Oxygen Management During Cardiopulmonary Bypass: A Single-Center, 8-Year Retrospective Cohort Study

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Abstract

Objective: To characterize the institutional oxygen management practices during cardiopulmonary bypass (CPB) in patients undergoing cardiac surgery, including any potential changes during an 8-year study period.

Design: A retrospective cohort study.

Setting: A tertiary care cardiac surgical program.

Participants: Patients who underwent cardiac surgery involving CPB, with or without hypothermic circulatory arrest (HCA), between January 1, 2010, and December 31, 2017.

Measurements and Main Results: In addition to baseline patient characteristics, the authors recorded the partial pressures of arterial oxygen (Pa o_2), fraction of inspired oxygen, and mixed venous oxygen saturation during CPB of 696 randomly selected patients during an 8-year study period. The overall mean Pa o_2 was 255 ± 48 mmHg, without any significant change during the 8-year study period ($p = 0.30$). The mean Pa o_2 of HCA patients was significantly higher than in patients without HCA (327 ± 93 mmHg *v* 252 ± 45 mmHg, respectively; $p < 0.001$).

Conclusions: The current approach to oxygen management during CPB at the authors' institution is within the range of hyperoxemic levels, and these practices have not changed over time. The impact of these practices on patients' outcomes is not fully understood, and additional studies are needed to establish firm evidence to guide optimal oxygen management practice during CPB.

Key Words: hyperoxia; cardiopulmonary bypass; oxygen management; cardiac surgery

ADEQUATE TISSUE oxygenation is essential for the maintenance of normal cellular activity and preservation of organ function during cardiac surgery.[1]Cardiopulmonary bypass (CPB) often exposes tissues to inadequate oxygen delivery, in part due to hemodilution, lack of pulsatile flow, and hemodynamic compromise.[2,3] The use of hypothermic circulatory arrest (HCA) also poses further oxidative stress during cardiac surgery. To counteract these adverse physiologic conditions, supranormal levels of oxygen (fraction of inspired oxygen [Fio_2]) are administered to increase the partial pressure of oxygen in arterial blood (Pao_2). [4,5] Despite these benefits, there is now concern regarding the possible harms of hyperoxia. There is some evidence that its use exacerbates reperfusion injury through oxygen free radical production in the context of cardiac surgery, for example. Growing controversy surrounds the use of hyperoxia, with no evidence-based guidelines to support or refute its use during CPB (with or without HCA).[6]

Although some research indicated possible adverse effects of hyperoxia, a recent systematic review by Heinrichs et al. did not find evidence that its avoidance (ie, by administering normoxia) significantly affected clinical outcomes. However, those authors attributed the poor evidence base to heterogeneity in how hyperoxia has been defined. For example, the normoxic targets in some trials exceeded the hyperoxic targets in others, with threshold values usually being arbitrarily assigned.[4,7,8]This heterogeneity is detrimental to an understanding of hyperoxia's effects and, therefore, the construction of evidence-based guidelines for its use during cardiac surgery.

It is possible that emerging recognition of the harms of hyperoxia has led to a decrease in the levels of oxygen used during CPB. Yet, with the growing use of brain monitors (eg, cerebral oximetry), one of the first-line therapies for reversing cerebral desaturation has been to increase Fio_2 . As this gains more traction in the operating room, a general increase in Pa o_2 also could be reasonably expected. Despite this likely variability, intraoperative oxygen management practices are poorly documented and may be using levels associated with harm. Without the data to fully understand this, however, a state of uncertainty exists.

The aim of this study was to determine the current approach to oxygen management during CPB (with or without HCA) in a tertiary care cardiac surgical program. The authors hypothesized that the mean Pao_2 levels would exhibit change over time, given the absence of guidelines or a definition as to what constitutes hyperoxia versus normoxia during surgery. They also hypothesized that Pa o_2 levels would differ between those who underwent HCA versus those who did not.

Methods

After approval from the University of Manitoba Research Ethics Board (September 18, 2017), this 8-year retrospective study was undertaken at a tertiary care cardiac surgical center (St. Boniface Hospital in Winnipeg, Manitoba, Canada). It included adult (age ≥18 years) patients who underwent cardiac surgery using CPB (with or without HCA) from January 1, 2010, to December 31, 2017. The starting date was selected based on the availability of archived handwritten perfusionist documents at the authors' institution.

The authors extracted the data from the patients' medical records (handwritten perfusion records). They selected each record to be reviewed using an online random date generator,[9] such that 100 dates per year were chosen for each of the 8 years of the study (target, N = 800). Random number generator software (Microsoft Excel 2010) was used to randomly select 1 patient for each of the chosen dates (eg, if Excel generated the number 4, the fourth patient to have surgery on the particular date was chosen, based on the order of records filed in the perfusion database). The authors limited their search to only weekdays to capture as many surgeries as possible, while still keeping within their randomization process. As surgeries are less likely to take place on weekends, their inclusion of the weekend could have limited the number of patients available to study (eg, if the randomization sequence indicated a Sunday and no cases occurred, they would have had fewer total patients to analyze).

In addition to baseline patient characteristics (age, sex, body mass index, and type of surgery), the authors recorded the Pao_2, Fio_2, and venous oxygen saturation (Svo_2) for each patient just after the commencement of CPB and then at approximately 15-minute intervals during CPB. Other surgical and bypass-related data points collected included average and lowest bypass temperature, average partial pressure of carbon dioxide in arterial blood, base deficit, pH, glucose, hemoglobin, and length of CPB, cross-clamp, and HCA. Arterial blood gas values were monitored using the Radiometer ABL Flex (Radiometer Canada, Mississauga, Canada), and Svo_2 values were monitored using a BioTrend device (Medtronic, Minneapolis, MN).

Statistical Analysis

The data were reported as the mean ± standard deviation (SD) for continuous variables, with categorical variables expressed as percentage (%). To detect differences between the study years, the authors used analysis of variance for continuous variables and chi-square tests for categorical variables. Univariate logistic regression models were used to determine the significance of linear Pa o $_2$ trends over time.

As an exploratory analysis, the authors also compared the CPB Pa o $_2$ levels in the HCA versus non-HCA patients; a *t* test for was used to detect differences between these 2 groups. All analyses were performed using SAS software (version 9.3, Statistical Analysis System Institute) and a $p < 0.05$ was considered significant. Due to the exploratory nature of this study, the authors did not adjust for multiple comparisons.

Results

The study population consisted of 696 patients. This sample was smaller than the planned 800 patients, as a number of the records from the randomly selected dates could not be located in the perfusion archives. Baseline characteristics, including demographics and surgery type, are summarized in Table 1 . The mean ± SD age across cohorts was 65 ± 12 years, with 26% of the sample being female. The majority of patients (n = 387; 56%) underwent coronary artery bypass grafting, with the remaining groups undergoing isolated valve (n = 141; 20%), coronary artery bypass grafting plus valve (n = 88; 13%), thoracic aortic (n = 40; 6%), or other procedures (n = 33; 5%). Of note, there were 7 patients for whom this

data were not available, including 6 who underwent CPB and 1 who underwent HCA. There were no significant differences in patient characteristics across cohorts from each respective year.

Table 1. Baseline Characteristics

Characteristic	**Total N = 696***	**Non-HCA N = 668***	**HCA N = 28***	**p value**
Age, y	65 ± 12	65 ± 12	61 ± 17	0.20 †
Female	179 (26)	173 (26)	6 (21)	0.60 ‡
BMI, kg/m^2	29 ± 5	30 ± 5	28 ± 6	0.17 †
Surgery type				
Isolated CABG	387 (56)	387 (58)	0 (0)	< .001 §
Isolated valve	141 (20)	139 (21)	2 (7)	0.09 §
CABG + valve	88 (13)	85 (13)	3 (11)	1.00 §
Aortic	40 (6)	22 (3)	18 (67)	< 0.001 ‡
Other	33 (5)	29 (4)	4 (15)	0.04 §

Data are presented as mean ± standard deviation or number of patients (%) for individuals with nonmissing values (thus, the surgery type totals may not add up to the corresponding column totals*).

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; HCA, hypothermic circulatory arrest.

† Student *t* test.

‡ Chi-square test.

§ Fisher exact test.

As shown in Table 2, the overall mean ± SD Pao_2, Svo_2, and Fio_2 were 255 ± 45 mmHg, 76 ± 5%, and 69 ± 7%, respectively. During the 8 years studied, there was no significant change in the Pao_2 levels during CPB (β = 0.90 per year *;* p = 0.30) (Fig 1).

Table 2. Intraoperative Characteristics

Variable	Total N = 696	Non-HCA N = 668	HCA N = 28	p Value
Average bypass temperature,°C	35.4 ± 1.0	35.6 ± 0.6	30.2 ±1.9	< 0.001
Lowest bypass temperature,°C	34 ± 3	35 ± 1	21 ± 4	< 0.001
Pao_2, mmHg	255 ± 48	252 ± 45	327 ± 93	< 0.001
Fio_2, %	69 ± 7	70 ± 10	70 ± 10	0.82
Svo_2, %	76 ± 5	76 ± 5	82 ± 4	< 0.001
$Paco_2$	39 ± 3	39 ± 3	39 ± 3	0.44
Base deficit	–3 ± 2	–3 ± 2	–4 ± 4	0.31
pH	7.36 ± 0.04	7.36 ± 0.04	7.35 ± 0.05	0.02
Glucose, mmol/L	8.3 ± 1.6	8.3 ± 1.6	8.8 ± 1.4	0.11
Hemoglobin, g/L	96 ± 14	96 ± 14	88 ± 11	0.003
CPB time, min	125 ± 58	121 ± 54	239 ± 100	< 0.001
Cross-clamp time, min	87 ± 43	87 ± 45	140 ± 63	< 0.001
HCA time, min	-	-	28 ± 20	-

Data are presented as mean ± standard deviation for individuals with nonmissing values. p Values are from the Student *t* test.

Abbreviations: CPB, cardiopulmonary bypass; Fio_2, fraction of inspired oxygen; HCA, hypothermic circulatory arrest; Pao_2, average partial pressure of oxygen in arterial blood; $Paco_2$, average partial pressure of carbon dioxide in arterial blood; Svo_2, mixed venous oxygen saturation.

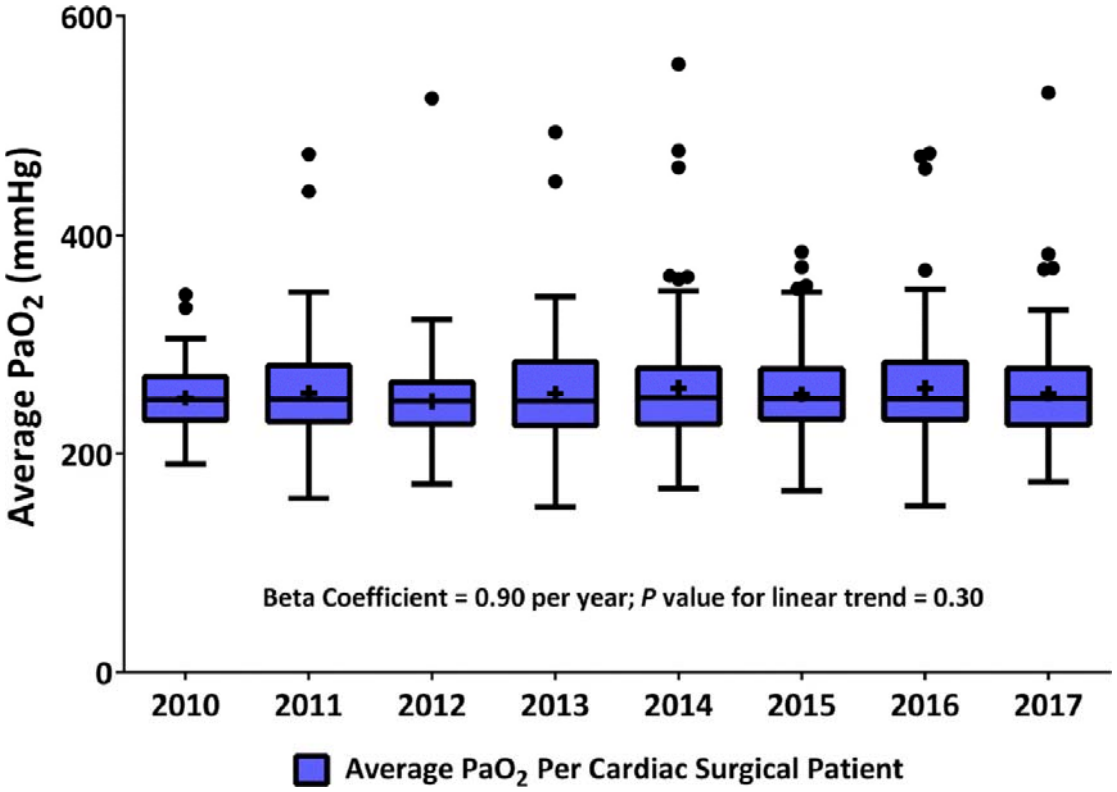

Fig 1. The partial pressure of arterial oxygen (Pao_2) during cardiopulmonary bypass in 696 patients undergoing cardiac surgery. The median and interquartile range for Pao_2 values across the 8-year study period are illustrated in this box and whisker plot. There was no change in Pao_2 during the 8 years studied (linear trend in the univariable logistic regression model; *β* = 0.90 per year*;* p = 0.30).

The Pao_2 of patients who underwent HCA was significantly higher than in those who did not (327 ± 93 mmHg *v* 252 ± 45 mmHg, respectively; p < 0,001) (Table 2). There were also significant differences in the Svo_2 values between these groups (82 ± 4 mmHg, HCA *v* 76 ± 5 mmHg, non-HCA; p < 0,001). The Fio_2 was 70 ± 10% in both HCA and non-HCA groups.

Discussion

The study results indicated that the authors' institutional oxygen management practices have not changed during the course of the 8-year study period, with the Pao_2 averaging 255 ± 48 mmHg. They also found that patients undergoing procedures requiring HCA had higher Pao_2 during CPB compared with the non-HCA patients despite both groups receiving the same Fio_2 (approx. 70%).

Enhanced oxygen therapy, though with widely variable levels of hyperoxia, is ubiquitous during intraoperative care. Yet, data that systematically document these practices during CPB are relatively lacking. The authors could not find any other reports that might allow for comparison of their institutional oxygen management practices during CPB with others. However, their levels far exceeded those reported by Morkane et al., who studied patients' general surgery[10] —their average Pao_2 being 184 ± 8 mmHg, with a mean Fio_2 of 50%.

The inconsistent definition of what constitutes "hyperoxia" can be seen in several recent trials in the context of cardiac surgery. The authors' Pa o $_2$ values were consistent with definitions of hyperoxia adopted in several of the recently reported randomized controlled trials (RCTs), including Belboul et al. (Pao_2 = 190-300 mmHg), Abdel-Rahman et al. (Pao_2 >250 mmHg), and Smit et al. (Pao_2 = 200-220 mmHg).[7,11,12] However, the authors' levels were consistent with some normoxia groups in the reported RCTs as well.[4,8] For example, Inoue et al. defined normoxia as a Pa o $_2$ between 200 and 250 mmHg.[4,8] This wide variability in definitions of hyperoxia likely points to additional equipoise as to what the optimal Pa o $_2$ should be during CPB.

Arguments have been made both for and against the use of supra-physiologic Pao_2 during cardiac surgery.[4,7,13] The prospect of infection prevention led the World Health Organization to recommend the routine intraoperative use of hyperoxia, though a recent meta-analysis failed to find sufficient evidence to support these guidelines.[6,14] Arterial hyperoxia may also be efficacious in reducing the size of gaseous microemboli that are a near-ubiquitous occurrence during CPB, particularly during valvular and other open-ventricular procedures.[15,16,17] Yet, possible harms thought to be associated with elevated levels of oxygen (such as within the range observed at the authors' institution) may arise through direct tissue injury from increased production of reactive oxygen species (ROS) and enhancement of ischemia-reperfusion injury.[17,18,19] The formation of ROS during CPB may be exacerbated after removal of the aortic cross-clamp and during the restoration of flow after HCA, but even more so in a hyperoxic milieu.[18] Peripheral and coronary vasoconstriction also may occur from hyperoxemia, alongside an attenuated cardiac output.[20,21]

As mentioned, however, the systematic review by Heinrichs et al. did not find consistent evidence of hyperoxia's impact on clinical outcomes. Those authors attributed this finding not only to the heterogeneous evidence base, but to the way that previous trials have been designed. Most opted for the global administration of either normoxia or hyperoxia before, during, and after commencement of CPB. It may be that exposure to hyperoxia just prior to or during CPB might circumvent the subsequent ischemia and, thus, reperfusion injury that normally occurs in patients exposed to normoxia during this time. On the other hand, patients exposed to normoxia may avoid other undesirable impacts of hyperoxia, such as those related to its vasoconstrictive properties. Therefore, the generalized use of intraoperative hyperoxia might balance its relative harms versus benefits, thus preventing either from translating to any discernible clinical impact. This illustrates a need for study methodologies that look beyond global comparisons of hyperoxia versus normoxia in favor of a more nuanced temporally adjusted approach.

The authors also investigated the oxygen levels used during procedures using HCA. Surgery requiring HCA presents its own unique oxygen management issues, with HCA reports suggesting a benefit to hyperoxia.[15,22,] For example, despite the intuitive argument that hyperoxia might increase ROS, there is also some evidence that hyperoxia levels just before commencement of HCA may decrease the overall ischemic injury by providing optimal pre-HCA tissue oxygen stores. Pearl et al. found that patients with a higher Pao_2 before HCA demonstrated reduced acid generation during the arrest period, an indicator of tissue hypoxia.[23] According to oxygen pressure field theory, this use of hyperoxia allows tissues to accumulate a buffer of oxygen in the event of subsequent ischemia.[24] This mechanism is

also enhanced with the concomitant use of hypothermia that increases oxygen solubility while also reducing its consumption. Therefore, an elevated Fio_2 prior to HCA to enhance the Pao_2 can reduce ischemia and its related tissue acidosis. This partially might explain why the average Pao_2 in the authors' study significantly varied between the HCA (higher Pao_2) and non-HCA groups, despite their receiving the same Fio_2.

The authors did not find any significant change in oxygen levels during the 8-year period of their study. They had hypothesized that with overall increasing use of tissue oxygen monitoring availability (ie, cerebral oximetry) that this might have occurred. Their increased use of cerebral oximetry itself could have raised the awareness of the practitioners to the influence of Fio_2 on cerebral oximetry signals. For example, when the cerebral oximetry saturation was lower than expected, part of the intuitive algorithm that the authors routinely used included increasing the Fio_2 . Thus, as cerebral oximetry use expanded at their institution (as it has expanded more globally), they had expected to see the overall Fio_2 and thus Pao_2 to also increase over time. The authors did not have specific data on the use of this device in their patients, though it is generally a routinely used monitor at their institution. Of note, they also recorded Svo_2 values and found no changes over time. The clinical decision to increase Pao_2 to increasingly hyperoxic levels can, in part, be theoretically influenced by monitoring the Svo_2 .

One limitation inherent to the present study was its single-center nature. This may restrict the generalizability of the results to other institutions. Other limitations stemmed from the use of the handwritten perfusionist records as a data source. The authors' use of these records did not allow for analysis of comorbidities, which may have influenced clinicians' intentions in titrating intraoperative oxygen levels. Due to the nature of the perfusion database queried, the authors were also unable to collect data regarding outcomes associated with the Pao_2 levels recorded during the study period. Furthermore, they were limited in the numbers of patients' records that they were able to locate for each year, thereby making their sample size slightly smaller than intended. The handwriting on these documents may additionally have led to some minor inaccuracies during data collection. Furthermore, perfusionists at their institution generally recorded values intraoperatively at 15-minute intervals on average, with some inevitable inconsistencies. However, this is unlikely to have made a significant difference in the overall data collected given the relatively large sample size.

Before any further study into the clinical impact of hyperoxia is undertaken, this concept must be universally defined. Two clinical trials currently registered in ClinicalTrials.gov (NCT03939832; NCT04144205) aim to study the effects of hyperoxia during CPB.[25,26] Yet both plan to titrate normoxic patients to an Fio_2 of 50%, which Toramen et al. previously defined as hyperoxic.[27] This highlights the inconsistencies that will likely persist until a global definition of hyperoxia occurs. For this to happen, more studies that document current approaches to oxygen management during CPB are needed to establish a baseline. This information then can be used to more clearly differentiate hyperoxic versus normoxic levels of oxygen. Using these definitions, future trials can begin to address the clinical equipoise that surrounds the use of intraoperative hyperoxia. This will facilitate the construction of evidence-based guidelines that optimize the care of cardiac surgery patients.

Conclusions

The authors' findings indicated that their institution has consistently been using significantly elevated levels of oxygen during CPB in cardiac surgery. The impact of this practice on patient outcomes is not fully understood due to the paucity of well-designed trials comparing hyperoxia with normoxia during cardiac surgery. Future research will require a universal definition of hyperoxia to better study its effects; studies that describe institutional practices aside from the authors' own will facilitate this objective. This information then can be used to design trials that expose patients to a wider variation of oxygen strategies, thereby understanding the impact of oxygen levels during CPB on patient outcomes after cardiac surgery.

Conflict of Interest

None.

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References

1. Murphy G.S., Hessel E.A., Groom R.C.: Optimal perfusion during cardiopulmonary bypass: An evidence-based approach. Anesth Analg 2009; 108: pp. 1394-1417.

2. DeBlasi R.A., Tonelli E., Arcioni R., et. al.: In vivo effects on human skeletal muscle oxygen delivery and metabolism of cardiopulmonary bypass and perioperative hemodilution. Intens Care Med 2012; 38: pp. 413-421.

3. Kemming G.I., Meisner F.G., Kleen M., et. al.: Hyperoxic ventilation at the critcal haematocrit. Resuscitation 2003; 56: pp. 289-297.

4. Heinrichs J., Lodewyks C., Neilson C., et. al.: The impact of hyperoxia on outcomes after cardiac surgery: A systematic review and narrative synthesis. Can J Anesth 2018; 65: pp. 923-935.

5. Moradkhan R., Sinoway L.I.: Revisiting the role of oxygen therapy in cardiac patients. J Am Coll Cardiol 2010; 56: pp. 1013-1016.

6. Wetterslev J., Meyhoff C.S., Jorgensen L.N., et. al.: The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. Cochrane Database System Rev 2015; 2015:

7. Smit B., Smulders Y.M., de Waard M.C., et. al.: Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: A randomised controlled trial. Crit Care 2016; 20: pp. 55.

8. Inoue T., Ku K., Kaneda T., et. al.: Cardioprotective effects of lowering oxygen tension after aortic unclamping on cardiopulmonary bypass during coronary artery bypass grafting. Circ J 2002; 66: pp. 718-722.

9. Haahr M.Random calendar date generator. Available at: https://www.random.org/calendar-dates/ . Accessed September 18, 2017.

10. Morkane C.M., McKenna H., Cumpstey A.F., et. al.: Intraoperative oxygenation in adult patients undergoing surgery (iOPS): A retrospective observational study across 29 UK hospitals. Perioper Med (Lond) 2018; 7: pp. 17.

11. Belboul A., Al-khaja N., Ericson C., et. al.: The effect of hyperoxia during cardiopulmonary bypass on blood cell rheology and postoperative morbidity associated with cardiac surgery. J Extracorp Technol 1991; 23: pp. 43-48.

12. Abdel-Rahman U., Aybek T., Moritz A., et. al.: Graded reoxygenation limits lipid peroxidation during surgical reperfusion. Med Sci Mon 2002; 9: pp. CR389-CR391.

13. McGuinness S.P., Parke R.L., Drummond K., et. al.: A multicenter, randomized, controlled phase iib trial of avoidance of hyperoxemia during cardiopulmonary bypass. Anesthesiology 2016; 125: pp. 465-473.

14. Allegranzi B., Zayed B., Bischoff P., et. al.: New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: An evidence-based global perspective. Lancet Infect Dis 2016; 16: pp. e288-e303.

15. Nollert G., Nagashima M., Bucerius J., et. al.: Oxygenation strategy and neurological damage after deep hypothermic circulatory arrest. I. Gaseous microemboli. J Thorac Cardiovasc Surg 1999; 117: pp. 1172-1179.

16. Georgiadis D., Wenzel A., Lehmann D., et. al.: Influence of oxygen ventilation on Doppler microemboli signals in patients with artifical heart valves. Stroke 1997; 28: pp. 2189-2194.

17. Young R.: Hyperoxia: A review of the risks and benefits in adult cardiac surgery. J Extracorp Technol 2012; 44: pp. 241-249.

18. Frank A., Bonney M., Bonney S., et. al.: Myocardial ischemia reperfusion injury: From basic science to clinical bedside. Semin Cardiothorac Vasc Anesth 2012; 16: pp. 123-132.

19. Caputo M., Mokhtari A., Rogers C.A., et. al.: The effects of normoxic versus hyperoxic cardiopulmonary bypass on oxidative stress and inflammatory response in cyanotic pediatric patients undergoing open cardiac surgery: A randomized controlled trial. J Thorac Cardiovasc Surg 2009; 138: pp. 206-214.

20. Bak Z., Sjoberg F., Rousseau A., et. al.: Human cardiovascular dose-response to supplemental oxygen. Acta Physiol (Oxf) 2007; 191: pp. 15-24.

21. Guensch D.P., Fischer K., Shie N., et. al.: Hyperoxia exacerbates myocardial ischemia in the presence of acute coronary artery stenosis in swine. Circ Cardiovasc Interv 2015; 8:

22. Nollert G., Nagashima M., Bucerius J., et. al.: Oxygenation strategy and neurologic damage after deep hypothermic circulatory arrest. II. Hypoxic versus free radical injury. J Thorac Cardiovasc Surg 1999; 117: pp. 1172-1179.

23. Pearl J.M., Thomas D.W., Grist G., et. al.: Hyperoxia for management of acid-base status during deep hypothermia with circulatory arrest. Ann Thorac Surg 2000; 70: pp. 751-755.

24. Grist G.: Oxygen pressure field theory: A detailed description of vital gas exchange at the capillary level for perfusionists. Prog Pediatr Cardiol 2008; 24: pp. 89-99.

25. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT03939832, FiO2 and Outcomes After Cardiac Surgery With Cardiopulmonary Bypass; 2019 May 7 [cited 2020 Mar 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT03939832?titles=Fio+and+outcomes+after+cardiac+surgery+with+cardiopulmonary+bypass&draw=2&rank=1 .

26. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT04144205, Effect of Arterial Oxygen Partial Pressure on Mixed Venous Oxygen Saturation; 2019 Oct 30 [cited 2020 Mar 15]. Available from: https://clinicaltrials.gov/ct2/show/NCT04144205?titles=Effect+of+arterial+oxygen+partial+pressure+on+mixed+venous+oxygen+saturation&draw=2&rank=1 .

27. Toraman F., Evrenkaya S., Senay S., et. al. Adjusting oxygen fraction to avoid hyperoxemia during cardiopulmonary bypass. Asian Cardiovasc Thorac Ann 2007; 15: pp. 303-306.