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Severity of hyperoxia as a risk factor in patients undergoing on-pump cardiac surgery

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Background. Hyperoxia has long been perceived as a desirable or at least an inevitable part of cardiopulmonary bypass. Recent evidence suggest that it might have multiple detrimental effects on patient homeostasis. The aim of the study was to identify the determinants of supra-physiological values of partial oxygen pressure during on-pump cardiac surgery and to assess the impact of hyperoxia on clinical outcomes.

Materials and methods. Retrospective data analysis of the institutional research database was performed to evaluate the effects of hyperoxia in patients undergoing elective cardiac surgery with cardiopulmonary bypass, 246 patients were included in the final analysis. Patients were divided in three groups: mild hyperoxia (MHO, PaO_2 100–199 mmHg), moderate hyperoxia (MdHO, PaO_2 200–299 mmHg), and severe hyperoxia (SHO, PaO_2 >300 mmHg). Postoperative complications and outcomes were defined according to standardised criteria of the Society of Thoracic Surgeons.

Results. The extent of hyperoxia was more immense in patients with a lower body mass index (p = 0.001) and of female sex (p = 0.005). A significant link between severe hyperoxia and a higher incidence of infectious complications (p – 0.044), an increased length of hospital stay (p – 0.044) and extended duration of mechanical ventilation ($p < 0.001$) was confirmed.

Conclusions. Severe hyperoxia is associated with an increased incidence of postoperative infectious complications, prolonged mechanical ventilation, and increased hospital stay.

Keywords: Hyperoxia, cardiac surgery, cardiopulmonary bypass, reactive oxygen species, infectious complications

INTRODUCTION

Over the past few decades, cardiopulmonary bypass (CPB) has been successfully used for millions cardiac procedures around the world. Recognition of CPB-related complications has led to major advances in technology and improved outcomes. However, there is still considerable evidence of a negative systematic effect of the artificial blood flow that alters the delivery of oxygen to tissues (1–3). In everyday practice physicians attempt

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to minimize cellular hypoxia by keeping partial arterial oxygen pressure (PaO_2) above the physiological value (>100 mmHg). However, a number of clinical trials and meta-analyses revealed a negative impact of hyperoxia after cardiac surgery with cardiopulmonary bypass (4–6). Hyperoxia can cause vasoconstriction, compromise perfusion, increase the oxidative stress, and fuel the systemic inflammatory response syndrome (SIRS) (7). On the other hand, there are some reported benefits of hyperoxia since it may act as a preconditioner, attenuate the ischemia-reperfusion injury (8, 9), counteract systemic inflammation-induced vasoplegia, and lower the damage by gas-microemboli (10). Therefore identification of the effects of hyperoxia on postoperative outcomes might be important in clarifying the role of excessive oxygen use during cardiac surgery. The aim of our study was to identify determinants of the supra-physiological values of PaO_2 during on-pump cardiac surgery and to assess the impact of hyperoxia on clinical outcomes.

MATERIALS AND METHODS

We conducted a retrospective data analysis of adult patients undergoing elective cardiac surgery requiring cardiopulmonary bypass (CPB) at a tertiary university hospital. An approval to conduct the study was granted by the Regional Bioethics Committee. Exclusion criteria were: high preoperative risk defined as EuroSCORE > 5, non-elective or transplant surgery. Patients were divided into three groups according to PaO_2 levels achieved during CPB: mild hyperoxia (MHO, PaO_2 100–199 mmHg), moderate hyperoxia (MdHO, PaO_2 200–299 mmHg), and severe hyperoxia (SHO, PaO_2 >300 mmHg).

Intraoperative management

Routine surgical and anaesthetic techniques were applied in all cases. Non-pulsatile cardiopulmonary bypass (CPB) was performed according to the institutional protocol. While on CPB, all patients were treated under moderate hypothermia (32–34°C), the mean arterial pressure was kept above 60–70 mmHg, and the blood flow was maintained at 2.4 L min^{-1} m^{-2} of the body surface area. Myocardial protection during the aortic cross-clamping period was achieved by minimally diluted tepid blood cardioplegia. Anticoagulation was induced using an unfractionated heparin loading dose of 300 IU kg^{-1} and additional doses, if needed, to maintain an activated clotting time of 450–480 seconds. Heparin reversal was achieved with protamine sulphate. Arterial blood gas measurements were taken every 15 minutes during CPB and analysed using the on-site arterial blood-gas analysis machine, RAPIDPoint 500 (Siemens, Germany). An average and peak values of partial oxygen pressure (PaO_2) were obtained together with the peak lactate concentration.

After surgery, patients were admitted to the ICU and weaned from mechanical ventilation according to standard protocol. Criteria for tracheal extubation were: patient's awakening, body core temperature >36°C, PaO_2 >80 mmHg and $PaCO_2$ <49 mmHg during a spontaneous breathing trial, hemodynamic stability or low doses of inotropic support, drainage <100 ml/h for at least 2 hours, no shivering, and adequate diuresis. Postoperative analgesia was achieved using opioid analgesics administered intravenously, combined with non-steroidal anti-inflammatory drugs. The prophylactic antibiotic regimen included the intravenous administration of 2 g. Ceftriaxone one hour preoperatively and six hours postoperatively. Ceftriaxone was continued in all patients for 48 hours postoperatively.

Postoperative complications and outcomes were defined according to standardised definitions of Society of Thoracic Surgeons, including: surgical (unplanned re-operation for bleeding), renal (acute renal failure, requiring dialysis), neurologic, infectious (wound or sternal infection, mediastinitis, septicaemia), pulmonary, cardiovascular (cardiac arrest, arrhythmia, low cardiac output), and other post-operative complications.

Statistical analysis

We used Chi-square tests in intergroup comparisons of categorical variables. The correlation between two quantitative variables was tested with Pearson's correlation coefficient. We used Kolmogorov-Smirnov test to check for normality of the data for the following variables: O_2 partial pressure, duration of surgery, CPB time, minimal nasopharyngeal temperature, cardioplegia time, aortic clamp time, age, body mass index (BMI), left ventricle ejection fraction (LVEF), EuroSCORE, ICU time, total hospitalization time, ventilator time, lactates, and intraoperative

haemoglobin. Analysis of variance (ANOVA) was used to interpret the differences among group means. For variables that were marginally skewed, we performed a nonparametric Kruskal-Wallis test for the differences in the medians between three hyperoxia groups. *P* values <0.05 were considered as statistically significant. All data in the tables are shown as mean ± SD. Statistical analysis was performed using an IBM SPSS v23.0 statistical package program.

RESULTS

A total of 246 patients underwent an elective cardiac surgery requiring cardiopulmonary bypass. Forty-seven (19.1%) patients fell to the MHO group, 124 (50.4%) to the MdHO group, and 75 (30.5%) to the SHO group. Patients' baseline characteristics are summarized in Table 1.

No significant differences were observed between the three patient groups regarding the prevalence of major comorbidities such as myocardial infarction, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, stroke, and peripheral vascular diseases. Patients in all three study groups were of similar age with males forming the majority. The degree of hyperoxia was higher in patients with a low body mass index (BMI) (p = 0.001), higher EuroSCORE value (p = 0.007) and in female patients (p = 0.005).

None of the procedural properties – duration of surgery, CPB time, aortic clamp time, cardioplegia time, and minimal nasopharyngeal temperature reached – showed significant differences between the study groups. Standard CPB protocol resulted in mean PaO_2 of 263.09 ± 66.00 mmHg with variation from 102.0 mmHg to 407.01 mmHg (Table 2).

Over the study period, the mortality remained very low and did not differ between hyperoxia groups. Multivariate analysis confirmed that there was a statistically significant link between severe hyperoxia and a higher incidence of postoperative infectious complications (p – 0.044), increased length of hospital stay (p – 0.044) and extended duration of mechanical ventilation (p < 0.001). No differences between the study groups were observed in terms of intensive care unit stay and other postoperative complications: reoperation for bleeding, perioperative myocardial infarction, acute kidney damage, and multi-organ failure.

Table 1. Patients' demographic data

	Severe hyperoxia (SHO) *n* = 75	**Moderate hyperoxia (MdHO) *n* = 124**	**Mild hyperoxia (MHO) *n* = 47**	***p*-value**
Females, *n* (%)	35 (14.2%)	35 (14.2%)	10 (4.1%)	**0.005**
Age, years	66.01 ± 10.06	64.33 ± 10.71	64.30 ± 10.63	0.661
BMI	*28.00 ± 4.69	28.57 ± 5.03	*31.58 ± 5.41	**0.001**
EuroSCORE	*2.10 ± 1.07	1.74 ± 0.09	*1.56 ± 0.76	**0.007**
Diabetes mellitus, *n* (%)	15 (6.1%)	23 (9.3%)	16 (6.5%)	0.081
Arterial hypertension, *n* (%)	58 (23.6%)	103 (41.9%)	41 (16.7%)	0.353
Coronary artery disease, *n* (%)	46 (18.7%)	86 (35.0%)	41 (16.7%)	**0.009**
Peripheral vascular disease, *n* (%)	9 (3.7%)	24 (9.8%)	3 (1.2%)	0.075
History of stroke, *n* (%)	12 (4.9%)	8 (3.3%)	4 (1.6%)	0.085
Currently smoking, *n* (%)	16 (6.5%)	31 (12.6%)	14 (5.7%)	0.573
Ejection fraction (%)	50.27 ± 8.76	51.61 ± 10.44	50.44 ± 9.89	0.260
Previous myocardial infarction (<90 days), *n* (%)	12 (4.9%)	17 (6.9%)	11 (4.5%)	0.308
Intra-aortic balloon pump before surgery, *n* (%)	1 (0.4%)	6 (2.5%)	1 (0.4%)	0.358

Table 2. Intraoperative and postoperative variables

	Severe hyperoxia (SHO) *n* = 75	**Moderate hyperoxia (MdHO) *n* = 124**	**Mild hyperoxia (MHO) *n* = 47**	***p*-value**
Intraoperative				
PaO_2, mmHg	336.18 ± 29.45	256.35 ± 27.90	164.25 ± 30.15	**<0.001**
Haemoglobin, g/l	*99.90 ± 13.97	104.49 ± 16.98	*109.42 ± 13.71	**0.002**
Duration of surgery, minutes	228.06 ± 64.45	210.28 ± 59.65	203.61 ± 45.98	0.058
CPB time, minutes	126.25 ± 51.37	116.53 ± 44.60	107.36 ± 35.71	0.084
Aortic clamp time, minutes	78.92 ± 32.81	75.76 ± 28.85	66.66 ± 28.56	0.249
Minimal nasopharyngeal temperature, °C	30.83 ± 2.90	31.17 ± 3.30	31.78 ± 2.77	0.233
Lactate, mg/dL	2.64 ± 2.30	2.36 ± 2.13	2.29 ± 2.22	0.159
Cardioplegia time, minutes	19.46 ± 8.13	23.01 ± 13.23	21.58 ± 9.30	0.117
Postoperative				
ICU stay, days	4.02 ± 5.90	2.75 ± 1.66	2.57 ± 1.44	0.157
CMV duration, hours	*28.24 ± 99.31	8.59 ± 10.41	*6.22 ± 3.87	**<0.001**
Reoperation for bleeding, *n* (%)	7 (2.8%)	6 (2.4%)	1 (0.4%)	0.211
Perioperative myocardial infarction, *n* (%)	39 (16.0%)	58 (23.8%)	17 (7.0%)	0.271
Infectious complications, *n* (%)	9 (3.7%)	4 (1.6%)	5 (2.0%)	**0.044**
Renal failure (creatinine >2.0 mg/dL)	3 (1.2%)	8 (3.3%)	2 (0.8%)	0.710
Multi-organ failure, *n* (%)	1 (0.4%)	0	0	0.318
Atrial fibrillation, *n* (%)	29 (11.8%)	44 (17.9%)	15 (6.1%)	0.747
Hospital length of stay, days	*16.16 ± 13.77	13.02 ± 5.38	*11.70 ± 3.88	**0.044**
Mortality, *n* (%)	1 (0.4%)	1 (0.4%)	0	0.727

DISCUSSION

Our data suggest that significant hyperoxia is common in elective cardiac surgery. There has been little change in this practice in spite of an extensive debate on the potential harm and doubts whether hyperoxia might be beneficial in critically ill and surgical patients (4–7).

Our key findings are increased hospital stay, duration of mechanical lung ventilation, and infectious complications rate in patients subjected to severe hyperoxia during CPB (SHO group).

According to the predefined criteria, high risk, emergency, and transplant cases were excluded. This allowed us to achieve a relatively homogenous study population. Analysis of peri-operative data suggests that there was no statistically significant difference in major co-morbidities, type or duration of surgery, or surgical complications. The incidence of diabetes and peripheral vascular and coronary artery disease was significantly higher in the MdHO group, whereas the difference between MHO and SHO groups was non-significant. We noted a statistically significant difference in EuroSCORE between SHO and MHO groups, but believe that an overall difference of 0.5 point is clinically insignificant and does not represent an increased pre-operative risk in the SHO group. Therefore the outcomes in the SHO group are unlikely to be affected by the difference in pre-operative status.

We hypothesize that increased rate of infectious complications might be related to CPB-inflicted immense oxidative stress precipitated by severe hyperoxia. Cardiopulmonary bypass activates a complex cascade of humoral and cell-mediated inflammatory responses, which lead to an increased number of circulating neutrophils (11). Alongside with reperfusion injury, neutrophils are the main source of reactive oxygen species (ROS) production during and after CPB (12). In some cases ROS may promote infections via metabolic effects on pathogen physiology, damage to the immune system, and ROS-induced activation

of immune defence mechanisms that are subsequently hijacked by particular pathogens to act against more effective microbicidal mechanisms of the immune system (13). It is possible that CPB with severe hyperoxia may induce changes in ROS homeostasis, alter the functions of immune system, and increase a patient's susceptibility to infections.

Prolonged duration of postoperative lung ventilation in patients exposed to severe hyperoxia can also be a consequence of altered ROS homeostasis. Some studies have demonstrated a deleterious effect of ROS on the contractile function of respiratory muscles, especially diaphragm, with a potential to prolong the time of mechanical ventilation (14).

Another interesting finding is that a lower BMI and female sex are independent predictors of hyperoxia. This phenomenon is most likely due to the fact that DuBois and other calculations of the body surface area are based on a patient's height and weight and cannot possibly reflect variations in individual metabolic rates.

Adipose tissue (AT) is characterized by a lower oxygen consumption, which leads to a higher partial oxygen pressure despite a lower AT blood flow. Therefore, it would be a logical assumption that a higher BMI should be a risk factor for hyperoxia and not vice versa. We hypothesize that a lower BMI is a risk factor for hyperoxia because of multiple effects of obesity on the cardiovascular system. In addition to increasing stroke volume that leads to the rise of cardiac output, obesity also enhances the total blood volume and oxygen consumption at rest (15). However, augmented circulation is still insufficient to meet the needs of proliferated AT and enlarged adipocytes (16, 17). Therefore a lot more oxygen is needed to achieve high PaO_2 in obese patients (18). Since women have lower basal and sleep metabolic rates compared to men, they are at a higher risk of hyperoxia (19).

Our study had a few limitations. It was a non-randomised retrospective study. We were unable to take into account such human factors as experience of the anaesthesiologist or the surgical team that may influence postoperative outcomes. This study measured the severity of hyperoxia, but not the time of exposure, which may play an important role. Finally, we could only assess the outcomes during hospitalization and have no data on possible long-term effects of severe hyperoxia.

In spite of the limitations, our study demonstrates harmful effects of severe hyperoxia. Patients may benefit from tighter PaO_2 controls during CPB and PaO_2 levels above 300 mmHg should be avoided.

CONCLUSIONS

Hyperoxia is a frequent finding during cardiac surgery with cardiopulmonary bypass. Severe hyperoxia is associated with an increased rate of postoperative infectious complications, prolonged mechanical ventilation, and increased hospital stay.

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HIPEROKSIJA KAIP RIZIKOS VEIKSNYS PACIENTAMS, KURIEMS ATLIEKAMOS ŠIRDIES OPERACIJOS SU DIRBTINE KRAUJO APYTAKA

Santrauka

Įvadas. Hiperoksija ilgą laiką buvo suvokiama kaip neišvengiamas reiškinys dirbtinės kraujo apytakos metu. Pastaraisiais dešimtmečiais atliktų tyrimų duomenimis, per didelė deguonies koncentracija audiniuose gali turėti nepageidaujamų poveikių paciento homeostazei.

Tyrimo tikslas. Nustatyti veiksnius, nulemiančius suprafiziologines parcialinio deguonies reikšmes širdies operacijų, atliekamų su dirbtine kraujo apytaka, metu ir įvertinti hiperoksijos poveikį klinikinėms išeitims.

Darbo objektas ir metodai. Į tyrimą įtraukti ir retrospektyviai išanalizuoti 246 pacientų, kuriems atliekamos širdies operacijos su dirbtine kraujo apytaka, duomenys. Atsižvelgiant į didžiausią arterinį parcialinio deguonies slėgį, pacientai suskirstyti į nedidelės (PaO_2 100–199 mmHg), vidutinės (PaO_2 200–299 mmHg) ir ryškios (PaO_2 > 300 mmHg) hiperoksijos grupes.

Rezultatai. Hiperoksijos rizikos veiksniai buvo žemas kūno masės indeksas (p = 0,001) ir moteriška lytis (p = 0,005). Didelis deguonies parcialinis slėgis statistiškai reikšmingai susijęs su infekcinių komplikacijų dažniu (p – 0,044), ilgesne gulėjimo ligoninėje trukme (p – 0,044) bei prailginta mechaninės plaučių ventiliacijos trukme (p < 0,001).

Išvados. Didelė hiperoksija susijusi su dažnesnėmis pooperacinėmis infekcinėmis komplikacijomis, ilgesne mechaninės plaučių ventiliacijos ir gulėjimo ligoninėje trukme.

Raktažodžiai: hiperoksija, širdies chirurgija, dirbtinė kraujo apytaka, reaktyvus deguonis, infekcinės komplikacijos