Myocardial protection: standard versus insulin cardioplegia and glucose-insulin-potassium solutions

Miyokardiyal koruma: Standarda karşı insülin kardiyopleji ve glikoz-insülin-potasyum solüsyonu

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Background: This study determined the hemodynamic and metabolic effects of insulin cardioplegia, glucose-insulin-potassium (GIK) solution combined with insulin cardioplegia, and blood-only cardioplegia on postoperative recovery in coronary artery bypass grafting (CABG).

Methods: One-hundred and twenty patients with normal ventricle function and no history of diabetes mellitus (DM) were randomly divided into three groups. During the operation, 10 IU/L of crystalized insulin-added blood cardioplegia was administered to the patients in group 1 (n=40) and group 2 (n=40), and standard blood cardioplegia was used in group-3 (n=40). In addition, GIK solution was started before the removal of cross-clamp (CC) period in group 2. The blood samples from arterial and coronary sinus were collected before CC application (T_0), before CC removal (T_1) and 0, 5th, 10th, and 15th minutes (T_2-T_3-T_4-T_5) after CC removal. Hemodynamic parameters were measured at the 30th minute after anesthesia induction and 1st and 24th hours following surgery. During the peri- and postoperative course, the need for defibrillation, inotropic and intraaortic balloon pump support, the incidence of postoperative arrythmias, duration of intubation, intensive care unit stay and hospitalization were recorded.

Results: The levels of arterial and coronary sinus lactate were significantly lower in group 2 compared to group 3 in the 5th, 10th, and 15th minutes. The blood glucose levels of arterial and coronary sinus were significantly higher in group 3. In group 2, the incidence of postoperative arrythmias and requirement for inotropic support was less than that of group 1 and group 3 ($p<0.05$).

Conclusion: After CABG, in the reperfusion period, persistant release of lactate or higher lactate levels demonstarate that myocardial protection was unsatisfactory and the recovery of aerobic metabolism was diminished perioperatively. Glucose-insulin-potassium solution combined with insulin cardioplegia decreases the myocardial lactate level, incidence of arrythmias, and requirement for inotropic support and leads to better myocardial protection.

Key words: Coronary artery bypass surgery; glucose; insulin; intraaortic balloon pumping; metabolism; myocardium; neurosecretory system; potassium.

Amaç: Bu çalışmada, koroner arter bypass greftleme (KABG) cerrahisinde insülin kardiyoplejisi, glikoz-insülin-potasyum (GİK) solüsyonu ile kombine edilmiş insülin kardiyoplejisi ve yalnız kan kardiyoplejisinin ameliyat sonrası derlenme üzerine olan hemodinamik ve metabolik etkileri belirlendi.

Çalışma planı: Diyabet öyküsü olmayan ve sol ventrikül fonksiyonları normal olan 120 hasta randomize olarak üç gruba ayrıldı. Ameliyat sırasında grup 1 (n=40) ve 2'deki (n=40) hastalara 10 IU/L kristalize insülin ilave edilmiş kan kardiyoplejisi ve grup 3'deki (n=40) hastalara standart kan kardiyoplejisi uygulandı. Grup 2'de kros-klemp (KK) açılmadan önce ilave olarak GİK solüsyonu başlandı. Arteryel ve koroner sinüs kan örnekleri, KK uygulamasından önce (T_0), KK açılmadan önce (T_1) ve KK açıldıktan sonraki 0, 5, 10. ve 15. dakikalarda (T_2-T_3-T_4-T_5) alındı. Hemodinamik parametreler anestezi indüksiyonunu takiben 30. dakikada ve ameliyat sonrası 1. ve 24. saatlerde ölçüldü. Ameliyat sırası ve sonrasında, defibrilasyon gereksinimi, inotropik ve intraaortik balon pompası desteği, ameliyat sonrası aritmi insidansı, entübasyon süresi, yoğun bakım ve hastanede kalış süreleri kaydedildi.

Bulgular: Arteryel ve koroner sinüs laktat düzeyleri grup 3 ile karşılaştırıldığında grup 2'de 5, 10. ve 15. dakikalarda anlamlı şekilde düşük bulundu. Arteryel ve koroner sinüs kan glikoz seviyeleri grup 3'de anlamlı olarak yüksek bulundu. Ameliyat sonrası aritmi insidansı ve inotropik destek ihtiyacı grup 2'de, grup 1 ve grup 3'den daha düşük bulundu ($p<0.05$).

Sonuç: Koroner arter bypass greftleme sonrası reperfüzyon periyodunda persistan laktat salınımı ve yüksek laktat düzeyleri, miyokard korumasının yetersiz olduğunu ve aerobik metabolizmanın ameliyat sırası dönemde geriye dönüşünün yavaşladığını göstermektedir. İnsülin kardiyoplejisi ile birlikte uygulanan GİK solüsyonu miyokard laktat seviyesi, aritmi insidansını ve inotropik destek gereksinimini azaltır ve daha iyi miyokard koruması sağlar.

Anahtar sözcükler: Koroner arter bypass cerrahisi; glikoz; insülin; intraaortik balon pompası; metabolizma; miyokard; nörosekretör sistem; potasyum.

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In the presence of adequate oxygen stores, oxidative phosphorylation is the main pathway for energy requirement in tissues including myocardium. The energy is provided by oxidation of fatty acids, glucose, aminoacids and ketone bodies. Aerobic glycolysis is inhibited by high arterial fatty acids levels. Whereas, a decrease in fatty acid oxidation is compensated by increased levels of glycolysis.[1] During exercise, instead of free fatty acids, lactate acts as a main energy supplier for myocardium.[2]

During the aortic cross-clamp (CC) period, hypothermia and cardioplegia are the most widely accepted methods for myocardial protection. However, myocardial ischemia and postischemic reperfusion injury has still been observed. The most sensitive parameter that demonstrates myocardial preservation are coronary sinus blood lactate levels.

In the period of reperfusion, glucose-insulin-potassium (GIK) solution has been tried for the prevention of myocyte injury, reflected by contractile dysfunction and/or intractable malign arrhythmias.[3] High dose insulin administration shifts the myocardial metabolism towards glycogenesis and glycolysis. By favoring the use of glucose from the glycogen stores, this shift diminishes the rise of coronary sinus lactate levels during the ischemic period. In addition, GIK solution has been shown to decrease the incidence of malignant arrhythmias.[4]

In this study, we aimed to investigate the hemodynamic and metabolic effects of insulin cardioplegia, GIK solution combined with insulin cardioplegia and only blood cardioplegia on peri- and postoperative recovery periods of patients who underwent elective coronary artery bypass grafting (CABG).

PATIENTS AND METHODS

Study population

After the Research, Planning and Coordination Council of the Ministry of Health approval of our study, 120 patients who underwent isolated CABG between January 2005 and November 2005, were randomized in three groups. All patients had left ventricular ejection fraction (EF) of above 45%, no history of diabetes mellitus and/or valve insufficiency requiring any other procedures.

In group 1 (n=40); cardiac arrest was induced with antegrade and retrograde cold intermittent blood cardioplegia with insulin concentration of 10 IU/L.

In group 2 (n=40); cardiac arrest was achieved by antegrade and retrograde cold intermittent blood cardioplegia with insulin at the concentration of 10 IU/L. In this group, GIK solution consisting of 10% 500 ml dextrose, 20 IU crystalized insulin, 60 mmol 22.5% potassium chloride (KCL) was started before the removal of CC and infused at the rate of 0.75 ml/kg/hour for 24 hours following surgery.

In group 3 (n=40); cold intermittent blood cardioplegia was used. According to a sliding scale, insulin was given to maintain blood glucose levels between 150-200 mg peroperatively.

Anesthetic and surgical technique

Patients were premedicated with oral diazepam (0.15 mg/kg), intramuscular morphine sulfate (0.15 mg/kg) and scopolamine (0.01 mg/kg) 45 minutes prior to surgery. Routine electrocardiography (ECG) monitoring with two derivations including DII and V5 was performed. Left radial arterial catheter and Swan-Ganz catheter (Biosensors International 7 F TD 1703 HX, Philadelphia, Penn, USA) were placed under local anesthesia. After induction of anesthesia using 15 mcg/kg fentanyl, 2 mg/kg propofol, 0.1 mg/kg pancuronium, the patients were mechanically ventilated with the settings of: FiO_2=1.0, tidal volume (TV)=8-10 ml/kg, respiratory rate 12/minute, inspiration/expiration=1/2. For maintenance, propofol (2 mg/kg/h) and fentanyl (4 mcg/kg/h) infusions were used. In order to keep hemodynamics in normal range, 1 MAC (minimum alveolar concentration) of sevoflurane was added on requirement. Hemodynamic parameters measured at 30 minutes after induction (T_0), 30 minutes after bypass period (T_1), postoperative first hour (T_2), and 24 hours after surgery (T_3) were mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP). In each group, arterial and coronary sinus blood samples were obtained at the following time settings; before cross-clamp application (T_2), just before cross-clamp removal (T_1), immediately after cross-clamp removal (T_2) and at following 5^{th} (T_3), 10^{th} (T_4), 15^{th} (T_5) minutes. The collected blood samples were processed in the Stat profile 5 (Nova Biomedical, seri no: MA 02454-9141 Waltham, USA) instrument for measurement of lactate and glucose levels.

All patients were operated by the same surgeon. Cardiopulmonary bypass (CPB) was achieved using a roller pump and membrane oxygenator on mild hypothermia at 32 °C. Cardiac arrest was maintained by insulin-added blood cardioplegia in group 1 and 2, and only cold blood cardioplegia in group 3. After the each anastomosis was completed, 150-200 ml cold blood cardioplegia was additionally given through the saphenous vein grafts. 200 ml cold blood cardioplegia was given retrogradely with coronary sinus route in every

Table 1. The distribution of the demographic data of groups

	Group 1	Group 2	Group 3	*p*
Age (year)	60.7±4.1	61.2±3.9	62.2±5.5	NS
Height (cm)	172.6±8.4	170.8±7.1	172.9±8.5	NS
Weight (kg)	72.7±7.2	71.7±8.9	70.6±10.5	NS

NS: Non-significant.

20 minutes periods. Terminal blood cardioplegia, hot shot, was given antegradely while LAD-LIMA anastomosis was performed. Blood cardioplegia contains blood in 1/3 concentration.

Inotropic agents were administered if the patients' systolic blood pressure was below 80 mmHg and PCWP was above 18 mmHg.

Besides demographics, the data collected and analyzed included; duration of cross-clamp and CPB, defibrillation, requirement of inotropic support, intraaortic baloon pump placement, the incidence of atrial fibrillation, duration of intubation, ICU and hospital stay.

Statistical analysis

The parameters in this study were analyzed statistically using the SPSS (Statistical Package for Social Sciences, SPSS, Inc., Chicago, IL, USA) for Windows 13.0 version. The data was presented as mean ± standard deviation (SD). For the assessment of data, qualitative statistical tests as well as quantitative Kruskal Wallis and Mann-Whithney U-tests were used. The differences between repetitive measures at different time settings were compared by Student t-test and Wilcoxon correlated two sample test.

Qualitative data were compared using Chi-square and Fisher's exact Chi-square tests. The relations between parameters were evaluated by the Spearman's correlation coefficient. The significance was reported at the level of $p<0.05$.

RESULTS

All the groups were similar in demographics ($p>0.05$; Table 1). Hemodynamic parameters were shown in table 2. There were no significant differences in hemodynamic parameters between the study groups. The levels of arterial and coronary sinus glucose are shown in figures 1 and 2. Both parameters were found to be significantly higher in group 3 compared to others, in all points of measurement except T_0 period ($p<0.05$).

Arterial and coronary sinus lactate levels were significantly lower in group 2 compared to group 3 at T_3, T_4, T_5 periods ($p<0.05$; Fig. 3, 4).

The duration of aortic cross-clamp, CPB, ICU and hospital stay were similar ($p>0.05$). Although statistically not significant patients in group 2 were extubated earlier than in other groups. The requirement for inotropic support was significantly higher in group 3 compared to group 2 ($p<0.05$). The incidence of postoperative arrythmias were found to be statistically higher in group 3 than in group 2 ($p<0.05$; Table 3).

DISCUSSION

In cardiac surgery, cardioplegia, systemic and local hypothermia have been used for myocardial protection for many years.[5-6] In order to prevent or decrease myocardial cellular injury during ischemia-reperfusion, transformation of lipolytic energy sources that can not be utilized in

Table 2. The comparison of hemodynamic parameters between groups at different time settings

	T_0	T_1	T_2	T_3
Heart rate				
Group 1	74.1±17.8	85.9±16.7	96.6±13.7	95.7± 14.8
Group 2	70.2±12.8	86.4±8.6	87.6±16.7	88.3±12.3
Group 3	67.2±9.1	94.2±15.9	91.0±19.4	87.2±11.4
Mean arterial pressure				
Group 1	98.7±15.3	79.5±11.0	87.6±13.3	88.4±14.1
Group 2	87.6±11.4	82.4±12.4	96.5±17.3	78.4±13.3
Group 3	97.6±11.6	72.6±14.3	89.7±16.7	81.5±12.2
Central venous pressure				
Group 1	9.2±3.2	9.1±3.6	7.1±3.2	8.3±2.4
Group 2	7.5±2.4	8.1±3.3	7.3±3.2	8.9±3.3
Group 3	8.9±2.8	10.8±2.7	8.9±3.2	9.5±3.4
Pulmonary capillary wedge pressure				
Group 1	10.0±2.4	9.4±3.6	8.8±4.3	9.5±3.3
Group 2	8.2±3.4	8.9±3.9	8.0±4.1	9.0±4.2
Group 3	8.5±3.7	10.0±2.6	9.0± 3.3	10.1± 4.4

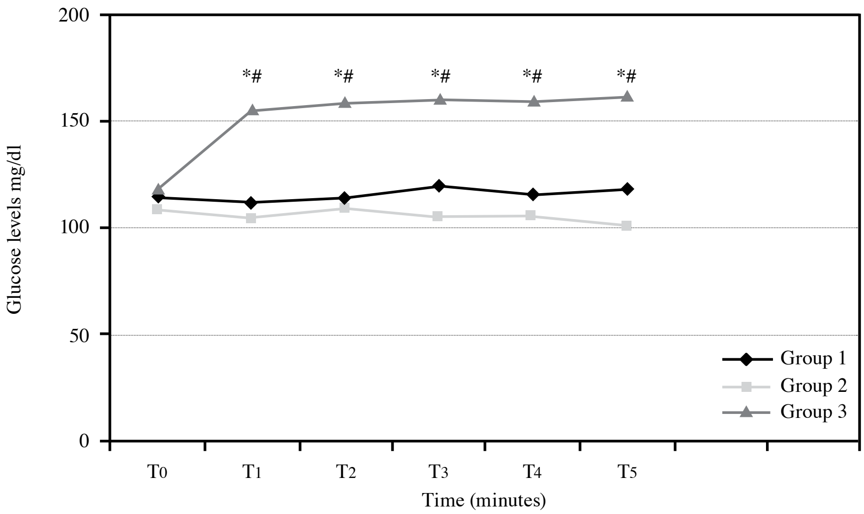

Fig. 1. Arterial glucose levels.

ischemic conditons, to anaerobic glycolytic sources might be needed.[7] However, since glycogen stores are limited, this process can not be sustained. For the continuance of myocyte viability and adenosine triphosphate (ATP) production, the amount of glycogen has to be increased. The surgical stress produces neuroendocrine response in the human body. These responses have secondary metabolic effects. The stress hormones not only cause a reduction in insulin secretion, but also antagonize their effects by stimulating systemic lypolysis and glyconeogenesis.[8] Svensson et al.[9] showed that during the reperfusion period, utilization of myocardial glucose and lactate decreased. In addition, systemic glucose utilization was also found to be reduced. They explained this phenomenon in terms of insulin resistance caused by stress hormones.

Under normal circumstances, lactate utilization by myocardial tissue is high and lactate is an acceptable substrate in the heart. The rate of its entry into the myocyte depends on the concentration gradient between blood and cytosol. Intracellular lactate concentration is related to the rate of pyruvate production and the reduction of pyruvate to lactate or its utilization via the Krebs cycle. At the beginning of reperfusion, myocardial lactate release is caused by increased glycogenolysis and anaerobic glucose oxidation.[10]

The positive contribution of insulin to the post-ischemic myocardium results from activation of PDH activity which triggers aerobic metabolism. Insulin neutralizes “insulin resistance ”caused by the increased concentration of free fatty acids and reduced myocardial glucose uptake. The increased concentration of free fatty acids and reduced myocardial glucose uptake leads to impairment of insulin neutralization or insulin resistance.[9] It was reported that IV (intravenous)

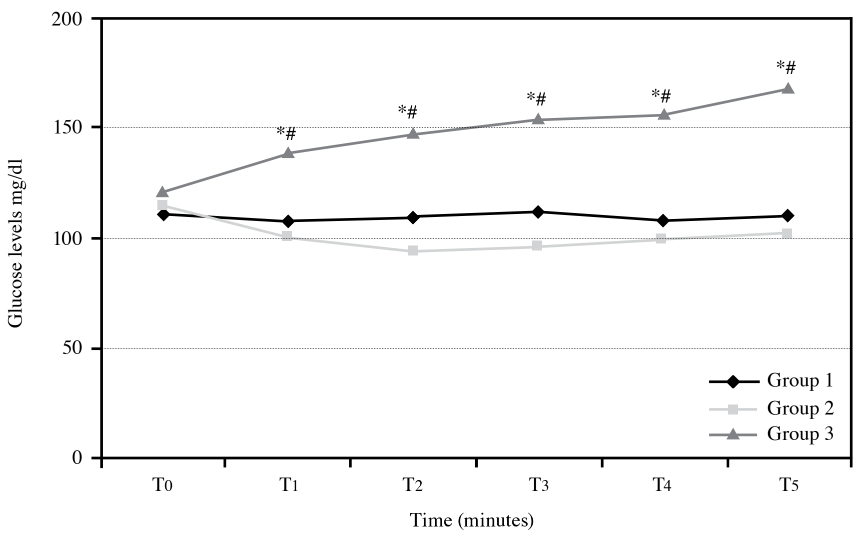

Fig. 2. Coronary sinus glucose levels.

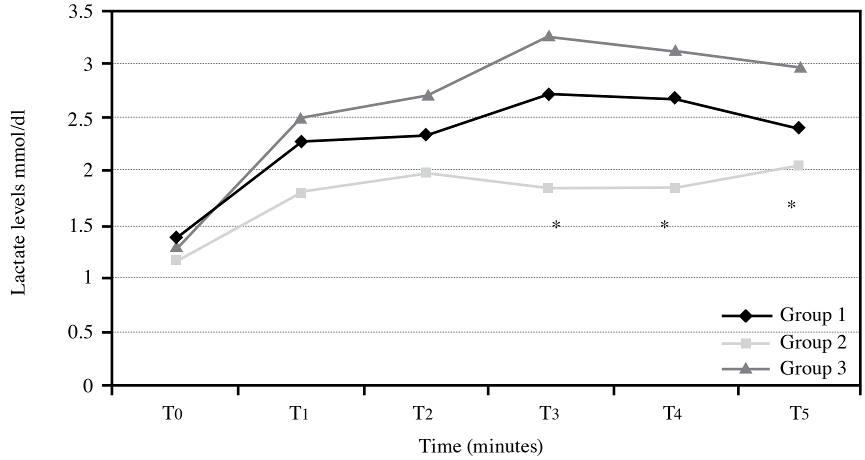

Fig. 3. The comparison of arterial lactate levels between groups at different time settings.

infusion of insulin following CABG operations and/or addition of insulin to blood cardioplegia stimulated the aerobic metabolism during reperfusion, prevented the plasma lactate release and improved left ventricular output work index.[11]

The main reason to the use of GIK solution in myocardial revascularization is that exogenous glucose increases ATP production via glycolytic pathway, decreases free fatty acid concentration in circulation and protects cellular viability. During reperfusion, both insulin and glucose renovates the substrates of the citric acid cycle thus supports the production of high energy phosphates. The resultant effect is protection of myocardial contractile function. The experimental and clinical studies showed that during ischemia and reperfusion periods the use of GIK has been effective in the production of substrates.[3,12,13]

In experimental studies it was shown that GIK infusion decreases tissue acidosis, the incidence of arrhythmias, protects contractile function and limits the necrotic areas. Glucose-insulin-potassium solution given during ischemia and reperfusion caused a significantly better positive response than the one given only during reperfusion. The other group of reperfusion only.[14] In a study on patients undergoing CABG due to unstable angina pectoris, GIK infusion resulted in higher cardiac index, less weight gain, shorter duration of intubation, ICU and hospital stay compared to the others.[15]

Rao et al.[16] compared the data from four groups of patients receiving either one of the four different solutions including; high or low dose glucose-added cardioplegic solutions with or without 10 IU/L of insulin. Patients receiving insulin cardioplegia with low dose glucose showed a better hemodynamic response than others. In another study, Rao et al.,[17] compared patients who developed low cardiac output syndrome following isolated CABG and those who did not. They reported that myocardial lactate release was higher in patients with low cardiac output syndrome. During the

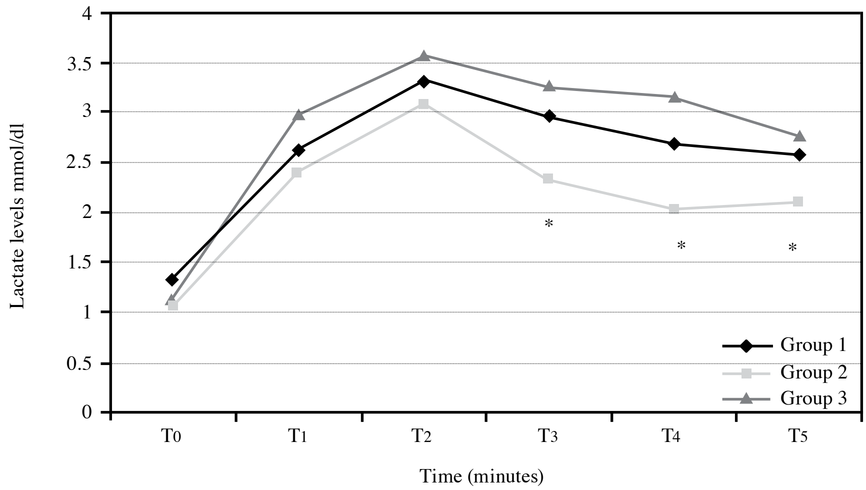

Fig. 4. The comparison of coronary sinus lactate levels at different time settings.

Table 3. The comparison of other variables during and after surgery

	Group 1	Group 2	Group 3	*p*
Cross-clamp time (minutes)	58.5±28.4	61.2±26.2	58.5±26.6	NS
Pump time (minutes)	98.5±40.2	92.3±34.3	89.2±28.5	NS
Entubation time (hours)	12.2±2.4	9.5±3.4	12.4±4.3	NS
Postoperative stay (hour)	28.2±8.3	27.4±11.1	31.3±14.4	NS
Hospital stay (day)	8.3±2.2	7.2±1.1	10.2±6.3	NS
Inotropic support				
Yes	5	1	9	p<0.05
No	35	39	31*	p<0.05
Defibrillation				
Yes	3	2	9	p<0.05
No	37	38	31*	p<0.05
Postoperative arrythmias				
Yes	5	3	11	p<0.05
No	35	38	27*	p<0.05

*: The comparison of group 2 and 3 demonstrates p<0.05.

reperfusion period, persistant lactate release caused late recovery of aerobic myocardial metabolism.[17]

In a previous study performed in our clinic, we demonstrated that the administration of a single dose of insulin before cross-clamp removal caused a reduction in arterial and coronary sinus lactate levels and decreased the incidence of postoperative arrythmias.[18]

Rao et al.[19] reported no differences in the frequency of low cardiac output and peroperative myocardial infarction in high risk patients whether or not they received insulin cardioplegia. However, Lazar[20] criticised this paper due to the fact that the control group also received a similar amount of insulin because of high blood glucose levels. They argued that this might have affected the results and recommended substrate support continuously from the beginning of anesthesia to the reperfusion period. In our study, parallel to the Lazar's results, the requirement for inotropic support was found to be significantly lower in patients receiving both insulin cardioplegia and GIK solution.

Lazar et al.[21] demonstrated in patients undergoing CABG for unstable angina that GIK solution decreased the incidence of atrial fibrillation and requirement for inotropic support.

Hynninen et al.[22] investigated the effects of insulin cardioplegia on postoperative atrial fibrillation incidence in high risk patients and found no difference. They posited that the differences of atrial fibrillation incidence could be related to the style of insulin administration. In order to prevent atrial fibrillation, they suggested insulin be given with blood cardioplegia and continued during the postoperative period.

In our study, the requirement for inotropic support and postoperative arrhythmias were significantly less in group 2 (insulin cardioplegia and postoperative infusion group) than the other groups. These findings are correlated with that of Lazar's. In group 1 (insulin only cardioplegia group) the results were similar to those of group 2 but did not achieve statistical significance. Therefore, we thought that results from group 1 also resemble those of Hynninen, and insulin cardioplegia should be followed by GIK infusion for the best results.

In conclusion, insulin cardioplegia followed by GIK solution improves metabolic parameters, accelerates postoperative recovery, decreases the requirement for defibrillation, inotropic agents and incidence of arrythmias. On the other hand, insulin cardioplegia alone does not achieve changes that are statistically significant in the same parameters, but still results in an overall clinical improvement. For this reason, we believe that in patients with low risk who are undergoing elective coronary artery surgery, insulin cardioplegia can be administered with GIK solution because of an improvement in metabolic parameters and postoperative intensive care recovery and stay. Hovewer, there is need for larger group studies to show the benefits of this regimen on high risk patients.

Declaration of conflicting interests

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