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Oxygen Fraction Adjustment According to Body Surface Area during Extracorporeal Circulation

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ABSTRACT

Background: The inspiratory oxygen fraction (FiO_2) is usually set between 60% and 100% during conventional extracorporeal circulation (ECC). However, this strategy causes partial oxygen pressure (PaO_2) to reach hyperoxemic levels (>180 mmHg). During anesthetic management of cardiothoracic surgery it is important to keep PaO_2 levels between 80-180 mmHg. The aim of this study was to assess whether adjusting FiO_2 levels in accordance with body temperature and body surface area (BSA) during ECC is an effective method for maintaining normoxemic PaO_2 during cardiac surgery.

Methods: After approval from the Ethics Committee of the University of Acıbadem, informed consent was given from 60 patients. FiO_2 adjustment strategies applied to the patients in the groups were as follows: FiO_2 levels were set as 0.21 × BSA during hypothermia and 0.21 × BSA + 10 during rewarming in Group I; 0.18 × BSA during hypothermia and 0.18 × BSA + 15 during rewarming in Group II; and 0.18 × BSA during hypothermia and variable with body temperature during rewarming in Group III. Arterial blood gas values and hemodynamic parameters were recorded before ECC (T1); at the 10th minute of cross clamp (T2); when the esophageal temperature (OT) reached 34°C (T3); when OT reached 36°C (T4); and just before the cessation of ECC (T5).

Results: Mean PaO_2 was significantly higher in Group I than in Group II at T2 and T3 (P = .0001 and P = .0001, respectively); in Group I than in Group III at T1 (P = .02); and in Group II than in Group III at T2, T3, and T4 (P = .0001 for all).

Conclusion: Adjustment of FiO_2 according to BSA rather than keeping it at a constant level is more appropriate for keeping PaO_2 between safe level limits. However, since oxygen consumption of cells vary with body temperature, it would be appropriate to set FiO_2 levels in concordance with the body temperature in the rewarming period.

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INTRODUCTION

Inspired oxygen fraction (FiO_2) during conventional extracorporeal circulation (ECC) is set between 60% and 100%, which consequently results in hyperoxemia (partial oxygen pressure [PaO_2] > 180 mmHg). The pathological processes that occur during hyperoxemia are well known [Boveris 1977; Beckman 1990; Pizov 2003]. These may augment the undesired effects of ECC and increase postoperative mortality and morbidity in cardiac surgery [Belboul 1993; Joachimsson 1996]. Clinicians currently prefer to decrease FiO_2 levels during hypothermic periods of ECC [Toraman 2007; Brodie 2007]. However, even with these decreased levels of FiO_2, hyperoxemia may be encountered during some periods of cardiac surgery [Toraman 2007, Brodie 2007].

It is well known that the need for and consumption of oxygen by tissues vary with body temperature, which changes rapidly during ECC. Thus, one strategy for preventing hyperoxemia and hypoxemia during cardiac surgery might be to adjust FiO_2 according to patient body surface area (BSA) and body temperature. The aim of this study was to assess whether adjusting FiO2 levels in accordance with body temperature during ECC is an effective and safe method for maintaining PaO_2 levels between 80-180 mmHg during cardiac surgery.

MATERIALS AND METHODS

Patient Selection

This prospective study was approved by the Ethics Committee of the Medical Faculty of Acıbadem University. Informed consent was obtained from 60 patients who were scheduled to undergo first-time elective aortocoronary bypass grafting surgery at Acıbadem Healthcare Group, Kadıkoy Hospital.

Patients who were hemodynamically unstable (mean arterial pressure <60 or >110 mmHg, or heart rate <50 or >120 beats/min) or significantly anemic (hemoglobin [Hb] <8 g/dL) were excluded.

Anesthetic and Surgical Protocol

As part of our routine practice, patients were hospitalized one day prior to surgery and underwent a standardized preoperative workup. All surgeries were performed under general anesthesia with extracorporeal circulation (ECC), and through a midsternal incision. Anesthetic management and

Table 1. The Groups' FiO2 Protocols during Extracorporeal Circulation and Rewarming

	FiO_2 during normothermic and hypothermic extracorporeal circulation	FiO_2 during Rewarming
Group 1 (n = 20)	0.21 × BSA	0.21 × BSA + 10
Group 2 (n = 20)	0.18 × BSA	0.18 × BSA + 15
Group 3 (n = 20)	0.18 × BSA	0.18 × BSA + 10 (to ET 34°C)
		0.18 × BSA + 15 (to ET 36°C)
		0.18 × BSA + 20 (once ET >36°C)

BSA indicates body surface area in m^2; ET, esophageal temperature.

ECC strategies were tailored to each patient. Prior to anesthetic induction, arterial cannulation for invasive blood pressure monitorization, peripheral venous cannulation for fluid and drug administration, and central venous cannulation were performed, and electrodes and sensors were placed for electrocardiography and monitoring of peripheral tissue oxygen saturation (SpO_2). The regional cerebral oxygen saturation (rSO_2) of the right and left cerebral hemispheres ($RrSO_2$ and $LrSO_2$) were monitored via near infrared spectroscopy (NIRS) (Invos Somanetics 5100 C, Somanetics Corp, Troy, MI, USA) throughout each operation. Midazolam 125 µg/kg intramuscularly (IM) was administered 30 minutes before the operation. Anesthetic induction was performed by midazolam 50 µg/kg, vecuronium 0.15 mg/kg, and fentanyl 25-35 µg/kg intravenously (IV). After endotracheal intubation, 50% O_2, 50% N_2O, and 3-4% desflurane were used for all hemodynamically stable patients. Maintenance of anesthesia and muscle relaxation were accomplished with midazolam and vecuronium 80 µg/kg/h IV, for both. Furosemide 0.5 mg/kg IV was routinely administered. Priming solution for CPB included 900 mL Ringer's lactate solution, 150 mL 20% mannitol, and 60 mL sodium bicarbonate (8.4%). During CPB, hematocrit, mean arterial pressure, and pump flow were kept between 20-30%, 50-80 mmHg, and 2-2.5 L/min/m^2, respectively. Adequacy of tissue perfusion was monitored with lactate level, urine output, and base deficit. Moderate hypothermia (30-32°C) was maintained during ECC. The doses of midazolam and vecuronium were decreased to 60 µg/kg/h IV (for both) when body temperature reached 32°C. Myocardial viability was preserved with antegrade cold hyperkalemic crystalloid cardioplegia (Plegisol, Abbott Laboratories, Abbott Park, IL, USA). Rewarming was initiated during left internal mammary artery grafting. When body temperature reached 36.5°C and the patient was hemodynamically stable, ECC was discontinued and heparin was reversed with protamine sulphate. Infusions of both midazolam and vecuronium were restored to 80 µg/kg/h IV during rewarming and were reduced to 50 µg/kg/h IV after termination of ECC. They were discontinued at skin closure.

Table 2. Group Means for BSA, CCT, and ECCT

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)
BSA, m^2	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.2
CCT, min	35 ± 11	46 ± 19	40 ± 17
ECCT, min	61 ± 15	74 ± 22	71 ± 27

BSA indicates body surface area; CCT, cross-clamp time; ECCT, extracorporeal circulation time.

Adjustment of FiO_2 Levels

In order to develop the protocol for the study, 5380 patients who had undergone aortocoronary bypass surgery in our clinic since 1999 were analyzed. For these 5380 patients, the same oxygenator and tubing sets (Dideco Evo Compact Flo, Sorin Group, Italy) were used. The mean BSA of these 5380 patients was 1.9 m^2 and the mean PaO_2 per square meter BSA was 128 mmHg during normothermia; these values obtained from 5380 patients had revealed a negative correlation between PaO_2 during normothermy period and BSA ($r = -0.338$, $P < .01$). Based on this finding, a formula to determine FiO_2 for each patient was defined. Assuming FiO_2 100% at 1 atm pressure and based on 713 mmHg pressure of PaO_2 (ie water vapor pressure subtracted from gas pressure of air), equations for PaO_2 and FiO_2 relative to BSA during ECC were created:

PaO_2 per m^2 BSA = 713 x FiO_2 per m^2 BSA

FiO_2 per m^2 BSA = PaO_2 per m^2 BSA ÷ 713

Inserting the mean PaO_2 per m^2 BSA for the 5380 patients during normothermy (128 mmHg) into the above equation revealed a value of 0.18 for FiO_2 per m^2 BSA in the normothermy period of ECC. (This data set was published in a preliminary report.) The result of this mathematical equation showed us a rate of 0.18 FiO_2 per m^2 BSA in the normothermy period of ECC. We accepted this value as the lowest limit and the 0.21 FiO_2 as the highest limit.

Based on this result and assuming that oxygen demand rises with body temperature during rewarming, we established three study groups based on FiO_2 adjustment regimes. FiO_2 levels were set as 0.21 × BSA during hypothermia and 0.21 × BSA + 10 during rewarming in Group I; 0.18 × BSA during hypothermia and 0.18 × BSA + 15 during rewarming in Group II; and 0.18 × BSA during hypothermia and variable with body temperature during rewarming period in Group III (Table 1). The aim was to keep normoxemic levels with the lowest FiO_2 values possible. Patients were assigned to groups randomly.

Data Collection

During each patient's operation, arterial blood-gas samples were collected and hemodynamic parameters were recorded at 5 time points: before ECC (T1); at the 10th minute of cross-clamping (CC) (T2); when esophageal temperature (OT) reaches 34°C (T3); when OT reaches 36°C (T4); and just before the end of ECC (T5).

Table 3. Group Results for Arterial Blood Gas Analyses and Hemodynamic Parameters

	MAP, mmHg	Lactate, mg/dL	pH	$PaCO_2$, mmHg	PaO_2, mmHg	SaO2, %	HCT, %	Hb, mg/dL	CPB Flow, L/dk
T1									
G1	76 ± 10	0.9 ± 0.4	7.4 ± 0.05	37 ± 5	215 ± 36	99 ± 0.6	39 ± 4.5	12.8 ± 1.8	–
G2	76 ± 9	1 ± 0.4	7.4 ± 0.04	38 ± 7	190 ± 58	99 ± 0.5	39 ± 6	12.5 ± 1.9	–
G3	74 ± 11	0.8 ± 0.2	7.41 ± 0.03	37 ± 4	176 ± 56	99 ± 0.6	41 ± 6	13.2 ± 2	–
T2									
G1	67 ± 13	1 ± 0.4	7.42 ± 0.03	36 ± 2	144 ± 20	99 ± 0.6	27 ± 4	8.8 ± 1.4	2.2 ± 0.1
G2	67 ± 12	1 ± 0.4	7.41 ± 0.03	36 ± 4	194 ± 35	99 ± 0.6	27 ± 1	8.7 ± 1.5	2.2 ± 0.1
G3	72 ± 12	0.9 ± 0.1	7.42 ± 0.03	38 ± 3	130 ± 28	99 ± 0.5	28 ± 5	9.2 ± 1.8	2.2 ± 0.1
T3									
G1	75 ± 14	1 ± 0.4	7.43 ± 0.03	36 ± 2	127 ± 21	99 ± 0.6	29 ± 5	9.4 ± 1.5	2.2 ± 0.1
G2	73 ± 13	1.1 ± 0.5	7.42 ± 0.04	36 ± 4	184 ± 38	99 ± 0.5	28 ± 5	9 ± 1.5	2.2 ± 0.2
G3	75 ± 13	0.9 ± 0.2	7.42 ± 0.03	37 ± 3	113 ± 27	99 ± 1	30 ± 6	9.8 ± 2	2.1 ± 0.1
T4									
G1	70 ± 15	1.2 ± 0.3	7.45 ± 0.03	33 ± 2	151 ± 44	99 ± 1	30 ± 6	9.7 ± 1.8	2.2 ± 0.1
G2	70 ± 11	1.5 ± 0.5	7.44 ± 0.05	32 ± 4	177 ± 41	99 ± 1	29 ± 5	9.2 ± 1.7	2.2 ± 0.1
G3	75 ± 13	1.1 ± 0.3	7.42 ± 0.04	35 ± 3	132 ± 33	99 ± 0.8	30 ± 6	9.8 ± 2	2.1 ± 0.1
T5									
G1	70 ± 13	1.5 ± 05	7.42 ± 0.04	34 ± 4	134 ± 45	99 ± 1	31 ± 6	9.9 ± 1.8	2.2 ± 0.1
G2	68 ± 12	1.6 ± 0.6	7.42 ± 0.05	33 ± 4	135 ± 44	99 ± 1	30 ± 6	9.6 ± 1.8	2.2 ± 0.1
G3	71 ± 13	1.3 ± 0.3	7.42 ± 0.04	34 ± 4	140 ± 49	99 ± 1	31 ± 6	10 ± 2	2.1 ± 0.1

Statistical Analysis

Results of the groups were presented as mean ± SD. Standard repeated-measures analysis of variance were used to determine change across time. A significance level of 0.05 was used throughout. Statistical calculations were performed with use of SPSS version 20 (IBM Corporation; Armonk, NY).

RESULTS

Results of the groups BSA, CC, and ECC times are shown in Table 2. There were no statistically significant differences between mean BSA values of the groups. Mean CC and ECC times were significantly longer in Group II than in Group I ($P = .018$ and $P = .03$, respectively).

Table 3 lists the arterial blood gas values and hemodynamic parameters of the groups at 5 time points. Mean $PaO_2$was significantly higher in Group I than in Group II at T2 and T3 ($P = .0001$ and $P = .0001$, respectively), in Group I than in Group III at T1 ($P = .02$), and in Group II than in Group III at T2, T3, and T4 (P = .0001 for all). Mean arterial partial carbon dioxide pressure (PaCO2) was significantly lower in Groups I and II than in Group III at T4 ($P = .04$ and $P = .0001$, respectively). Mean lactate level was significantly lower in Group III than in Group II at T1 and T2 ($P = .019$ and $P = .004$, respectively).

As seen in Table 4, the percentage of hyperoxic patients was 70% at T2, 50% at T3, 45% at T4, and 20% at T5 in Group I; 15% at T2, 25% at T3, 25% at T4, and 30% at T5 in Group II, whereas none of the patients in Group III were hyperoxic at any time point.

DISCUSSION

Adjustment of inspired oxygen fraction (FiO_2) during conventional ECC is a controversial issue and usually set between 60%-100%, which consequently results in hyperoxemia (PaO_2 > 180 mmHg). Regarding the importance of adjustment of optimal FiO_2 during ECC, a novel formula in this study is used to adjust FiO_2 levels in accordance with body temperature during ECC, and is tested as to whether it is an effective and safe method for maintaining PaO_2 levels between 80-180 mmHg during cardiac surgery.

Arterial blood oxygen level is one of the most important determinants of blood flow. The specific mechanism for this involves production of metabolites by parenchymal cells that use oxygen [Alston 1989], and reactions that these metabolites trigger through receptors in endothelium and other vessel wall structures. Most studies on cardiopulmonary bypass have investigated the effects of hyperoxemia and hypoxemia, and some have identified the mechanisms by which hyperoxemia affects capillary blood flow [Busse 1983; Jackson 1987]. Thorborg et al [Thorborg 1990] examined the capillary blood flow of skeletal muscle during hyperoxemia, and found that

Table 4. Proportion of Patients with Hypoxemia and Hyperoxemia at the Time Points Studied

	T1		T2		T3		T4	
	Hypoxemic, %	Hyperoxemic, %	Hypoxemic, %	Hyperoxemic, %	Hypoxemic, %	Hyperoxemic, %	Hypoxemic, %	Hyperoxemic, %
Group 1 (n = 20)	–	70 (14/20)	–	50 (10/20)	–	45 (9/20)	10 (2/20)	20 (4/20)
Group 2 (n = 20)	–	15 (3/20)	–	25 (5/20)	–	25 (5/20)	–	30 (6/20)
Group 3 (n = 20)	–	–	–	–	–	–	–	–

tissue oxygen levels decreased under these conditions due to reduced capillary flow. Conditions such as anemia, pulseless arterial flow, hypothermia, and changes in vascular permeability that occur during ECC present particular challenges for maintaining tissue oxygen levels in the normal range (80-180 mmHg). ECC alters capillary blood flow directly (and tissue oxygenation secondarily), in addition to various other undesired effects (increased inflammatory mediators and platelet activation, increased oxygen-derived free radicals and serotonin release, low blood flow, and other impacts) that occur when a patient becomes hyperoxic during ECC [Edmunds 1993; Cavarocchi 1984].

Oxidant injury to tissues, and particularly to myocardium during hyperoxemia, can occur via two pathways. The mechanism best understood is via oxygen-derived free radicals (O_2, H_2O_2, and OH) [Gauduel 1989], and research has shown that blood levels of these radicals are directly proportionate to PaO_2 [Boveris 1977, Littauer 1992]. Hyperoxemia results in excessive amounts of oxygen dissolved in the membrane lipid matrix, which leads to more interactions between oxygen and carrier molecules with reduced electrons, thus accentuating free-radical production [Boveris 1977]. The other pathway for hyperoxemic injury to tissues (especially the myocardium) is via interaction between nitric oxide and superoxide. Production of nitric oxide is PaO_2-dependent, and nitric oxide interacts with superoxide to form cytotoxic oxygen products that alter blood flow to the tissues, causing tissue damage [Beckman 1990].

Ihnken et al [Ihnken 1995] observed that tissue injury from oxygen-derived free radicals is associated with increased activity of neutrophil elastase, an enzyme that is also elevated in tissues under hyperoxemic conditions. In another study by Ihnken et al [Ihnken 1998] that involved 40 patients who underwent cardiac surgery, the authors found that normoxemia during ECC lowered the risk of intraoperative myocardial injury. Specifically, compared to findings in the hyperoxemic group, they observed that patients who were kept normoxemic during ECC had significantly lower blood levels of oxygen-derived free radicals, neutrophil elastase, creatine kinase, and lactate dehydrogenase. Moreover, Pizov et al [Pizov 2003] reported that higher FiO_2 causes increased production and release of proinflammatory cytokines, which may increase the risk of infection of the patient. The latter was documented by Pryor et al [Pryor 2004] in a study of 165 general surgery patients who had one or more periods of hyperoxemia during their operations. Also, hyperoxemia is known to increase hemolysis and thus reduce numbers of functional circulating erythrocytes [Belboul 1993]; therefore, hyperoxemia during cardiac surgery can increase the requirement for blood and blood products of the patients. Both loss of erythrocyte and reduced capillary flow resulting from hyperoxemia could also have undesired postoperative outcomes such as postoperative arrhythmias, prolonged intubation, and extended hospitalization [Belboul 1993; Joachimsson 1996]. The above-noted issues underline the need for strategies that ensure normoxemia during cardiopulmonary bypass. At our clinic, based on our preliminary report [Toraman 2007], we have been initiating ECC with FiO_2 0.60 and increasing to 0.70 during the rewarming period. As stated in our initial study relating to the FiO_2 levels during cardiac surgery, 90 patients undergoing open heart surgery were studied and the results showed that PaO_2 levels of 80-180 mmHg could be maintained with FiO_2 of 0.35 during CPB and 0.45 during rewarming [Toraman 2007]. We had applied this FiO_2 protocol. However, we observed that patients with similar respiratory and cardiac conditions but different BSAs had different PaO_2 levels. For us, this implied that it might be possible to regulate FiO_2 levels during cardiac surgery according to patient BSA. Hence, we analyzed retrospectively the patient data to derive the formulas described in this study.

We observed hyperoxemia in Groups I and II (Group I with higher FiO_2 levels than Group II for all periods of the surgery). Our findings suggest that patients subjected to these FiO_2 regimes are at greater risk for myocardial damage, infection, and/or systemic inflammatory reactions during or after cardiac surgery, even though their lactate levels are similar to the patients who are normoxemic throughout the operation. We also observed that all of our Group III patients (n = 20), those subjected to variable FiO_2 regime in accordance with body temperature, were normoxemic during all periods of CPB. Thus, we conclude that adjusting FiO_2 levels according to BSA variable with body temperature during ECC and rewarming is an effective method for maintaining normoxemia during cardiac operations. We suggest that FiO_2 settings follow this regime during cardiac surgery: 1) 0.18 × BSA in the normothermic and hypothermic periods; 2) 0.18 × BSA + 10 during rewarming until OT reaches 34° C; 3) 0.18 × BSA + 15 during rewarming when OT is between 34-36°C; 4) 0.18 × BSA + 20 during rewarming when OT is >36°C.

Conclusion

Usage of a formula to adjust FiO_2 during CPB that takes into account both BSA and patient temperature reduces unwanted variations in arterial PO_2 and the undesired effects of hyperoxemia.

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