Effects of Arterial Oxygen Pressure Values During Cardiopulmonary Bypass on Postoperative Outcomes in Paediatric Patients

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Abstract

Aim: To investigate the effects of supraphysiological arterial oxygen pressure (PaO2) levels during cardiopulmonary bypass (CPB) on clinical outcomes in children undergoing open heart surgery.

Methods: Intraoperative and postoperative data of patients aged 16 years and younger undergoing open heart surgery were retrospectively reviewed. Patients were divided into three groups according to maximum PaO2 values determined by blood gas analysis during CPB. Group I was defined as maximum PaO2 = 100-199 mmHg during CPB; group II, PaO2 = 200-299 mmHg; and group III, PaO2 ≥ 300 mmHg.

Results: The maximum PaO2 values achieved during CPB increased with increasing duration of CPB and cross-clamp duration (p=0.001, p=0.028). In the postoperative period, no significant difference was found between the groups in terms of maximum PaO2 levels achieved during CPB, duration of mechanical ventilation, hospital and intensive care unit (ICU) stay and complications (p = 0.307). There was no difference between systemic inflammatory response syndrome and PaO2 levels assessed at 6, 24 and 48 hours postoperatively in the ICU (p = 0.706, p = 0.926, p = 0.876). An increase in the maximum PaO2 achieved during CPB was associated with an increase in mortality (p = 0.039). When analysing the subgroup of cyanotic patients, ICU length of stay ≤ 10 days was associated with high oxygen levels (p = 0.028).

Conclusions: The results of our study indicate that supraphysiological oxygen levels used during CPB cause an increase in mortality.

Keywords: *Paediatric patient; cardiopulmonary bypass; hyperoxia; oxygen; mortality*

1. Introduction

As a consequence of scientific developments in the domains of paediatric cardiac surgery, anaesthesia and perfusion, the number of paediatric patients undergoing surgical intervention for congenital heart disease is rising annually. The recognition of complications associated with cardiopulmonary bypass (CPB) has led to significant developments in technology and improved patient prognosis. Nevertheless, there is substantial evidence indicating the detrimental effects of artificial perfusion, which result in altered oxygen delivery to tissues[1,2]. In order to prevent these adverse effects, it is generally recommended that cellular hypoxia be minimised by maintaining the partial arterial oxygen pressure (PaO_2) above the physiological value (> 100 mmHg). However, a series of clinical studies and meta-analyses conducted in recent years have demonstrated the adverse effects of hyperoxia following cardiac surgery utilising CPB[3,4]. Hyperoxia has been demonstrated to cause vasoconstriction and impairment of perfusion, increase oxidative stress and trigger a systemic inflammatory response syndrome (SIRS)[5]. Conversely, some beneficial effects of hyperoxia have also been documented. It may act as a preconditioner and attenuate ischaemia-reperfusion injury, prevent systemic inflammation-induced vasoplegia and reduce gas-microembolism injury[6,7]. It is therefore important to determine the effects of hyperoxia on postoperative outcomes in paediatric cardiac patients in order to clarify the role of excessive oxygen use during congenital cardiac surgery. The objective of our study was to evaluate the impact of supra-physiological values of PaO_2 on clinical outcomes during CPB in children undergoing open heart surgery for congenital heart disease.

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2. Materials and Methods

This study was conducted retrospectively at Cukurova University, Department of Anaesthesiology and Reanimation. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of T.C. Çukurova University Faculty of Medicine (15/06.11.2020). In this study, we retrospectively reviewed the intraoperative and postoperative data of patients aged 16 years and younger who underwent open heart surgery for cyanotic and acyanotic congenital heart disease between January 2017 and December 2019. Patients with preoperative renal failure or hepatic disease, emergence surgeries and reoperations were excluded from the study. The following data were recorded in the retrospective file scans of the patients: patient demographic data, preoperative haematocrit (htc) value, diagnosis of the disease causing surgery, and preoperative RACHS1 (Risk Adjustment For Surgery for Congenital Heart Disease) score[8]. From the intraoperative records of the patients, the following data were recorded: the operation performed, CPB duration, aortic cross-clamp duration, circulatory arrest duration, body temperature during CPB and the lowest body temperature reached, amount of cardioplegia, amount of urine and diuretic use. The PaO_2 values, lactate levels and blood glucose values were recorded at the outset of the procedure, at 30-minute intervals throughout the operation, upon exiting the pump and at the conclusion of the procedure. The mean arterial pressure values were duly recorded. The values of ACT (activated coagulation time) at the commencement and conclusion of the surgical procedure, along with the quantity of heparin and protamine administered, were documented. In the postoperative intensive care period, the following variables were recorded at the 6th, 24th and 48th postoperative hours: blood gas and lactate values, haematocrit value, amount of fluid (crystalloid and colloid) and blood products administered, and vasoactive inotrope score[9]. The duration of mechanical ventilation, intensive care unit (ICU) treatment, and hospitalisation were documented.

The following major complications were identified and documented: cardiac arrest, neurological deficit (stroke, seizure), acute renal failure necessitating dialysis treatment, arrhythmias requiring a permanent pacemaker, and multiple organ dysfunction. In the postoperative period, data pertaining to the systemic inflammatory response syndrome (SIRS) were obtained from the medical records at the 6th, 24th and 48th postoperative hours. This was achieved through the utilisation of age-specific SIRS criteria, which had been previously established by the International Paediatric Sepsis Consensus Conference[10] (Table 1).

The PaO_2 values determined by blood gas analysis during CPB were classified into three groups. The maximum PaO_2 level attained during CPB was 100-199 mmHg in the group I, 200-299 mmHg in the group II, and ≥300 mmHg in the group III. The statistical evaluation of the relationship between the PaO_2 values determined by blood gas analysis during CPB and the parameters in the postoperative period was conducted. Lactate and urine volume records were employed as perfusion parameters, and their correlation with PaO_2 values was examined. The impact of PaO_2 levels during CPB on mechanical ventilation therapy, intensive care unit (ICU) and hospitalisation duration was examined. The relationship between PaO_2 values during CPB and the subsequent development of SIRS in the postoperative period was investigated.

Table 1

Paediatric SIRS Criteria

Age	Tachycardia	Bradycardia	Respiratory rate	Leukocyte count	Body temperature
Newborn (1-7 days)	180<	100>	50<	34x103/mm3<	38oC< or 36oC>
Newborn (7-30 days)	180<	100>	40<	>19,5 or <5x103/mm3	38oC< or 36oC>
Infant (1 month -1 year)	180<	90>	34<	>17.5 or <5x103/mm3	>38,5°C or <36°C
Play child (1-5 years)	140<	Criteria unclear	22<	>15.5 or <6x103/mm3	>38.5°C or <36°C
School child (5-12 years)	130<	Criteria unclear	18<	>13.5 or <4.5x103/mm3	>38.5°C or <36°C
Adolescent (12-18 years)	110<	Criteria unclear	14<	>11 or <4.5x103/mm3	>38.5°C or <36°C

**SIRS is diagnosed when 2 or more criteria are present. One of the criteria must be changes in body temperature or white blood cell count.*

2.1. Anaesthesia Management

Following a six-hour period of preoperative fasting, infants younger than six months of age were sedated without the administration of premedication, whereas older children were sedated intravenously (iv) with either 2 mg/kg ketamine (Ketalar, Pfizer) or 0.05 mg/kg midazolam (Dormicum amp, Deva), before being transferred to the operating room. Following the administration of routine monitoring agents (electrocardiography (ECG), $Sa0_2$, non-invasive blood pressure measurement), anaesthetic induction was achieved via intravenous (iv) administration of propofol (2 mg/kg, Propofol 1%, Fresenius) or inhalation induction with sevoflurane (Sevorane, Abbot). Furthermore, all patients received 5 µg/kg fentanyl (Talinat amp, Vem pharmaceuticals) and 0.6 mg/kg rocuronium (Esmeron, MSD) as a muscle relaxant. The anaesthetic was maintained with sevoflurane inhalation (2-3%) and fentanyl infusion (5 µg/kg/h).

2.2. Cardiopulmonary Bypass Management

In the context of cardiopulmonary bypass management, the initial solution employed was a combination of ES and supplementary electrolyte solution. Following cross-clamping,

cardiac arrest was induced with antegrade hypothermic blood cardioplegia. The centrifugal pump flow (non-pulsatile) was set to 150-200 ml/min/m^2 for patients weighing up to 10 kg and 2.4-2.6 L/min/m^2 for patients weighing over 10 kg. Blood gas analysis was conducted using the α-stat method.

2.3. Intraoperative Blood Transfusion

The objective htc level during CPB was established at 28-30%. Following the conclusion of the cardiopulmonary bypass procedure, a red blood cell (RBC) transfusion was conducted with a htc level of 25-30% in children with no cyanotic conditions and 30% in those with cyanotic conditions. In instances where haemorrhage was observed, a total of 10 ml/kg of fresh frozen plasma (FFP), 10 ml/kg of apheresis and 10 ml/kg of cryoprecipitate were administered. For the purpose of providing postoperative analgesia, iv 0.15 mg/kg of morphine was administered at the time of closure of the sternum.

2.4. Postoperative Follow-up

A complete blood count, biochemical parameters, arterial blood gas analysis and lactate level were conducted as part of the routine assessment upon admission to the ICU. In cases of metabolic acidosis, manifested by hypotension, lactate increase or base deficit, and bleeding causing haemodynamic instability, RBC transfusion was performed. In the treatment of coagulopathy, 10 ml/kg apheresis platelet and 10 ml/kg cryoprecipitate were employed. In the event of persistent bleeding, 10 ml/kg FFP was administered.

2.5. Primary and Secondary Outcomes

The primary objective was to ascertain the impact of varying PaO_2 levels during CPB on in-hospital mortality, ICU and hospitalisation duration. The secondary objective was to ascertain the impact of varying PaO_2 levels during CPB on postoperative acute kidney injury, mechanical ventilation duration, transfusion necessity, postoperative lactate and serum creatinine levels, and the emergence of SIRS.

2.6. Statistical Analysis

Categorical variables were summarized as frequencies and percentages, while numerical variables were summarized as means and standard deviations (medians and minimum-maximum values when applicable). A chi-square test was employed to ascertain whether there were any significant differences between the categorical measurements observed in the various groups. The assumption of normal distribution was tested for each numerical measurement using the Shapiro-Wilk test. The Kruskal-Wallis test was employed for the general comparison of numerical measurements that did not demonstrate a normal distribution between the PaO_2 groups. The Mann-Whitney U test with Bonferroni correction was employed for the pairwise comparisons of the groups for which a significant result was obtained in the aforementioned comparisons. A repeated-measures analysis was employed to ascertain the temporal change in the numerical measurements taken prior to and during the surgical procedure. The IBM SPSS Statistics Version 20.0 package programme was employed for the statistical analysis of the data. In all tests, the statistical significance level was set at 0.05, in accordance with the SPSS reference. IBM Corp. Published in 2011. IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp.)

3. Results

In the present study, the medical records of 260 patients, comprising both cyanotic and acyanotic individuals, who had undergone open heart surgery for congenital heart disease, were retrospectively reviewed. While the medical records evaluation of 259 patients was successfully completed, the data for one patient could not be accessed. The diagnoses of congenital heart disease, the comorbidities present, and the RACHS1 scores for each patient are presented in Table 2.

Table 2

Demographic data 1

Congenital Heart Anomalies			
ASD	25(9,60%)	PMOVSD+ASD+PS	1(%0,38)
ASD+PS	4(%1,5)	PAPVDA	4(%1,5)
VSD	55(%21,1)	PAPVDA+PS	1(%0,38)
VSD+PA	10(%3,8)	TAPVDA	14(%5,3)
VSD+PS	6(%2,3)	MR	1(%0,38)
VSD+PS+APCA	1(%0,38)	MS	2(%0,76)
ASD+VSD	12(%4,6)	AR	1(%0,38)
VSD+ASD+PS	7(%2,6)	TR+PS	2(%0,76)
AVSD	22(%8,4)	TA	2(%0,76)
Aortic coarctation+VSD	1(%0,38)	PA	2(%0,76)
Double outlet right ventricle	17(%6,5)	TA+PA	2(%0,76)
Double outlet Left ventricle	2(%0,76)	AS+PS	1(%0,38)
TGA	7(%2,6)	Subaortic stenosis	13(%5)
Tetralogy	24(%9,2)	Ebstein anomaly+PS+CTGA	1(%0,38)
Fallot+MAPCA	1(%0,38)	Subpulmonic membrane	1(%0,38)
PMOVSD	8(%3,07)	Truncus arteriosus	10(%3,8)
RACHS1 Score (n,%)		**Comorbidities (n,%)**	
1	25(%9,6)	Down Syndrome	29(%11,1)
2	91(%35)	Hypothyroidism	8(%3)
3	133 (%51,1)	Epilepsy	6(%2,3)
4	10(%3,8)	Bilateral hydroureteronephrosis	1(%0,38)
5	1(%0,38)	Mental retardation	2(%0,76)
		Tip I DM	2(%0,76)
		Cystic fibrosis	1(%0,38)

ASD: Atrial septal defect, VSD: Ventricular septal defect, PS: Pulmonary stenosis, PA: Pulmonary atresia, APCA: Aortopulmonary collateral artery, AVSD: Atrioventricular septal defect, TGA: Transposition of the great arteries, MAPCA: Multiple aortopulmonary collateral arteries, PMOVSD: Perimembranous outlet VSD, PAPVDA: Partial anomalous pulmonary venous return, TAPVDA: Total anomalous pulmonary venous return, MY: Mitral regurgitation, MS: Mitral stenosis, AY: Aortic regurgitation, TY: Tricuspid regurgitation, TA: Tricuspid atresia.

The demographic and intraoperative data of the patients are presented in Table 3. No statistically significant correlation was identified between the age or body weight of the patient and the maximum PaO_2 levels achieved during CPB (p=0.649, p=0.420). The relationship between CPB duration, cross-clamp duration, total surgical time and maximum PaO_2 levels reached during CPB was evaluated during the intraoperative period. It was observed that the maximum PaO_2 levels attained during CPB demonstrated a positive correlation with prolonged CPB duration (p=0.001).

Table 3

Demographic and intraoperative data

	Group I	Group II	Group III	p
Age (month)	42.1 ± 42.9	45.2 ± 49.2	37.1 ± 39.5	0.69
Weight (g)	13187.5 ± 9508.8	14605.9 ± 12944.1	11933.0 ± 9070.9	0.420
Gender	M:%62.5 (n=15) F:%37.5 (n=9)	M:%54.7 (n=81) F:%45.3 (n=67)	M:%56.8 (n=50) F:%43.2 (n=38)	0.760
Acyanotic Cyanotic	%66.7 (n=16) %33.3 (n=8)	%66.2 (n=98) %33.8 (n=50)	%61.4 (n=54) %38.6 (n=34)	0.475
Preoperative htc (%)	39.4 ± 7.8	39.1±8.2	39±9.7	0.706
CPB duration (min)	55 ± 34	76±42.3	83.7±45.6	0.001
Cross clamp time (min)	33.2 ± 26.1	49.3±31.5	45.7±30.6	0.028
Total operation time (min)	168.1 ± 42.3	195.9 ± 57.4	207.5 ± 77.4	0.101

Categorical variables were summarized as frequencies and percentages, while numerical variables were summarized as means and standard deviations (medians and minimum-maximum values when applicable). Htc: hematocrit, CPB: Cardiopulmonary bypass

Table 4

Comparison of groups classified according to PaO2 levels and maximum PaO2 levels achieved during CPB.

	Group I		Group II		Group III		
	Mean±sd	Min-max	Mean±sd	Min-max	Mean±sd	Min-max	p
Preoperative PaO2	181.1 ± 95.9	44-350	156.7 ± 82.3	47- 390	166.6 ± 96.7	26 - 439	0.446
Before CPB PaO2	165.6±107.7	46.3 - 475	161.6 ± 87.5	30.9-430	172.7±114.4	27.3 - 601	0.370
30.min PaO2	157.6 ± 38	30.5 - 198	247.9 ± 31.3	153-299	304.9 ± 60.8	137 - 410	0.0
60. min PaO2	153 ± 21.1	128 - 179	226.5 ± 46.3	44-296	291.1 ± 51.2	126 - 378	0.0
90. min PaO2	181.3 ± 15.2	165 - 195	222.4 ± 44.1	102-281	247.1 ± 66	101 - 410	0.034
120.min PaO2	184 ± 2.8	182 - 186	231.5 ± 50.7	125-297	275 ± 65.4	120 - 359	0.008
End of operation PaO2	168.1 ± 96.1	47 - 378	154.3 ± 89.4	29.3-454	166.3 ± 109	25 – 711.9	0.746

(min: minimum, max: maximum, min: minute, PaO2: Partial oxygen pressure)

Similarly, the maximum PaO_2 levels reached during CPB increased with prolongation of the cross-clamp duration (p=0.028). Nevertheless, no statistically significant difference was observed when the total operation time and the maximum PaO2 levels reached during CPB were compared (p=0.101) (Table 3). No statistically significant difference was observed between the groups with regard to intraoperative crystalloid fluid, RBC, FFP, apheresis, and cryoprecipitate consumption (p > 0.05).

No statistically significant difference was identified between the maximum PaO_2 levels reached during CPB in patients with cyanotic and acyanotic congenital heart disease (p = 0.475) during the intraoperative period.

No significant difference was observed in the blood gas values analysed during the intraoperative period between the PaO_2 levels in the arterial blood gas examination taken at the beginning of the operation and before the pump, and the maximum PaO_2 levels reached during CPB (p = 0.365; p = 0.253). Nevertheless, a notable discrepancy was observed in the comparison of PaO_2 levels at 30., 60., 90. and 120. min between the two groups (p = 0.0; p = 0.0; p = 0.034; p = 0.008). (Table 4).

A comparison of the lactate values in the blood gas samples obtained at the beginning of the operation, before CPB, at 30, 60, 90, 120 minutes of CPB, after CPB and at the end of the operation revealed no significant difference between the groups. (p = 0.313; p = 0.659; p = 0.849; p = 0.606; p = 0.291; p = 0.454; p = 0.481, respectively). Furthermore, no significant differences were observed between the groups in the volume of urine collected at the corresponding time points (p = 0.695; p = 0.522; p = 0.109; p = 0.200; p = 0.677; p = 0.279; p = 0.857, respectively).

The maximum PaO_2 levels reached during CPB in patients with cyanotic and acyanotic congenital heart disease were compared. No statistically significant difference was identified between the two groups (p = 0.475).

In the postoperative period, no significant difference was observed between the groups when the maximum PaO_2 levels reached during CPB and the duration of mechanical ventilation, hospitalisation and ICU stay were compared (p > 0.05, Tables 5). No statistically significant difference was identified between the groups with regard to complications that developed during the postoperative period in the ICU follow-up period (p = 0.307).

No statistically significant difference was observed between the groups in the comparison of maximum PaO_2 levels reached during CPB and inotrope scores calculated at the postoperative 6th, 24th and 48th hours (p = 0.565, p = 0.285, p = 0.241).

Table 5

Effects of maximum PaO2 levels achieved during CPB on the duration of stay in the intensive care unit, the duration of hospital stay and the duration of mechanical ventilation.

	Cyanosis	Group I	Group II	Group III	p
Length of stay in ICU (days)	No	8.1 ± 10.2	5.5 ± 3.6	5.2 ± 3.2	0.982
	Yes	5.3 ± 2.4	5.2 ± 4	7.6 ± 6.1	0.439
Length of hospital stay (days)	No	12.5 ± 10.2	9.9 ± 6.2	10.3 ± 8.4	0.884
	Yes	8.4 ± 1.1	10.5 ± 7.3	11.6 ± 7.9	0.825
Mechanical ventilation time (hours)	No	39.7 ± 79.4	16.7 ± 33.2	24.2 ± 44.3	0.491
	Yes	16.3 ± 13.6	30.6 ± 51.6	23.2 ± 29.1	0.702

Table 6

Comparison of cyanotic and acyanotic groups in patients with mortality

	Cyanosis	Group I	Group II	Group III	p
Mortality	No	%0 (n=0)	%53,8 (n=7)	%46,2 (n=6)	0.416
	Yes	%3,8 (n=1)	%50 (n=13)	%46,2 (n=12)	
No Mortality	No	%10,3 (n=16)	%58,7 (n=91)	%31(n=48)	0.468
	Yes	%10,6 (n=7)	%56,1 (n=37)	%33,3 (n=22)	

Table 7

Effect of maximum PaO2 levels achieved during CPB on the length of stay ICU in cyanotic patients

Length of stay ICU	Group I	Group II	Group III	p
7 days	%0.0, n=0	%25, n=12	%25, n=8	0.028
7-9 days	%85.7, n=6	%25, n=12	%28.1, n=9	
≥ 10 days	%14.3, n=1	%50, n=24	%46.9, n=15	

No statistically significant difference was observed between the groups in the incidence of SIRS and the maximum PaO2 levels achieved during CPB at the postoperative 6th, 24th and 48th hours in the ICU (p = 0.706, p = 0.926, p = 0.876).

The mortality rates in the postoperative period were compared with the maximum PaO_2 values reached during CPB and a statistically significant difference was found. The increase in the maximum PaO_2 values reached during CPB increased mortality rate (p = 0.039). No significant relationship was found between the mortality and cyanotic patient groups. (p = 0.416, p = 0.468, Table 6) However, when the relationship between the duration of ICU stay of cyanotic patients and the maximum PaO_2 values reached during CPB was examined, it was observed that ICU stays ≥ 10 days were significantly associated with high oxygen levels. (p = 0.028, Table 7)

4. Discussion

Although many congenital cardiac anomalies can be successfully treated with open heart surgery performed with CPB, surgical stress, cross-clamping, artificial circulation and contact of blood with a foreign surface may result in a widespread inflammatory response and systemic complications[1]. Maintenance of arterial partial oxygen pressure in the appropriate range and oxygen delivery to the tissue constitute key points in successful CPB management. In clinical applications, high oxygen levels have been frequently used in the perioperative period to avoid the adverse effects of hypoxia, especially in cardiac surgery[11]. Recent studies demonstrate that high oxygen levels are still employed in the perioperative period in cardiac surgery to safeguard against hypoxia that may arise during CPB[12,13]. In our retrospective study, in which we reviewed the perioperative records of 259 patients, we found that high PaO_2 levels were also preferred in our clinic. Nevertheless, elevated oxygen levels lead to augmented formation of free oxygen radicals in the circulation and a reduction in antioxidant capacity[13,14]. Furthermore, it causes vasoconstriction in myocardial microcirculation, decreased coronary flow, decreased cardiac output and increased systemic vascular resistance, which in turn results in increased mortality and morbidity[14,15,16]. In addition to all these effects, the fact that the organ systems of paediatric patients continue to mature after birth and the structural and physiopathological differences present in paediatric patients with congenital heart disease cause further exacerbation of clinical outcomes[17]. The results of our study demonstrated a significant correlation between the administration of supraphysiological oxygen levels during CPB and mortality in children undergoing open

heart surgery for congenital heart disease, in accordance with the findings of the existing literature.

In addition to the negative evidence, the controversy about oxygen levels persists, with preclinical and clinical studies advancing disparate arguments. It has been proposed that both hyperoxia and hypoxia exert comparable effects on cardiovascular functions[16,17]. Additionally, hyperoxia has been demonstrated to protect the heart against ischaemia-reperfusion injury by providing preconditioning[7,19,20]. Conversely, evidence has been presented indicating that intraoperative hyperoxia may induce oxidative stress[21,22,23]. Despite the extensive discourse, a consensus has yet to be reached. In an experimental study conducted by Fujii et al.[23] on rats, it was observed that hyperoxia during CPB resulted in an increase in pro-inflammatory cytokine production and lung fluid, while the anti-inflammatory cytokines was suppressed. A study (n=22) conducted in paediatric patients undergoing cardiac surgery for acyanotic congenital heart disease demonstrated that normoxic and hyperoxic CPB management did not affect postoperative outcomes. However, inflammatory markers (TNF-α, IL-6) were significantly higher in the hyperoxic group[17]. In the present study, we investigated whether there was a relationship between postoperative SIRS and intraoperative PaO_2 during follow-up in the intensive care unit. However, no significant correlation was found between the incidence of SIRS and PaO_2 levels in statistical analysis.

Cyanotic congenital heart disease is associated with chronic hypoxia and stress. It is established that endogenous antioxidant levels are diminished in cyanotic patients, rendering their myocardium particularly vulnerable to ischaemia-reperfusion injury[22]. A comparative study of antioxidant reserve capacities and CPB-related oxidative stress formation in cyanotic and acyanotic groups of children with congenital heart disease revealed no significant difference between the control group and the acyanotic groups. However, the cyanotic group exhibited increased oxidative stress formation, decreased antioxidant capacities and significantly elevated oxidant levels[22-25]. In a study by Allen et al.[26], the effects of different FiO_2 levels applied during CPB on oxidative stress and antioxidant markers in cyanotic and acyanotic paediatric patients were investigated. No significant difference was found between the antioxidant reserve capacities measured before CPB in both groups. However, significant decreases in antioxidant capacities were observed in the cyanotic group after CPB. The researchers observed that reperfusion with hyperoxia (FiO_2: 1.0) following ischemia resulted in a notable increase in free radical formation in cyanotic patient groups, when compared to reperfusion with normoxia (FiO_2: 0.21). As previously stated, inflammatory reaction was evaluated by SIRS formation in the postoperative period in our study. However, we could not determine that the oxygen levels administered in cyanotic and acyanotic patient groups created a significant difference in terms of the development of inflammatory reaction, which we evaluated by SIRS formation.

In experimental studies investigating the effects of normoxic (ReO_2 = 100 mmHg) and hyperoxic (ReO_2 = 400 mmHg) CPB applications on infantile myocardial injury, hyperoxic CPB applications were demonstrated to result in an increase in myocardial injury[27,28]. Furthermore, Caputo et al.[29] (2000) demonstrated that controlled reoxygenation (PaO_2 = 50–80 mmHg) during CPB may result in a reduction of oxygen-induced myocardial injury compared to standard/hyperoxic (PaO_2 = 150–200 mmHg) applications. In a further study conducted on cyanotic patients (n=67), troponin-I levels were observed to be lower in patients who underwent controlled reoxygenation (50-80 mmHg) compared to those who underwent hyperoxic reoxygenation (150-180 mmHg)[30]. Modi et al.[31] observed that in cyanotic (n=20) and acyanotic (n=9) paediatric patients, hyperoxic CPB was associated with early myocardial injury in the former group and prolonged CPB duration exacerbated myocardial injury in the latter. In the present study, myocardial activity was evaluated based on the necessity for inotropic agents and the inotropic score during the ICU stay. No notable correlation was identified between intraoperative high PaO_2 levels and inotropic scores in the postoperative period.

In paediatric patients undergoing open heart surgery, the target haemoglobin (Hb) level is frequently determined according to the cardiac anomaly, age and general condition of the patient. In randomised controlled trials, a lower postoperative cardiac index, higher lactate levels and poor neurological development results have been reported in paediatric patients who were transfused with htc = 20% during CPB compared to patients transfused with htc = 30%[32]. It has been demonstrated that a 24% htk level during CPB is adequate in terms of clinical outcomes and neurological development[33,34]. Nevertheless, higher htc levels may be necessary in neonates, cyanotic patients and those with markedly disparate cardiac profiles. In our clinic, the htc value is ensured to be at the level of 24-25% during CPB and transfusion is planned to be at the level of htc = 27-30% in acyanotic children and htk: 30-35% in cyanotic children and newborns when leaving CPB. In this study, no significant statistical relationship was found between high oxygen levels administered during CPB and htc levels.

Cardiopulmonary bypass is closely associated with lung injury caused by oxidative stress and inflammation[35]. Reber et al.[36] demonstrated that elevated oxygen levels (FiO_2 = 1.0) administered following CPB during the intraoperative period in adult patients (n = 20) undergoing cardiac surgery were significantly associated with an increased incidence of pulmonary complications in the postoperative period when compared with the control group (FiO_2 = 0.35). This increment may be attributed to alveolar collapse and pulmonary shunt formation. The present study revealed no statistically significant difference between the high oxygen levels administered during CPB and the mechanical ventilation requirement. Furthermore, no statistically significant correlation was observed between oxygen levels and length of hospital stay. Nevertheless, the ICU length of stay was found to be longer than ten days in cyanotic patients with PaO_2 levels of +300 mmHg.

In 2016, the World Health Organization recommended that the fraction of inspired oxygen (FiO_2) level should be maintained at 0.8 in intubated patients to reduce wound site infection[37]. However, recent studies conducted on patients in intensive care units have demonstrated that hyperoxygenation is associated with increased mortality. Xu et al.[16] reported a significant increase in mortality in the presence of hypoxia (PaO_2 <80 mmHg) and hyperoxia (PaO_2 >140 mmHg) in intensive care patients. The optimal PaO_2 for reducing mortality was reported to be 100-120 mmHg. A study conducted on paediatric patients admitted to the ICU following surgery revealed that hyperoxia (PaO_2 > 250 mmHg) was associated with significantly elevated mortality rates[38]. In this study, hypoxic groups (PaO_2 = 1–50 mmHg, 51–100 mmHg) were also included[38]. It was observed that mortality rates were higher in hyperoxic groups than in hypoxic groups, and the best results were observed in patients with PaO_2 = 101–150 mmHg. The present study demonstrated that elevated oxygen levels were associated with an increased mortality rate. The mortality rate was 20.5% in Group III, which exhibited the highest PaO_2 level during CPB at +300 mmHg, and 4.3% in Group I, which demonstrated a PaO_2 level of 100-199 mmHg.

4.1. Limitations

Our study has some important limitations. The retrospective nature of our study is a limiting factor. The heterogeneity of the patient population in terms of both cardiac anomalies and patient ages is an important limiting factor. Additionally, patients with

severe comorbidities, such as cystic fibrosis, were included in the study, and comorbidities may affect oxygenation. Other important limitations of our study include variations in intraoperative and postoperative management and the lack of long-term patient outcome data.

5. Conclusion

In the context of cardiac surgery, the use of supraphysiological oxygen levels is a common practice during the perioperative period. Although there is evidence that hyperoxia is neuroprotective and reduces gas microemboli and myocardial ischaemia, it is also known to increase oxidative stress and increase mortality and morbidity in the postoperative period. The findings of our study also indicate that elevated PaO_2 values during CPB are associated with an increased risk of mortality. Further comprehensive studies on the administration of supraphysiological oxygen are required, given the association between this practice and mortality, and the lack of sufficient evidence to support its clinical benefits.

Statement of ethics

The study received approval from the Cukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee on (15/06.11.2020).

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Both authors contributed equally to the article. Both authors read and approved the final manuscript.

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