Preconditioning with glucose-insulin-potassium solution and restoration of myocardial function during coronary surgery

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Abstract. The administration of glucose-insulin-potassium (GIK) solution has beeen shown to exert cardioprotective and immunomodulatory properties in coronary disease.

49 patients (pts.) for coronary surgery were randomly assigned to receive high-dose GIK treatment (30% glucose, insulin 2 IU·kg^{-1}·l^{-1} and K^+ 80 mmo/l solution; 1 ml/kg/h); low-dose GIK treatment (10% glucose, insulin 32 IU l^{-1} and K^+ 80 mmol/l solution; 1 ml/kg/h) or control treatment (Ringer solution 1 ml/kg/h). Haemodynamic measurements were done for four time points: T1 – after induction of anaesthesia; T2 – after the operation; T3 – 6 h after the operation and T4 – 24 h after the operation.

Significant recovery of cardiac function was evident in high-dose GIK (H-GIK) and low-dose GIK (L-GIK) groups after 24 h (cardiac index improved considerably ($p = 0.0002$)), with a statistically significant difference between the groups ($p = 0.005$). LVSWI covariated with PCWP, improved over time in group H-GIK ($p = 0.0008$) and between the groups ($p = 0.046$). Oxygen supply-consumption ratio evidently improved in the GIK groups, while inotropic drug support was used in 5.5% pts. in group H-GIK vs. 13% in group L-GIK and 31% pts. in control (C) group.

Glucose-insulin treatment has a potential cardioprotective effect in coronary surgery. The effect is independent of the glucose-insulin concentration and amount.

Key words: Coronary surgery — GIK — Haemodynamic parameters — Oxygen profile

Introduction

From the first clinical investigation by Sodi-Pallares and colleagues, clinical trials were directed to assess the influence of the glucose-insulin-potassium (GIK) solution on myocardium in acute ischemic event (Sodi-Pallares et al. 1962). Early studies found that GIK treatment in patients (pts.) with acute myocardial ischemia reduces electrocardiographic changes, decreases infarct size and improves ventricular function. Subsequent multicentric studies, ECLA (Dias et al. 1998) as well as DIGAMI (Malmberg et al. 1996) study in diabetic pts., documented favorable effect of the GIK solution in pts. with acute ischemic syndrome. They reported a remarkable decrease in the mortality rate in pts. treated with GIK solution. The idea of GIK's protective role and beneficial effect on myocardium during coronary surgery was revitalized (Gradinac et al. 1989; Svedjeholm et al. 1991; Lazar et al. 1997). Some experimental and some clinical studies suggested that the viability of ischaemic myocardium depends on the glucose supply. Providing glucose to the critically ischaemic cell has been hypothesized to have multiple beneficial effects, and despite the inhibition of fatty acid metabolism, it increases the production of anaerobic ATP while maintaining a protective role on the threatened cell membrane (Opie 1998). Many clinical reports were strongly suggestive of the protective effect of GIK administration on myocardial function, during acute myocardial ischaemia, coronary angioplasty or coronary surgery. The importance of insulin for coronary blood supply and its role on vasodilatation have been implicated in some experimental studies (Downing et al. 1977). Recently,

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a clinical study by Laine et al. (2000) has also reported that insulin acts as a true vasodilatory horomone in the myocardial vasculature. The sensitivity of GIK echocardiography (GIK solution administration during echocardiography) in detection of myocardial viability seems to be very similar to low-dose dobutamine stress echocardiography (Van Wezel et al. 2006).

GIK treatment has been used in cardiac surgery, mainly because of its potentially beneficial effects on myocardial metabolism during ischaemia. Lazar et al. (1997) reported results from a random study of urgent coronary bypass grafting for unstable angina. GIK infusion was given prior to bypass and for 12 h afterwards. Cardiac indexes (CI) of the GIK groups improved significantly with less inotropic support and with dramatically reduced incidence of perioperative atrial fibrillation. Results in another blind, controlled study conformed that GIK initiated prior to the bypass produced marked improvement in CI with the most beneficial effect in those pts. with the worst left ventricular function (Girard et al. 1992). Our study was primarily based on the encouraging results from earlier trials, where GIK was infused during the coronary surgery. Even in diabetic pts., this treatment had a supportive effect on left ventricular function and postoperative outcome (Szabo et al. 2001). Furthermore, recent human (Hansen et al. 2003) and experimental studies (Brix-Christiansen et al. 2008) have shown that the administration of insulin may also have immunomodulation effects and potential to reduce the production of proinflamatory cytokines. Our hypothesis states that a high-dose GIK treatment could enhance myocardial preconditioning as well as improve the postischaemic recovery and restoration of myocardial function.

Materials and Methods

The aim of the study

The aim of the study was: i) to evaluate the beneficial effect of GIK on left ventricular performances and haemodynamics during and after the coronary artery bypass surgery in pts. with poor left ventricular function, ii) to determine whether the difference in glucose-insulin amount and concentration has an impact on left ventricular recovery and haemodynamics restoration.

Open, prospective, randomized study was performed in 49 pts. for coronary artery bypass graft (CABG) surgery with poor left ventricular function (EF < 40%). All pts. were clinically examined. Following the usual examination, coronarography with ventriculography, evaluation was completed with dobutamine-stress test echocardiography on myocardial viability in 56 pts. Forty nine pts. with positive dobutamine-stress test and conformed myocardial viability in one or more segments were included in study and divided in three groups, a high-dose GIK (H-GIK), low-dose GIK (L-GIK) and a control (C) .

Table 1. Patients' assessment

	H-GIK group	L-GIK group	C group
Sex m/f	17/0	12/3	15/2
Age	58.5 ± 6.5	58.2 ± 4.61	54.75 ± 9
Smoking (%)	94.4	46.6	68.75
Hypertension (%)	72.2	73. 3	68.75
Diabetes (%)	44.4	12.5	37.5
Arrhythmia (%)	11.1	20.0	0
COPD (%)	11.1	0	31.25
MI (%)	83.3 (22.2*)	73.3	93.75 (6.24*)
AICS (%)	0	0	0

m, male; f, female; COPD, chronic obstructive pulmonary disease; MI, preoperative myocardial infarction; AICS, preoperative acute coronary syndrome; * percentage of pts. with two or more preoperative myocardial infarctions.

There were no significant differences between groups. The majority were male pts., while only 10.2% were female. About two thirds were treated of hypertension and most of them were smokers. Most of the pts. had a previous history of myocardial infarctions (83.3% in group H-GIK and 73.3% in group L-GIK and 93.75 in group C) and about 40% were on oral medication due to diabetes (Table 1).

Dobutamine stress echocardiography protocol

After usual transthoracic echocardiography examination, pts. received dobutamine 5 $\mu g/kg^{-1}\cdot min^{-1}$ during 3 min with additional 10 $\mu g\cdot kg^{-1}\cdot min^{-1}$ for next 3 min. During the test, global and regional left ventricular function and wall motion was assessed. Hypokinesia was defined as systolic left ventricular wall thickening less then 40%, while systolic left ventricular wall thickening less then 10% was defined as akinesia. Dyskinesia was observed as lateral wall movement with wall thinning. Regional wall movement analyses were done according to the American Society of Echocardiography Recommendations.

Anaesthesia

Premedication for all pts. included: atropine 0.5 mg, midazolam 0.1 $mg\cdot kg^{-1}$, and dolantin 50 mg intramuscularly, thirty minutes prior to operation. After preoxygenation FiO_2 1.0 and induction of anaesthesia with midazolam 0.3–0.4 $mg\cdot kg^{-1}$, fentanil 10–15 $\mu g\cdot kg^{-1}$ and pancuronium 0.1 $mg\cdot kg^{-1}$ pts. were intubated endotrachealy. Intermittent doses of the same drugs were used for anaesthesia

maintenance. Arterial pressure was measured *via* arterial catheter inserted into the left radial artery. Central venous catheter (three ports) was inserted trough the right subclavian vein while the pulmonary artery catheter (five lead Arrow 7.5 F) was inserted through right internal jugular vein.

Haemodynamic study

Haemodynamic measures and calculations were done for four time points. First (T1) – before the surgery, after the induction of anaesthesia (pre OP), the second (T2) – at the end of the surgery (after the chest closure) (post OP), the third (T3) – 6 h after the operation (6 h post OP) and the fourth (T4) – 24 h after the operation (24 h post OP). Cardiac output was measured three times at every time point, the average value was used as a definitive value for the actual time point. Calculated haemodynamic parameters included: cardiac output, CI, stroke volume, stroke volume index (LVSWI), left ventricular stroke work index, right ventricular stroke work index (RVSWI), systemic vascular resistance, and pulmonary vascular resistance simultaneously with oxygen profile parameters: arterial oxygen content, venous oxygen content, arterio-venous oxygen difference, oxygen consumption (VO_2), oxygen delivery (DO_2) and oxygen extraction.

Study design – GIK protocol

Pts. were divided, prospectively, in three groups:

H-GIK group – 17 pts. received a GIK infusion, 30% glucose, insulin 2 IU·kg^{-1}·l, K^+ 80 mmol/l at 1 ml/kg/h rate, after the induction of anaesthesia until aortic cross-clamping. After the distal anastomoses has been completed, and aortic cross-clamp has been released, GIK infusion was continued until the end of surgery. Prior aortic cross-clamping, additional doze of insulin 24 IU was given. After initial 500 ml 30% GIK infusion was terminated, additional 10% glucose, 32 IU·l^{-1} of insulin and K^+ 80 mmol/l was infused up to 24 h after operation at same rate 1 ml/kg/h.

L-GIK group – 17 pts. received a GIK infusion, 10% glucose, insulin 32 IU·kg^{-1}·l, K^+ 80 mmol/l at 1 ml/kg/h rate, after the induction of anaesthesia until aortic cross-clamping. After the distal anastomoses has been completed, and aortic cross clamp has been released, low-GIK infusion was continued until the end of surgery and up to 24 h after operation at same rate 1 ml/kg/h.

C group – 15 pts. received Ringer solution 1 ml/kg/h during the operation and 24 h postoperatively. St. Thomas cold crystalloid cardioplegia was used in all pts. after aortic cross-clamping.

Blood glucose and potassium levels were assessed simultaneously every 60 min.

Statistical analysis

Statistical analyses were performed with a statistical software package for Windows (Statistic 4.5). Data are presented as the mean ± S.D. Mann-Whitney U test was used for simple comparison of clinical and haemodynamic data. ANOVA for repeated measures and Newman-Keuls *post hoc* analysis were used to study the trend, of haemodynamic parameter data. Significance was defined as a p value less then 0.05.

Ethical aspects

The study was performed according to the principles of the Helsinki Declaration of Human Rights and the Ethics Committee, "Dedinje" Cardiovascular Institute, Medical School, University of Belgrade approved the protocol of the study. Signed informed consent was obtained from each patient.

Results

Echocardiography

There were no differences between the groups on preoperative echocardiography examination. Average left ventricular end-diastolic diameter, average left ventricular end-systolic diameter was 40.8 in H-GIK group vs. 44.5 in L-GIK group vs. 41.8 mm in C group; left atrial diameter 39 mm with mitral insufficiency $1–2^+$. Average left ventricular ejection fraction was 34%.

Operative procedures

There were no significant differences between the groups. Average grafts number was 2.6 in group H-GIK, vs. 2.3 in group L-GIK vs. 2.8 in group C. Bypass duration was as follows: group H-GIK 76.7 min; group L-GIK 73.6 min vs. group C 69.1 min with cross-clamping time 43.6 min in group H-GIK, 47.2 min in group L-GIK and 38.8 min in group C.

Hemodynamic data

There was no difference between groups at first (pre OP) measurement. CI changes for the GIK groups were insignificant during the first six postoperative hours, with a significant improvement between the third and fourth time point measurement ($p = 0.002$). Total improvement was found to be 2.14 ± 0.36 l·min^{-1}·m$^{2-1}$ to 3.05 ± 0.55 l·min^{-1}·m$^{2-1}$ ($p = 0.00002$) in H-GIK group vs. 2.24 ± 0.40 l·min^{-1}·m$^{2-1}$ to 3.16 ± 0.43 l·min^{-1}·m$^{2-1}$ ($p = 0.00003$) in L-GIK group.

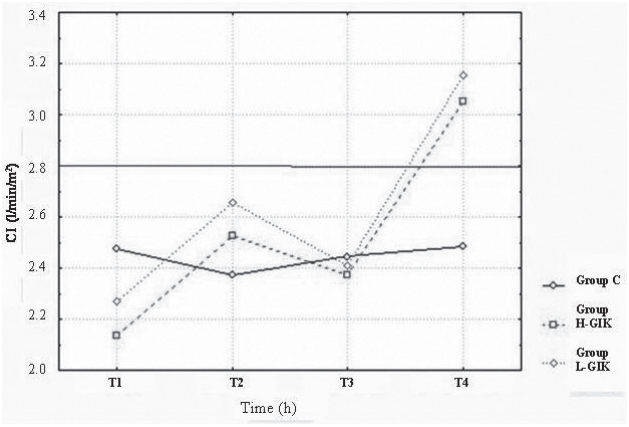

Figure 1. In GIK groups were significant cardiac index (CI) improvement between T3–T4 (p = 0.002). Total improvement was found to be 2.14 ± 0.36 l·min^{-1}·m$^{2-1}$ to 3.05 ± 0.55 l·min^{-1}·m$^{2-1}$ (p = 0.00002) in H-GIK group vs. 2.24 ± 0.40 l·min^{-1}·m$^{2-1}$ to 3.16 ± 0.43 l·min^{-1}·m$^{2-1}$ (p = 0.00003) in L-GIK group. Four time points: T1 – before the surgery (after the induction of anaesthesia), T2 – at the end of the surgery (after the chest closure), T3 – 6 h after the operation, T – 24 h after the operation.

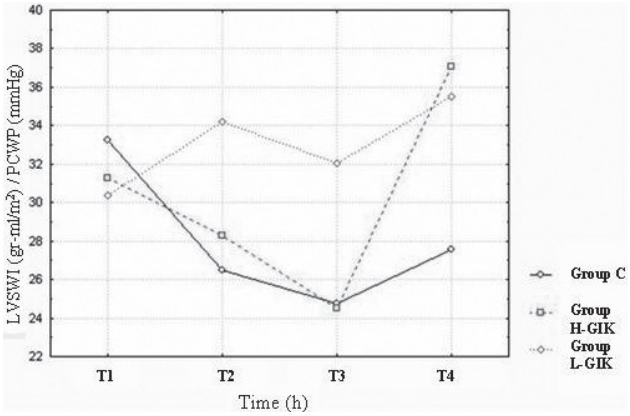

Figure 2. Trend of changes over time was more significant (p = 0.0016) then the difference between the groups (p = 0.014). The improvement in H-GIK group was significant in the interval between T3–T4 (p = 0.0039). LWSWI, left ventricle stroke work index; PCWP, pulmonary capillary wedge pressure. Four time points: T1 – before the surgery (after the induction of anaesthesia), T2 – at the end of the surgery (after the chest closure), T3 – 6 h after the operation, T4 – 24 h after the operation.

In the C group, CI changes had a linear trend 2.47 ± 0.39 l·min^{-1}·m$^{2-1}$ to 2.48 ± 0.50 l·min^{-1}·m$^{2-1}$. Difference between the groups were found to be statistically significant in the postoperative period, during last two time points, 6 h to 24 h post OP (p = 0.005) (Figure 1).

We assessed the GIK influence on the global left ventricular function by comparing LVSWI as an index of left ventricular work and pulmonary capillary wedge pressure (PCWP) as an index of ventricular loading. Covariation of LVSWI with PCWP was performed. Calculated values were individually more sensitive than each parameter by itself. Trend of LVSWI-PCWP changes over time was more significant (p = 0.0016) then the difference between the groups (p = 0.014). Segmental analyses emphasizes the improvement in H-GIK group in interval between 6 and 24 h after surgery (p = 0.0039) (Figure 2).

By comparing right ventricle work and loading (RVSWI/CVP) we found a significant improvement in GIK groups (p = 0.000017), with a considerable deference between groups during the time interval (p = 0.015). Significant improvement was observed in H-GIK group between T1 and T4 (p = 0.019) vs. L-GIK group between T1 and T4 (p = 0.022) vs. stagnation in group C (Figure 3).

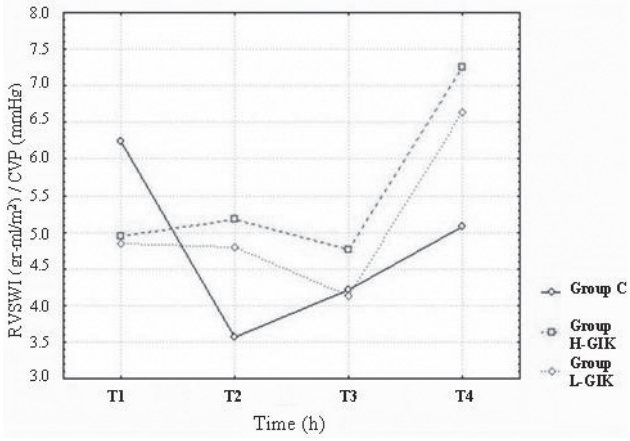

Figure 3. Remarkable deference between groups during the time interval (p = 0.015). Significant improvement in H-GIK group between T1–T4 p = 0.019 vs. L-GIK group between T1–T4 p = 0.022 vs. stagnation in group C. RVSWI, right ventricle stroke work index; CVP, central venous pressure. Four time points: T1 – before the surgery (after the induction of anaesthesia), T2 – at the end of the surgery (after the chest closure), T3 – 6 h after the operation, T4 – 24 h after the operation.

Oxygen delivery-consumption relationship

Analysis of the DO_2-VO_2 relationship during the time intervals and comparing the differences between groups resulted in interesting results. Shift to the left of the DO_2-VO_2 relationship curve to the critical, supply dependent VO_2, was evident immediately after the surgery in both groups. In an interval between 6 and 24 h after operation, we observed a shift to the right and a marked improvement in GIK groups, from baseline values DO_2-VO_2

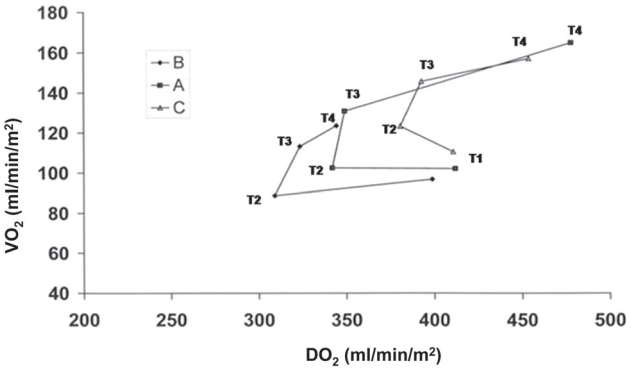

Figure 4. There was no difference in the behavior between groups during the time intervals. The difference in achieved levels of DO_2-VO_2 balance between groups was extremely significant (p = 0.00073). There was no difference between H-GIK and L-GIK groups. VO_2, oxygen consumption; DO_2, oxygen delivery. Four time points: T1 – before the surgery (after the induction of anaesthesia), T2 – at the end of the surgery (after the chest closure), T3 – 6 h after the operation, T4 – 24 h after the operation.

(430–101 ml·m$^{2-1}$·min^{-1}) toward normal ratio (500–156 ml·m$^{2-1}$·min^{-1}). There was no difference in the behavior between groups during the time intervals, but the difference in achieved levels of DO_2-VO_2 balance between groups was extremely significant (p = 0.00073). There was no difference between H-GIK and L-GIK groups, while the group C ratio DO_2-VO_2 was at the borderline level, 349–136 ml·m$^{2-1}$·min^{-1} (Figure 4).

Blood glucose and serum potassium levels were assessed every 4 h. Only in three pts., in group H-GIK and group C, glucose level was over 12 mmol/l at the second reading, while the potassium levels in both groups were between 3.77–4.29 mmol/l.

Postoperative treatment

During the ICU treatment, duration of mechanical ventilation was same for all pts., 15.58 ± 3.09 h in H-GIK group vs. 16.78 ± 4.04 h in L-GIK group vs. 17.40 ± 2.41 h in C group. The difference was in ICU stay, 1.14 days for group H-GIK vs. 1.73 for group L-GIK vs. 2.3 days for group C. The inotropic support (dopamine 5–10 μg·kg^{-1}·min^{-1} or epinephrine 0.03–0.1 μg·kg^{-1}·min^{-1}) was needed in 5.5% of pts. in H-GIK group vs. 13% of pts. in L-GIK group vs. 31% of pts. in C group. Statistical significance was determined using the binomial sampling distribution analysis, such that the exact probability was calculated to be p = 0.01391 for the H-GIK group and p = 0.05 for the L-GIK group. The mechanical assist device was not necessary.

Morbidity-mortality rate was the same for all three groups. One patient in H-GIK group died 34 h postoperatively, after reintervention due to surgical bleeding and consequent myocardial insufficiency. Another patient in the C group died on 13th postoperative day due to the myocardial infarction and subsequent cardiorespiratory insufficiency.

Discussion

During prolonged coronary insufficiency, myocardial hibernation overcomes the persistent energy deficit through adaptation to reduced myocardial blood flow. Reduced energy reserves act to maintain myocardial integrity and viability (Opie 1988).

Myocardial stunning and reperfusion injury during the coronary surgery as well as a great number of incorporated intracellular mechanisms and disorders all occur due to the energy deficit. The anaerobic metabolism with reduced energy production in mitochondria and deterioration in energy consumption in myofibrils are critical for this process (Opie 1988). Cascade of intra-mitochondrial events, namely calcium ion metabolism disorders, oxygen free radicals production, free fatty acids mobilization, pyruvate dehydrogenase inactivation and Krebs cycle dysfunction, all have an influence on myocardial contractility (Downing et al. 1977; Svedjeholm et al. 1991; Laine et al. 2000; Van Wezel 2006). The role for mitochondria during preconditioning and reperfusion is becoming increasingly clear. During ischemia, oxidative phosphorylation is maintained while the process of oxidation is impaired (mitochondrial uncoupling). During reperfusion, energy production is restored. Restored energy stimulates the calcium overload, with the consequence of uncontrolled force generation followed by hypercontractility of myofibrils (mitochondrial paradox). Subsequently it leads to self-destruction and myocyte dysfunction after prolonged ischemia (Lazar et al. 1997).

In extensive coronary disease with preserved myocardial viability, detection of hibernated myocardium and its protection can be extremely beneficial during the reperfusion or revascularization procedures. Hibernated myocardium must be recognized and identified by appropriate diagnostic procedures. In our study we preferred a dobutamine-stress echocardiography for detection and assessment of hibernated myocardium. This was potentially advantageous in evaluating the myocardial functional reserve (Girard et al. 1992) and as such was important for the study. The restoration and protection of high-energy phosphate stores in the viable myocardium was the target of the GIK protective action.

Previous studies with GIK

Many of GIK studies assessed GIK effects on myocardium in acute myocardial infarction (Sodi-Pallares et al. 1962;

Malmberg et al. 1996; Dias et al. 1998; Bertrand et al. 2008; Nesto and Lago 2008), during PTCA (percutaneous transluminal coronary angioplasty) (Van der Horst et al. 2003) or during the CABG surgery (Svedjeholm et al. 1991; Girard et al. 1992; Lazar et al. 1997; Szabo et al. 2001), considering mortality rate, heart failure or recurrence of ischemic event. Following the initial study and experience with GIK solution of Sodi-Pallares and coworkers (1962), many studies have been performed. Most of them were nonprospective and nonrandomized, with modest design. Controversial results in these studies are the consequence of the employed strategy. They reported various criteria for GIK usage, difference in glucose concentration and insulin doses as well as in selection of the proper moment for the treatment. In some of them glucose was given peroraly with subcutaneous insulin while in others GIK infusion was induced 48 h after the onset of angina. In a meta-analysis of randomized, placebo-controlled trials, the benefits of GIK therapy in acute myocardial infarction have been demonstrated. In the four studies GIK has been administered intravenously at a high-dose resulting in mortality reduction of 48% relative to the placebo group (Szabo et al. 2001). In nonrandomized study pts. with acute myocardial infarction were treated with thrombolysis. Some of them were given GIK, carnitin and magnesium by peripheral venous infusion. Pts. treated with metabolic support had significantly lower incidence of heart failure development or death, compared to control pts. treated only with thrombolysis (Ganc and Braunwald 1997). Despite the controversy of the GIK beneficial effects (Kloner and Nesto 2008) and results of some clinical studies, in pts. with ST elevation myocardial infarction (Rasoul et al. 2007) and on diastolic dysfunction after coronary-bypass grafting (Tsang et al. 2007) where GIK infusion did not improve the outcome, metabolic modulation still attracted attention (Yetkin et al. 2002).

Ischemia and reperfusion lead to desirable pharmacological effects of metabolic modulation with GIK infusion such as decreased fatty acid oxidation, increased glucose oxidation, maintaining the coupling of glycolysis to glucose oxidation with increased glycolysis, increased efficiency in oxygen utilization for supporting ATP synthesis and increased efficiency of ATP utilization for contractile function (Bolli et al. 1989; Bolli 1990). Aforementioned processes are associated with simultaneous improvement in the cardiac contractile function.

Recent evidence was strongly suggestive of the insulin signaling K_{ATP} channel activation. K_{ATP} channels are crucial and critical mediators of ischaemic preconditioning, the process of importance for powerful protection against myocardial infarction, ischaemia-reperfusion injury and apoptosis (Gross 1992; Akao et al. 2001). Their activity is modulated by several intracellular kinases as well as by insulin (Chai et al. 2008). Insulin has also been shown to regulate K_{ATP} channel activity by increasing the open-state probability of the channel and by decreasing the channel sensitivity to ATP (Tricarico et al. 1997). Recent studies have suggested that under pathological conditions, such as type-2 diabetes, myocardial ischaemia, and cardiac hypertrophy, insulin signal transduction pathways and action are modified (Bertrand et al. 2008). Results of the recent experimental study confirm protective effects of GIK administration immediately before the reperfusion independently of blood glucose level (Laine et al. 2000). However, presented findings support previous observations in rats that GIK or insulin administered immediately before reperfusion reduced the ischemic area. High-dose insulin treatment was known to have potential anti-inflammatory properties in coronary revascularization surgery (Koskenkari et al. 2006). The efficacy of GIK may be modulated under these conditions because of the glucose-impaired K^+ channel activation or due to metabolic effects of insulin and glucose.

This idea was an inspiration for our study. Pts. about to undergo the coronary artery bypass surgery with poor left ventricular function and detected hibernated myocardium were selected in order to evaluate efficiency of GIK infusion on preconditioning and intraoperative protection of myocardial function. The intention was to evaluate haemodynamic parameters and DO_2-VO_2 relationship as direct effect of left ventricular function. The primary function of the left ventricle is to generate a flow and distribution of oxygenated blood to sustain aerobic metabolism. The relationship between DO_2 and VO_2 is in very sensitive balance. Oxygen can not be stored and any disturbances in haemodynamics with consequences on perfusion, affect the delivery/consumption ratio. Cardiac output and left ventricular pump function are essential in achieving this goal. With that in mind our intention was to evaluate the left ventricular function indirectly, considering that the oxygen supply becomes limited with depressed left ventricular performances, resulting in VO_2 becoming almost supply dependent. Furthermore, simultaneously with haemodynamic calculations, DO_2, VO_2 and their respective ratios were calculated.

In this study we used high concentration glucose (30%) insulin 1 IU·kg^{-1}·h^{-1} and single dose 24 IU of insulin prior to aortic cross-clamping, without any extreme blood glucose values during the study. Only in three pts. in each group's blood glucose level was over 12 mmol/l at T2.

Considering an importance and influence of the GIK infusion on haemodynamic and intraoperative outcome, difference between groups is evident and significant. Postoperative improvement of CI, LVSWI and LVSWI/PCWP in GIK groups is emphasized during last hours, between T3–T4 (6 to 24 h after the surgery). During the ICU treatment, duration of mechanical ventilation was

same for all pts. The difference was in ICU stay, 1.14 days for group H-GIK vs. 1.73 for group L-GIK vs. 2.3 days for group C what is in correlation with inotropic support. A significant difference in the need for inotropic support was demonstrated (5.5 vs. 13 vs. 31%; $p = 0.01391$ for the H-GIK group and $p = 0.05$ for the L-GIK group) which may indicate favorable effects of GIK. Advanced surgical skills, modern anesthetic techniques and improved myocardial protection are essential to achieving a better outcome of coronary artery by pass surgery in advanced left ventricular dysfunction (Trachiotis et al. 1998). However, surgical coronary revascularization in pts. with poor left ventricle still remains a challenge for a surgical team. Two large studies of postoperative treatment after coronary artery bypass surgery in pts. with low EF, reported usage of IABP in 10.7–20% of pts. with intrahospital mortality rate 3.8–10% (Elefteriadis and Kron 1995; Kaul et al. 1996; Trachiotis et al. 1998). Considering this, metabolic modulation might serve as an alternative to standard procedures in intraoperative myocardial protection used in our study.

The importance of DO_2-VO_2 relationship has been investigated as a predictive factor for an outcome in critically ill and septic pts. for years (Boyd et al. 1993). Shoemaker et al. reported the importance of increasing blood volume, CO, DO_2 and VO_2 in treatment of oxygen debt and for the postoperative outcome (Shoemaker et al. 1988, 1992a). This poses a dilemma whether the DO_2-VO_2 ratio can be used as an outcome-prediction factor in CABG surgery and it can be interpreted as a supplement to haemodynamic parameters (Shoemaker et al. 1992b). Despite the difficulties of evaluating regional blood flow, distribution and regional DO_2-VO_2 relationship, our idea was to test DO_2-VO_2 relationship in the context of haemodynamics, considering that left ventricular function and cardiac output are the main contributing factors to oxygen metabolism balance in a tissue.

Preoperatively all pts. exhibited a borderline level of DO_2-VO_2 relationship. During the postoperative period it deteriorated, shifted to the left, and near to the critical levels (VO_2 supply-dependent). Six hours after the operation improvement was obvious, with a rightward shift observed in all three groups. Pts. in group C retained near-initial levels while the GIK groups exhibited DO_2-VO_2 ratios (shifted to the right), significantly above the starting levels, and close to the normal levels.

In the presented study we have performed an assessment of haemodynamic parameters during and after the surgery. Considering the volume loading, LVSWI, DO_2-VO_2 ratio and the need for inotropic support, evaluation of myocardial working capabilities were provided during reperfusion period, 24 h after surgery. The difference between GIK groups and control were significant.

Study limitations

The present results should be interpreted within the constraints of several potential limitations. With the observed low mortality rates in the GIK groups and control group, our study could not detect a significant difference in mortality. Nevertheless, myocardial VO_2 was not directly measured in the current study; DO_2-VO_2 ratio was measured as factor dependent on haemodynamics and left ventricular pump capability.

This is a report of clinical experience and not a formal scientific trial. The comparatively earlier haemodynamic recovery, improvement of oxygen supply-consumption relationship and minimal inotropic support in GIK groups, are consistent with the assumption that the course of recovery was influenced by metabolic support.

Results of our study should be an encouragement for further randomized, controlled metabolic and clinical studies, even multicentric, in order to define metabolic strategies for intraoperative myocardial protection and for broader use of GIK metabolic support.

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