

## The role of regional cerebral oxygen saturation on adjustment of fraction of inspired oxygen during coronary artery bypass graft surgery

*Koroner arter baypas greft cerrahisi sırasında inspire edilen oksijen fraksiyonunun ayarlanmasında rejyonel serebral oksijen satürasyonunun rolü*

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**Background:** The aim of the study is to detect the regional cerebral oxygen saturation by the help of near infrared spectroscopy (NIRS) monitorization and to diagnose the hypoxemic or hyperoxemic episodes for the assessment of the effects of hypoxia episodes on cerebral perfusion during cardiopulmonary bypass (CPB) as early as possible.

**Methods:** The study had been performed in Acibadem Kadıköy Hospital during February 2011 and June 2011. Seventy patients who were admitted with coronary heart disease (CHD) and scheduled for coronary artery bypass graft (CABG) surgery were included in the study. The patients were divided into two equal groups. Thirty five percent of the 35 patients (n=12) were female in group 1, 50% of 50 patients (n=18) were female in group 2. The mean age was 60±10 years and 57±11 years in group 1 and group 2, respectively. Group 1 consisted of 35 patients with adjusted inspired oxygen fraction (FiO<sub>2</sub>) at 0.35-0.45 during CABG. Group 2 consisted of 35 patients with adjusted FiO<sub>2</sub> at 0.40-0.50 during surgery. In addition to the standard monitorization, cerebral cortical oxygen saturation of all patients was monitored by NIRS. The measurements were done five times during the course of CABG.

**Results:** In group 1, hypoxia was detected in five patients (14%) in at least one of the five measurement periods. In these patients, FiO<sub>2</sub> value increased accompanied by increased ScO<sub>2</sub>. In group 2, hyperoxemia was observed in at least one of the measurement periods in 15 (42.8%) patients. Hypoxia was not observed in any of the patients in group 2.

**Conclusion:** It is possible to detect hypoxic periods and to adjust FiO<sub>2</sub> accordingly by means of noninvasive cerebral cortical oxygen saturation measurement in nonpulsatile flow of CPB.

**Key words:** Cardiopulmonary bypass; cerebral oxygen saturation; cerebral oximeter; inspired oxygen saturation.

**Amaç:** Bu çalışmada yakın kızılötesi spektroskopi (NIRS) monitörizasyonu ile rejyonel serebral oksijen satürasyonunun saptanması ve kardiyopulmoner baypas (KPB) sırasında hipoksi epizotlarının serebral perfüzyon üzerindeki etkilerinin değerlendirilebilmesi için mümkün olduğunca en kısa sürede hipoksemik veya hiperoksemik epizotların tespit edilmesi amaçlanmıştır.

**Çalışma planı:** Bu çalışma Şubat 2011 ve Haziran 2011 tarihleri arasında Acibadem Kadıköy Hastanesi'nde yürütüldü. Çalışmaya koroner kalp hastalığı (KKH) nedeniyle başvuran ve koroner arter baypas greft (KABG) cerrahisi yapılması planlanan 70 hasta dahil edildi. Hastalar iki eşit gruba ayrıldı. Grup 1'deki 35 hastanın %35'i (n=12) ve grup 2'deki 50 hastanın %50'si (n=18) kadındı. Hastaların ortalama yaşı grup 1'de 60±10 yıl, grup 2'de ise 57±11 yıl idi. Grup 1'de KABG cerrahisi sırasında inspire edilen oksijen fraksiyon (FiO<sub>2</sub>) değeri 0.35-0.45'e ayarlanmış 35 hasta vardı. Grup 2'de ise, cerrahi sırasında FiO<sub>2</sub> değeri 0.40-0.50'ye ayarlanmış 35 hasta bulunuyordu. Standart monitörizasyonun yanı sıra, tüm hastaların serebral kortikal oksijen satürasyonu NIRS ile izlendi. Ölçümler, KABG cerrahisi sırasında beş kere tekrarlandı.

**Bulgular:** Grup 1'de beş ölçüm süresinden en az birinde beş hastada (%14) hipoksi saptandı. Bu hastalarda FiO<sub>2</sub> değeri yükselen ScO<sub>2</sub>'ye eşlik ederek yükselmişti. Grup 2'de, beş ölçüm süresinden en az birinde on beş hastada (%42.8) hiperoksemi saptandı. Grup 2'deki hastaların hiçbirinde hipoksi görülmedi.

**Sonuç:** Pulsatil olmayan KPB akışında noninvaziv serebral kortikal oksijen satürasyonu ölçümü ile hipoksik epizotları saptamak ve buna göre FiO<sub>2</sub> değerini ayarlamak mümkündür.

**Anahtar sözcükler:** Kardiyopulmoner baypas; serebral oksijen satürasyonu; serebral oksimetre; inspire edilen oksijen satürasyonu.



The majority of cardiac operations are still performed under cardiopulmonary bypass (CPB), and patients undergoing cardiac surgery with CPB are often thought to have tissue hypoxia. Therefore, it is usually assumed that a supranormal partial arterial oxygen tension (PaO<sub>2</sub>) will improve oxygen delivery to peripheral tissues. With regard to these safety measures, very high values of PaO<sub>2</sub> are frequently observed during CPB. However, these can be detrimental. Animal studies have shown that oxygen reduces the heart rate and cardiac output and increases systemic vascular resistance,<sup>[1,2]</sup> and this has been confirmed in patients with congestive heart failure in whom the effect is more pronounced.<sup>[3]</sup> The adverse influences of hyperoxemia (PaO<sub>2</sub> >180 mmHg) on red blood cells and tissue oxygenation during CPB along with subsequent perioperative complications and morbidity have been reported.<sup>[4-6]</sup> Although CPB has been used for more than half a century, there is still no consensus regarding the ideal levels of fraction of inspired oxygen (FiO<sub>2</sub>) and PaO<sub>2</sub>. There seems to be a wide range of practice in relation to the optimum oxygen settings during CPB, and the perfusionist usually adjusts the oxygen by trial and error. The most frequently recommended FiO<sub>2</sub> at the initiation of CPB is 0.80, with this being decreased to 0.70-0.60 during hypothermia.<sup>[7]</sup> However, with such an application, hyperoxemia is almost inevitable.<sup>[8]</sup>

In order to avoid hyperoxemia and keep the partial oxygen level (pO<sub>2</sub>) <180 mmHg, the FiO<sub>2</sub> should be lowered accordingly; however, some patients may then run the risk of hypoxia (pO<sub>2</sub> <80 mmHg). Thus, it is necessary to keep in mind the risk of hypoxia and take the necessary precautions to diagnose it when adjusting the FiO<sub>2</sub>.<sup>[9]</sup> In addition, preventing hyperoxia from occurring during coronary artery bypass grafting (CABG) is also crucial. If the perfusion during CABG is nonpulsatile, the efficacy of the pulse oximeter when attempting to diagnose hypoxia is reduced. However, near infrared spectroscopy (NIRS), which is unaffected by the nonpulsatile flow, provides useful knowledge about ischemic changes in the brain tissue by measuring regional cerebral oxygen saturation.

Hypoxic attacks can occur during CABG while trying to refrain from hyperoxemia. In order to assess the effects of hypoxia episodes on cerebral perfusion during CPB as early as possible and make the necessary adjustments to the FiO<sub>2</sub> in time, we aimed to detect the regional cerebral oxygen saturation with the help of NIRS monitorization and diagnose the hypoxic or hyperoxic episodes. Our goal was to keep the FiO<sub>2</sub> at the lowest safe level by this noninvasive method of monitorization.

## PATIENTS AND METHODS

After approval of the ethics committee of our hospital, the study was started. Seventy patients who were scheduled for CABG surgery alone were included in the study after obtaining their informed consent. The patients were then divided into two groups.

Group 1 consisted of 35 patients whose FiO<sub>2</sub> would be 0.35 in the normothermic and hypothermic periods of CABG and 0.45 at the beginning of rewarming. Group 2 was composed of 35 patients whose FiO<sub>2</sub> would be 0.40 in the normothermic and hypothermic periods of CABG and 0.50 at the beginning of rewarming (Table 1). In addition to the standard monitorization, cerebral cortical oxygen saturation (ScO<sub>2</sub>) of all the patients was monitored by NIRS through the INVOS Model 5100 C cerebral/somatic oximeter (Somanetics Corporation, Troy, Michigan, USA), and five measurements were taken with this device during CABG. The first was obtained before the induction of anesthesia (T<sub>1</sub>=basal), the second at the fifth minute of CPB (T<sub>2</sub>), the third at 15 minutes after cross-clamping (T<sub>3</sub>), the fourth after the cross-clamp had been removed (T<sub>4</sub>), and the fifth just before the end of extracorporeal circulation (T<sub>5</sub>).

A decrease in the ScO<sub>2</sub> values of more than 20% from the basal value was accepted as significant. When there was a decrease of more than 20% from the basal value, an arterial blood gas analysis was done in addition to the what was planned in the five time periods, and the pO<sub>2</sub> levels were kept above 90 mmHg. Furthermore, when the ScO<sub>2</sub> levels decreased by more than 20% from the baseline and the pO<sub>2</sub> levels were >90 mmHg, the pump blood flow and mean arterial pressure (MAP) were increased successively. Despite all these maneuvers, if there was no improvement in the ScO<sub>2</sub> levels and the hematocrit was <20%, red blood cell transfusion were planned for the patients.

The INVOS monitor has a probe with two photodetectors and a light source which are placed on the right and left frontal hemispheres on the forehead. The photodetector closest to the light source absorbs the superficial rays (from skin, bone, and fat tissue), whereas the other photodetector absorbs the rays from the deep tissues of the brain. Oxymetric studies are based principally on the Beer-Lambert Law which states the following.

$$A = -\log(I_1/I_0) = \alpha \lambda \cdot C \cdot L$$

A=attenuation; I<sub>1</sub>= detected light intensity; I<sub>0</sub>= incident light intensity;  $\alpha$ = specific extinction coefficient ( $\mu\text{M}^{-1}\cdot\text{cm}^{-1}$ ); C= the molar concentration C of absorbing species in the material; L= distance light enters and leaves solution (cm).

In addition, the modified Beer-Lambert Law is used during the measurement of ScO<sub>2</sub>, in which the oxygen saturation values of the right and left hemispheres are stated as a percentage (%). When evaluated as biological spectroscopy, the INVOS oximeter emits a light that contains a light emitting diode (LED) at a wavelength of 660-940 nm. A light at this wavelength is absorbed strongly by oxyhemoglobin and deoxyhemoglobin and very weakly by water, bone, fat, and skin tissue. Therefore, this feature of the infrared light provides some beneficial knowledge. For instance, the differentiation between oxyhemoglobin and deoxyhemoglobin is made by a specific extinction coefficient value ( $\mu\text{M}^{-1}\cdot\text{cm}^{-1}$ ) which shows the absorption degree of masses that absorb light at a certain wavelength. The absorption degree of the oxyhemoglobin molecule of a light at a wavelength of 680 nm is  $0.4 \mu\text{M}^{-1}\cdot\text{cm}^{-1}$ , whereas the absorption degree of deoxyhemoglobin is  $2.4 \mu\text{M}^{-1}\cdot\text{cm}^{-1}$ . This difference provides the distinction.

### Anesthesia and operative technique

The night prior to the operation, all patients received alprazolam 0.5 mg by mouth (PO), and midazolam 125  $\mu\text{g}/\text{kg}$  intramuscular (im) was given 30 minutes before the operation. A 16-gauge (G) intravenous (i.v.) cannula was inserted into all patients in the operating room, and induction of anesthesia was performed using midazolam 50  $\mu\text{g}/\text{kg}$ , pancronium 0.15 mg/kg, and fentanyl 25 to 35  $\mu\text{g}/\text{kg}$ . After endotracheal intubation, 50% oxygen (O<sub>2</sub>), 50% nitrous oxide (N<sub>2</sub>O), and 3-4% desflurane were used for all hemodynamically stable patients, but the desflurane and N<sub>2</sub>O were discontinued at times of hemodynamic instability. Anesthesia was maintained and muscle relaxation was achieved through the use of midazolam and vecuronium, both 80  $\mu\text{g}/\text{kg}/\text{hr}$ . Furosemide 0.5 mg/kg was also routinely administered. A Dideco Compactflo Evo microporous, hollow-fiber membrane oxygenator (Sorin Group Italia

S.r.l.-Cardipulmonary Business Unit, Mirandola, Italy) was used for extracorporeal circulation. The priming solution for CPB included 900 ml Ringer's lactate solution, 150 ml 20% mannitol, and 60 ml sodium bicarbonate (8.4%).

During CPB, the MAP and pump flow were kept between 50-70 mmHg, and 2.2-2.5 L/m<sup>2</sup>, respectively. Sweep gas flow was kept at 1.5 L·min<sup>-1</sup>·m<sup>-2</sup>, and blood gas analyses were carried out with an ABL 700 analyzer (Radiometer Medical, Brønshøj, Denmark). Tissue perfusion adequacy was monitored via veno-arterial carbon dioxide partial pressure difference (P<sub>v-a</sub> CO<sub>2</sub>), lactate level, urine output, and base deficit. Moderate hypothermia (32 °C) was used during CPB. Myocardial viability was preserved with antegrade cold hyperkalemic crystalloid cardioplegia (Plegisol®, Abbott Laboratories, Abbott Park, Illinois, USA). After the termination of CPB, the midazolam and vecuronium doses were decreased to 50  $\mu\text{g}/\text{kg}/\text{hr}$  and then were discontinued at skin closure.

The results were analyzed via a chi-square test (or Fisher's exact test where applicable), and the independent samples t-test. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 10 software program. Values of  $p < 0.05$  were considered to be statistically significant, and all data was presented as mean  $\pm$  standard deviation.

### RESULTS

In group 1, hypoxia (pO<sub>2</sub> <80 mmHg) was detected in five patients (14%) in at least one of the five measurement periods. In 12 patients (34%), the ScO<sub>2</sub> levels decreased by more than 20%. In five of these patients, the FiO<sub>2</sub> levels were higher. By making an adjustment to account for these higher levels, the decrease in the ScO<sub>2</sub> was calculated as being lower than 20%. In group 1, hyperoxemia (pO<sub>2</sub> >180 mmHg)

**Table 1. Demographic data**

	Group 1 (FiO <sub>2</sub> : 0.35-0.45) (n=35)			Group 2 (FiO <sub>2</sub> : 0.40-0.50) (n=35)			p
	n	%	Mean $\pm$ SD	n	%	Mean $\pm$ SD	
Age (years)			60 $\pm$ 10			57 $\pm$ 11	NS
Gender							
Female	12	35		18	50		NS
Male	23			17			
Cardiopulmonary bypass time (minutes)			66 $\pm$ 22			62 $\pm$ 23	NS
Cross-clamp time (minutes)			43 $\pm$ 20			40 $\pm$ 18	NS

FiO<sub>2</sub>: Fraction of inspired oxygen; SD: Standard deviation; NS: Not significant.

**Table 2. The values of cerebral cortical oxygen saturation**

	Group 1 RScO <sub>2</sub>	Group 2 RScO <sub>2</sub>	<i>p</i>	Group 1 LScO <sub>2</sub>	Group 2 LScO <sub>2</sub>	<i>p</i>	Group 1 Hct	Group 2 4Hct	<i>p</i>
	(%)	(%)		(%)	(%)		(%)	(%)	
T <sub>1</sub>	64±9	60±10	NS	65±9	62±10	NS	39±6	39±6	NS
T <sub>2</sub>	56±8	55±9	NS	56±8	54±12	NS	27±6	27±6	NS
T <sub>3</sub>	53±7	54±8	NS	55±8	54±9	NS	27±6	27±6	NS
T <sub>4</sub>	53±8	53±9	NS	54±9	55±8	NS	27±7	28±6	NS
T <sub>5</sub>	54±8	54±8	NS	56±9	56±9	NS	28±6	28±6	NS

RSc: Right cerebral oxygen saturation; Hct: Hematocrit; NS: Not significant.

was observed in eight patients (22.8%) in at least one of the five measurement periods; however, in group 2, it was observed in at least one of the measurement periods in 15 patients (42.8%). In eight of these (22.8%), the decrease in the ScO<sub>2</sub> was greater than 20%. Two of these eight patients, whose pO<sub>2</sub> levels were between 87-90 mmHg, had increased FiO<sub>2</sub> values and in one of these patients, the ScO<sub>2</sub> levels were also higher (Table 2). The change in partial pressure of O<sub>2</sub> and CO<sub>2</sub> in relation to the five time periods is seen in Table 3. Hypoxia (pO<sub>2</sub> <80 mmHg) was not observed in any of the patients in group 2. The hemodynamic parameters are given in Table 4.

## DISCUSSION

Peripheral tissue perfusion deteriorates and is reduced during hypothermic CPB because of both a continuous flow pattern and a reduced flow.<sup>[4,5]</sup> Under such circumstances, it may be tempting to assume that a higher PaO<sub>2</sub> level would provide improved oxygen delivery to the peripheral tissue and an increased margin of safety. In fact, hyperoxemia increases global oxygen delivery and oxygen saturation in mixed venous blood during CPB.<sup>[5]</sup> However, this increase is not associated with improved tissue perfusion or clinical outcome.<sup>[4]</sup> In their *in vivo* study, Parolari et al.<sup>[10]</sup> showed that oxygen extraction occurs at a rate

of 19% during hypothermia, and this increases to 27% during rewarming, reflecting a three- to four-fold safety margin. Therefore, oxygen extraction ratios were not affected by FiO<sub>2</sub> levels.<sup>[9]</sup>

Indeed, hyperoxemia is associated with many side effects. An excess level of PaO<sub>2</sub> has been implicated in the deterioration of capillary flow, decreased cardiac index, increased systemic vascular resistance and hemolysis.<sup>[11,5,7]</sup> Moreover, in several investigations in which tissue oxygenation was studied, decreased oxygenation, sometimes even to hypoxic levels, together with signs of maldistribution of capillary flow were found as a response to hyperoxemia.<sup>[5,11-13]</sup> Another deleterious effect of hyperoxemia was reported by Pizov et al.<sup>[4]</sup> in which they determined there was a larger increase of proinflammatory cytokines in patients treated with 100% oxygen compared with the 50% oxygen group. A delayed recovery in patients treated with 100% oxygen was reported in our study. The use of a high FiO<sub>2</sub> in the perioperative period of general surgical procedures was reported to be associated with increased surgical site infection.<sup>[14]</sup>

On the other hand, we have known for years that on reperfusion, oxygen is detrimental, yet we still have PaO<sub>2</sub> rates of up to 300 or 375 mmHg when

**Table 3. The change in partial pressure of O<sub>2</sub> and CO<sub>2</sub> in relation to the five time periods**

Periods	Group 1 (FiO <sub>2</sub> : 0.35-0.45) (n=35)	Group 2 (FiO <sub>2</sub> : 0.40-0.50) (n=35)	<i>p</i>	Group 1 (FiO <sub>2</sub> : 0.35-0.45) (n=35)	Group 2 (FiO <sub>2</sub> : 0.40-0.50) (n=35)	<i>p</i>
	pO <sub>2</sub>	pO <sub>2</sub>	NS	pCO <sub>2</sub>	pCO <sub>2</sub>	NS
T <sub>1</sub>	194±48	184±41	NS	39±4	37±4	0.02
T <sub>2</sub>	158±54	177±49	NS	37±3	36±3	NS
T <sub>3</sub>	163±51	183±43	NS	37±3	36±3	NS
T <sub>4</sub>	160±52	184±43	0.03	36±4	35±4	NS
T <sub>5</sub>	160±54	184±43	NS	36±5	35±4	NS

NS: Not significant.

**Table 4 . The hemodynamic parameters**

	Group 1 MAP (mmHg)	Group 2 MAP (mmHg)	<i>p</i>	Group 1 Lactate (mmol/l)	Group 2 Lactate (mmol/l)	<i>p</i>	Group 1 CI (L/dk/m <sup>2</sup> )	Group 2 CI (L/dk/m <sup>2</sup> )	<i>p</i>
T <sub>1</sub>	78±14	75±11	NS	0.9±0.3	0.9±0.3	NS	–	–	
T <sub>2</sub>	65±17	71±13	NS	1±0.4	1.1±0.4	NS	2.5±0.2	2.3±0.2	0.001
T <sub>3</sub>	66±17	68±19	NS	1±0.4	1.1±0.4	NS	2.4±0.3	2.2±0.2	0.034
T <sub>4</sub>	51±12	59±15	0.015	1.2±0,5	1.2±0.4	NS	2.3±0.3	2.3±0.2	NS
T <sub>5</sub>	53±12	55±15	NS	1.3±0,6	1.3±0.6	NS	2.3±0.3	2.4±0.3	NS

MAP: Mean arterial pressure; CI: Confidence interval; NS: Not significant.

the cross-clamp is removed. Ihnken et al.<sup>[15]</sup> showed that hyperoxemic CPB during cardiac operations in adults results in oxidative myocardial damage related to oxygen-derived free radicals and N<sub>2</sub>O. In their prospective randomized double-blind study, hyperoxemic bypass resulted in higher levels of polymorphonuclear leukocyte elastase, creatine kinase, lactic dehydrogenase, antioxidants, malondialdehyde, and nitrate in coronary sinus blood. In addition, a reduction in lung vital capacity and forced expiratory volume in one second (FEV<sub>1</sub>) compared with normoxemic management was noted. The clinical reflections of these findings were a 57% longer duration of ventilator support and an extra day spent in the hospital.<sup>[15]</sup> In recent years, more data has been accumulated regarding the cardioprotective effect of lowering oxygen tension after aortic declamping on CPB.<sup>[16,17]</sup>

Hyperoxemia and hypoxia during CPB should be avoided because of the many disadvantages. During the rewarming period of CPB, the oxygen demand increases. Therefore, according to a study by Toraman et al.,<sup>[9]</sup> it is necessary to work with higher FiO<sub>2</sub> values (PaO<sub>2</sub> >80 mmHg) during hypothermia. If these higher values remain constant during CPB, it is inevitable that hyperoxia during hypothermia will occur. However, if the hypothermia period is used as a guide for FiO<sub>2</sub> adjustment, then hypoxia during rewarming will take place. Hence, it is inappropriate to work with a constant FiO<sub>2</sub> value during CPB. The evidence from the study by Toramal et al.<sup>[9]</sup> indicates that if FiO<sub>2</sub> ratios are kept between 35-45%, the risk of hypoxia during rewarming and hyperoxemia during hypothermia are reduced. However, it is rare to observe hypoxemia with an FiO<sub>2</sub> level of 0.35, and levels of 0.40 are normally used in order to minimize the possibility of having inadequate levels of oxygen in the blood. Nevertheless, hyperoxemia occurred in 43% of the patients of the study by Toramal et al. This leads to the conclusion that increasing FiO<sub>2</sub> levels does not solve this problem

during hypothermia and that it would be safer to keep them at 0.35 instead of 0.40.

In order to diagnose and treat the hypoxic periods in timely manner, close monitorization is mandatory. For example, connecting the devices to the arterial part of the CPB so that blood gas analysis can be done online is beneficial, but the cost of this monitorization limits its widespread use. The use of high FiO<sub>2</sub> values has become widespread for safety reasons. In our study, measurement of the ScO<sub>2</sub> levels was used as a tool to diagnose systemic tissue hypoxia and as an alternative method to online blood gas analysis or use a pulse oximeter. When the ScO<sub>2</sub> levels in our study were measured during CPB, hypoxia was detected in five of the patients in group 1 (14%), and they were treated by increasing the FiO<sub>2</sub> level by 10%. In 80% of the patients in this group, no hyperoxemia period was detected, and the detected hypoxemic periods were treated. In group 2, there were hyperoxemia attacks during CPB in 43% of the patients.

We believe that measuring the levels of ScO<sub>2</sub> in the nonpulsatile flow of CPB can be an effective noninvasive method of monitorization. If this occurs, it would allow for hypoxic periods to be detected and treated appropriately and on time. Additionally, our data revealed that the use of lower FiO<sub>2</sub> values leads to less hyperoxemia during CPB.

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#### REFERENCES

- Anderson KJ, Harten JM, Booth MG, Kinsella J. The cardiovascular effects of inspired oxygen fraction in anaesthetized patients. *Eur J Anaesthesiol* 2005;22:420-5.

2. Thomson AJ, Webb DJ, Maxwell SR, Grant IS. Oxygen therapy in acute medical care. *BMJ* 2002;324:1406-7.
3. Harten JM, Anderson KJ, Angerson WJ, Booth MG, Kinsella J. The effect of normobaric hyperoxia on cardiac index in healthy awake volunteers. *Anaesthesia* 2003;58:885-8.
4. Pizov R, Weiss YG, Oppenheim-Eden A, Glickman H, Goodman S, Koganov Y, et al. High oxygen concentration exacerbates cardiopulmonary bypass-induced lung injury. *J Cardiothorac Vasc Anesth* 2000;14:519-23.
5. Joachimsson PO, Sjöberg F, Forsman M, Johansson M, Ahn HC, Rutberg H. Adverse effects of hyperoxemia during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1996;112:812-9.
6. Chartrand C, Langevin L, Forest F, Stanley P. Hyperoxemia in extracorporeal circulation. *Can J Surg* 1975;18:84-7. [Abstract]
7. Brodie JE, Johnson RB. Conduct of perfusion. In: Halligan M, Moore P, Richards K, Brodie J, editors. *The manual of clinical perfusion*. 2nd ed. Georgia, USA: Glendale; 1997. p. 67-79.
8. Karabulut H, Toraman F, Tarcan S, Demirhisar O, Alhan C. Adjustment of sweep gas flow during cardiopulmonary bypass. *Perfusion* 2002;17:353-6.
9. Toraman F, Evrenkaya S, Senay S, Karabulut H, Alhan C. Adjusting oxygen fraction to avoid hyperoxemia during cardiopulmonary bypass. *Asian Cardiovasc Thorac Ann* 2007;15:303-6.
10. Parolari A, Alamanni F, Gherli T, Bertera A, Dainese L, Costa C, et al. Cardiopulmonary bypass and oxygen consumption: oxygen delivery and hemodynamics. *Ann Thorac Surg* 1999;67:1320-7.
11. Lund N, Jorfeldt L, Lewis DH, Odman S. Skeletal muscle oxygen pressure fields in artificially ventilated, critically ill patients. *Acta Anaesthesiol Scand* 1980;24:347-53.
12. Lund N, Jorfeldt L, Lewis DH. Skeletal muscle oxygen pressure fields in healthy human volunteers. A study of the normal state and the effects of different arterial oxygen pressures. *Acta Anaesthesiol Scand* 1980;24:272-8.
13. Thorborg P, Gustafsson U, Sjöberg F, Harrison DK, Lewis DH. Effect of hyperoxemia and ritanserin on skeletal muscle microflow. *J Appl Physiol* 1990;68:1494-500.
14. Pryor KO, Fahey TJ 3rd, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *JAMA* 2004;291:79-87.
15. Ihnken K, Winkler A, Schlensak C, Sarai K, Neidhart G, Unkelbach U, et al. Normoxic cardiopulmonary bypass reduces oxidative myocardial damage and nitric oxide during cardiac operations in the adult. *J Thorac Cardiovasc Surg* 1998;116:327-34.
16. Abdel-Rahman U, Aybek T, Moritz A, Kleine P, Matheis G. Graded reoxygenation limits lipid peroxidation during surgical reperfusion. *Med Sci Monit* 2003;9:CR389-91.
17. Inoue T, Ku K, Kaneda T, Zang Z, Otaki M, Oku H. Cardioprotective effects of lowering oxygen tension after aortic unclamping on cardiopulmonary bypass during coronary artery bypass grafting. *Circ J* 2002;66:718-22.