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>9.0%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>3.8±1.2</td>
<td>3.8±1.2</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>53±17</td>
<td>53±17</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>81±25</td>
<td>83±30</td>
</tr>
</tbody>
</table>
Outcome for patients with CCS class IV angina undergoing isolated CABG

The primary composite endpoint did not differ significantly between the groups. Regarding secondary endpoints significantly fewer patients in the glutamate group developed severe circulatory failure (1.3% v 6.9%; p=0.004). Primary and major secondary endpoints for this subgroup analysis of the GLUTAMICS-trial are shown in Table 9.

Table 9. Outcome for patients with CCS class IV angina undergoing isolated CABG (mean±SD or count n %).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Glutamate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV-failure at weaning from CPB</td>
<td>5.2%(12)</td>
<td>5.3%(12)</td>
<td>1.0</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>2.2%(5)</td>
<td>2.7%(6)</td>
<td>0.77</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.3%(3)</td>
<td>0.9%(2)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes at weaning from CPB</td>
<td>12.0%(28)</td>
<td>11.2%(25)</td>
<td>0.88</td>
</tr>
<tr>
<td>SvO2 at weaning from CPB</td>
<td>71.7±7.1</td>
<td>71.6±7.6</td>
<td>0.82</td>
</tr>
<tr>
<td>a-Lactate mmol/L 5 minutes after protamine</td>
<td>1.8±0.6</td>
<td>1.6±0.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Hemodynamic state at completion of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Stable without inotropes</td>
<td>80.9%(188)</td>
<td>79.8%(180)</td>
<td>0.81</td>
</tr>
<tr>
<td>-Stable with inotropes</td>
<td>17.0%(40)</td>
<td>19.7%(44)</td>
<td>0.47</td>
</tr>
<tr>
<td>-Unstable with inotropes / IABP</td>
<td>2.2%(5)</td>
<td>0.5%(1)</td>
<td>0.22</td>
</tr>
<tr>
<td>IABP on admission to ICU</td>
<td>2.1%(5)</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Severe circulatory failure</td>
<td>6.9%(16)</td>
<td>1.3%(3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stroke within 24h post op</td>
<td>0.8%(2)</td>
<td>0.9%(2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dialysis post op</td>
<td>2.6%(6)</td>
<td>0.4%(1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cardiac mortality (in hospital or 30-day)</td>
<td>0.9%(2)</td>
<td>0.4%(1)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Multivariable analysis was added to exclude that significant results obtained in the subgroup analysis were due to a skewed distribution of risk factors. This analysis showed that glutamate infusion was independently associated with a reduced risk of developing severe circulatory failure (OR 0.2; 95% confidence interval 0.04-0.72; p=0.02) (Table 10).

**Table 10. Multivariable analysis of risk factors for severe circulatory failure in patients with CCS class IV angina undergoing isolated CABG.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR</th>
<th>CI(95%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative troponin-T level*</td>
<td>2.2</td>
<td>1.3-3.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Extra-cardiac vascular disease</td>
<td>6.5</td>
<td>1.8-23.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Severe systolic LV-dysfunction</td>
<td>7.3</td>
<td>1.6-34.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>5.1</td>
<td>1.4-18.9</td>
<td>0.01</td>
</tr>
<tr>
<td>ST-depression ≥ 1 mV</td>
<td>3.8</td>
<td>1.0-14.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Intravenous glutamate infusion</td>
<td>0.2</td>
<td>0.04-0.72</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* complete data available from two of the participating centers (n=780)
** data from all three participating centers (n=1222)

Hosmer-Lemeshow goodness-of-fit test-χ² (df 5) = 3.51, p = 0.62.
CI = confidence interval; LV = left ventricular; OR = odds ratio; * per unit change.

**Results for the non-study cohort during the GLUTAMICS-trial period**
During the study period of the GLUTAMICS-trial a total of 2087 patients underwent surgery for acute coronary syndrome at the three participating centers. Of these 2087 patients 1064 were assessed for eligibility. An overview of patient characteristics and outcome for the patients that never were assessed is presented in Table 11.
Table 10. Multivariable analysis of risk factors for severe circulatory failure in patients with CCS class IV angina undergoing isolated CABG.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR</th>
<th>CI (95%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative troponin-T level*</td>
<td>2.2</td>
<td>1.3-3.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Extra-cardiac vascular disease</td>
<td>6.5</td>
<td>1.8-23.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Severe systolic LV-dysfunction</td>
<td>7.3</td>
<td>1.6-34.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>5.1</td>
<td>1.4-18.9</td>
<td>0.01</td>
</tr>
<tr>
<td>ST-depression ≥ 1 mV</td>
<td>3.8</td>
<td>1.0-14.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Intravenous glutamate infusion</td>
<td>0.2</td>
<td>0.04-0.72</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Hosmer-Lemeshow goodness-of-fit test- $\chi^2$ (df 5) = 3.51, $p = 0.62$.

CI = confidence interval; LV = left ventricular; OR = odds ratio; * per unit change.

Results for the non-study cohort during the GLUTAMICS-trial period

During the study period of the GLUTAMICS-trial a total of 2087 patients underwent surgery for acute coronary syndrome at the three participating centers. Of these 2087 patients 1064 were assessed for eligibility. An overview of patient characteristics and outcome for the patients that never were assessed is presented in Table 11.

Table 11. Preoperative, intraoperative and outcome data for patients operated for acute coronary syndrome during the study period but not included in the GLUTAMICS-trial (mean±SD or count n %).

<table>
<thead>
<tr>
<th>Patients operated for acute coronary syndrome during the study period but not included in the GLUTAMICS-trial $(n=780\ast)$</th>
<th>Patients operated for acute coronary syndrome during the study period but not included in the GLUTAMICS-trial $(n=1222\ast\ast)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±9</td>
</tr>
<tr>
<td>Female gender</td>
<td>26.3%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28.1%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8.6%</td>
</tr>
<tr>
<td>Extra-cardiac arterial disease</td>
<td>11.4%</td>
</tr>
<tr>
<td>COPD</td>
<td>7.1%</td>
</tr>
<tr>
<td>Moderate-severe LV-dysfunction</td>
<td>25.9%</td>
</tr>
<tr>
<td>Intravenous nitroglycerine preop</td>
<td>11.5%</td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>44.1%</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>6.1±3.9</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>11.5%</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>3.5±1.2</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>58±29</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>95±47</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>30-day mortality**</td>
<td>4.0%</td>
</tr>
<tr>
<td>Hemodynamic state at completion of surgery</td>
<td></td>
</tr>
<tr>
<td>- Stable without inotropes</td>
<td>65.4%</td>
</tr>
<tr>
<td>- Stable with inotropes</td>
<td>29.7%</td>
</tr>
<tr>
<td>- Unstable with inotropes / IABP</td>
<td>4.3%</td>
</tr>
<tr>
<td>Dialysis post op</td>
<td>2.2%</td>
</tr>
<tr>
<td>Stroke during hospital stay</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

* complete data available from two of the participating centers $(n=780)$

** data from all three participating centers $(n=1222)$
Comment
The GLUTAMICS-trial was terminated after interim analysis, as prespecified stopping criteria (Appendix) were fulfilled with no absolute between group differences regarding the composite primary endpoint or significant difference regarding markers for myocardial injury or postoperative renal function in favor of glutamate. However, subsequent analysis revealed significant between group differences in favor of the glutamate group regarding secondary endpoints related to hemodynamic recovery.

Patients with weaning problems from CPB had substantially shorter ICU-stay and ventilator treatment if they received intravenous glutamate infusion. In more ischemic patients (CCS class IV angina) significantly fewer patients developed severe circulatory failure in the glutamate group. Arterial lactate after weaning from CPB was lower in the glutamate group. No increase in serious or non-serious adverse events in patients receiving intravenous glutamate was detected.
4.4 The influence of inotropes in the GLUTAMICS-trial (Paper IV)

Two of the three participating centers in the GLUTAMICS-trial accounted for 91% of the recruited patients. These centers exhibited markedly different policies regarding preemptive use of inotropic drugs to facilitate weaning from CPB. Inotropic drugs were used preemptively in 23.4% of the patients at Center A compared to 4.5% of the patients at Center B (p<0.0001)

Of all the patients in the GLUTAMICS-trial (n=861), 166 patients received inotropic drugs intraoperatively. These patients were analyzed with regard to the influence of intravenous glutamate infusion on primary and secondary outcome variables.

Comparison of Center A and Center B

A total of 788 patients were included in the GLUTAMICS-trial at center A (n=252) and center B (n=536). Patient characteristics and intraoperative data for centers A and B are given in Table 12.
Table 12. Demographic and intraoperative data for patients at center A and B (mean±SD or count n %).

<table>
<thead>
<tr>
<th>Outcome Center A versus Center B</th>
<th>Center A n=252</th>
<th>Center B n=536</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69±9</td>
<td>68±9</td>
<td>0.63</td>
</tr>
<tr>
<td>Female gender</td>
<td>20.6%</td>
<td>16.6%</td>
<td>0.17</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83±15</td>
<td>82±14</td>
<td>0.46</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>174±9</td>
<td>173±8</td>
<td>0.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.1%</td>
<td>24.8%</td>
<td>0.51</td>
</tr>
<tr>
<td>p-creatinine (µmol/L)</td>
<td>92±34</td>
<td>102±25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6.8%</td>
<td>9.4%</td>
<td>0.22</td>
</tr>
<tr>
<td>Extra-cardiac arterial disease</td>
<td>8.8%</td>
<td>13.4%</td>
<td>0.06</td>
</tr>
<tr>
<td>Active smokers</td>
<td>10.4%</td>
<td>20.5%</td>
<td>0.004</td>
</tr>
<tr>
<td>COPD</td>
<td>6.6%</td>
<td>6.9%</td>
<td>0.94</td>
</tr>
<tr>
<td>LV-dysfunction: moderate</td>
<td>11.2%</td>
<td>16.4%</td>
<td>0.05</td>
</tr>
<tr>
<td>LV-dysfunction: severe</td>
<td>6.4%</td>
<td>3.5%</td>
<td>0.09</td>
</tr>
<tr>
<td>CCS class IV angina</td>
<td>40.9%</td>
<td>68.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina at rest &lt;48h preop</td>
<td>22.5%</td>
<td>21.8%</td>
<td>0.80</td>
</tr>
<tr>
<td>Intravenous nitroglycerine preop</td>
<td>6.0%</td>
<td>9.7%</td>
<td>0.10</td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>49.0%</td>
<td>36.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>5.0±2.8</td>
<td>5.3±2.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>8.7%</td>
<td>3.5%</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>3.6±1.0</td>
<td>3.9±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other operation than isolated CABG</td>
<td>6.4%</td>
<td>3.4%</td>
<td>0.05</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>52±23</td>
<td>55±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>86±32</td>
<td>83±30</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Outcome Center A versus Center B
The incidence of the composite primary endpoint was significantly lower at Center A (4.0% v 8.1%; p=0.03) mainly explained by a lower rate of LV-failure at weaning from CPB. However, the incidence of the secondary endpoint severe circulatory failure did not differ (3.6% v 2.6%). Thirty-day mortality was 1.2% v 1.1%. Primary and major secondary endpoints for Centers A and B are given in Table 13.
Table 13. Outcome for patients at Center A and B (mean±SD or count n %)

<table>
<thead>
<tr>
<th></th>
<th>Center A</th>
<th>Center B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV-failure at weaning from CPB</td>
<td>2.8%</td>
<td>5.4%</td>
<td>0.14</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>1.6%</td>
<td>2.3%</td>
<td>0.79</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.6%</td>
<td>1.5%</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes at weaning from CPB</td>
<td>25.9%</td>
<td>7.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SvO2 at weaning from CPB</td>
<td>74.0±8.2</td>
<td>70.9±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>a-Lactate mmol/L 5 minutes after protamine</td>
<td>1.68±0.7</td>
<td>1.72±0.5</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Hemodynamic state at completion of surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stable without inotropes</td>
<td>57.9%</td>
<td>86.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Stable with inotropes</td>
<td>41.3%</td>
<td>11.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Unstable with inotropes / IABP</td>
<td>0.8%</td>
<td>1.1%</td>
<td>1.0</td>
</tr>
<tr>
<td>IABP on admission to ICU</td>
<td>0.4%</td>
<td>0.7%</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe circulatory failure</td>
<td>3.6%</td>
<td>2.6%</td>
<td>0.5</td>
</tr>
<tr>
<td>Stroke within 24h post op</td>
<td>1.2%</td>
<td>1.1%</td>
<td>1.0</td>
</tr>
<tr>
<td>Dialysis post op</td>
<td>1.6%</td>
<td>0.8%</td>
<td>0.28</td>
</tr>
<tr>
<td>Postop increase of p-Creatinine (Δ µmol/L)</td>
<td>12±43</td>
<td>6±33</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiac mortality (in hospital or 30-day)</td>
<td>0.8%</td>
<td>0.6%</td>
<td>0.66</td>
</tr>
</tbody>
</table>

**Influence of glutamate in patients receiving inotropes intraoperatively**

Inotropic drugs were instituted intraoperatively in 166 patients. The most commonly used inotropic drugs were milrinone (58.8%) and epinephrine (46.4%). Levosimendan (7.3%), dopamine (4.2%) and dopexamine (1.8%) were also used. Of the 166 patients 78 were in the control group and 88 in the glutamate group. Patient characteristics and intraoperative data are given in Table 14.
Table 14. Demographic and intraoperative data for patients receiving inotropic drugs intraoperatively (n=166), (mean±SD or count n %).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo n=78</th>
<th>Glutamate n=88</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71±9</td>
<td>70±8</td>
<td>0.80</td>
</tr>
<tr>
<td>Female gender</td>
<td>26.9%(21)</td>
<td>25.0%(22)</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37.2%(29)</td>
<td>29.5%(26)</td>
<td>0.33</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>9.1%(7)</td>
<td>10.2%(9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Extra-cardiac arterial disease</td>
<td>11.8%(9)</td>
<td>15.3%(13)</td>
<td>0.65</td>
</tr>
<tr>
<td>COPD</td>
<td>9.2%(7)</td>
<td>14.1%(12)</td>
<td>0.47</td>
</tr>
<tr>
<td>LV-dysfunction: moderate</td>
<td>25.6%(20)</td>
<td>28.4%(25)</td>
<td>0.73</td>
</tr>
<tr>
<td>LV-dysfunction: severe</td>
<td>25.6%(20)</td>
<td>15.9%(14)</td>
<td>0.13</td>
</tr>
<tr>
<td>CCS class IV angina</td>
<td>52.6%(41)</td>
<td>47.7%(42)</td>
<td>0.64</td>
</tr>
<tr>
<td>Angina at rest &lt;48h preop</td>
<td>26.7%(21)</td>
<td>25.6%(23)</td>
<td>1.0</td>
</tr>
<tr>
<td>Intravenous nitroglycerine preop</td>
<td>10.3%(8)</td>
<td>10.2%(9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>47.4%(37)</td>
<td>39.8%(35)</td>
<td>0.35</td>
</tr>
<tr>
<td>Additive EuroSCORE</td>
<td>7.2±3.4</td>
<td>6.8±2.8</td>
<td>0.64</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>9.0%(7)</td>
<td>3.4%(3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Number of bypassed vessels</td>
<td>3.8±0.9</td>
<td>4.1±1.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Other operation than isolated CABG</td>
<td>11.5%(9)</td>
<td>10.2%(9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cross clamp time (minutes)</td>
<td>61±28</td>
<td>61±24</td>
<td>0.79</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>102±40</td>
<td>100±35</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**Outcome**

The primary endpoint did not differ significantly between the glutamate group and the control group in the cohort of patients receiving inotropic drugs intraoperatively (22.7% v 21.8%; p=1.0). Thirty-day mortality was 1.1% in the glutamate group and 2.6% in the control group.

Secondary endpoints showed that significantly fewer patients in the glutamate group were hemodynamically unstable at completion of surgery (1.3% v 9.9%; p=0.03), or arrived to the ICU with IABP (0% v 6.4%; p=0.02). Cardiac mortality was 0% in the glutamate group v 3.8% in the control group (p=0.10).

Primary and major secondary endpoints for patients receiving inotropic drugs intraoperatively are given in Table 15. The postoperative NT-proBNP levels were significantly lower in the glutamate group (Figure 6).
Table 14. Demographic and intraoperative data for patients receiving inotropic drugs intraoperatively (n=166), (mean±SD or count n %).

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<th>p-value</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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Primary and major secondary endpoints for patients receiving inotropic drugs intraoperatively are given in Table 15. The postoperative NT-proBNP levels were significantly lower in the glutamate group (Figure 6).
Comment
This post-hoc analysis suggests that a liberal policy regarding preemptive use of inotropic drugs to facilitate weaning from CPB had a significant influence on the primary endpoint of the GLUTAMICS-trial since LV-failure at weaning from CPB constituted the major component of the composite primary endpoint in the trial. Preemptive use of inotropic drugs did not, however, lower the incidence of severe circulatory failure.

Glutamate infusion was associated with significantly lower postoperative NT-proBNP levels, fewer patients hemodynamically unstable at completion of surgery or in need of IABP on arrival to the ICU.
5 General discussion

Postoperative heart failure precipitated by myocardial ischemia remains a major cause of postoperative morbidity and mortality after CABG\textsuperscript{2, 6, 13}. Conventional treatment with inotropic drugs is poorly documented with regard to outcome and carries potential hazards due to increased myocardial oxygen demand\textsuperscript{13-5, 9, 26}. In this thesis an alternative approach with the aim to prevent ischemic injury and promote post-ischemic myocardial recovery was studied.

A metabolic strategy to prevent and treat postoperative heart failure involving adherence to physiological principles to minimize myocardial and systemic oxygen expenditure, and metabolic interventions with glutamate and high-dose GIK to increase myocardial tolerance to ischemia and facilitate myocardial recovery after ischemia was evolved during a five-year period\textsuperscript{100}. Based on encouraging clinical results in patients with LV-dysfunction the GLUTAMICS-trial was initiated. In this trial 861 patients undergoing surgery for acute coronary syndrome were randomly allocated to blinded intravenous infusion of L-glutamic acid or saline. The trial was conducted at three cardiac surgery centers in Sweden according to the principles of Good Clinical Practice including professional external monitoring. The event rate in the GLUTAMICS-trial was lower than anticipated reducing the power of the trial and no difference regarding the primary endpoint – a composite of postoperative mortality, perioperative myocardial infarction or LV-failure on weaning from CPB – was detected. However, regarding secondary endpoints significant differences compatible with a beneficial effect of glutamate on post-ischemic myocardial recovery was found.
5.1 Metabolic strategy in CABG patients with LV-dysfunction

This is one of few studies to address this category of patients from a perspective of perioperative management and it raises important questions that deserve to be addressed in future studies. The metabolic strategy evolved during a five-year period and the study cohort of patients with LV-dysfunction comprises 104 patients from a cohort of 775 patients operated for ischemic heart disease by two surgeons.

Figure 7. Demonstrating the shift in preferred therapy from 1991-1995 in 775 patients when the metabolic strategy was introduced.

The metabolic strategy was associated with lower 30-day mortality (1.0%) than previously reported in patients with severe LV-dysfunction undergoing CABG. It was also substantially lower than the expected risk adjusted mortality of 8.3% according to logistic EuroSCORE. Long-term survival was an even more encouraging with a crude 5-year survival of 89.4%.
Alternative measures that can enhance myocardial recovery and function without putting further strain on the heart are particularly desirable in patients with limited myocardial reserve. Our experience demonstrates that traditional pharmacological inotropic support for weaning from CPB can be replaced by alternative measures even in patients with severely compromised LV-function without jeopardizing renal function. As the confidence in the metabolic strategy grew the use of inotropes for weaning from CPB during the latter half of the studied period was reduced to 2.6%. The average doses of inotropes when used were low (Paper I), usually in the dose interval known to enhance renal perfusion.

Some degree of extended CPB was employed in virtually all patients and CPB was substantially extended in patients with weaning difficulty with an average reperfusion time of approximately 80 minutes to permit myocardial recovery during metabolic support. The potential adverse effects of CPB are well known and many surgeons advocate short perfusion times and even avoidance of CPB. However, our results suggest that under certain circumstances the benefits of unloading the heart may outweigh the drawbacks of CPB. These results are in agreement with Royster et al who found that long pump times were associated with lower need for inotropes after coronary surgery on patients with LVEF ≤ 0.45. In animals premature use of inotropic drugs for weaning from CPB has been shown to impede metabolic and functional recovery of the heart.

It can be argued that a strategy that accepts low cardiac outputs could jeopardize perfusion of vital organs. Renal function is a sensitive marker of the adequacy of hemodynamic treatment. This report and previous experience show that patients with compromised ventricular function and even overt postoperative heart failure can be treated with a low incidence of renal complications. In this study an increase of s-creatinine by 50% or more compared to preoperative values was found in 2.9% of the cases, which is substantially lower than the 16% overall incidence after CABG surgery reported from a comparable Scandinavian Center.

The metabolic strategy comprises a multimodal approach and although it is difficult to discern the relative importance of each issue from the present study, all major aspects have been addressed separately by our group and others. To elucidate the clinical role of glutamate or high-dose GIK adequately powered randomized trials are necessary. From other areas of surgical research it has been argued that it may be difficult to improve clinical outcome with single measures and that a multimodal approach might be necessary to achieve such aims.
5.2 The GLUTAMICS-trial

Several hundred experimental interventions have been reported to protect the ischemic myocardium in animals; however, with the exception of early reperfusion, none has been translated into clinical practice according to Bolli et al.\textsuperscript{108}. Lack of commercial interest in substances not protected by patents may have limited the conductance of adequately powered randomized controlled trials. Glutamate is one of these substrates that has been claimed to protect the heart from ischemia and facilitate metabolic and hemodynamic recovery after ischemic insults\textsuperscript{58, 59, 76-83, 85, 87, 92-94, 98, 109, 110}.

Based on the encouraging clinical experience with the metabolic strategy the GLUTAMICS-trial was initiated (Paper III). In this trial we decided to focus on the clinical effects of intravenous glutamate infusion rather than high-dose GIK because of several reasons. Intravenous glutamate is easy to administer, it does not require specific monitoring and it can be studied in a blinded fashion\textsuperscript{111}. Furthermore, it would have been difficult to interpret the results if both interventions had been investigated simultaneously and the sample size required to investigate both interventions separately was beyond our resources. Also, in our clinical practice based on the Leuven experience, high-dose GIK had been replaced by a modified blood glucose protocol similar to the STS guidelines\textsuperscript{22, 112}.

Patients with acute coronary syndrome were chosen for the GLUTAMICS-trial as they represented the largest risk group in our practice. Since the planning of the trial the proportion of patients with unstable angina undergoing CABG decreased in favor of patients accepted for urgent surgery due to non-STEMI. Patients requiring emergency surgery were not eligible because of ethical reasons further contributing to lower than anticipated event rates. Thus, it is questionable if the cohort studied can be regarded a high-risk group. The incidence of the primary endpoint was also influenced by clinical management, as will be discussed below.

No significant between group differences were found regarding the composite primary endpoint or markers for myocardial injury or postoperative renal function. The latter finding implied that prespecified stopping criteria were fulfilled at interim analysis and, hence, the study was terminated. Subsequent analysis revealed significant between group differences in favor of the glutamate group regarding secondary endpoints related to hemodynamic recovery.

The results are compatible with the hypothesis that glutamate mitigates postoperative heart failure by enhancing myocardial recovery. Although the incidence of LV-failure at weaning from CPB did not differ between the groups, post-hoc analysis revealed that patients with weaning problems treated with glutamate had substantially shorter ICU stay and ventilator

\begin{table}
\centering
\begin{tabular}{lcl}
\hline
 & Placebo & Glutamate \\
\hline
n & 18 & 20 \\
\hline
a-Lactate mmol/L 5 minutes after protamine & 2.5±1.0 & 1.7±0.5 \\
\hline
Hemodynamic state at completion of surgery & & \\
- Unstable with inotropes / IABP & 31\% (5/16) & 0 \%
- Severe circulatory failure & 56\% (10/18) & 15\% (3/20) \\
\hline
Postop increase of ∆p-Creatinine (µmol/L) & 58±87 & 19±34 \\
\hline
Ventilator treatment (hours) & 7.4 [5.8-49] & 5.0 [3.3-8.0] \\
\hline
ICU stay (hours) & 92 [41-139] & 25 [18-57] \\
\hline
\end{tabular}
\caption{Outcome data for patients with LV-failure at weaning from CPB (median + interquartile range, mean±SD or count n \%)}
\end{table}
treatment (Figure 5). Patients with heart failure at weaning from CPB were those in whom the first encouraging clinical experience with intravenous glutamate was obtained in our practice. Unpublished clinical results for this category of patients in the GLUTAMICS-trial, further support the above suggested mechanism (Table 16).

Table 16. Outcome data for patients with LV-failure at weaning from CPB (median+ interquartile range, mean±SD or count n %).

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=18</th>
<th>Glutamate n=20</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-Lactate mmol/L 5 minutes after protamine</td>
<td>2.5±1.0</td>
<td>1.7±0.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemodynamic state at completion of surgery - Unstable with inotropes / IABP</td>
<td>31% (5/16)</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Severe circulatory failure</td>
<td>56%(10/18)</td>
<td>15%(3/20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Postop increase of p-Creatinine (Δ μmol/L)</td>
<td>58±87</td>
<td>19±34</td>
<td>0.08</td>
</tr>
<tr>
<td>Ventilator treatment (hours)</td>
<td>7.4 [5.8-49]</td>
<td>5.0 [3.3-8.0]</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU stay (hours)</td>
<td>92 [41-139]</td>
<td>25 [18-57]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Patients with CCS class IV angina undergoing isolated CABG were analyzed separately to address the issue of unstable angina. In this cohort significantly fewer patients developed severe circulatory failure in the glutamate group. Multivariable analysis identified intravenous glutamate infusion as the only independent variable associated with a reduced incidence of severe circulatory failure.

To conclude, in this investigator initiated trial on 861 patients with acute coronary syndrome undergoing CABG glutamate did not prevent perioperative myocardial infarction or postoperative heart failure but the results are compatible with a beneficial effect of glutamate on post-ischemic myocardial recovery.
5.3 The influence of inotropic drugs in the GLUTAMICS-trial

The aim of this study (Paper IV) was to investigate if preemptive use of inotropic drugs influenced the primary endpoint of the GLUTAMICS trial and if glutamate influenced outcome in patients receiving inotropes intraoperatively.

At an early stage of the GLUTAMICS-trial the clinical endpoints committee identified that preemptive use of inotropic drugs in patients with anticipated circulatory problems often prohibited the diagnosis of heart failure on weaning from CPB even in patients that later developed severe circulatory failure.

The fact that the two major centers participating in the trial exhibited markedly different policies regarding preemptive use of inotropic drugs permitted us to assess its implications on the primary endpoint. The results of our post-hoc analysis agree with the clinical impression of the clinical endpoints committee.

A liberal policy for preemptive use of inotropic drugs to facilitate weaning from CPB was associated with more patients developing severe circulatory failure than fulfilled criteria for LV-failure at weaning from CPB. A restrictive policy was associated with the opposite finding. Given that LV-failure at weaning from CPB constituted the major component of the composite primary endpoint we conclude that preemptive use of inotropic drugs had substantial implications on the primary endpoint of the GLUTAMICS-trial.

The choice of primary endpoint was based on clinical experience with metabolic interventions employing restrictive use of inotropic drugs. However, participating centers and individual clinicians were free to institute inotropic drugs according to their choice and usual practice. In retrospect, the discrepancy in the use of inotropic drugs between center A and B is not unexpected given the lack of generally accepted guidelines for inotropic therapy.

The secondary endpoint late circulatory failure was added to the protocol as an amendment to identify these cases. In conjunction with the secondary endpoint severe circulatory failure it allowed discrimination of mild short-lasting heart failure at weaning from CPB from clinically significant heart failure requiring substantial circulatory support and leading to prolonged ICU stay or death.

The patients that received inotropic drugs intraoperatively were those in whom circulatory failure was anticipated or manifest. Patients at higher risk are obviously better suited to evaluate metabolic intervention assumed to enhance myocardial recovery (Figure 8). In patients that received ino-
tropic drugs intraoperatively, intravenous glutamate infusion was associated with significantly fewer patients hemodynamically unstable at completion of surgery or in need of IABP on admission to ICU.

Postoperative NT-proBNP levels were also significantly lower in the glutamate group (Figure 6).

Figure 8. Proportion of patients hemodynamically unstable at completion of surgery despite inotropes or in need of IABP.

To conclude, a liberal policy regarding preemptive use of inotropic drugs to facilitate weaning from CPB had a significant influence on the primary endpoint of the GLUTAMICS-trial but did not lower the incidence of severe circulatory failure. Intravenous glutamate infusion was associated with a beneficial effect on hemodynamic outcome in patients receiving inotropic drugs intraoperatively.
5.4 Defining postoperative heart failure

Although postoperative heart failure is a major cause for postoperative mortality there are no generally accepted criteria for this diagnosis, and the criteria used are inevitably debatable.

In the GLUTAMICS-trial we addressed this issue by using criteria based on variables documented with regard to outcome and we provided the blinded clinical endpoints committee with strict prespecified criteria to minimize bias from individual clinical judgement\textsuperscript{100, 113-115}.

The clinical endpoints committee consisted of consultants in cardiothoracic surgery and cardiothoracic anesthesiology from each of the participating centers. The members of the committee were blinded to the treatment assignment and prespecified criteria reported in the Appendix were used to reach a consensus decision.

All cases with suspected postoperative heart failure based on SvO\textsubscript{2} and other hemodynamic data, use of inotropic drugs or mechanical circulatory support, extended ICU stay, circulatory problems reported by anesthesiologists or surgeons in the clinical database were reviewed. Based on prespecified criteria (Appendix) the committee decided whether circulatory problems had occurred, if these circulatory problems were severe and if they were cardiac in origin, if they were evident at weaning from CPB or presented later in the postoperative course. The committee also decided if events leading to death were cardiac in origin.

LV-failure at weaning from CPB constituted a major component of the composite primary endpoint in the GLUTAMICS-trial. The complexity of defining heart failure at weaning from CPB and postoperative heart failure in general emphasizes the need for robust endpoints and definitions in both clinical management and when evaluating novel circulatory treatment. To discriminate mild short-lasting heart failure at weaning from CPB from clinically significant heart failure requiring substantial circulatory support and leading to prolonged ICU stay or death we introduced the secondary endpoint severe circulatory failure as an amendment to the study protocol.

With increasing acknowledgement of NT-proBNP as a reliable marker of the severity of heart failure\textsuperscript{116-123}, an amendment was filed to the Swedish MPA to add this marker to the study protocol. The results of NT-proBNP analyses were blinded to the clinical endpoints committee and, hence, permitted evaluation of the clinical endpoint committee decisions with an unbiased marker (Figure 9).
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All cases with suspected postoperative heart failure based on SvO2 and other hemodynamic data, use of inotropic drugs or mechanical circulatory support, extended ICU stay, circulatory problems reported by anesthesiologists or surgeons in the clinical database were reviewed. Based on prespecified criteria (Appendix) the committee decided whether circulatory problems had occurred, if these circulatory problems were severe and if they were cardiac in origin, if they were evident at weaning from CPB or presented later in the postoperative course. The committee also decided if events leading to death were cardiac in origin.

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5.5 Biochemical mechanisms of glutamate

Intravenous glutamate infusion according to the protocol in the GLUTAMICS-trial could influence postoperative outcome by two different biochemical mechanisms. First, glutamate could improve myocardial tolerance to ischemia by facilitated anaerobic metabolism during ischemia. In the present study, no clinical evidence for this mechanism was detected by markers of myocardial injury or the incidence perioperative myocardial infarction.

The second mechanism by which glutamate could improve postoperative outcome after coronary surgery is related to the anaplerotic role of glutamate. Glutamate contributes to replenishment of Krebs cycle intermediates lost during ischemia, which enhances recovery of myocardial metabolism.
and function. The results of this trial are compatible with enhanced post-ischemic myocardial recovery.

Promoting recovery represents a different and more appealing concept than the use of inotropic drugs, which increase oxygen expenditure regardless of the state of myocardial recovery. This may have contributed to the low cardiac mortality in the glutamate group and could explain the encouraging clinical outcomes previously reported with metabolic interventions.

5.6 Adverse events

There have been concerns regarding the safety of intravenous administration of glutamate. In the central nervous system glutamate acts as an excitatory neurotransmitter. Under certain conditions it may act as an excitotoxin and participate in events leading to neurological damage. Glutamate administration has been shown to cause neurological injury in rodents but not in primates due to the blood-brain barrier that prevents passage of exogenous glutamate to the brain. Furthermore, the concentration of glutamate in the brain is fifty-fold higher than in human plasma.

The pathophysiological role of exogenously administered glutamate in patients undergoing cardiac surgery with CPB and potential blood brain barrier dysfunction remains to be clarified. Assessment of this issue is obscured by the fact that cardiac surgery per se is associated with a substantial risk of neurological injury. Available data have not demonstrated any increase in clinically evident neurological injury when glutamate enhanced cardioplegic solutions or intravenous infusions have been used in clinical practice.

In our clinical practice neurological complications have been monitored continuously. As an early safety measure in the GLUTAMICS trial a specified subgroup of patients were analyzed with regard to postoperative S-100B levels to detect potential subclinical neurological injury related to intravenous glutamate infusion (Paper II).

The Swedish Medical Products Agency requested surveillance and unblinding in cases of CT-verified stroke within 24 hours of surgery, mortality and suspected unexpected serious adverse reactions (SUSAR). Before unblinding was done the case was reviewed by the Clinical endpoints committee if suspected circulatory problems had occurred.

The S-100B substudy of the GLUTAMICS trial and the outcome data from the whole GLUTAMICS trial show no differences in neurological outcome and there was no evidence of subclinical neurological injury associated with intravenous glutamate infusion.

Regarding other serious and non-serious adverse events no statistically significant differences were found between the glutamate group and control group (Appendix).

To conclude we found that intravenous glutamate infusions in the dosages employed can be safely administered to patients undergoing cardiac surgery.
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To conclude we found that intravenous glutamate infusions in the dosages employed can be safely administered to patients undergoing cardiac surgery.
5.7 Limitations
This thesis consists of data from an observational study and from a randomized clinical trial. A major limitation regarding Paper I is of course that it, like most studies on patients with severe LV-dysfunction undergoing CABG, is retrospective and observational.

The major limitation of Paper IV is that although the same inclusion criteria were employed demographics of patients included at center A and center B differed. Demographics for patients randomized to glutamate infusion or placebo receiving inotropes intraoperatively were more comparable but the results have to be interpreted cautiously as they are based on a post-hoc analysis.

Regarding the GLUTAMICS-trial there are certain study limitations that deserve comment. The issues concerning patient selection and the definition of postoperative heart failure have been discussed above.

The major findings in the GLUTAMICS-trial are related to secondary outcomes and subgroup analyses, which are somewhat provisional even when prespecified. However, the results should be regarded in the context of current evidence. Treatment for postoperative heart failure is based on expert opinion and the need for large studies to assess the optimal way to manage postoperative heart failure has been emphasized.

5.8 Clinical perspectives
The importance of clinical trials is receiving increased attention in cardiac surgery but there is still a chasm to bridge before our practice is permeated by evidence-based medicine.

Without a generally accepted definition of myocardial infarction the rapid evolution in the cardiological management of myocardial infarction would never have occurred. To some extent the situation in cardiac surgery resembles the situation in cardiology fifty years ago when cardiologist GE Burch stated that it was interesting that nobody wanted to define myocardial infarction but that everybody talked about it and all seemed to know what they were talking about129. In cardiac surgery several of the most important complications such as postoperative renal failure, postoperative myocardial infarction and postoperative heart failure lack generally accepted definitions6, 7, 103, 104, 130. A recent paper demonstrated that by choosing different definitions of renal failure the incidence, patient identification and risk-factors were influenced104. Before the issue of definitions is addressed evaluation of treatment of these conditions will be impeded and dissemination of progress may be delayed.
In 1979 E. Rau proposed that use of glutamate could provide an important step in efforts to protect cardiac tissue during stress induced at cardiac surgery or by ischemia. Despite this and other animal experimental data suggesting a beneficial effect of glutamate in association with myocardial ischemia further exploration of clinical benefits in humans has been sparse. Lack of commercial interest and fears of potential neurological adverse effects could explain this.

Our long-standing clinical experience and a prospective randomized double-blind clinical trial in 861 patients suggest that intravenous glutamate infusion could provide a novel and clinically important way of promoting myocardial recovery after ischemic injury.

Further studies are warranted to confirm these results and to elucidate the role of metabolic intervention with glutamate for other high-risk groups in cardiac surgery. Eventually glutamate could find a role in the management of acute post-ischemic heart failure in cardiology practice.

Intravenous glutamate infusion in the dosages employed in our experience provides a safe and inexpensive treatment. Paradoxically, the latter may be an issue due to the lack of commercial interest and obstruct clinical exploration in the future.
A metabolic strategy to prevent and treat postoperative heart failure involving adherence to physiological principles to minimize myocardial and systemic oxygen expenditure, and metabolic interventions with glutamate and high-dose GIK to increase myocardial tolerance to ischemia and facilitate myocardial recovery after ischemia was evolved during a five-year period. The metabolic strategy allowed restrictive use of inotropes and was associated with short-term and long-term survival that compares favorably with the literature in patients with LV-dysfunction undergoing CABG. The metabolic strategy was associated with particularly encouraging results regarding preservation of renal function. The GLUTAMICS-trial was an investigator-initiated randomized clinical trial investigating if intravenous glutamate infusion given in association with surgery for acute coronary syndrome can reduce mortality and prevent or mitigate myocardial injury and postoperative heart failure. The trial was conducted according to the principles of Good Clinical Practice including professional external monitoring. The composite primary endpoint did not differ between the glutamate group and the control group. The event rates in the GLUTAMICS-trial were substantially lower than calculated reducing the power of the trial. A liberal policy regarding preemptive use of inotropic drugs to facilitate weaning from CPB influenced the primary endpoint of the GLUTAMICS-trial further reducing the power of the trial. Patients with LV-failure on weaning from CPB had significantly shorter ventilator treatment and ICU-stay if they received intravenous glutamate infusion.
Summary

- A metabolic strategy to prevent and treat postoperative heart failure involving adherence to physiological principles to minimize myocardial and systemic oxygen expenditure, and metabolic interventions with glutamate and high-dose GIK to increase myocardial tolerance to ischemia and facilitate myocardial recovery after ischemia was evolved during a five-year period.

- The metabolic strategy allowed restrictive use of inotropes and was associated with short-term and long-term survival that compares favorably with the literature in patients with LV-dysfunction undergoing CABG.

- The metabolic strategy was associated with particularly encouraging results regarding preservation of renal function.

- The GLUTAMICS-trial was an investigator-initiated randomized clinical trial investigating if intravenous glutamate infusion given in association with surgery for acute coronary syndrome can reduce mortality and prevent or mitigate myocardial injury and postoperative heart failure.

- The trial was conducted according to the principles of Good Clinical Practice including professional external monitoring.

- The composite primary endpoint did not differ between the glutamate group and the control group.

- The event rates in the GLUTAMICS-trial were substantially lower than calculated reducing the power of the trial.

- A liberal policy regarding preemptive use of inotropic drugs to facilitate weaning from CPB influenced the primary endpoint of the GLUTAMICS-trial further reducing the power of the trial.

- Patients with LV-failure on weaning from CPB had significantly shorter ventilator treatment and ICU-stay if they received intravenous glutamate infusion.
- In patients with unstable angina (CCS class IV) undergoing isolated CABG intravenous glutamate infusion was associated with significantly lower arterial lactate early after weaning from CPB.

- In patients with unstable angina (CCS class IV) undergoing isolated CABG intravenous glutamate infusion was associated with significantly lower incidence of severe circulatory failure.

- In patients with unstable angina (CCS class IV) undergoing isolated CABG multivariable analysis identified intravenous glutamate infusion as the only independent variable associated with a reduced incidence of severe circulatory failure.

- In patients receiving inotropic drugs intraoperatively intravenous glutamate infusion was associated with significantly fewer patients hemodynamically unstable or in need of IABP.

- In patients receiving inotropic drugs intraoperatively intravenous glutamate infusion was associated with significantly lower postoperative NT-proBNP.

- Intravenous glutamate infusion during surgery for acute coronary syndrome did not initiate a sustained elevation of plasma S-100B postoperatively.

- Intravenous glutamate infusion during surgery for acute coronary syndrome was not associated with an increased incidence of neurological injury or other adverse events.
Conclusions

- The metabolic strategy was associated with encouraging clinical results, unsurpassed in the literature, in patients with LV-dysfunction undergoing CABG.

- Intravenous glutamate infusion did not improve the composite primary endpoint but was associated with secondary outcomes compatible with a beneficial effect on post-ischemic myocardial recovery.

- The putative effect on post-ischemic myocardial recovery was seen in more ischemic patients (CCS class IV) and in patients with evident or anticipated LV-failure on weaning from CPB.

- Intravenous glutamate infusion in association with surgery for acute coronary syndrome was safe in the dosages employed.

- Intravenous glutamate infusion could provide a novel and important way of promoting myocardial recovery after ischemic injury.
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The work in this thesis was carried out at the Departments of Cardiothoracic Surgery and Anesthesiology at Örebro University Hospital, the University Hospital of Linköping and at Blekinge County Hospital, Karlskrona.

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I would like to express my gratitude to all who have helped and supported me to complete the studies that have resulted in this thesis.

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My second supervisor, Örjan Friberg, for leading me over the first thresholds in scientific work. Your great support has helped me a lot, and your knowledge regarding the Carath database has been invaluable.

My co-authors Erik Håkanson, Jonas Holm, Farkas Vanky, Lena Sunnermalm, Rajiv Sharma, Jan-Olov Borg and Sören Juhl-Andersen for your important contributions to this work.

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### Table 8

Patients operated for acute coronary syndrome during the study period but not included in the Glutamics trial (n=780*)

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>4.0%</td>
</tr>
<tr>
<td>Inotropes in OR &gt; 30 minutes</td>
<td>34.2%</td>
</tr>
<tr>
<td>Hemodynamic state at completion of surgery</td>
<td></td>
</tr>
<tr>
<td>- Stable without inotropes</td>
<td>65.4%</td>
</tr>
<tr>
<td>- Stable with inotropes</td>
<td>29.7%</td>
</tr>
<tr>
<td>- Unstable with inotropes / IABP</td>
<td>4.3%</td>
</tr>
<tr>
<td>CK-MB µg/L day 1 post op</td>
<td>15 (10-27)</td>
</tr>
<tr>
<td>Troponin-T µg/L day 3 post op</td>
<td>0.4 (0.1-1.4)</td>
</tr>
<tr>
<td>Peak p-Creatinine µmol/L</td>
<td>121 ± 86</td>
</tr>
<tr>
<td>Dialysis post op</td>
<td>2.2%</td>
</tr>
<tr>
<td>Length of ICU stay (hours)</td>
<td>22 (18 -37)</td>
</tr>
<tr>
<td>Time on ventilator (hours)</td>
<td>5.3 (3.5-8.8)</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>32.8%</td>
</tr>
<tr>
<td>Reoperation due to bleeding/tamponade</td>
<td>5.8%</td>
</tr>
<tr>
<td>Reoperation sternal infection/dehiscense</td>
<td>1.7%</td>
</tr>
<tr>
<td>Stroke during hospital stay</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

*complete data available from two of the participating centers (n=780) **data from all three participating centers (n=1222)


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