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Myocardial protection by glucose–insulin–potassium in acute coronary syndrome patients undergoing urgent multivessel off-pump coronary artery bypass surgery

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Editor's key points

- Effects of glucose–insulin–potassium (GIK) infusion on myocardial damage during coronary artery surgery were studied.
- Biomarkers of myocardial damage were measured after reperfusion of the heart in patients with or without the ongoing infusion.
- GIK attenuated the levels of creatinine kinase-MB and troponin-T.
- This study provides biochemical evidence of myocardial protective role of GIK infusion.

Background. The aim of this randomized and controlled trial was to investigate the effect of a glucose–insulin–potassium (GIK) solution on myocardial protection in acute coronary syndrome (ACS) patients undergoing urgent multivessel off-pump coronary artery bypass (OPCAB) surgery.

Methods. Sixty-six patients were randomly allocated either to receive 0.3 ml kg^{-1} h^{-2} GIK solution (potassium 80 mEq and regular insulin 325 IU in 500 ml of 50% glucose) or equivalent volume of normal saline (control) upon anaesthetic induction until 6 h after reperfusion. The primary endpoints were to compare the concentrations of creatine kinase-MB (CK-MB) and troponin-T between the groups after reperfusion. The secondary endpoints were to compare the incidences of postoperative troponin-T >0.8 ng ml^{-1} and myocardial infarction (MI) between the groups.

Results. Highest CK-MB [8.7 (4.4) *vs* 13.1 (7.9) ng ml^{-1}, P=0.006] and troponin-T [0.20 (0.13–0.49) *vs* 0.48 (0.18–0.91) ng ml^{-1}, P<0.0001] values after reperfusion were significantly lower in the GIK group compared with the control group. The area under the curve of serially measured troponin-T was also significantly smaller in the GIK group compared with the control group [0.83 (0.43–1.81) *vs* 0.46 (0.31–1.00), P=0.036]. Significantly fewer patients in the GIK group showed troponin-T >0.8 ng ml^{-1} after reperfusion compared with the control group (3 *vs* 11, P=0.033). The incidence of postoperative MI was similar between the groups.

Conclusions. GIK administration in ACS patients undergoing urgent multivessel OPCAB significantly attenuated the degree of ensuing myocardial injury without complications related to glycaemic control.

Clinical Trial Registry. URL: http://clinicaltrials.gov/ct2/show/NCT01384656?term=GIK+AND+OPCAB&rank=1. Unique identification number NCT01384656.

Keywords: acute coronary syndrome; insulin; myocardial injury; OPCAB; troponin T

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In patients with multivessel coronary artery disease and acute coronary syndrome (ACS), urgent coronary artery bypass surgery (CABG) is a well-established treatment. Unfortunately, these patients are at increased risk of myocardial infarction (MI), rehospitalization, and cardiac death after CABG compared with patients with stable angina pectoris.[1 2]

Recently, off-pump CABG (OPCAB) is gaining renewed interest for being associated with improved outcome in high-risk patients compared with on-pump CABG.[3 4] In patients with ACS presenting for emergent CABG, OPCAB was also associated with improved hospital outcome.[5] Moreover, in the era of dual antiplatelet therapy, OPCAB may especially be valuable for ACS patients, as it has been safely performed without increased risk of procedural bleeding in patients on continued clopidogrel therapy close to surgery.[6 7]

Although different from the global myocardial ischaemia–reperfusion injury observed in on-pump CABG, multivessel OPCAB produces cumulative warm regional myocardial ischaemia–reperfusion injury.[8] Accordingly, the myocardium remains vulnerable to various degrees of injury with unavoidable periods of regional myocardial stunning and impaired cardiac performance.[9] Thus, an effective myocardial

protective strategy, especially in high-risk patients such as ACS patients requiring urgent surgical revascularization, seems to be mandatory.

In order to minimize ischaemic myocardial injury, glucose–insulin–potassium (GIK) solution has been used for almost five decades in various clinical settings for its metabolic and non-metabolic cardioprotective mechanisms. GIK as an adjunct to revascularization after acute MI has been shown to offer significant survival benefit.[10] In the cardiac surgical setting, a recent meta-analysis also showed beneficial effects of GIK solution in terms of reduced myocardial injury and improved haemodynamic performance.[11] Yet, evidence regarding the myocardial protective effect of GIK in ACS patients undergoing OPCAB is lacking.

The aim of this prospective, single-site, double-blind, randomized, and parallel-arm controlled trial was to investigate the effect of a GIK solution on myocardial protection in ACS patients undergoing urgent OPCAB. The primary endpoints were to compare the concentrations of creatine kinase-MB (CK-MB) and troponin-T between the groups during the perioperative period as markers of myocardial injury. The secondary endpoints were to compare the incidences of troponin-T >0.8 ng ml^{-1},[12] postoperative MI, and outcome between the groups.

Methods

Patients

After Institutional Review Board approval and written informed consent was obtained, 66 patients with ACS requiring urgent multivessel OPCAB between February 2011 and October 2011 at Severance Hospital were prospectively studied. This study was registered with ClinicalTrials.gov (*Ref: NCT01384656*). Urgency was defined as OPCAB performed during the index admission within 2 days of diagnosis-confirmation by coronary angiography. Patients were randomly allocated to either the GIK or the control group in 1:1 ratio by means of random numbers generated by a computer. An anaesthesiologist not involved in the current trial performed randomization and assignment. Exclusion criteria were emergent and/or redo surgery, insulin-dependent diabetes, serum fasting blood glucose concentration >13.8 mmol litre^{-1}, liver dysfunction, confirmed renal impairment [serum creatinine (Cr) >2 mg dl^{-1}], mechanical cardiopulmonary support (patients who are already on mechanical ventilation, intra-aortic balloon pump, or both before operation), and emergency conversion to an on-pump CABG. We had not excluded patients with recent MI as we enrolled ACS patients, which encompass patients with non-ST elevation MI, ST elevation MI, and unstable angina (data provided in Table 1). There was no lower limit for the left ventricular ejection fraction (LVEF). However, we excluded patients who were already on intra-aortic balloon pump before operation due to severe heart failure and haemodynamic compromise as described above.

Table 1 Patients' characteristics. Values are mean (range) for age, mean (SD) or number of patients (%). GIK, glucose–insulin–potassium; MI, myocardial infarction

	Control ($n=33$)	GIK ($n=33$)	*P*-value
Age (yr)	67 (7–79)	64 (48–76)	0.157
Gender (M/F)	23/10	20/13	0.606
Body mass index (kg m^{-2})	24 (3)	24 (3)	0.949
Left ventricular ejection fraction (%)	39 (9)	35 (11)	0.089
Diabetes	12 (36)	19 (58)	0.138
Hypertension	17 (52)	19 (58)	0.805
Recent MI (<1 month)	13 (39)	16 (49)	0.620
Unstable angina/non ST-elevation MI	31 (94)	30 (91)	1.000
ST-elevation MI	2 (6)	3 (9)	1.000
Left main disease	3 (9)	5 (15)	0.708
Degree of stenosis (%)			
Left anterior descending	82 (13)	86 (10)	0.195
Left circumflex	80 (21)	77 (26)	0.684
Right coronary artery	83 (14)	85 (15)	0.773
Creatinine (mg dl^{-1})	1.0 (0.2)	1.0 (0.2)	0.321
Medications			
Nitrates	5 (15)	7 (21)	0.751
β-Blockers	22 (67)	22 (67)	1.000
Calcium channel blockers	12 (36)	8 (24)	0.422
Renin–angiotensin system antagonists	17 (52)	20 (61)	0.620
Statins	11 (35)	9 (28)	0.595

Treatment

Patients in the GIK group received 0.3 ml kg^{-1} h^{-2} GIK solution (potassium 80 mEq and regular insulin 325 IU in 500 ml of 50% glucose) via the central venous route upon anaesthetic induction until 6 h after reperfusion. Patients in the control group received equivalent volume of normal saline for the same duration. Solutions were prepared by an anaesthesia nurse and administered by an anaesthesiologist who were both not involved in this study. Attending surgeon and anaesthesiologist involved in the patient care were blinded to the patients' groups.

In all patients, arterial blood gas analyses were performed every hour until discontinuation of the treatment or placebo. Serum glucose concentration was serially measured by arterial blood gas analysis and was maintained between 4 and 11 mmol litre^{-1} using regular insulin or 50% glucose, as necessary. Serum potassium concentration was also serially measured by arterial blood gas analysis and maintained between 3.5 and 5.5 mEq litre^{-1}.

Perioperative management

All patients received standardized perioperative care. Standard monitoring included a pulmonary artery catheter (Swan–Ganz CCOmbo CCO/SvO$_2$^{TM}, Edwards Lifesciences

LLC, Irvine, CA, USA) and transoesophageal echocardiography. Anaesthesia was induced with midazolam (0.05–0.07 mg kg^{-1}) and sufentanil (1.5–2 $\mu g\ kg^{-1}$), and then maintained with sufentanil (1.0–1.5 $\mu g\ kg^{-1}\ h^{-2}$) with sevoflurane (0.8–1.5%) to maintain the bispectral index score between 40 and 60. Neuromuscular block was achieved with rocuronium.

All surgical procedures were performed by a single surgical team through a full sternotomy incision. During grafting, the heart was displaced using a posterior pericardial stitch, large gauze (12×70 cm) swabs, and a suction-type tissue stabilizer. Routine sequence of revascularization was as follows. The left internal thoracic artery was grafted to the left anterior descending coronary artery first, followed by revascularizations of the diagonal branch, left circumflex coronary artery, and the right coronary artery as required. These were achieved by way of composite graft reconstruction using the radial artery or the saphenous vein to the left or the right internal thoracic artery, and/or by using the saphenous vein anastomized to the ascending aorta, or both, as necessary.

Major goals of haemodynamic management were to maintain mixed venous oxygen saturation (Sv_{O_2}) > 60% and the mean systemic arterial pressure between 60 and 80 mm Hg. Milrinone (0.3–0.5 $\mu g\ kg^{-1}\ min^{-2}$) was infused in patients with Sv_{O_2} < 60% for >10 min, despite the optimization of preload and haematocrit and/or newly developed mitral regurgitation ≥grade 3 with a concomitant increase in the mean pulmonary arterial pressure >30 mm Hg during grafting. During grafting, emergency conversion to an on-pump CABG was considered when Sv_{O_2} < 50% or newly developed mitral regurgitation ≥grade 3 persisted, despite aggressive treatment or when intractable dysrhythmia had developed. All patients were transferred to the intensive care unit (ICU) after the operation. In the ICU, milrinone was infused when cardiac index was <2.0 litre $min^{-1}\ m^{-2}$ or Sv_{O_2} was <60%, despite the optimization of other determinants of cardiac output. An intra-aortic balloon pump was inserted when cardiac index <2.0 litre $min^{-1}\ m^{-2}$ or Sv_{O_2} < 60% persisted with worsening lactic acidosis, despite aggressive treatment. Packed erythrocytes were transfused when haematocrit was <25% throughout the study period.

Endpoints

The primary endpoints were to compare the highest concentrations of CK-MB and troponin-T between the groups after reperfusion as markers of myocardial injury. Also, the area under the curve (AUC) of serially measured troponin-T was compared between the groups. CK-MB (normal range <5 ng ml^{-1}) and troponin-T (normal range <0.1 ng ml^{-1}) were measured immediately before operation, and at 12, 24, and 48 h after reperfusion.

The secondary endpoints were to compare the incidences of postoperative troponin-T >0.8 ng ml^{-1},[12] MI, and composite morbidity endpoint between the groups. MI was defined as the occurrence of increase in troponin-T >0.5 ng ml^{-1} (five times above the upper normal limit) and the development of new pathological Q-waves or new left bundle branch block.[13] Composite morbidity endpoint was defined as the presence of any of the following major morbidity endpoints including MI and in-hospital mortality: (i) permanent stroke, (ii) renal dysfunction, (iii) haemostatic reoperation, (iv) deep sternal wound infection, and (v) prolonged ventilation >48 h.[14]

Clinical evaluations

Assessed preoperative variables included patient characteristic data, co-morbid conditions, LVEF, history of recent MI (<1 month), presence of left main disease, degree of stenosis of the diseased coronary arteries, and medications.

Assessed intraoperative variables included the duration of the operation, number of grafts performed, total graft reconstruction time, fluid balance, and use of milrinone. Also, haemodynamic variables including Sv_{O_2}, cardiac index, heart rate, mean systemic arterial pressure, central venous pressure, mean pulmonary arterial pressure, and pulmonary artery occlusion pressure were recorded at 10 min after anaesthetic induction (T1), 10 min after stabilizer application for grafting at the obtuse marginalis branch (T2), and 10 min after sternum closure (T3).

Assessed postoperative variables included the use of milrinone, amount of blood loss for postoperative 24 h (mediastinal and chest tube drainage), and length of ICU and hospital stay.

Statistical analysis

Continuous variables are presented as mean (SD) or median (inter-quartile range), and dichotomous variables are presented as number (percentage). The AUC of the serially measured troponin-T (four times during 48 h) was calculated using the trapezoid rule. Dichotomous variables were compared using the χ^2 or Fisher's exact tests, as appropriate. For continuous variables, the normality of distribution was tested with the Kolmogorov–Smirnov test. Intergroup comparisons of parametric data were performed by the independent *t*-test. Intergroup comparisons of non-parametric data were performed by the Mann–Whitney *U*-test. Inter- and intragroup comparisons of parametric data measured at multiple time points were analysed using the linear mixed model with patient indicator as a random effect, group, time, and group by time as fixed effects. Inter- and intragroup comparisons of non-parametric data measured at multiple time points were analysed using the Mann–Whitney *U*-test with the Bonferroni correction of the resulting *P*-values. All statistical tests were two-tailed. *P*-values of <0.05 were considered statistically significant. This study was designed to validate the superiority of GIK treatment. Based on the results of a previous study, a sample size of 32 patients in each group was determined with 80% power to detect a 5 ng ml^{-1} (SD 7 ng ml^{-1}) difference of CK-MB between the groups at an α-level of 0.05 using the

Table 2 Operative data. Values are mean (SD), number of patients (%), or median (inter-quartile range). GIK, glucose–insulin–potassium

	Control ($n=33$)	GIK ($n=33$)	*P*-value
Operation time (min)	320 (44)	334 (47)	0.242
Number of grafts per patient	3 (3–4)	3 (3–4)	0.653
Total graft reconstruction time (min)	35 (9)	35 (10)	0.881
Input			
Crytalloid (ml)	2391 (729)	2526 (760)	0.511
Colloid (ml)	1074 (255)	1059 (312)	0.842
Packed erythrocytes (unit)	0.4 (0.8)	0.6 (0.8)	0.451
Urine output (ml)	676 (491)	680 (434)	0.978
Milrinone	7 (22)	6 (19)	1.000
Glucose concentration (mmol litre^{-1})			
10 min after anaesthetic induction	6.6 (1.0)	7.1 (1.3)	0.132
Composite Y graft construction	7.1 (1.2)	7.0 (1.7)	0.887
10 min after sternum closure	6.7 (0.9)	6.3 (0.8)	0.134
Potassium concentration (mmol litre^{-1})			
10 min after anaesthetic induction	4.1 (0.3)	4.1 (0.3)	0.577
Composite Y graft construction	4.1 (0.3)	4.2 (0.3)	0.857
10 min after sternum closure	4.1 (0.2)	4.1 (0.2)	0.931

Table 3 Intraoperative hemodynamic data. Values are mean (SD). GIK, glucose–insulin–potassium; T1, 10 min after anaesthetic induction; T2, 10 min after stabilizer application for grafting at the obtuse marginalis branch; T3, 10 min after sternum closure. *$P<0.05$, intergroup comparison; †$P<0.05$, intragroup comparison *vs* T1

	Group ($n=33$, each)	T1	T2	T3
Mixed venous oxygen saturation (%)	Control	78 (5)	66 (9)†	74 (6)
	GIK	78 (5)	71 (9)*,†	76 (7)
Cardiac index (litre min^{-1} m^{-2})	Control	2.8 (0.6)	2.0 (0.4)†	2.6 (0.5)
	GIK	2.7 (0.4)	2.2 (0.5)†	2.7 (0.6)
Heart rate (beats min^{-1})	Control	60 (6)	65 (11)	70 (8)†
	GIK	63 (9)	67 (12)	70 (14)
Mean systemic arterial pressure (mm Hg)	Control	73 (8)	70 (14)	74 (8)
	GIK	73 (8)	68 (8)	73 (7)
Central venous pressure (mm Hg)	Control	9 (2)	12 (9)	10 (2)
	GIK	8 (3)	11 (4)†	10 (3)
Mean pulmonary arterial pressure (mm Hg)	Control	19 (5)	22 (5)†	20 (4)
	GIK	19 (4)	23 (7)†	21 (5)
Pulmonary artery occlusion pressure (mm Hg)	Control	13 (4)	16 (4)†	15 (3)
	GIK	14 (3)	16 (5)	16 (5)

independent *t*-test.[15] All statistical analyses were performed using SAS (version 9.2, Cary, NC, USA).

Results

OPCAB could be successfully performed in all patients without requiring emergency conversion to an on-pump procedure. Also, none of the patients required intra-aortic balloon pump placement during the perioperative period. Patients' preoperative characteristics were all similar between the groups except LVEF which showed a trend towards being lower in the GIK group compared with the control group (Table 1).

Operative data including the number of grafts performed and total graft reconstruction time were similar between the groups. Serially measured glucose and potassium concentrations during the operations were also all similar between the groups and could be maintained within the predefined target range in all patients (Table 2). In detail, three patients in the GIK group received both additional 5–10 ml of 50% glucose solution and potassium supplementation (<10 mEq), and one patient in the control group received 3 IU of regular insulin.

Baseline haemodynamic data were all similar between the groups. Intraoperative haemodynamic data showed similar trends of deterioration and recovery during and after mechanical heart displacement in both groups. However, Sv_{O_2} was significantly higher in the GIK group compared with the control group at T2 (Table 3).

Perioperative changes in myocardial enzymes are listed in Table 4. Baseline CK-MB concentrations were similar between the groups, whereas baseline troponin-T was higher in the GIK group compared with the control group. Highest CK-MB and troponin-T values after reperfusion reflecting the intensity of myocardial injury were both significantly lower in the GIK group compared with the control group. All CK-MB and troponin-T values were significantly increased compared with each baseline value in both groups ($P<0.0001$). The AUC of serially measured troponin-T was also significantly smaller in the GIK group compared with the control group [0.83 (0.43–1.81) *vs* 0.46 (0.31–1.00), $P=0.036$]. The number of patients with troponin-T >0.8 ng ml^{-1} after reperfusion was significantly less in the GIK group compared with the control group.

The number of patients with postoperative MI was, however, not statistically different between the groups. The incidence of composite morbidity endpoint and the length of ICU and hospital stay were also not different between the groups. One patient died in the control group due to intractable ventricular dysrhythmia (Table 5).

Discussion

In this randomized and controlled trial addressing the myocardial protective effect of a GIK solution in patients with

Table 4 Perioperative changes in myocardial enzymes. Values are mean (SD), number of patients (%), or median (inter-quartile range). GIK, glucose–insulin–potassium

	Control ($n=33$)	GIK ($n=33$)	*P*-value
Creatine kinase-MB (ng ml^{-1})			
Preoperative	4.0 (0.9)	3.9 (1.3)	0.871
Highest value after reperfusion	13.1 (7.9)	8.7 (4.4)	0.006
Troponin-T (ng ml^{-1})			
Preoperative	0.02 (0.01–0.05)	0.04 (0.01–0.08)	<0.001
12 h after reperfusion	0.34 (0.12–0.83)	0.19 (0.12–0.49)	0.183
24 h after reperfusion	0.36 (0.16–0.72)	0.17 (0.11–0.34)	<0.001
48 h after reperfusion	0.28 (0.12–0.51)	0.10 (0.06–0.23)	<0.001
Highest value after reperfusion	0.48 (0.18–0.91)	0.20 (0.13–0.49)	<0.001
Troponin-T >0.8 ng ml^{-1}	11 (33)	3 (9)	0.033

Table 5 Postoperative data and outcome. Values are mean (SD) or number of patients (%). GIK, glucose–insulin–potassium; ICU, intensive care unit

	Control ($n=33$)	GIK ($n=33$)	*P*-value
Glucose at 4 h after ICU arrival (mg dl^{-1})	150 (29)	147 (31)	0.659
Potassium at 4 h after ICU arrival (mmol litre^{-1})	4.1 (0.2)	4.2 (0.3)	0.567
Milrinone	8 (24)	6 (18)	0.764
Postoperative 24 h bleeding (ml)	543 (251)	522 (281)	0.761
Composite morbidity endpoint	12 (36)	7 (21)	0.277
Stroke	0	0	1.000
Haemostatic reoperation	1 (3)	1 (3)	1.000
Deep sternal wound infection	1 (3)	2 (6)	1.000
Renal dysfunction	3 (9)	3 (9)	1.000
Ventilator care > 48 h	2 (6)	0	0.492
Myocardial infarction	4 (12)	1 (3)	0.355
In-hospital mortality	1 (3)	0	1.000
Length of ICU stay (days)	3.6 (1.5)	3.4 (1.7)	0.540
Length of hospital stay (days)	15.9 (6.0)	15.4 (4.3)	0.676

ACS undergoing urgent multivessel OPCAB, we observed a significant attenuation in myocardial injury in terms of significant reduction in both peak concentrations of CK-MB and troponin-T after reperfusion, and also the AUC of the serially measured troponin-T in the perioperative period in patients treated with GIK.

Multiple mechanisms involved in attenuating myocardial ischaemia–reperfusion injury have been proposed advocating the use of GIK solution in cardiac surgical setting. The principal metabolic mechanism involves the optimal provision of glycolytic adenosine triphosphate, which plays a pivotal role in maintaining membrane integrity during ischaemia. Accordingly, GIK infusion before myocardial ischaemia improves resistance against myocardial ischaemia.[16 17] Another potential key metabolic mechanism involves the suppression of the amount of circulating free fatty acids. This promotes the use of glucose as the primary myocardial fuel source which is less oxygen consuming,[18] and also prevents subsequent membrane damage.[19] Moreover, GIK improves myocardial perfusion and activates intracellular signalling pathways involved in inhibiting apoptosis and promoting cell survival suggesting its additional role in attenuating subsequent myocardial injury after reperfusion.[20 21] Other non-metabolic effects include improved cardiac output by decreasing systemic vascular resistance and direct positive inotropic effect on the post-ischaemic heart.[22 23]

Despite these theoretical advantages, however, the widespread use of GIK solution in cardiac surgical setting had been limited by inconclusive clinical results.[24 25] This controversy may be attributable to wide ranges of insulin dosages used and the inconsistent duration and timing of GIK administration. Earlier studies administered suboptimal insulin dosage not sufficient enough to suppress circulating free fatty acid concentrations or failed to administer GIK solution into the reperfusion period. Also, inconsistent glycaemic control may have masked the beneficial effects conveyed by the GIK solution, since hyperglycaemia is known to independently aggravate the extent of myocardial injury.[26] Nevertheless, neither serious nor life-threatening complications have been reported so far,[14 27 28] and a more recent meta-analysis addressing the effects of GIK solution in adult cardiac surgical patients revealed significant reduction in myocardial injury and improvement in haemodynamic performance.[11]

With regard to GIK application in OPCAB, however, only a limited number of studies exist reporting either neutral or negative results.[29–31] Although all of these studies used appropriate insulin dosages to suppress free fatty acids (≥5 IU h^{-1}),[18] and administered GIK solution into the reperfusion period, none of these studies could demonstrate attenuation of myocardial injury. In these studies, the lack of beneficial influence was explained by including low-risk patients and the absence of evident myocardial ischaemia–reperfusion injury associated with OPCAB. This was supported by the

findings of previous studies demonstrating less myocardial injury associated with OPCAB compared with on-pump CABG.[32 33]

Patients with ACS display a high-risk entity among patients undergoing CABG, and OPCAB is gaining renewed interest in those patients as it has been safely performed with better results compared with on-pump CABG.[5 34] However, OPCAB requires brief obligatory periods of regional myocardial ischaemia for target vessel anastomosis leading to various degrees of myocardial injury. In addition, mechanical heart displacement results in reduced cardiac output which may further aggravate the regional ischaemic insult imposed on the myocardium. As these insults become cumulative in the case of multivessel grafting, patients with evolving MI, unstable angina, or both requiring urgent multivessel OPCAB would be more prone to develop significant myocardial injury. These aspects have led us to our hypothesis that ACS patients requiring urgent multivessel OPCAB would most likely benefit from metabolic myocardial protection with GIK solution, yet it has never been addressed heretofore.

As our results indicate, insulin infusion at a rate of ~0.195 IU kg^{-1} h^{-2} starting immediately after anaesthetic induction until 6 h after reperfusion offered significant ischaemic benefit in terms of postoperative myocardial enzyme release in ACS patients undergoing urgent multivessel OPCAB. Both, highest CK-MB and troponin-T after reperfusion indicating the intensity of myocardial injury were significantly higher in the control group compared with the GIK group, despite higher baseline troponin-T values in the GIK group. Moreover, the AUC of the serially measured troponin-T was also significantly smaller in the GIK group compared with the control group. In addition, significantly fewer patients showed troponin-T >0.8 ng ml^{-1} in the GIK group compared with the control group in the current trial.

Notwithstanding the lack of statistically significant clinical benefit in the current trial, cardiac enzymes have been used as surrogate markers of myocardial injury and patients' outcome after CABG. Troponins have the improved ability to diagnose subtle ischaemic injuries and perioperative myocardial ischaemia compared with CK-MB, and are considered as the preferred biomarkers for assessing myocardial injury.[35] Indeed, a recent retrospective analysis involving a large contemporary cohort of adult cardiac surgical patients revealed that troponin-T concentrations of more than 0.8 ng ml^{-1} were independently associated with major adverse cardiac events after surgery with the largest odds risk ratio (2.7, 95% confidence interval: 2.08–3.5) compared with other independent risk factors.[12] Thus, the results of the current trial suggest the beneficial influence of the GIK solution on attenuating OPCAB-related myocardial injury in ACS patients.

More importantly, these benefits could be observed without the occurrence of insulin-resistant hyperglycaemia which was reported by a previous study applying GIK in OPCAB.[30] In that study, patients with higher preoperative glucose concentrations up to 19.4 mmol $litre^{-1}$ were included, and a different regimen and infusion rate of GIK solution was applied compared with our study. In the current trial, we used a modified GIK regimen from our previous study which delivers a concentration of insulin sufficient to suppress circulating free fatty acids and yielding improved glycaemic control.[29] Accordingly, none of our patients was exposed to a blood glucose concentration of more than 11 mmol $litre^{-1}$ throughout the study period. However, as noted above, we excluded patients with preoperative fasting glucose concentration >13.8 mmol $litre^{-1}$. Since, acute systemic inflammatory response associated with an evolving MI may evoke hyperglycaemic episodes, caution should be exercised not to extrapolate the results of the current trial to patients with poorly controlled blood glucose concentrations in the preoperative period.

Of interest, Sv_{O_2} was significantly higher in the GIK group during grafting at the obtuse marginalis branch with a concomitant trend towards a higher cardiac index in the GIK group. This may be the consequence of a possible direct inotropic action of insulin rather than the consequence of metabolic protection of the myocardium, considering that Sv_{O_2} was similar between the groups during other periods of grafting and that haemodynamic deterioration by mechanical heart displacement is most severe during exposure of the obtuse marginalis branch.[9]

The limitation of this study is as follows. Contrary to the definite benefit observed in terms of myocardial injury as reflected by CK-MB and tropoinin-T, the sample size may have been too small to identify differences in actual clinical outcome such as the incidence of postoperative MI.

In conclusion, continuous infusion of GIK solution starting upon anaesthetic induction until 6 h after reperfusion in ACS patients undergoing urgent multivessel OPCAB could significantly attenuate the degree of ensuing myocardial injury as assessed by CK-MB and troponin-T. As this regimen was devoid of insulin-resistant hyperglycaemia, consideration should be given to use this simple and inexpensive therapeutic measure of metabolic myocardial protection for patients at increased risk of developing major adverse cardiac events after OPCAB.

Declaration of interest

None declared.

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