Açık Kalp Cerrahisinde Glikoz Leptin Metabolizmasında İnsulin Uygulamasının Rolü

THE EFFECT OF INSULIN ADMINISTRATION ON GLUCOSE LEPTIN METABOLISM IN OPEN HEART SURGERY

Nehir Sucu, *Zeliha Koçak, Barlas Aytaçoğlu, İlhan Mavioğlu, **Lülüfer Tamer, Kerem Karaca, Murat Dikmengil, **UğurAtik, *Uğur Oral

Mersin Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi Ana Bilim Dalı, Mersin
** Mersin Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Ana Bilim Dalı, Mersin*
*** Mersin Üniversitesi Tıp Fakültesi, Biyokimya Ana Bilim Dalı, Mersin*

Özet

Amaç: Hipotermik kardiyopulmoner bypassda glikoz-leptin arasındaki ilişkiyi ve normoglisemi sağlamak amacıyla uyguladığımız insulinin serum glikoz-leptin düzeyine olan etkisini belirlemeyi amaçladık.
Materyal ve Metod: Hastalar kontrol ve çalışma grubu olmak üzere ikiye ayrıldı. Çalışma grubundaki hastalara peroperatif insülin uygulandı. Anestezi öncesi dönemden başlayarak sternum kapatılıncaya kadar geçen süreçte hastalardan 20 dakikada bir kan alındı. Son kan örnekleri yoğun bakımda alındı. Tüm örneklerde glikoz ve leptin değerleri kaydedildi.
Bulgular: Çalışma grubunda 71 ± 12 ünite insülin uygulandı. İki grupta da intraoperatif hiperglisemi gelişmekle birlikte çalışma grubunda glikoz değerleri daha düşüktü. Kardiyopulmoner bypass süreci ve sonrasındaki değerler arasındaki fark istatiksel olarak anlamlıydı ($p < 0.05$). Aynı süreçte glikoz değerleri ile leptin değerleri arasında ters bir korelasyon mevcuttu.
Sonuç: Bu çalışmada hipotermik kardiyopulmoner bypassta glukoz düzeyinin insulin infüzyonu ile daha düşük düzeylere çekilebileceğini gösterdik. Ayrıca glukoz leptin arasında saptadığımız ters korelasyon nedeniyle kardiyopulmoner bypassta leptinin hiperglisemi gelişiminde etkili faktörlerden biri olabileceği sonucuna vardık.

Anahtar kelimeler: Leptin, hiperglisemi, kardiyopulmoner bypass

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Summary

Background: We aimed to put forward the relation between glucose and leptin under hypothermic cardiopulmonary bypass and effect of insulin administered to achieve normoglycemia on glucose – leptin levels.
Methods: Patients were divided into two groups as control and study groups. Insulin was given to the patients in the study group. Blood samples were collected from all of the patients with 20 minutes intervals beginning at the preanesthesia period until the closure of the sternum and the last sample was taken in the intensive care unit. Glucose and leptin levels were recorded.
Results: In the study group 71 ± 12 units of insulin was given. Intraoperative hyperglycemia was present in both groups but in the study group the levels were lower. The difference between the values during and after cardiopulmonary bypass was statistically significant ($p < 0.05$). During the same process there was inverse correlation between glucose and leptin levels.
Conclusions: In this study we demonstrated that glucose levels are lowered by crystallized insulin application under hypothermic cardiopulmonary bypass. Furthermore as we estimated an inverse correlation between glucose and leptin we are convinced that leptin is one of the influential factors in the development of hyperglycemia under hypothermic cardiopulmonary bypass.

Keywords: Leptin, hyperglycemia, cardiopulmonary bypass

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Introduction

The role of insulin and insulin antagonist hormones (glucagon, epinephrine, norepinephrine and cortisol) in the development of hyperglycemia under hypothermic cardiopulmonary bypass (CPB) has been documented [1,2]. Leptin is another hormone discovered recently both in vivo and in vitro studies, and it is also effective in glucose metabolism [3-6]. Leptin is not only important in the regulation of food intake and energy balance, but it also functions as a metabolic and neuroendocrine hormone. It is especially involved in glucose metabolism, as well as in normal sexual maturation and reproduction [7]. While adipose tissue mediated leptin blockades insulin secretion at the pancreatic level, insulin increases leptin levels [3,4,6,8-10]. In this study we aimed to put forward the relation between glucose and leptin under hypothermic cardiopulmonary bypass and effect of insulin administered to achieve normoglycemia on glucose – leptin levels.

Adres: *Dr. Nehir Sucu, Mersin Universitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi Ana Bilim Dalı, 33079, Mersin*
e-mail: *nehirsucu@superonline.com*

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Materials and Methods

Patients

After obtaining approval of the ethics committee of our institution and informed consent, 35 patients underwent CABG surgery. Patients with diabetes mellitus or requiring emergency surgery was excluded. Any patient exhibiting significant pulmonary, endocrine, metabolic or neurologic pathology was also excluded. All cardiac medications were continued until the day before surgery. Patients were randomly separated into two groups as the control (n = 20) and study groups (n = 15). In all patients, a baseline measurement of blood glucose and leptin levels was performed before induction of anaesthesia and was continued to be measured in every 20 minutes until the sternal closure. Final samples were obtained in the intensive care unit and only normal saline was administered for perioperative and postoperative i.v. infusions in any phase of these operations. Intravenous insulin application started simultaneously with the induction of anaesthesia in the study group and lasted with the closure of the sternum. We modified the insulin administration protocol of Chaney and coworkers [12] since they encountered hypoglycemia attacks and applied insulin as described in Table 1.

Table 1. Insulin protocol.

Blood glucose level	
< 50 mg/dL	administer 12.5 g of dextrose IVP, stop infusion
50-100 mg/dL	stop infusion
100-150 mg/dL	maintain current infusion rate
150-200 mg/dL	5 units of regular insulin IVP, increase infusion by 3 units/hr
200-250 mg/dL	7.5 units of regular insulin IVP, increase infusion by 4units/hr
250-300 mg/dL	10 units of regular insulin IVP, increase infusion by 5 units/hr
> 300 mg/dL	12.5 units of regular insulin IVP, increase infusion b 5units/hr

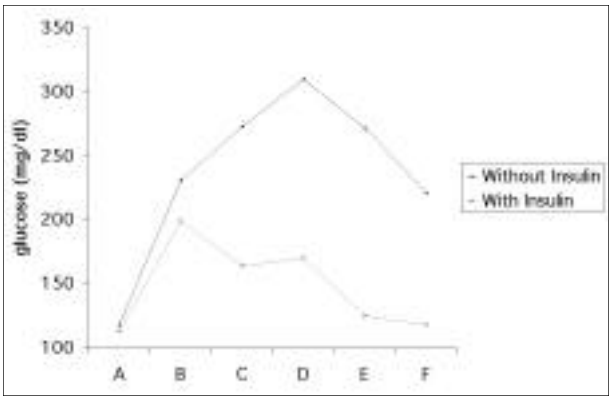
IVP= Intravenous push

Table 2. Demographics and surgical data.

	Control (n = 20)	**Study (n = 15)**
Age	57 ± 6	59 ± 4
Sex ratio (male/female)	14/6	11/4
BMI ≤ 25	13 (65%)	9 (60%)
> 25	7 (35%)	6 (40%)
Preoperative treatment		
Digoxine	2	2
Diuretic	3	2
Nitrate	11	9
Calcium-channel blocker	5	4
Beta blocker	6	5
Amiodarone	2	4
CPB time (min)	111 ± 14	120 ± 20
Duration of aortic cross-clamping (min)	57 ± 9	60 ± 11
Lowest temperature (°C)	28 ± 0	28 ± 0
Htc before induction	0.41 ± 0.3	0.43 ± 0.4
Minimum level of Htc during CPB	0.26 ± 0.2	0.27 ± 0.3
Saphenous vein grafts	2.3 ± 0.4	2.5 ± 0.3
Internal mammary artery	18	13
Inotropic support after CPB	6	5
Perioperative MI	1	0

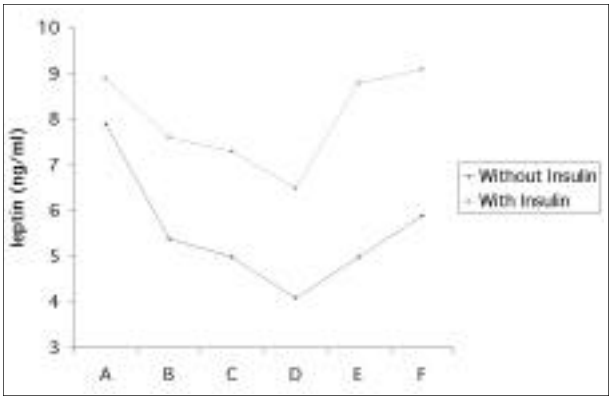
BMI = body mass index; CPB = cardiopulmonary bypass; Htc = haematocrit; MI = myocardial infarction

Figure 1. Glucose levels in control and study group.



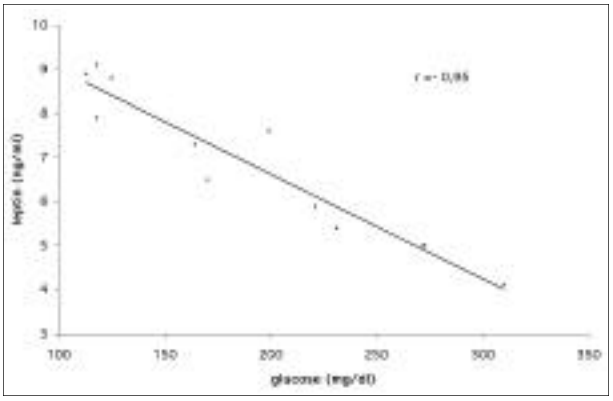
A. Preinduction of anaesthesia, B. Time between entubation and commencement of CPB, C. Cooling period during CPB, D. Rewarming period during CPB, E. Time from the cessation of CPB to the sternal closure, F. Intensive care period

Figure 2. Leptin levels in control and study group.



A. Preinduction of anaesthesia, B. Time between entubation and commencement of CPB, C. Cooling period during CPB, D. Rewarming period during CPB, E. Time from the cessation of CPB to the sternal closure, F. Intensive care period

Figure 3. Relation between leptin and glucose.



Anaesthesia Management

After pre-oxygenation, anaesthesia was induced with 0.3 mg/kg etomidate, 1mg/kg remifentanil and 0.15 mg/kg vecuronium. Maintenance of anaesthesia was obtained with 0.7-1% sevoflurane in 50% N_2O + 50% O_2 with a continuous infusion of remifentanil at 0.2-0.25 mg/kg/min until the beginning of CPB. During CPB remifentanil infusion was reduced to 0.1 mg/kg/min, inhalation anaesthesia was stopped and the patients' lungs were allowed to deflate. After completion of CPB remifentanil infusion was continued at 0.2-0.25 mg/kg/min and 0.7-1 % sevoflurane in 100% O_2 without N_2O was started.

Cardiopulmonary Bypass

All patients underwent coronary artery bypass surgery with CPB by using a roller pump (Stockert SIII, Munich, Germany) and disposable membrane oxygenator (Dideco D708, Mirandola, Italy). The system was primed with crystalloid solutions. Approximately 1500 cc of priming solution which usually consisted of 1000 cc Isolyte S and 500 cc gelatine (Gelafusine, Braun, Germany) was used for all patients. Unless the patients were anaemic, blood was generally not added to the system. The patients'haematocrit was kept in the range of 25-28%. During perfusion, additional perfusate (Ringer´s solution) was added when necessary to run the system safely. Activated clotting time (ACT) was maintained over 400 sec. Standard cardiopulmonary techniques were used during extracorporeal circulation.

Blood Sampling

Arterial blood samples were collected from the patients in every twenty minutes in six different phases of the operation; a) preinduction of anaesthesia, b) time between the entubation and CPB, c) cooling period during CPB, d) rewarming period during CPB and e) the time from the cessation of CPB to sternal closure, and f) in the intensive care unit were evaluated by taking the mean values.

Glucose measurement

Blood glucose levels were determined by blood glucose meter (Prestige and Prestige Smart System HDI Home Diagnostics, Inc. Ft. Landerdale, Florida, U.S.A.) Leptin measurement: Each sample was collected into a precooled tube, centrifuged at 4000 rpm for 2 min and serum was stored at –20°C. The levels of leptin were measured with a commercial enzyme-linked immunosorbent assay kit (Accucyte Human Leptin, European patent NO. EP 0 598 758 B1).

Statistics

SPSS 10.0 was used as the statistics program. Results are expressed as mean ± SD. A p value of < 0.05 is accepted to be statistically significant. We used the Student-t test and the Pearson´s correlation analysis tests for evaluation.

Results

The groups were not significantly different for demographic and clinical characteristics and intraoperative data (Table 2).
The base mean value of glucose being 118 ± 36 mg/dLduring the preinduction of anaesthesia phase has reached to a mean

level of 231 ± 112 mg/dL during the time between entubation and the commence of CPB. During hypothermic phase the mean glucose values obtained turned out to be 273 ± 92 mg/dL and the highest levels were found during the rewarming phase of CPB to be as high as 310 ± 104 mg/dL The glucose levels showed a tendency to fall to the levels of 272 ± 125 mg/dL from the cessation of CPB until the closure of the sternum. The glucose level found in the samples taken in the intensive care unit was 221 ± 97mg/dL The following glucose levels were obtained in the study group respectively: 113 ± 29 mg/dL, 199 ± 43 mg/dL, 164 ± 29 mg/dL, 170 ± 32 mg/dL, 125 ± 24 mg/dL, 118 ± 18 mg/dL (Figure 1).

The levels of leptin were synchronously recorded and their progress'were found to be as follows; leptin: for phase (a) 7.9 ± 3.7 ng/mLversus 8.9 ± 3.5 ng/mL, phase (b) 5.4 ± 1.7 ng/mL versus 7.6 ± 2.3 ng/mL, phase (c) 5.0 ± 1.9 ng/mL versus 7.3±1.4 ng/mL, phase (d) 4.1 ± 1.9 versus 6.5 ± 1.3 ng/mL phase (e) 5.0 ± 2.3 ng/mL versus 8.8 ± 1.7 ng/mL and last phase (f) 5.9 ± 2.2ng/mL, 9.1 ± 1.1 ng/mL (Figure 2).

As the glucose levels in the control and study groups were compared before, during and after CPB periods it was found that before CPB glucose levels in the study group was low, but there was no statistically diferent from the control group; during the CPB and post CPB periods the glucose levels between the two groups turned out to be statistically significant ($p < 0.05$). When leptin values were evaluated it is seen that the difference in the control and study groups after the start of surgery was statistically significant ($p < 0.05$).

Analyzing the relation between leptin and glucose in the control and study groups with Pearson Correlation analysis test the results were found to be significant ($p < 0.05$) during intraoperative and postoperative periods (Figure 3).

Conclusions

The human response to surgical stress is characterised by massive release of neuroendocrine hormones, provoking catabolism, thermogenesis and hyperglycemia [11]. Reasons for hyperglycemia under CPB seem to be decreased secretion of insulin and peripheral glucose use (hypothermia, pancreatic hypoperfusion) and/or increased activity of insulin antagonist hormones [12]. Recent studies put forward that leptin is one of the hormones, which is effective in hyperglycemia [3-6]. Functional leptin receptors were shown to be present on insulin-secreting pancreatic beta cells [4,13]. Leptin has been shown to inhibit basal and glucose stimulated insulin secretion at the pancreatic level [4,6,13]. On the other hand, this is most evident from studies with isolated adipocytes, which all showed that in vitro insulin clearly stimulates the mRNA expression and secretion of leptin in cultured rat and human adipocytes [8-10]. Serum leptin levels are raised by insulin treatment, in type 2 as well as in type 1 diabetic patients [14]. In our study, we have demonstrated an inverse correlation between glucose and leptin ($p < 0.05$). In the control group, leptin levels decreased as glucose levels increased. This decrease in leptin levels can be explained by the response of the neuroendocrine system to surgical stress. In a study with the patients undergoing surgery Kain and associates [11] estimated a decrease in leptin levels while there was an increase in cortisol levels. Previously it has been shown that leptin secretion by the adipocyte is partly regulated by insulin, cortisol, and sex steroids [7]. According to these findings leptin's role in hyperglycemia that occurred in the control group can be explained by its insulin secretion decreasing effect. In the study group, we could not achieve normoglycemia by insulin administration but managed to lower the glucose levels, which was significant for the CPB, and post CPB periods ($p < 0.05$). The increase in leptin levels was significant from the beginning of surgery ($p < 0.05$). Chaney and associates [12] reported that they could not achieve a response to insulin administration during CPB therefore indicated that instead of decrease in insulin secretion hyperglycemia would be due to insulin resistance and temperature. Gill and associates [15] reported that during CPB insulin secretion and sensitivity is decreased and the glucose metabolism is continued partially. Other studies demonstrated that in hyperglycemia besides insulin resistance glucagons, growth hormone, catecholamines and cortisol are also effective [1,2].

In our study we found out that leptin levels are increased by insulin administration and a decrease in glucose levels is achieved therefore deducing that under hypothermic CPB a) there isn't a complete insulin resistance, b) the glucose metabolism still carries on and c) leptin is also effective in glucose metabolism. The inverse correlation we estimated between glucose and leptin in study and control groups indicates that in hyperglycemia that develops under hypothermic CPB leptin should also be taken into consideration.

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