Glucose, insulin and potassium for heart protection during cardiac surgery

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Background. Coronary artery bypass grafting with hypothermic cardiac arrest and cardiopulmonary bypass (CPB) is associated with myocardial injury. Our study investigated whether an infusion of glucose, insulin and potassium (GIK) during elective coronary artery bypass surgery decreases myocardial cell death.

Methods. We measured cardiac troponin I (cTnI), a myofibrillar structural protein, which is a sensitive and specific indicator of myocytic injury. With ethics committee approval, 42 patients were enrolled into a randomized, prospective, double-blinded study. In the GIK group, 500 ml of 50% dextrose solution containing 100 IU insulin and potassium 80 mmol was infused at the rate of 0.75 ml kg⁻¹ h⁻¹. Patients in the non-GIK group received 5% dextrose solution at the same rate. Arterial blood samples were taken before induction of anaesthesia, after removal of the aortic clamp and 6 and 12 h after CPB.

Results. In both groups there was an increase in cTnI concentration (P<0.05), which was greatest about 6 h after CPB. At no time did the cTnI concentration differ between the two groups.

Conclusion. The results suggest that GIK does not decrease the irreversible myocardial damage associated with routine coronary artery bypass surgery.

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Table 1  Patient characteristics. Values are mean (SD), number (%) or ratio

<table>
<thead>
<tr>
<th></th>
<th>GIK group (19 patients)</th>
<th>Non-GIK group (20 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.3 (9.9)</td>
<td>66.3 (10.4)</td>
</tr>
<tr>
<td>Gender ratio (M:F)</td>
<td>19:0</td>
<td>15:5</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>80.3 (22.3)</td>
<td>69.5 (20.3)</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>50.7 (13.7)</td>
<td>45.2 (12.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (90%)</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>14 (74%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Preoperative ejection fraction &lt;45%</td>
<td>9 (47%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>10 (53%)</td>
<td>8 (40%)</td>
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</table>

Methods

With local ethics committee approval and informed patient consent, we conducted a double-blinded prospective randomized study of 42 patients scheduled for elective coronary artery bypass grafting. Three patients were excluded from analysis, two because of incomplete sampling and one because of missing randomization. All patients who electively received at least two bypass grafts were included in the study. Exclusion criteria were an abnormal creatinine concentration and type 1 and type 2 diabetes. Assessment of ejection fraction was part of the routine preoperative evaluation.

Patients received either 50% glucose 500 ml containing insulin 100 IU and potassium 80 mmol at a rate of 0.75 ml kg⁻¹ h⁻¹ (GIK group) or an equivalent rate of 5% dextrose (non-GIK group), given into a central vein. The infusion started immediately after induction of anaesthesia and stopped at the end of surgery. Blood glucose was measured hourly and insulin was given according to a sliding scale to maintain blood glucose between 4 and 10 mmol litre⁻¹. Potassium was added to achieve a plasma concentration of 4–6 mmol litre⁻¹. Peripheral arterial blood samples were collected for cTnI analysis before induction of anaesthesia, after removal of the aortic cross-clamp and 6 and 12 h after CPB.

Surgical and anaesthetic technique

A standardized anaesthetic technique was used for all patients. Premedication consisted of oral temazepam 20 mg and ranitidine 150 mg. Anaesthesia was induced with fentanyl 10–15 µg kg⁻¹ and propofol 2 mg kg⁻¹. A single dose of vecuronium 0.15 mg kg⁻¹ was used for muscle relaxation. Anaesthesia was maintained with 30% oxygen in nitrous oxide and isoflurane before CPB. End-expiratory isoflurane concentration was held between 0.6 and 0.8%. Thereafter, a propofol infusion of 100–350 mg h⁻¹ was used to maintain anaesthesia until transfer to the recovery area. Supplementary i.v. fentanyl was administered according to the discretion of the anaesthetist up to a maximum of 500 µg. Inotropic drugs were administered only when required to facilitate separation from CPB.

The same surgeon operated on all patients. Cardiopulmonary bypass was achieved with a roller pump and membrane oxygenator with mild hypothermia of 32°C. Multiple anterograde doses of St Thomas’ cardioplegia solution in cold (6°C) oxygenated blood were infused for myocardial preservation. St Thomas’ solution contains magnesium chloride BP 3.253 g, potassium chloride BP 1.193 g and procaine hydrochloride BP 272.8 mg in 20 ml.

CPB time, aortic cross-clamp time and reperfusion time were noted. Mean arterial pressure was maintained between 50 and 60 mm Hg either by adjusting pump flow or with small boluses of phenylephrine. Anticoagulation was with heparin 300 IU kg⁻¹ and further doses to maintain an activated clotting time greater than 480 s.

Blood sampling and laboratory analysis

Blood samples were taken into tubes without anticoagulant and centrifuged at 2500 g for 20 min. The serum obtained was then stored at −70°C until analysis.

Quantitative cTnI analysis was performed using the Bayer Immuno-1 assay (Bayer, Leverkusen, Germany), a heterogeneous sandwich magnetic separation system using mouse monoclonal and goat polyclonal anti-cTnI antibodies. Both antibodies were directed to epitopes at the centre of the cTnI molecule. The detection antibodies were labelled with alkaline phosphatase and addition of substrate subsequently gives a colour change directly proportional to the cTnI concentration. The assay had a detection limit of 0.1 µg litre⁻¹ and an analytical range up to 200 µg litre⁻¹. The interassay coefficient of variation was 6% at a concentration of 0.2 µg litre⁻¹, which was the manufacturer’s recommended clinical discriminatory level for myocardial injury (cTnI ≥0.9 µg litre⁻¹ is considered diagnostic of acute myocardial infarction).

Statistical analysis

A power analysis showed that 17 patients in each group would be required to detect a mean difference of 0.9 (SD 0.8) µg litre⁻¹ in cTnI concentration between the two groups at any of the time points with a power of 90% and a P value of 0.05. The cTnI data were assessed with the Shapiro–Wilk test of normality and were distributed asymmetrically. Non-parametric statistical tests were therefore used for cTnI analysis. The Mann–Whitney U-test was used to test for differences in cTnI concentration between groups at each time point. Changes in cTnI concentration over time within groups were assessed by Friedman analysis of variance (ANOVA) and the Wilcoxon signed ranks test. Fisher’s exact test was used to determine whether there was a significant difference in the proportion of patients with a low ejection fraction (<45%) in the GIK group compared with the non-GIK group. Other categorical data, including all patient proportions (hypertension, hypercholesterolaemia, preoperative myocardial infarction, gender ratio), were
also assessed with Fisher’s exact test. The Mann–Whitney U-test was used to determine whether cTnI concentrations were greater in patients with low ejection fractions. The relationship between cross-clamp time and cTnI concentration was evaluated by Spearman correlation analysis. Patient age, CPB time, aortic cross-clamp time and blood glucose and blood potassium concentrations were normally distributed and were assessed with parametric statistical tests. Differences in these variables between the GIK and non-GIK groups were assessed with the unpaired t-test. Changes in potassium and glucose concentrations over time within groups were examined by ANOVA and paired t-tests. P<0.05 was regarded as significant for all tests. All statistical tests were carried out with Analyse-it software (Analyse-it, Leeds, UK).

**Results**

The groups were well matched for age and number of bypass grafts (Table 1). Four patients in group 1 and three patients in group 2 each had four grafts, and four in each group each received two grafts. All other patients had three coronary artery grafts with at least one internal mammary artery graft.

Randomization did not give an equal distribution of male and female patients. Ten patients (53%) in the GIK group and eight (40%) in the non-GIK group had suffered a previous myocardial infarct. Nine out of 19 patients (47%) in the GIK group had an ejection fraction less than 45%, compared with only three out of 20 (15%) in the non-GIK group (P=0.06). Mean operation times, cross-clamp times and CPB times did not differ between the two groups (Table 1).

Before operation, all patients were on beta-blockers and aspirin; the latter was stopped 5 days before surgery. A large number were also taking cholesterol-lowering medications and angiotensin-converting enzyme inhibitors.

**Inotropic support**

In the GIK group, two patients received an epinephrine infusion and two patients required ventricular pacing to facilitate weaning from CPB. In the non-GIK group, one patient received epinephrine, one patient received dopamine 2 μg kg⁻¹ min⁻¹ and one patient needed ventricular pacing. No patient developed ECG changes after surgery that were suggestive of acute myocardial infarction.

**Blood glucose concentration**

None of the patients in the non-GIK group needed insulin to maintain blood sugar within the normal range. Twelve patients in the GIK group required additional doses of insulin. Blood glucose concentrations in the recovery phase were within the normal range in both groups (Figs 1 and 2). There were significant changes in blood concentrations in both the GIK and the non-GIK group over time (P<0.05). Glucose concentrations were greater in the GIK than in the non-GIK group during the entire intraoperative period (P<0.05). Three hours and 12 h after CPB, the blood glucose concentration was slightly lower in the GIK than in the non-GIK group (P<0.05).

There were significant changes in blood potassium concentration in both the GIK and the non-GIK group over time (P<0.05). Potassium concentration was lower in the GIK than in the non-GIK group from 1 h after induction of anaesthesia until the time of arrival in the intensive care unit (P<0.05) (Fig. 1).
cTnI concentration (Fig. 3)

No patient had a significantly raised baseline cTnI concentration. In both groups there was an increase in cTnI concentration (P<0.05), in keeping with myocardial cell injury after cardiac surgery, which peaked about 6 h after CPB. At no time was there a significant difference in cTnI between the two groups (P>0.05) (Fig. 3). There was also no difference in cTnI concentration at any time point between patients with low and those with normal ejection fractions (P>0.05). There was a strong correlation between cross-clamp time and peak cTnI concentration (rS=0.57, P<0.001) (Fig. 4).

Discussion

Cardiac surgery with hypothermic cardioplegic arrest causes some myocardial cell death, even in patients with no ECG changes and uneventful recovery.13 Perioperative myocardial infarction is a clinically recognizable form of such damage and has an adverse effect on outcome.12

There is reason to believe that GIK infusion should aid recovery of the heart and decrease ischaemic injury during cardiac surgery using bypass. The possible benefits of GIK include the following.

(i) A glycogen-sparing effect by the supply of substrate to the cells during ischaemia.4 5

(ii) Increased ATP synthesis. During hypoxia there is depletion of energy-rich phosphates such as ATP, and glycolysis is important in the maintenance of myocardial viability.14 ATP produced by oxidative phosphorylation is used preferentially to support myocyte contractile activity by supplying energy to the actin–myosin-ATPase.15 Under normal circumstances, oxidative metabolism of free fatty acids is the predominant energy source for the myocardium. After reperfusion, oxidative metabolism of free fatty acids resumes but seems to be reduced after ischaemia.6 14 16

Bunger and colleagues showed that, during the change from anaerobic to aerobic metabolism, glycolytic activity is critical for functional recovery of the heart and GIK could serve as a substrate.17

(iii) Maintenance of sarcoplasmic reticulum function and calcium homeostasis. Another explanation for a protective role of GIK is a possible compartmentation of glycolytic and oxidative ATPase.15 18 This renders ATP derived from glycolysis vital for the recovery of the sarcoplasmic reticulum (SR) function after hypoxia. In a study conducted by Xu and colleagues,15 sarcoplasmic reticulum vesicles from skeletal and cardiac muscle were isolated to investigate whether the energy derived from glycolysis was functionally coupled to active calcium transport in the SR. They found that the entire chain of glycolytic enzymes was associated with SR vesicles producing the ATP that was needed to maintain calcium pump function and thus SR membrane integrity. This suggests that there is functional coupling of glycolytic ATP to calcium transport and thus cell homeostasis.

(iv) Free radical scavenging activity.19

(v) Reduction in free fatty acid concentration. This is an insulin-related effect. Free fatty acids can harm cell membranes under hypoxic conditions, causing calcium overload, arrhythmias and cell death.5 6

(vi) Decreased coronary artery resistance leading to increased myocardial perfusion.3 4

We studied whether GIK decreases the amount of irreversible myocytic injury during coronary artery bypass grafting, in contrast to other studies, which assessed functional recovery of the heart.

To quantify the amount of myocardial damage perioperatively, we used cTnI, a sensitive and reliable marker for the detection of perioperative myocardial infarction.11 The maximum value can be used to quantify the extent of myocardial cell death.11 20 cTnI is accepted as a marker of perioperative risk stratification in cardiac risk patients.
undergoing non-cardiac surgery and in patients undergoing coronary bypass grafting, because its concentration is related to the amount of irreversible cell injury. Higher perioperative concentrations are associated with more postoperative complications. It has also been used to indicate underlying cardiac injury in intensive care patients and to examine the benefit of different solutions and temperatures of cardioplegia. The heart is most likely to sustain ischaemic injury when the aortic cross-clamp is applied. This is supported by our finding of a correlation between cross-clamp time and peak cTnI concentration.

In this study, despite the theoretical protective effects of GIK listed above and the reliability of cTnI as a marker of myocardial cell damage, no cardioprotective effect of GIK was observed. We did not find a significant difference in cTnI concentration between the two groups. The median values of both groups (Fig. 3) after 6 and 12 h showed that some myocardial death had occurred during surgery, supporting the findings of other studies, but there was no difference between GIK- and non-GIK-treated patients. Before concluding that GIK confers no protective effect on the myocardium during CABG surgery, other possible reasons for our negative findings should be considered.

We used a high dose of GIK, as recommended in other studies, but this was only given during surgery. It might be of more benefit if started before surgery and continued for 12–48 h after surgery, as suggested by other studies. Oldfield and colleagues examined the effect of GIK on complications of mitral valve replacement and demonstrated an increased myocardial glycogen content after an infusion of GIK 12 h before the operation. This reduced complications after surgery, such as hypothermia and arrhythmia. Lazar and colleagues found better cardiac performance and faster recovery from urgent coronary bypass grafting in patients with unstable angina given GIK infusion for 12 h after operation. These patients had greater cardiac output, a significantly lower incidence of atrial fibrillation (13.3 vs 53.3%; P = 0.02) and a shorter stay in intensive care.

GIK might be beneficial in patients with decreased cardiac reserve, poor left ventricular function and/or cardiogenic shock. Patients with a high risk of death may be more likely to benefit from metabolic therapy. Patients with insulin-dependent diabetes might benefit particularly from GIK, as shown in the DIGAMI study for patients with myocardial infarct. A recent study by Lazar and colleagues found better cardiac performance and faster recovery after coronary bypass grafting in a group of 40 diabetic patients. Postoperative GIK infusion for 48 h is of benefit in patients with refractory cardiac failure after hypothermic cardiac arrest for bypass grafting.

Limitations of our study
It is possible that our study was too small and the groups too poorly matched to reveal the benefit of GIK. The different proportions of male and female patients in the GIK and non-GIK groups is unlikely to have influenced the results, but this possibility cannot be excluded. The possible influence of the ejection fraction was analysed retrospectively. Nine out of 19 patients in our GIK group and only three in the non-GIK group had an ejection fraction of less than 45% (P = 0.06). The importance of the ejection fraction as a confounding factor is uncertain as there was no significant difference in cTnI concentration at any time point between patients with low and those with normal ejection fractions. It remains speculative whether those patients in the GIK group with poor cardiac function would have had higher cTnI concentrations without GIK infusion. Differences in preoperative ventricular function can affect postoperative recovery but not necessarily the postoperative cTnI concentration, which specifically indicates myocardial cell death. It would be useful to conduct a larger study in diabetic patients or patients with decreased left ventricular function, testing for an even smaller difference in cTn concentrations, and to relate cTnI to functional recovery of the heart. One problem with a high-concentration glucose infusion is hyperglycaemia during CPB, which could damage the brain and worsen neurological outcome. Hyperglycaemia may aggravate ischaemic brain injury and be harmful after acute head injury. The critical glucose concentration at which treatment should be initiated is not known. A confounding factor is that high glucose concentrations may indicate severe head injury, as hyperglycaemia is a general stress response. However, there is consensus that the blood glucose concentration should be maintained within the normal range. Measuring glucose and potassium concentrations regularly is necessary. Blood glucose concentrations were higher in the GIK group implying that, in future studies, more insulin should be added to the glucose solution. Another concern is that increasing glycolysis can increase the concentrations of end-products such as lactate. Lactate accumulation is associated with inhibition of glycolysis and mitochondrial changes leading to cell damage, but in an animal study treatment with glucose did not affect the lactate concentration.

Conclusion
We did not find that the use of GIK infusion during surgery reduced myocardial cell damage associated with cardiac surgery and CPB. However, it was associated with increased hyperglycaemia. As hyperglycaemia may worsen the neurological outcome, routine GIK infusions cannot be recommended until studies have been performed that demonstrate the value of this practice and determine which patients are most likely to benefit.
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