Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: A randomized controlled trial

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Supplemental material is available online.

Objective: We sought to assess the role of glucose-insulin-potassium in providing myocardial protection in nondiabetic patients undergoing coronary artery surgery with cardiopulmonary bypass.

Methods: A prospective, randomized, double-blind, placebo-controlled trial was conducted at a single-center university hospital performing adult cardiac surgery. Two hundred eighty nondiabetic adult patients undergoing first-time elective or urgent isolated multivessel coronary artery bypass grafting were prospectively randomized to receive glucose-insulin-potassium infusion or placebo (dextrose 5%) before, during, and for 6 hours after surgical intervention. Anesthetic, cardiopulmonary bypass, myocardial protection, and surgical techniques were standardized. The primary end point was postreperfusion cardiac index. Secondary end points were systemic vascular resistance index, the incidence of low cardiac output episodes, inotrope and vasoconstrictor use, and biochemical-electrocardiographic evidence of myocardial injury. The incidence of dysrhythmias and infections requiring treatment was recorded prospectively.

Results: The glucose-insulin-potassium group experienced higher cardiac indices ($P < .001$) throughout infusion and reduced vascular resistance ($P < .001$). The incidence of low cardiac output episodes was 15.9% (22/138) in the glucose-insulin-potassium group and 27.5% (39/142) in the placebo group ($P = .021$). Inotropes were required in 18.8% (26/138) of the glucose-insulin-potassium group and 40.8% (58/142) of the placebo group ($P < .001$). Fewer patients in the glucose-insulin-potassium group (12.3% [16/133]) versus those in the placebo group (23.4% [32/137]) had significant myocardial injury ($P = .017$). Noncardiac morbidity was not different.

Conclusion: Glucose-insulin-potassium therapy improves early postoperative cardiovascular performance, reduces inotrope requirement, and might reduce myocardial injury. These potential benefits are not at the expense of increased noncardiac morbidity.

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During coronary artery bypass grafting (CABG), the myocardium endures periods of ischemia and reperfusion. For on-pump CABG, ischemic protection is usually afforded by cardioplegia, which establishes electromechanical arrest and reduces myocardial oxygen consumption. Despite this, CABG might be followed by myocardial contractile dysfunction, which is associated with increased early and late morbidity and mortality and necessitates inotropic and mechanical circulatory support.^{1,2} Metabolic modulation with glucose-insulin-potassium (GIK) might improve myocardial protection, particularly in diabetic patients.³ A survival benefit has been noted when early high-dose GIK has been used after acute myocardial infarction,⁴⁻⁶ and GIK might reduce the requirement for

Abbreviations and acronyms

AF	= atrial fibrillation
ANOVA	= analysis of variance
CABG	= coronary artery bypass grafting
CI	= cardiac index
CPB	= cardiopulmonary bypass
cTnI	= cardiac troponin I
ECG	= electrocardiogram
GIK	= glucose-insulin-potassium
IQR	= interquartile range
ITU	= intensive therapy unit
LCOE	= episodes of low cardiac output
NYHA	= New York Heart Association
PMI	= perioperative myocardial infarction
SD	= standard deviation
SVR	= systemic vascular resistance
SVRI	= systemic vascular resistance index
WBG	= whole blood glucose

postsurgical circulatory support.⁷ Additionally, insulin therapy in intensive care patients has been associated with reduced mortality.⁸ A recent meta-analysis of 11 trials (n = 468) of GIK in cardiac surgery suggested that GIK improved cardiac index (CI) and reduced inotrope requirement and the incidence of atrial fibrillation (AF)⁹ and called for a multicenter randomized controlled trial of GIK in cardiac surgery. The aim of this study was to examine the effects of GIK on cardiovascular performance and myocardial injury in nondiabetic patients undergoing CABG.

Materials and Methods

A double-blind, prospective, randomized, placebo-controlled trial was conducted in 280 patients undergoing isolated CABG between January 2000 and August 2002. The study was approved by the local research ethics committee, and all patients provided written informed consent. Inclusion criteria were age of 18 years or older and an intention to perform first-time multivessel CABG. Exclusion criteria included diabetes mellitus, serum creatinine level of 200 $\mu\text{mol/L}$ or greater, recent (<6 weeks) cerebrovascular event, and emergency status. Before the trial, computer-generated randomization schedules were generated in advance, stratified by surgeon and left ventricular function, and placed in sequentially numbered sealed envelopes. Trial investigators and medical and nursing staff were blinded to allocation.

Trial Intervention

GIK and placebo (5% dextrose) solutions were independently prepared immediately preoperatively in identical containers and administered from sternotomy to 6 hours after release of the aortic crossclamp as a continuous central intravenous infusion at $0.75 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The GIK solution comprised 40% dextrose containing 70 IU/L human Actrapid insulin (Novo Nordisk A/S, Bagsvaerd, Denmark) and 80 mmol/L potassium chloride.

Anesthetic, Operative, and Postoperative Protocols

Anesthesia, cardiopulmonary bypass (CPB), myocardial protection, and surgical techniques were standardized. Anesthesia was induced with intravenous etomidate, fentanyl, and pancuronium and maintained with enflurane, propofol, and alfentanil. CPB (28°C) was instituted with a roller pump and membrane oxygenator with an asanguineous prime. Intermittent antegrade cold blood St Thomas' No. 2 cardioplegia (Martindale Pharmaceuticals, Essex, United Kingdom) containing no glucose was used for myocardial protection (12 mL/kg for induction and 6 mL/kg at 20-minute intervals). Distal anastomoses were constructed during a single crossclamp period, and proximal anastomoses were constructed during partial aortic occlusion. After rewarming with a 37°C maximal heat-exchanger temperature, CPB was discontinued at 36°C-37°C nasopharyngeal temperature. Intraoperative ventricular tachydysrhythmias were treated with internal cardioversion or lidocaine. Intravenous glycopyrrolate, atropine, and atrial or dual-chamber epicardial pacing were used to achieve a target heart rate of 70 to 110 beats/min. Arterial whole blood glucose (WBG) samples were drawn at baseline, every half hour before CPB, every 20 minutes during CPB, every hour for the initial 6 hours of reperfusion, and every 2 hours for the subsequent 6 hours. Supplemental insulin (human Actrapid, Novo Nordisk) was administered according to a simple standardized sliding scale with a target WBG value of 180 to 270 mg/dL. Patients with a WBG value of 180 to 270 mg/dL received a 4-IU intravenous bolus of insulin and 5 IU/h continuous intravenous infusion until the next test schedule, and patients with a WBG value of 271 to 360 mg/dL received an 8-IU intravenous bolus and 10 IU/h continuous intravenous infusion. Supplemental infused insulin was stopped 1 hour before trial solution cessation in both groups and restarted 1 hour later according to protocol. Inotropic support, initially with dopamine ($3\text{--}10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and secondly with epinephrine, was commenced if the mean arterial pressure was less than 65 mm Hg with a CI of $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or less in the presence of a central venous pressure of 12 mm Hg, a pulmonary capillary wedge pressure of 14 mm Hg, and a heart rate of 70 to 110 beats/min. Support was also permitted if the operating surgeon identified poor contractility at separation of CPB or if marginal hemodynamics were noted by attending physicians. Intravenous vasoconstrictors were used for a mean arterial pressure of less than 65 mm Hg, a systemic vascular resistance (SVR) of less than $800 \text{ dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$, and a CI of greater than $3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Bolus phenylephrine was used until the administration of protamine, after which norepinephrine infusion was used as a vasoconstrictor. Extubation, intensive therapy unit (ITU), and hospital discharge criteria and AF management were standardized.

Trial Investigations

Before surgical intervention, baseline demographic and clinical data were recorded. Hemodynamic studies were performed before infusion, before and 15 minutes after protamine administration, and 2, 4, 6, 9, and 12 hours after reperfusion. Cardiac troponin I (cTnI) samples were drawn at baseline and 6, 12, 24, 48, and 72 hours after reperfusion and analyzed in batches with a commercial assay (Bayer Corp, Tarrytown, NY). Preoperative, postoperative day 1, and postoperative 4 electrocardiograms (ECGs) were obtained.

Outcome Measures

The primary outcome measure was comparison of CI. Secondary outcomes included systemic vascular resistance index (SVRI), incidence of myocardial injury on ECG and enzymatic criteria, episodes of low cardiac output (LCOE), and inotrope and vasoconstrictor requirement. Perioperative myocardial infarction (PMI), assessed by an independent cardiologist, was defined by the presence of new left bundle branch block or new Q waves of 2 mm in depth in 2 contiguous leads by postoperative day 4. Myocardial injury was predefined as PMI, a cTnI value of 13.1 ng/mL, or both 6 hours after reperfusion.¹⁰ An LCOE, as assessed by a blinded committee, was defined as a CI of $2.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or less with a central venous pressure of 12 mm Hg and a pulmonary capillary

wedge pressure of 14 mm Hg in the presence of a native or paced synchronized heart rate of greater than 70 beats/min. The individual total weight-indexed dose of dopamine was calculated. Serial WBG concentrations and supplemental insulin requirements were recorded. Reperfusion ventricular fibrillation was noted. Postoperative atrial dysrhythmias were defined as those requiring pharmacologic or electrical cardioversion. Type I and II neurologic deficits were diagnosed according to published criteria by attending ITU physicians.¹¹

Statistical Analysis

For 280 patients, the study had a 95% power to detect a change in CI of $0.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ at a significance level of 1% (assumed

Figure 1. Cardiac index (CI), systemic vascular resistance index (SVRI), and pulmonary capillary wedge pressure (PCWP) in placebo (open diamonds) and glucose-insulin-potassium (GIK; solid circles) groups at predetermined time points (mean $\pm$ 95% confidence intervals). Data analysis was performed with repeated-measures analysis of variance (ANOVA; $P < .001$ for CI and SVRI). For individual time points, asterisks indicate a P value of less than .05. PCWP was not statistically different at any time point.

standard deviation [SD] of 0.6). Data were analyzed with SPSS software. Categorical or ordinal data were compared by using χ^2 tests or Kendall tau b, respectively. Continuous data are presented as means (95% confidence limits) unless stated otherwise. Normally distributed data were compared by means of independent t test. Repeated-measures analysis of variance (ANOVA) was used for serial measurements. Skewed data were either logarithmically transformed or analyzed nonparametrically (Mann-Whitney U test). The denominator for percentages accounts for missing data (<1.5% for any specific end point). We performed multivariable binary logistic and linear regression analyses to identify predictors of myocardial injury, LCOE, inotrope use, time to extubation, and ITU and hospital length of stay.

Results

From 284 patients initially enrolled, 4 were excluded (postponement of operation [$n = 2$], new diabetes [$n = 1$], and a requirement for aortic valve replacement [$n = 1$]). Of 280 patients studied, 138 were assigned to the GIK group, and 142 were assigned to the placebo group. There were no differences between groups for demographic or intraoperative variables, including angina status, priority, left ventricular function, and medications (Table E1). Specifically, there was no difference in the preischemic trial infusion time (GIK mean, 82 minutes [SD, 23.8 minutes]; placebo mean, 84 minutes [SD, 24.2 minutes]; $P = .527$), CPB time (GIK mean, 88.3 minutes [SD, 25.2 minutes]; placebo mean, 88.8 minutes [SD, 28.4 minutes]; $P = .858$), and aortic cross-clamp time (GIK mean, 48.9 minutes [SD, 15.6 minutes]; placebo, 47.5 minutes [SD, 18.5 minutes]; $P = .508$). There

were 5 (1.8%) deaths (GIK group, $n = 3$; $P = .68$), and 8 patients (GIK group, $n = 4$) required postoperative intra-aortic balloon pump support. Patients in both groups received a median of 3 grafts (interquartile range [IQR], 2-3).

Hemodynamic Effects

Baseline CI was not different (GIK group, $2.24 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ [95% confidence limits, $2.14\text{-}2.74 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$]; placebo group, $2.16 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, [95% confidence limits, $2.07\text{-}2.26 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$]; $P = .145$), but patients in the GIK group had a higher CI during infusion ($P < .001$). Baseline SVRI was similar (GIK group, $2607 \text{ dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ [95% confidence limits, $2459\text{-}2755 \text{ dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$]; placebo group, $2543 \text{ dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ [95% confidence limits, $2409\text{-}2677 \text{ dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$]; $P = .72$) but was significantly lower in the GIK group during the infusion ($P < .001$), increasing after infusion cessation ($P = .41$; time points 0, 9, and 12 hours after aortic crossclamp removal; Figure 1). Pulmonary capillary wedge pressure, central venous pressure, and heart rate were not different between groups at any time point.

Low Cardiac Output and Inotrope and Vasoconstrictor Requirements

During the first 6 hours of reperfusion, the incidence of LCOE was lower in the GIK group (GIK group, 22/138 [15.9%]; placebo group, 39/142 [27.5%]; $P = .021$; Figure 2). During this period, GIK particularly reduced the incidence of LCOE in patients in New York Heart Association

Figure 2. Incidence (%) of low cardiac output episodes (LCOE) and inotrope use 0 to 6 hours after reperfusion and myocardial injury in all patients, patients with New York Heart Association (NYHA) classes III or IV, and patients with a left ventricular ejection fraction (LVEF) of less than 50%. GIK, Glucose-insulin-potassium.

Figure 3. Incidence of dopamine and epinephrine use 0 to 6 and 6 to 12 hours after reperfusion and cumulative dosage of dopamine ($\text{mg/kg} \times 10^{-2}$) or epinephrine ($\mu\text{g/kg} \times 10^{-1}$) in all patients and in those receiving dopamine as an inotrope. Error bars represent upper 95% confidence limit. GIK, Glucose-insulin-potassium.

(NYHA) classes III and IV and in those with an ejection fraction of less than 50%.

Fewer patients in the GIK group received inotropic support in the first and subsequent 6 hours after reperfusion (Figures 2 and 3), including patients in NYHA class III or IV and with an ejection fraction of less than 50%, but more patients required norepinephrine (0-6 hours after removal of aortic crossclamp: GIK group, 96/138 [69.6%]; placebo group, 65/142 [45.8%]; $P < .001$; 6-12 hours after removal of aortic cross clamp: GIK group, 85/138 [61.6%]; placebo group, 55/142 [38.7%]; $P < .001$). However, CI was significantly higher in the GIK group before norepinephrine use ($P < .001$), and data were concordant, regardless of need for norepinephrine. If individual patients required inotropes, the cumulative dose received was not different between groups. Similarly, if norepinephrine was required, the dosage received was similar (GIK group, 20.9 mg/kg [95% confidence limits, 18.1-23 mg/kg]; placebo group 20.6 mg/kg [95% confidence limits, 15.6-25.6 mg/kg]; $P = .99$).

Myocardial Injury

The incidence of myocardial injury was lower in the GIK group (GIK group, 16/133 [12.3%]; placebo group, 32/137 [23.4%]; $P = .017$; Figure 2). Electrocardiographic PMI did not differ between groups (GIK group, 6/135 [4.4%]; placebo group, 10/140 [7.1%]; $P = .442$), but fewer patients in the GIK group had a cTnI value of 13.1 ng/mL (GIK group,

11/133 [8.3%]; placebo group, 26/137 [19.0%]; $P = .021$), and 6-hour mean cTnI values were lower (GIK group, 6 ng/mL [95% confidence limits, 5.2-6.8]; placebo group, 9.0 ng/mL [95% confidence limits, 7.5-10.6]; $P = .001$). ANOVA demonstrated a lower cTnI release over 12 hours ($P = .035$) but no difference over 72 hours ($P = .272$, Figure 4).

Metabolic Data

WBG concentration at baseline was similar but increased in both groups during infusion, despite an escalating protocol of supplemental insulin (Figure E1). More patients in the GIK group reached the criterion of a WBG concentration of 180 mmol/L or greater for supplemental insulin by the end of CPB (GIK group, 129/138 [93.5%]; placebo group, 29/142 [20.4%]; $P < .001$) and during the 12 hours after reperfusion (GIK group, 132/138 [95.7%]; placebo, 68/142 [47.9%]; $P < .001$). The total amount of supplemental insulin used in recipients was 5-fold higher in the GIK group (GIK group median, 49.6 IU [IQR, 37.1-72.5 IU]; placebo group median, 10 IU [IQR 7.1-23.4 IU]; $P = .001$). Fifteen patients in the GIK group but no patients in the placebo groups required intravenous 50% dextrose for a WBG value of less than 4 mmol/L.

Neurologic Outcomes

There was no difference in the incidence of type I or II neurologic deficits.

Figure 4. Serum cardiac troponin I (cTnI) levels (ng/mL; from baseline to 72 hours after aortic crossclamp release). Analysis was done with repeated-measures analysis of variance. *GIK*, Glucose-insulin-potassium.

Other Complications

There were no differences in the overall or specified incidence of infection episodes requiring treatment. Also, the incidence of reperfusion ventricular dysrhythmias and new postoperative atrial dysrhythmias was no different between groups. Extubation times and ICU and postoperative hospital lengths of stay were similar (Table 1).

Multivariable Analyses

By using binary logistic regression analysis, nonuse of GIK was an independent predictor of myocardial injury, low cardiac output episodes, and inotrope use (Table 2). Intra-aortic balloon pump use ($P = .001$), postoperative infection ($P = .004$), and use of vasoconstrictors (6-12 hours, $P = .003$) increased the time to extubation. Increasing ITU

TABLE 1. Postoperative results

Variable	GIK group	Placebo group	P value
Type I neurologic deficit, n (%)	2 (1.4)	5 (3.5)	.443
Type II neurologic deficit, n (%)	11 (8)	7 (4.9)	.336
Extubation time (min), median (IQR)	982 (708-1361)	1030 (687-1308)	.90
ITU stay (h), median (IQR)	28 (24-49)	28 (24-49)	.95
Hospital stay (d), median (IQR)	7 (6-10)	7 (6-11)	.41
Postreperfusion VF/VT, n (%)	20 (14.5)	19 (13.4)	.864
Postoperative AF, n (%)	77 (55.8)	66 (46.5)	.122
Treated infections, n (%)	42 (30.4)	33 (23.2)	.429
Chest infection	24 (17.4)	23 (16.2)	.873
UTI	4 (2.9)	7 (4.9)	.541
SSWI	4 (2.9)	4 (2.8)	1
DSWI	4 (2.9)	1 (0.7)	.209
LWI	11 (8.0)	7 (4.9)	.335

Data on extubation and discharge time were transformed. *GIK*, Glucose-insulin-potassium; *IQR*, interquartile range; *ITU*, intensive therapy unit; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *AF*, atrial fibrillation; *UTI*, urinary tract infection; *SSWI*, superficial sternal wound infection; *DSWI*, deep sternal wound infection; *LWI*, leg wound infection.

TABLE 2. Multivariable predictors of myocardial injury, LCOE, and inotrope use

Outcome	Factor	OR (95% CI)	P value
Myocardial injury	Nonuse GIK	2.86 (1.35-5.88)	.006
	NYHA class III/IV	2.9 (1.14-7.34)	.025
	Previous Q-wave MI	2.29 (1.09-4.79)	.028
	No preoperative ACE-I	2.22 (1.0-5.0)	.05
LCOE 0-6 h after AXC off	Nonuse GIK	2.22 (1.01-4.48)	.027
	Myocardial injury	3.3 (1.67-9.6)	.004
	Increasing age (per year)	1.06 (1.01-1.1)	.014
	NYHA III/IV	3.26 (1.4-7.62)	.002
Inotrope use	Nonuse GIK	3.57 (1.81-6.67)	<.001
	Myocardial injury	3.3 (1.48-7.38)	.013
	Male sex	2.52 (1.15-5.56)	.022
	Increasing age (per year)	1.05 (1.01-1.07)	.022
	Increasing clamp time (per minute)	1.04 (1-1.07)	.033
	NYHA III/IV	3.26 (1.4-7.62)	.006
	LMS disease	2.19 (1.02-4.7)	.045

Binary logistic regression analysis was used. *LCOE*, low cardiac output episodes; *OR*, odds ratio; *CI*, confidence interval; *GIK*, glucose-insulin-potassium; *NYHA*, New York Heart Association; *MI*, myocardial infarction; *ACE-I*, angiotensin-converting enzyme inhibitor; *AXC*, aortic crossclamp; *LMS*, left main stem coronary artery.

length of stay was predicted by intra-aortic balloon pump use ($P = .009$), postoperative infection ($P = .002$), extubation time ($P = .001$), and myocardial injury ($P = .05$). NYHA class III or IV ($P = .018$), angina requiring intravenous nitrates ($P = .026$), postoperative infection ($P < .001$), and ITU stay ($P = .003$) predicted overall postoperative length of stay.

Discussion

This study demonstrates that perioperative systemic GIK in on-pump CABG is associated with increased CI, lower vascular resistance, fewer low cardiac output episodes, and less cardiomyocyte injury. GIK treatment reduced the need for inotropic support, even beyond the duration of infusion, but increased vasoconstrictor use. In particular, the hemodynamic benefits of GIK were apparent in patients with heart failure symptoms and reduced ejection fraction, whereas the myocardial protection effect was demonstrable in the lower-risk patients. These findings are important because previous studies have demonstrated that low cardiac output, the need for inotropic support, and biochemical evidence of myocyte injury are important risk factors for prolonged ventilation, ITU stay, and early mortality after CABG.¹ Hyperglycemia after GIK administration was prevalent but was not associated with an increased incidence of brain injury or infection episodes nor did it preclude reduced biochemical markers of myocardial injury, as has been suggested by animal models of hyperglycemia during myocardial ischemia.¹² Postoperative cardiac surgical patients have significant insulin resistance after cooling, and strict glycemic control might be difficult to achieve in the perioperative period. Although active treatment of WBG

concentrations of greater than 120 mg/dL with intravenous insulin benefits patients with sepsis and multiorgan failure with longer ITU stays,⁸ the mechanism by which this is achieved and its relevance to ischemic myocardial protection during cardiac surgery is unclear.

In experimental in vitro and in vivo models, GIK has been shown to have both inotropic and vasodilator properties.¹³⁻¹⁵ Because we did not use load-independent methods to assess myocardial contractility, the relative contribution of these hemodynamic changes cannot be differentiated. Our results, however, are consistent with a mechanism of either improved protection or a vasodilator-inotropic response to GIK and are concordant with previous smaller studies of systemic GIK.^{16,17} Cardiomyocyte injury is a recognized sequel of CABG, and the incidence we observed is comparable with that seen in other studies.¹⁸ Previous work has demonstrated a close relationship between ECG evidence of ischemia-infarction and a cTnI level of 13.1 ng/mL, and this threshold was combined with ECG PMI as our index of myocardial injury.¹⁰ Six-hour postoperative cTnI levels of greater than 13.1 ng/mL were also predictive of low cardiac output and have previously been associated with increased early and 2-year cardiac mortality.^{18,19}

In this study there was an intentional protocol restriction of β -blocker use until postoperative day 4. The observed incidence of AF was high and, in contrast to previous open-label studies and the results from the meta-analysis,⁹ was not reduced by GIK.¹⁶ GIK alone does not confer AF protection, but our findings do not exclude a possible adjunctive antiarrhythmic effect.²⁰ There was no effect on reperfusion ventricular dysrhythmia.

CABG with CPB is associated with brain injury, which could be exacerbated by perturbations in WBG concentration. Although GIK therapy produced episodes of hypoglycemia and hyperglycemia requiring treatment, careful monitoring of WBG and discontinuation of supplemental insulin 1 hour before trial solution cessation minimized hypoglycemia, which, if detected, was promptly treated. We did not observe any greater incidence of type I or type II neurologic injury. However, any detrimental effect of hyperglycemia might have been ameliorated by hypothermia during CPB or by coadministration of insulin, which might be intrinsically neuroprotective.²¹

The dose of GIK is comparable with that used in 2 large acute myocardial infarction studies and in some surgical studies that have demonstrated hemodynamic benefit in postsurgical cardiogenic shock and in patients undergoing urgent CABG.^{5-7,17,22} The optimal timing of GIK infusion in relation to the myocardial ischemic period is undefined. We started the infusion approximately 80 minutes before aortic clamping and continued throughout ischemia and for 6 hours after reperfusion. The relative importance of pre-ischemic, peri-ischemic, and postischemic administration is unclear, but reperfusion of viable cardiomyocytes appears crucial to its efficacy.²³ Without reperfusion, hydrogen ion and lactic acid accumulation frustrate the beneficial metabolic and functional effects.²⁴ Further studies are necessary to discover its optimal timing, duration, and dosage and the effects of subsequent glycemic control on outcome.

If GIK truly improves clinical myocardial protection, its mechanisms of action might include metabolic protection through promotion of cardiac glycolysis, upregulation of glucose transport, and suppression of cardiac nonesterified fatty acid metabolism.^{25,26} These might result in preservation of intracellular glycogen and high-energy phosphates and a reduction of membrane lipid peroxidation.^{27,28} Finally, insulin might have anti-inflammatory, profibronolytic,²⁹ and antiapoptotic effects independent of known metabolic actions.³⁰ The individual clinical effect of these effects is unknown.

It is not known whether the findings are applicable to warm on-pump or off-pump CABG techniques, in which insulin resistance might be lower. It is possible that the administration of norepinephrine augmented the hemodynamic changes seen in the GIK group. However, norepinephrine was commenced once a low SVR–high CI state had been established at 15 minutes after protamine administration. Examination of CI over the time points before norepinephrine use showed that GIK still increased CI ($P < .001$). A subanalysis of norepinephrine recipients only demonstrated a higher CI in the GIK group ($P < .001$, repeated-measures ANOVA) and a lower SVRI ($P < .008$), despite similar doses of norepinephrine, suggesting it was not contributing to the increased CI. Finally, a subanalysis of the CI data

between groups in patients not requiring norepinephrine again demonstrates a higher CI in the GIK group, although statistical significance was not reached (GIK group, $n = 42$; control group, $n = 72$; $P = .111$, log-transformed data, repeated-measures ANOVA) and a significantly lower SVRI ($P = .035$). The magnitude of the change in CI between nonnorepinephrine and norepinephrine recipients was no different ($P = .807$). Thus on the basis of these data, we conclude that GIK truly increased CI but acknowledge the confounding effect of norepinephrine use.

Postoperative hyperglycemia was prevalent, despite supplemental insulin, and we did not change the insulin protocol once the study was in progress because this would have been likely to generate more hypoglycemia in the placebo group, thereby unblinding the study.

Systemic GIK has beneficial cardiovascular and myocardial protective effects when administered in the perioperative period in patients undergoing CABG without apparent increased morbidity, even in the presence of hyperglycemia. It can thus be considered an effective, inexpensive, and safe adjunctive myocardial protective technique but necessitates careful glucose monitoring. Further multicenter studies are required to examine the effect of GIK on mortality, wider aspects of morbidity, and resource use.

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Appendix 1. Study investigators.

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Figure E1. Whole blood glucose (g/m) at baseline, before cardiopulmonary bypass (*Pre CPB*), during cardiopulmonary bypass (*Intra CPB*), and 0-12 hours after aortic crossclamp release. *GIK*, Glucose-insulin-potassium.

TABLE E1. Preoperative and intraoperative variables

Variable	GIK group	Placebo group	P value
Age (y), mean (SD)*	64.4 (8.8)	63.6 (9.07)	.463
Sex* (male:female ratio)	6.3:1	4.3:1	.261
Body surface area (m ²), mean (SD)	1.91 (0.19)	1.91 (0.18)	.762
Treated hypertension, n (%)	71 (51.4)	64 (45.1)	.339
Previous Q-wave MI, n (%)*	55 (39.9)	49 (34.5)	.388
Angina requiring intravenous nitrates, n (%)*	6 (4.3)	8 (5.6)	.785
Previous TIA/CVA, n (%)	3 (2.2)	6 (4.2)	.501
Previous AF, n (%)	9 (6.5)	4 (2.8)	.164
Preoperative medications, n (%)			
Antiplatelets	128 (92.7)	137 (96.5)	.192
β -Adrenergic antagonists*	106 (76.8)	100 (70.4)	.278
Angiotensin-converting enzyme inhibitor*	50 (36.2)	46 (32.4)	.530
Potassium channel blocker*	40 (29)	29 (20.4)	.127
Calcium channel antagonists*	72 (52.2)	77 (54.2)	.811
Lipid-lowering agents*	108 (78.3)	122 (85.9)	.118
Elective:urgent*	2.37:1	2.55:1	.79
Preoperative cholesterol (mmol/L), mean (SD)	4.26 (1.1)	4.4 (1)	.123
CCS score, n (%)			.240
I	10 (7.25)	7 (4.9)	
II	41 (29.7)	60 (42.3)	
III	50 (36.2)	41 (28.9)	
IV	37 (26.8)	34 (23.9)	
NYHA class, n (%)*			.423
I/II	117 (84.8)	133 (86.7)	
III/IV	21 (15.2)	19 (13.3)	
Parsonnet score, median (IQR)	4 (2-8.25)	4 (1.75-10)	.89
LV function, n (%)*			.89
EF $\geq$ 50%	99 (71.7)	100 (70.4)	
EF <50%	39 (28.3)	42 (29.6)	
LMS stenosis $\geq$ 50%, n (%)*	33 (23.9)	22 (15.5)	.098
Preischemic infusion time (min), mean (SD)*	82 (23.8)	84 (24.4)	.527
CPB time (min), mean (SD)*	88.3 (25.2)	88.8 (28.4)	.858
AXC time (min), mean (SD)*	48.9 (15.6)	47.5 (18.5)	.508

GIK, Glucose-insulin-potassium; SD, standard deviation; MI, myocardial infarction; TIA, transient ischemic attack; CVA, cerebrovascular accident; AF, atrial fibrillation; Urgent, coronary artery bypass grafting performed during admission episode for unstable angina–acute coronary syndrome; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; IQR, interquartile range; LV, left ventricular; EF, ejection fraction (estimated by means of ventriculography or echocardiographically); LMS, left main stem; Preischemic infusion time, time from infusion start to aortic crossclamp; CPB, cardiopulmonary bypass; AXC, aortic crossclamp. *Factor that was included in the multivariable analyses. Significant myocardial injury was included as an additional factor for low cardiac output episodes and dopamine requirements 0 to 6 hours after release of aortic crossclamp.