

Effects of Perfusion Temperature on Inflammatory Response and Outcome Following Cardiopulmonary Bypass

Kardiyopulmoner Bypass Isısının İnflamatuar Cevap ve Sonuçlar Üzerine Etkileri

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ABSTRACT

Objective: To evaluate the effects of perfusion temperature on inflammatory response, and outcome in patients undergoing open heart surgery.

Methods: Forty nine patients were assigned to 2 groups, group I (n=24) normothermic cardiopulmonary bypass (CPB) and group II (n=25) hypothermic CPB. Blood samples were collected preoperatively and postoperatively for interleukin-6 (IL6) and high sensitive CRP (hsCRP). Concerning the variables, there were no significant preoperative differences between the groups.

Results: At the end of CPB, mean plasma levels of IL-6 was significantly lower in the normothermia group (Group 1: 34.0±14.9 vs. Group 2: 53.0±41. p<0.05). At postoperative 12h, IL6 concentrations were 25.2±9.2 in Group 1 and 34.0±21.2 in Group 2 (p>0.05). In 24 h, the IL-6 concentrations were 20.4±8.1 in Group 1 and 29.6±21.1 in Group 2 (p>0.05). High sensitive CRP levels were significantly higher at the end of CPB than the preoperative levels (Group 1: 16.1±3.4 vs. Group 2: 18.5±3.6, p<0.05). At postoperative 12 h and 24 h, hsCRP concentrations declined (Group 1: 12.8±2.6 vs. Group 2: 13.2±2.9 at 12h, p>0.05 and Group 1: 12.3±2.6 vs. Group 2: 14.2±2.8 at 24 h, p>0.05). Normothermic CPB resulted in a shorter CPB time; 63.1 ±19.1 min. vs 82.0 ±19.2 min. (p <0.01) and the interval up to extubation was 8.9±2.5 h vs. 11.6±4.6 h (p<0.05). Blood loss was 633.1±390.4 ml vs. 981.8±438.0 ml (p<0.05) and use of blood was 2.7±0.7 packages vs. 4.2±0.5 packages (p<0.01) in Group 1 and Group 2 respectively, as well as the length of ICU stay 2.5±0.5 vs. 4.0±0.6 days, (p<0.01). Length of hospital stay was significantly shorter in the normothermic group 7.2±0.5 days vs. 8.0±0.6 days (p<0.01).

Conclusion: A strategy of normothermic CPB seems to be as safe as hypothermic CPB and is associated with a reduced inflammatory response and offers a better outcome. (*JAREM 2012; 2: 10-4*)

Key Words: Normothermic CPB, Hypothermic CPB, Inflammatory response, cardiopulmonary bypass, open heart surgery, CABG

ÖZET

Amaç: Açık kalp cerrahisinde perfüzyon ısısının inflamatuar cevap ve sonuçlar üzerine etkilerinin araştırılması.

Yöntemler: Toplam 49 hasta iki gruba bölünmüştür, Grup 1 (n=24) normotermik opere edilmiş, grup 2 (n=25) hipotermik kardiyopulmoner bypass (KPB) altında opere edilmiştir. Preoperatif ve postoperatif dönemde interleukin-6 (IL6) ve high sensitive CRP (hsCRP) seviyeleri için kan örnekleri alınmıştır.

Bulgular: Kardiyopulmoner bypassın sonunda IL-6 değerleri normotermik opere edilmiş grupta hipotermik gruba oranla belirgin olarak düşük bulunmuştur (Grup 1: 34.0±14.9-Grup 2: 53.0±41. p<0.05). Postoperatif 12. saatte, IL6 seviyeleri düşmeye başlamıştır, Grup 1: 25.2±9.2, Grup 2: 34.0±21.2 (p>0.05). Yirmi dördüncü saatte IL-6 seviyeleri Grup 1: 20.4±8.1, Grup 2: 29.6±21.1 olarak bulunmuştur (p>0.05). High sensitive CRP değerleri Grup 1: 16.1±3.4, Grup 2: 18.5±3.6 (p<0.05). Postoperatif 12. ve 24. saatte, hsCRP seviyeleri düşmeye başlamıştır Grup 1: 12.8±2.6-Grup 2: 13.2±2.9 12 h. saat, p>0.05 ve Grup 1: 12.3±2.6-Grup 2: 14.2±2.8 24.saat, p>0.05). Grup 1'de KPB ve extubasyon süreleri Grup 2'ye göre belirgin kısadır (63.1±19.1 dakika-82.0 ±19.2 min. (p <0.01)) ve (8.9±2.5 saat - 11.6±4.6 saat (p<0.05). Grup 1 ve Grup 2 karşılaştırıldığında drenaj miktarı 633.1±390.4 mL - 981.8±438.0 mL (p<0.05), kan kullanımı 2.7±0.7 torba-4.2±0.5 torba (p<0.01), yoğun bakım süresi 2.5±0.5-4.0±0.6 gün, (p<0.01) bulunmuştur. Tüm bu sonuçlar normotermik grubun hastane yatış süresini olumlu etkilemiştir 7.2±0.5 gün-8.0±0.6 gün (p<0.01).

Sonuç: Normotermik KPB stratejisi en az hipotermik KPB kadar güvenli olmasının yanı sıra inflamatuar cevabı azaltmış ve daha iyi sonuçlar vermiştir. (*JAREM 2012; 2: 10-4*)

Anahtar Sözcükler: Normotermik KPB, Hipotermik KPB, inflamatuar yanıt, kardiyopulmoner bypass, açık kalp cerrahisi, CABG



INTRODUCTION

The deleterious effects of cardiopulmonary bypass are believed to be related to activation of neutrophils, various cytokines, complement, interleukin production, free radical generation and a wide variety of other responses collectively known as the systemic inflammatory response. This can lead to end-organ dysfunction that may affect the postoperative course of the patients and may limit surgical success (1-3). In the present investigation, a variety of surrogate markers of the inflammatory response were measured to determine the role of perfusion temperature on the magnitude and temporal nature of this response.

IL-6 is a multifunctional proinflammatory cytokine, which also plays an important role in ischemia-reperfusion injury (3-5). CRP is a member of the class of acute-phase reactants, and its levels rise dramatically during inflammatory processes. Its physiological role is to bind to phosphocholine in order to activate the complement system via the complex. The high-sensitivity CRP (hs-CRP) test measures low levels of CRP.

Cardiopulmonary bypass is a non-physiologic state associated with significant alterations in homeostatic mechanisms, hormone levels and organ perfusion which is astonishingly well tolerated during hypothermia. The response to normothermic CPB remains to be investigated. The purpose of this study is to evaluate the effects of temperature on inflammatory response and outcome during open heart surgery.

METHODS

Patient groups

Patients recruited for these prospectively controlled, randomized studies underwent elective coronary artery bypass grafting using normothermic or hypothermic CPB in Hacettepe University Faculty of Medicine, Department of Cardiovascular Surgery and Bağcılar Training and Research Hospital, Department of Cardiovascular Surgery. We enrolled 24 patients (mean age 58.0 ± 11.2 years) in the normothermia group and 25 patients (mean age 62.6 ± 9.9 years) in the hypothermia group. Patients with diabetes mellitus, unstable angina, chronic obstructive lung disease and renal disease were excluded from the study. Informed consent was obtained from each patient according to the protocol of the ethics committee. Patient preoperative data were shown in Table 1.

Operative techniques

After median sternotomy and heparinization, standard cannulation techniques through the ascending aorta and right atrium were used to complete the CPB circuit. Cardiopulmonary bypass was performed with a membrane oxygenator (Edwards Vital; Edwards Lifesciences, Irvine, CA, USA). An aortic antegrade cardioplegia cannula and a retrograde coronary sinus catheter were positioned using a closed transatrial technique. The heart was arrested either antegradely or retrogradely with blood with high potassium solution (K^+ 30 mmol/L). After cardiac arrest, retrograde low potassium blood (K^+ 10 mmol/L) was infused every 15 minutes in Group 1 and every 20 minutes in Group 2, with the infusion pressure at the cannula tip maintained at less than 40 mm Hg. In Group 1, warm cardioplegia was infused at 37°C and the CPB temperature was maintained at $>34^\circ\text{C}$. In Group 2 cold cardioplegia was infused at 4°C and the CPB temperature was maintained at 28°C . The CPB pump flow was adjusted to 2.4 l/min per m^2 during normothermia and to 1.8 l/min per m^2 during moderate hypothermia. The mean systemic pressure

was maintained at between 40-60 mmHg with the use of vasoactive drugs in hypothermic patients and attempted to maintain it above 60 mmHg in the normothermic patients (ephedrine, glyceroltrinitrate) where necessary. The internal mammary artery and saphenous vein grafts were used for coronary anastomosis. Heparin was neutralized with protamine hydrochloride (Protamin 1000; Roche, Istanbul, Turkey).

Measurements

Operative procedures and operative variables and intraoperative data were shown in Table 2, 3. Operative variables included the CPB time, need for vasopressors and volume during CPB. In the postoperative period, routine blood chemistry, IL6 and hsCRP parameters were analyzed: Postoperative variables; extubation time, chest tube drainage, transfusion of blood, length of ICU stay and length of hospital stay were also analyzed and shown in Table 4.

Table 1. Preoperative data

	Group 1 (n=24)	Group 2 (n=25)	p value
Age (years)	58.0 ± 11.2	62.6 ± 9.9	NS
Men/women	17/7	16/9	NS
NYHA class	2.7 ± 0.4	2.6 ± 0.2	NS
Smoking (on admission)	22 (%)	21 (%)	NS
Hypertension (patient history)	22 (%)	23 (%)	NS
Hyperlipidemia (requiring treatment)	22 (%)	19 (%)	NS
Obesity (> 10% normal body weight)	6 (%)	9 (%)	NS
Prior myocardial infarction	11 (%)	15 (%)	NS
Ejection fraction (%)	51 ± 3	48 ± 4	NS

NYHA: New York Heart Association

Table 2. Operative procedures

	Group 1 (n=24)	Group 2 (n=25)	p value
CABG	24	25	NS
No. of grafts	3.3 ± 0.2	3.5 ± 0.3	NS
Urgent procedures	3 (%)	2 (%)	NS

CABG: coronary artery bypass grafting

Table 3. Intraoperative data and variables

	Group 1 (n=24)	Group 2 (n=25)	p value
Ephedrine (mg)	10.3 ± 3.1	33.1 ± 4.1	$p < 0.05$
No. of patients with vasopressors	12 (50%)	14 (56%)	NS
CPB time (min)	63.1 ± 19.1	82.0 ± 19.2	$p < 0.01$
Cross-clamp time (min)	50.0 ± 15.0	46.6 ± 15.2	NS

Sample Collection and Laboratory Assays

Venopuncture was performed in the morning on the patients, all of whom had been fasting for >12 hours. Samples were also collected at the end of the CPB, 12 and 24 h postoperatively. Platelet-poor plasma fractions were obtained by centrifugation at 4°C for 20 minutes at 4000g, and soluble IL-6 was measured by an enzyme-linked immunosorbent assay Biosource immunoassay kit (Camarillo, CA, USA). hsCRP levels were assayed in serum samples by rate turbidimetry (Immagine 800 Immunochemistry System CRPH; Beckman Coulter, Brea, CA, USA).

Statistical Analysis

Data were expressed as means±the standard deviation. Unpaired t-test was used to compare data and a p value less than 0.05 was considered statistically significant.

RESULTS

The patients' preoperative characteristics are shown in Table 1. To assess the differences in outcome in regard to CPB temperature, Group 1 and Group 2 were compared. In respect to preoperative variables, there were no significant differences between Groups 1 and 2.

Patients in Group 1 and Group 3 were similar with respect to the number of grafts performed and type of operation (Table 2). To maintain defined systemic pressure during CPB, the hypothermic patients (group II) needed significantly higher doses of ephedrine HCL (10.3±3.1 vs 33.1±4.1mg, p<0.05). However, there were no differences in regard to the total number of patients who needed vasopressors during CPB (normothermic 12/24, 50%; hypothermic 14/25, 56%; NS). Cardiopulmonary bypass time was significantly shorter in the normothermic group (63.1±19.1 min vs 82.0±19.2 min, p<0.01) with similar cross-clamp times in the two groups (normothermic 50.0±15.0 min vs. hypothermic 46.6±15.2 min, NS) (Table 3). The postoperative extubation time was significantly shorter after normothermic CPB (8.9±2.5 h vs. 11.6±4.6 h, p<0.05), as well as the length of ICU stay (2.5±0.5 days vs. 4.0±0.6 days, p<0.01), total amount of chest tube drainage (633.1±390.4 ml vs. 981.8±438.0 ml, p<0.05) and blood requirements (2.7±0.7 packages vs. 4.2±0.5 packages, p<0.01). All these results affected the length of hospital stay, which was significantly shorter in the normothermia group 7.2±0.5 days vs. 8.0±0.6 days (p<0.01) (Table 4).

Preoperative IL6 and hsCRP levels did not show any difference between the groups. In samples taken at the end of CPB, both IL6 and hsCRP levels were significantly higher than the preoperative values (Tables 5 and 6). For IL6, this difference was significant (Group 1: 34.0±14.9 vs. Group 2: 53.0±41.6, p<0.05). At postoperative 12h, the concentrations declined in both groups but, although it was lower in group I, it was not statistically significant (Group 1: 25.2±9.2 vs. Group 2: 34.0±21.2 p>0.05). At 24h, as shown in Figure 1, the levels continued to decline but this also was not statistically significant (Group 1: 20.4±8.1 vs. Group 2: 29.6±21.1 p>0.05) (Table 5).

As in IL6, hsCRP levels were significantly higher than the preoperative values at the end of CPB and this difference was significant between the groups (Group 1: 16.1±3.4 vs. Group 2: 18.5±3.6 p<0.05). At postoperative 12h and 24h, hsCRP concentrations declined, (Figure 2) but they did not show any difference or statistical significance between the groups (Group 1: 12.8±2.6 vs. Group 2: 13.2±2.9 at 12h, p>0.05 and Group 1: 12.3±2.6 vs. Group 2: 14.2±2.8 at 24 h, p>0.05), (Table 6).

Table 4. Postoperative variables

	Group 1 (n=24)	Group 2 (n=25)	p value
Extubation time (h)	8.9±2.5	11.6±4.6 h	p<0.05
ICU stay (day)	2.5±0.5	4.0±0.6	p<0.01
Chest tube drainage (ml)	633.1±390.4	981.8±438.0	p<0.05
Blood (units)	2.7±0.7	4.2±0.5	p<0.01
Hospital stay (days)	7.2±0.5	8.0±0.6	p<0.01

Table 5. IL-6 levels

	Group 1	Group 2	p value
Preoperative	6.8±3.3	6.2±3.0	p>0.05
After CPB	34.0±14.9	53.0±41.6	p<0.05
12h	25.2±9.2	34.0±21.2	p>0.05
24h	20.4±8.1	29.6±21.1	p>0.05

Table 6. hsCRP levels

	Group 1	Group 2	p value
Preoperative	0.47±0.27	0.40±0.24	p>0.05
After CPB	16.1±3.4	18.5±3.6	p<0.05
12 h	12.8±2.6	13.2±2.9	p>0.05
24 h	12.3±2.6	14.2±2.8	p>0.05

DISCUSSION

The inflammatory response that accompanies open heart surgery is multifactorial (6). The foreign surfaces in the heart-lung machine, surgical trauma, anesthesia, and deviation from normal organ perfusion are important factors causing inflammatory activation (7, 8). It has also been suggested that the perfusion temperature may influence the inflammatory response and outcome (9). The influence of temperature during CPB on the incidence and severity of these injuries has not yet been established. There are several theoretical objections to warm CPB: (a) enzymatic reactions are temperature dependent. This may result in an extended cellular and humoral activation during CPB, (b) side effects due to nonhomogeneous organ perfusion may be more evident in normothermia because of reduced tolerance to ischemia, (c) higher blood flow rates during CPB lead to additional blood trauma (higher shear stress) (10, 11). Our study could not demonstrate any important adverse effects of warm CPB. Inflammatory response is much better in normothermia.

Normothermia may have reasonably been expected to produce an exaggeration of the inflammatory response to bypass because biochemical pathways are optimal at normal body temperature. However, the results of this study and others suggest the opposite (10, 12). Both IL6 and hsCRP levels showed a rapid increase at the end of CPB and in both IL6 and hsCRP this increase was significantly low in Group 1, showing an attenuated inflammatory response to normothermia. At postoperative 12h and 24h, all the concentrations declined but they did not show a major difference or statistical significance (p>0.05). The literature remains confusing

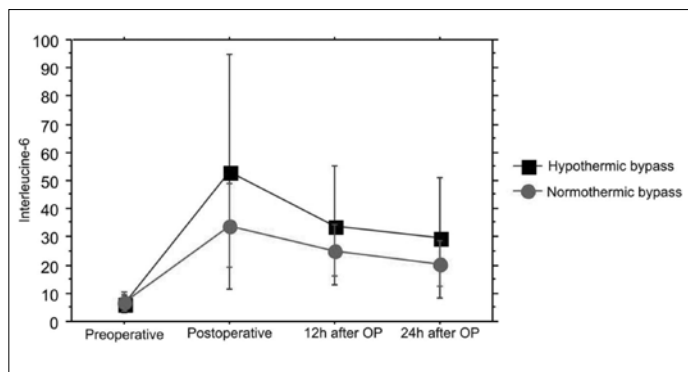


Figure 1. IL6 levels

with regard to the effects of perfusion temperature on the activity of the inflammatory response and even less is known about the clinical sequelae of these responses. Inconsistencies in definitions of normothermic bypass (35-37°C) only perpetuate the controversy. In a clinical study by Menasche and associates (13), normothermic bypass (35-37°C) was associated with significantly elevated levels of IL-1 β compared to hypothermic bypass (28-30°C). The incidence of vasodilatation, presumed to result from the presence of these mediators, was two-fold higher in the normothermic group, necessitating increased use of vasopressors (14). Steroid pre-treatment may prevent the vasodilatation associated with normothermic cardiopulmonary bypass by inhibition of IL-6 release (15). In contrast to these, in our study the total amount of vasopressors were higher in Group 2.

IL-6 concentrations have been shown to be much higher in patients undergoing heart transplantation, in which the duration of myocardial ischemia was much longer than in those undergoing coronary revascularization (16). There is evidence linking this cytokine to the pathogenesis of reperfusion injury, the post perfusion syndrome and the adult respiratory distress syndrome (17-19). While all the studies mentioned above have provided some insight into the effects of normothermic bypass upon the inflammatory response, the practical significance with regard to end organ dysfunction still requires further evaluation. Of interest would be the effects of normothermic bypass on the systemic response in higher risk patients and those enduring long aortic cross clamp and cardiopulmonary bypass times (12, 16, 20). Also, normothermic CPB resulted in a shorter extracorporeal perfusion time and, postoperative course with a shorter extubation time, less bleeding and shorter ICU stay (21, 22). Although not expressed herein; when we looked at our results on a patient basis, patients with a longer CPB time and longer aortic cross-clamp times had enhanced inflammation involving raised levels of interleukin-6 and hsCRP. This may need further investigation.

The short postoperative extubation time may reflect superior pulmonary function and/or improved hemodynamic stability after normothermic CPB, which could be explained by the attenuated inflammatory response. Similar results have been reported by several authors (23, 24). In a large observational study involving 2817 patients, Singh et al. (23) found no evidence of important side effects due to normothermic CPB.

Also, bleeding and blood transfusion were reduced with normothermia in this study, which was correlated with the study of others. This revealed that the normothermic heart surgery is as safe

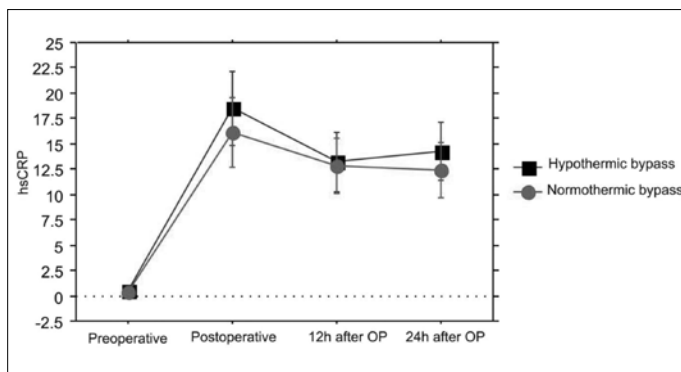


Figure 2. hsCRP levels

as hypothermic surgery, and associated with a reduced risk of allogeneic blood transfusion (10, 21, 22). This could be due to shorter CPB times and relatively less blood trauma.

The concept that normothermia may be associated with an exaggerated inflammatory response to bypass was therefore not demonstrated in this study. One possible reason may be that clearance of these markers may also have been more rapid at higher temperatures, although it is recognized that only circulating mediators can participate in end organ injury. As a result, this study suggests that, normothermic CPB provides better outcome, attenuates inflammatory response, shortens CPB time, ICU stay, decreases blood loss and usage of blood products. According to the data, although it needs further investigation, normothermic CPB seems to be a safe alternative.

Conflict of interest: No conflict of interest was declared by the authors.

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