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EFFECTS OF HYPEROXEMIC CARDIOPULMONARY BYPASS ON OXIDATIVE STRESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Original Article

KRONİK OBSTRÜKTİF AKCİĞER HASTALIĞINDA HİPEROKSEMİK KARDİYOPULMONER BAYPAS'IN OKSİDATİF STRES ÜZERİNDEKİ ETKİLERİ

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ABSTRACT

High arterial oxygen levels may aggravate oxidative stress associated with CPB (cardiopulmonary bypass). Most cardiac surgery patients have COPD (chronic obstructive pulmonary disease), complicating the relationship of hyperoxia and oxidative stress. In this study the effects of different oxygenation strategies on oxidative balance during CPB in patients with COPD was assessed. Forty patients with COPD underwent elective coronary bypass surgery, using CPB. In 20 patients, high arterial oxygen levels were maintained (PaO_2 between 300-400 mm Hg) during CPB, whereas 20 patients underwent normoxic (PaO_2 between 100-200 mm Hg) bypass. Oxidative balance was assessed by measurement of thiobarbituric acid reactive substance, paraoxanase and uric acid levels in blood. Thiobarbituric acid reactive substance, paraoxanase and uric acid levels obtained throughout the study period were similar among the two groups. In both groups, thiobarbituric acid reactive substance, paraoxanase and uric acid levels remained unchanged after CPB, compared to baseline values. High arterial oxygen levels during CPB do not cause alterations in oxidative balance in the blood of COPD patients.

Key words: *Chronic obstructive pulmonary disease; oxidative stress;cardiac surgery; TBARS; cardiopulmonary bypass.*

ÖZET

Yüksek arteriyel oksijen seviyeleri KPB (kardiyopulmoner baypas)' nin yol açtığı oksidatif stresi şiddetlendirebilir. Kalp cerrahisi planlanan hastaların çoğunda KOAH (kronik obstrüktif akciğer hastalığı) nedeniyle, hiperoksinin yol açacağı oksidatif stres bir sorun olarak karşımıza çıkmaktadır. Bu çalışmada farklı oksijenasyon stratejilerinin KOAH'lı hastalardaki oksidatif denge üzerine etkileri değerlendirilmiştir. Kırk adet KPB ile elektif koroner arter baypas cerrahisi planlanan KOAH tanılı hasta çalışmaya alındı. 20 hastada KPB sırasında yüksek arteriyel oksijen düzeyleri sürdürülürken, (PaO2: 300-400 mmHg), 20 hastada normoksik KPB (PaO2: 100-200 mm Hg) uygulaması yapıldı. Oksidatif denge için kan TBAR (Thiobarbituric acid reactive substance), paraoksanaz ve ürik asid düzeyleri çalışıldı. TBAR, paraoksanaz ve üric asit düzeyleri çalışma boyunca gruplar arasında benzer bulundu. Her iki grupta da bazal değerler ile karşılaştırıldığında KPB sonrası TBAR, paraoksanaz ve ürik asit düzeylerinin değişmediği gözlendi. Sonuç olarak KPB sırasında yüksek oksijen düzeyi idamesinin KOAH' lı hastalarda kandaki oksidatif dengeyi değiştirmediği gözlendi.

Anahtar Kelimeler: *Kronik obstrüktif akciğer hastalığı; oksidatif stress; kalp cerrahisi;TBARS; kardiyopulmoner.*

INTRODUCTION

Cardiac surgery using cardiopulmonary bypass (CPB) is often associated with disruptions in oxidative balance. The production of toxic reactive oxygen species and the resulting increase in lipid peroxidation products is dependent on the oxygen levels attained (1). However, there is a widespread tendency to maintain high arterial oxygen concentrations during CPB, based mainly on safety concerns. As more evidence on the adverse consequences of conducting CPB under hyperoxic conditions becomes evident, use of more conservative oxygenation strategies is being advocated. (2,3,4). Recent studies indicate the feasibility and safety of such a CPB management (5).

Chronic obstructive pulmonary disease (COPD) represents an additional challenge in cardiac surgery. Pathophysiologic changes in this disease have an intricate relationship with oxidative and antioxidant processes (6). The introduction of this entity into the equation, turns the problem into a four faceted one: CPB, oxygenation levels, oxidative balance and pulmonary disease.

In this study, we compared the effects of high versus low partial arterial oxygen concentrations on the oxidative balance during CPB, in this particular subset of patients having COPD, by means of plasma thiobarbituric acid reactive substance (TBARS), uric acid and paraoxanase (PON) levels.

MATERIALS-METHODS

After approval of Ethics Committee, 40 patients with COPD undergoing elective coronary artery bypass operations were enrolled in the study and randomly allocated to either group CH (n=20), with high arterial oxygen concentrations during CPB, or group CL (n=20), with low oxygen concentrations. Exclusion criteria included emergency operations, current nicotine use, age older than 65 years, ejection fraction below 40% and diabetes mellitus. The smokers who were enrolled had been asked to quit smoking at least one month before the surgery. In all patients the presence of COPD was confirmed

according to the American Thoracic Society/European Respiratory Society guidelines (7)**.** A written informed consent was obtained from each patient.

Anesthesia protocol and surgical techniques were identical for all patients. Following premedication with 0.04 mg/kg intravenous midazolam, anesthesia was induced with intravenous fentanyl 3-5 micg/kg, propofol 2 mg/kg and rocuronium 1 mg/kg, 50% oxygen in air. The maintenance was achieved with intravenous propofol (50-150 micg/kg/min adjusted according to bispectral index) and fentanyl (total dose 25 micg/kg) infusions and rocuronium boluses as needed. The radial artery was cannulated and blood was drawn for gas analysis before anesthesia induction. A central venous catheter was placed through the right internal jugular vein. Following endotracheal intubation, patients were ventilated with a fraction of inspired oxygen (FiO_2) of 0.4.

Following systemic heparinization (400 IU/kg), the aorta and right atrium were cannulated. A roller pump (Jostra, Lund, Sweden) and a membrane oxygenator (Dideco, Mirandola, Italy) were used for extracorporeal circulation. Priming of the extracorporeal circuit consisted of lactated Ringer's solution to achieve a hematocrit level of about 20-25%, 5000 IU heparin and 0.5 g/kg mannitol. A moderate hypothermia of 30 ^{o}C and flow rates of 1.8-2.4 L/m^2/min were used. Ventilation was stopped and the endotracheal tube was kept open to the atmospheric pressure during CPB. Myocardial protection was achieved by initial use of antegrade isothermic hyperkalemic blood cardioplegia followed by repeated antegrade infusions every 20 minutes. Before discontinuation of CPB, the lungs were manually inflated until visible atelectases disappear. Ventilation was started with a FiO_2 of 0.5, reduced to 0.4 fifteen minutes later. When necessary, packed red blood cell concentrates were transfused to achieve a hemoglobin level of about 9-10 g/dL following CPB. The left internal thoracic artery was used and the left pleura routinely opened in all the patients. Patients were transferred to the ICU under deep sedation with propofol infusion, on volume-controlled mechanical ventilation. Patient controlled analgesia by intravenous tramadol was routinely used for post-operative analgesia. A mediastinal and a left pleural drain were placed in all patients. None of the patients received inotropic agents. Nitroglycerin was infused at a range of 0.5-1.5 micg/kg/min for 24 hours postoperatively.

After the initiation of CPB, oxygen flow adjustments were done in order to achieve an arterial oxygen concentration ≤ 200 mm Hg (range 100-200 mmHg) in patients assigned to Group CL (n=20) , and an arterial oxygen concentration ≥300 mmHg (range 300-400 mm Hg) in patients in group CH (n=20).

Arterial blood samples were drawn to analyze the thiobarbituric acid reactive substance (TBARS), uric acid and paraoxanase (PON) levels after anesthesia induction, at the end of the CPB, 2 hours after the completion of CPB and 24 hours postoperatively. Plasma concentrations of lipid peroxides were estimated from measurement of TBARS using 1,1,3,3-tetra-ethoxypropane as a standard. Malondialdehyde (MDA), the end product of lipid peroxidation, was estimated from the spectrophotometric measurement of TBARS modified according to Yoshioka et al. (8) using 1,1,3,3-tetra-ethoxypropane (Sigma) as a standard. The amount of TBARS was expressed as nmol/ml. Blood samples were centrifuged at 3000 rpm x 10 minutes, before the PON analysis. Paraoxanase (U/L) activity was measured by an automated biochemistry analyzer

(Opera-Technicon, Bayer Inst.) using colorimetric method. Blood samples for uric acid (mg/dL) measurement were centrifuged at 3000 rpm x 10 minutes. Serum was analysed for uric acid using Opera Technicon Bayer autoanalyzer by Diasis diagnostic commercial kits. All the samples were stored at - 20 °C until analysis.

TBARS, PON and uric acid values are reported as median, 90% interquartile range, all the other variables are reported as mean (± SD). Chi-square test was used to compare non-parametric values. Comparisons between the groups were done by Mann-Whitney U-test, in-group comparisons were done with non-parametric Friedman test and $p<0.05$ was considered significant. Unistat version 5.0 for Windows (Unistat Ltd, London, UK) was used for the statistical analysis.

RESULTS

Demographic and operative data of the groups were statistically identical (**Table 1**).

Table 1. *Demographic and clinical data of the patients.*

	Group CH n= 20	Group CL n=20
Gender [M/F]	20 / 0	19 / 1
Age [year]	56 ± 9	58 ± 8
Weight [kg]	76 ± 9	75 ± 10
ACC time [min]	51 ± 17	48 ± 15
CPB time [min]	80 ± 19	83 ± 16
Graft number	3 ± 0.7	3 ± 0.6
MVD [h]	5.6 ± 0.67	6 ± 0.7
ICU stay [h]	32 ± 9	35 ± 8
Hospitalization [days]	6.8 ± 0.8	6.9 ± 0.7
Mortality	0	0

Abbreviations: CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; MVD, mechanical ventilation duration; ICU, intensive care unit; CH, high oxygen group; CL, low oxygen group.

None of the patients required reintubation in the postoperative period. Perioperative arterial lactate levels were similar among the groups (**Table 2**).

Table 2. *Arterial lactate levels of the patients (mmol/L).*

	Group CH n= 20	Group CL n=20
Baseline	1.2 ± 0.3	1.4 ± 0.4
At the end of CPB	2.3 ± 0.4	2.4 ± 0.3
2 hrs after CPB	2.1 ± 0.4	2.2 ± 0.5
24 hrs after CPB	1.6 ± 0.3	1.7 ± 0.3

Abbreviations: CPB, cardiopulmonary bypass; CH, high oxygen group; CL, low oxygen group.

The PaO_2/FiO_2 ratios of the groups were similar among the groups throughout the study period (**Table 3**).

Table 3. *PaO2/FiO2 ratios of the groups during the study period.*

	Group CH n= 20	Group CL n=20
Baseline	350 ± 65	345 ± 47
At the end of CPB	155 ± 44 *	179 ± 56 *
2 hrs after CPB	187 ± 49 *	204 ± 57 *
24 hrs after CPB	240 ± 50 *	267 ± 60 *

$p < 0.05$ compared to baseline values.

Abbreviations: CPB, cardiopulmonary bypass; CH, high oxygen group; CL, low oxygen group.

Median baseline TBARS values of group CH and CL were 1.4 and 2 nmol/ml respectively. These values were 2.6 and 3 nmol/ml immediately following CPB; 2.9 and 3 nmol/ml two hours after CPB; and 3.1 and 2.5 nmol/ml 24 hours after CPB,

respectively. Statistically, TBARS levels obtained throughout the study period were similar among the groups. In both groups, TBARS levels during and after CPB remained unchanged compared to baseline values. (**Figure 1**)

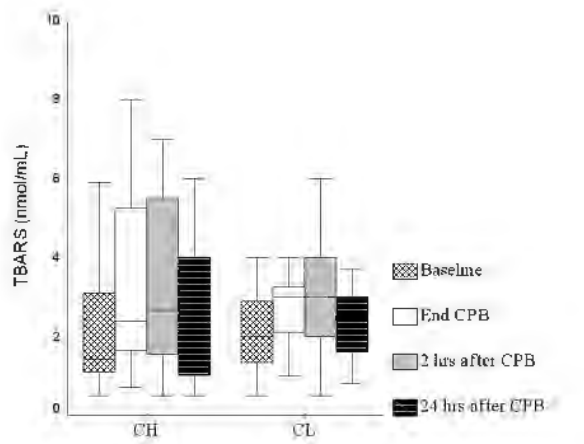

Figure 1. *Blood TBARS levels of the groups. Abbreviations: TBARS, thiobarbituric acid reactive substance; CPB, cardiopulmonary bypass; CH, high oxygen group; CL, low oxygen group. TBARS levels are expressed as median (inner line), 25/75 percentiles (box), and 10/90 percentiles (whiskers).*

PON and uric acid levels were also identical among the groups during the study period and did not change from the baseline values. Median baseline PON values of groups CH and CL were 28 and 22 U/L, respectively. Median PON values were 20 and 22 U/L at the termination of CPB; 21 and 22 U/L 2 hours after CPB; 35 and 26 U/L 24 hours after CPB, respectively for groups CH and CL (**Figure 2**).

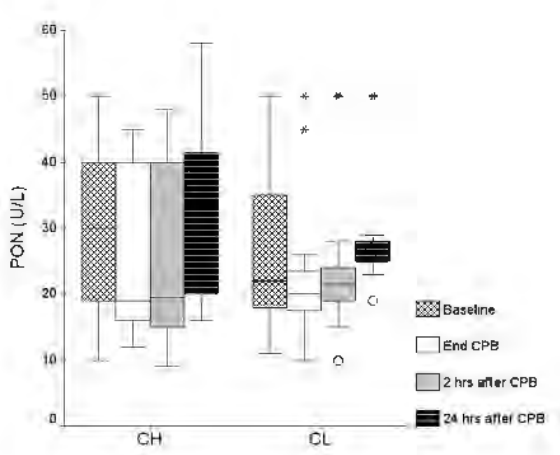

Figure 2. *Paraoxanase (PON) levels during the study period. Abbreviations: PON, paraoxanase; CPB, cardiopulmonary bypass; CH, high oxygen group; CL, low oxygen group. PON levels are expressed as median (inner line), 25/75 percentiles (box), 10/90 percentiles (whiskers) and the values out of these ranges (*), (o).*

Mean baseline uric acid values of groups CH and CL were 6.8±1.8 and 5.6±1 mg/dL; values at the termination of CPB were 6±1.4 and 6±1 mg/dL; 5.8±1.2 and 5.5±1.1 mg/dL 2 hours after CPB; 5.5±1.5 and 5±1 mg/dL 24 hours after CPB, respectively (**Figure 3**).

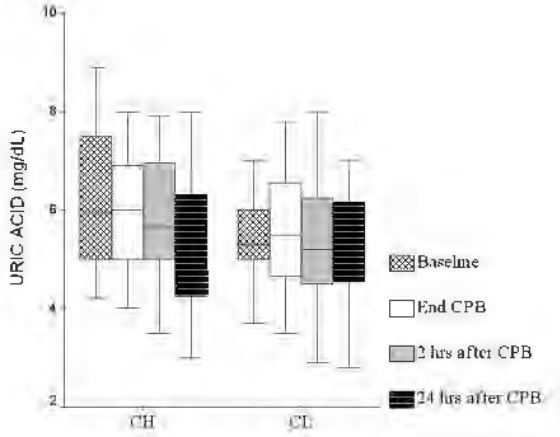

Figure 3. *Uric acid levels during the study period. Abbreviations: CPB, cardiopulmonary bypass; CH, high oxygen group; CL, low oxygen group. Uric acid levels are expressed as median (inner line), 25/75 percentiles (box), 10/90 percentiles (whiskers)*

Total operative fluid balance (725 ± 400 mL in CH group; 805 ± 350 mL in CL group) and red blood cell concentrate transfusion (1.6 ± 0.7 units in CH group; 1.2 ± 0.7 units in CL group) were not different among the groups.

DISCUSSION

In the present study the effects of high and low PaO_2 levels during CPB on oxidative stress in blood of patients with COPD were compared. Changing oxygen levels did not cause any significant difference between the two groups in terms of lipid peroxidation and antioxidant activity as assessed by plasma uric acid and paraoxanase levels. In both groups, no significant alteration in antioxidant activity and lipid peroxidation markers following CPB was observed.

CPB is a major cause of oxidative stress (9). To which extent hyperoxemic conditions usually present during CPB contributes to this outcome has been debated (10). However, increasing evidence pointing out hyperoxemia as an independent adverse factor in oxidative balance is becoming available.

Cellular metabolism is disturbed by high oxygen levels during CPB (2). The deleterious potential of oxygen becomes more prominent in the ischemia-reperfusion context. The harmful effect of high oxygen tensions during reperfusion of the ischemic myocardium is well studied. A series of animal studies investigating various aspects of the relationship between hyperoxic reperfusion and oxidative damage to the myocardium provides evidence for avoiding hyperoxia especially during the immediate reperfusion period (3,4). Accordingly, in the clinical setting, hyperoxemic CPB (PaO_2 >400 mm. Hg) results in marked oxidative myocardial damage when compared to normoxemic CPB (PaO_2 <140 mm. Hg) (1). Abdel-Rahman et al. reported significantly reduced levels of lipid peroxidation products in the systemic blood by further lowering the arterial oxygen tension (PaO_2 = 50-70 mm Hg) temporarily in the early myocardial reperfusion phase (11). In a recent study, they showed on a porcine model that hypoxemic CPB during early myocardial reperfusion results in reduced oxidative stress markers in the coronary sinus blood in parallel with improved cardiac function (12). Even if the direction of the causal relationship between oxidative stress and ischemia-reperfusion injury is still unclear, these findings demonstrate the benefits of a tight oxygenation management during CPB. An incentive to avoid high oxygen tensions throughout the CPB instead of focusing only on myocardial reperfusion period is encouraged by animal studies showing systemic effects of hyperoxemic CPB such as microvascular disfunction and well known systemic nature of oxidative stress caused by CPB in humans (13,14).

COPD is closely associated with oxidative stress. An oxidant-antioxidant imbalance in favour of oxidants can be detected both locally (in the exhaled air or bronchoalveolar lavage fluid) and systemically (in blood and urine) in patients with COPD. This imbalance reflects both an increase in oxidative activity and a decrease in antioxidant capacity (15). Again, cause and effect relationship connecting COPD and oxidative stress is possibly bidirectional. External factors such as smoking which frequently accompanies COPD have a major influence on the oxidative burden, but intrinsic factors such as inflammatory processes contribute to the oxidant-antioxidant imbalance (6,16). Regulatory and adaptative mechanisms, some not well elucidated, complicate this general scheme. Increased levels of the

antioxidant enzymes, superoxide dismutase and catalase in the circulating red blood cells of the smokers have been reported (17). Chronic smoking results in elevated levels of the antioxidant glutathione in bronchial epithelial cells (18). These changes are possibly due to an up-regulation of the enzymatic antioxidant activity as an adaptive response triggered by the increased oxidative burden and suggest an enhanced in vivo efficiency of antioxidants even in presence of decreased antioxidant activity demonstrated in vitro (19). Recent evidence shows that COPD patients may react better to increased oxygen exposure in terms of oxidative stress. In a study by Van Helvoort et al. supplemental oxygen administration at rest did not affect markers for systemic inflammation or oxidative stress in normoxemic patients with moderate to very severe COPD. In the same study supplemental oxygen prevented exercise-induced oxidative stress expected in COPD patients (20). In contrast, healthy subjects have evidence of increased oxidative stress in both their airways and plasma, as measured by lipid peroxidation, and superoxide dismutase activity after exposure to hyperoxia (21,22). Van Helvoort's results, interpreted in this context, point to the possibility that the increase of markers of inflammation and oxidative stress in COPD patients after supplemental oxygen is not expressed systemically. Although the PaO_2 limit defining high and low oxygen groups in our study far exceeds the PaO_2 levels considered in van Helvoort's, the idea that COPD patients may have different systemic responses to changing arterial oxygen levels makes sense with regard to the lack of the systemic changes in our study.

Most of the literature on the subject deals with effects of changing levels of inspired oxygen. In our study, where the systemic oxygen supply is directly controlled by the extracorporeal circulation, the lungs inflicted by COPD were no longer the first line of contact with oxygen. In a similar fashion, Frass et al. observed the inflammatory response to different arterial oxygen tensions attained during CPB, in cell samples from bronchoalveolar lavage fluid (BALF) and systemic blood separately (23). They found a correlation between oxygen levels and intracellular thiol depletion both in intraalveolar compartment and systemically, but noticed that the inflammatory response in BALF cells is much limited in comparison to systemic blood cells. They remark that the correlation of intracellular thiol depletion with the intraoperative PaO_2 is even stronger with increasing severity of COPD. This study differs from ours in that it focuses on intracellular oxidative balance. As the authors state in their article, oxidative stress may be expressed differently in various body compartments, which may account for the different results obtained in our study.

The definition of "high" and "low" PaO_2 levels is rather arbitrary in CPB practice, mainly due to the traditional tendency to keep an ample safety margin in oxygenation. Frass et al. chose the median of the PaO_2 values recorded which was 196 mm. Hg. In the light of significant oxidative stress changes they observed below and above this level, we designed our study in order to achieve a PaO_2 level of 300 mm. Hg in "high" oxygen patients, and not to exceed 200 mm. Hg in "low" oxygen patients. It is still possible that this cut-off value of PaO_2 = 200 mm. Hg is not "low" enough to make a difference, especially when relatively shorter CPB durations are considered. In Abdel-Rahman's study, PaO_2 levels were lowered to 50-70 mmHg during the myocardial reperfusion period. This study

was focused on the reperfusion associated myocardial oxidative damage, and the safety of further extending this period of clear hypoxia is questionable (11).

The limitations to our study include the sensitivity in interpreting the antioxidant state in the patients. The assessment of MDA by the TBARS assay is a non-specific technique and may not be as reliable as newer methods. Measurement of PON and uric acid levels provides only a restricted picture of the antioxidant activity. Uric acid concentrations depend largely on various factors including age, diet, heavy exercise, renal functions and metabolic state (24).

Although uric acid represents up to two thirds of the total serum antioxidant capacity tested in vitro, its physiologic role in oxidative balance is a matter of controversy (25).

CONCLUSION

In conclusion, in COPD patients undergoing coronary bypass surgery, hyperoxemic CPB did not result in any change in systemic lipid peroxidation markers and antioxidant activity, when compared to CPB under lower PaO2 levels.

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