The Effect of Hyperoxia During Cardiopulmonary Bypass on Blood Cell Rheology and Postoperative Morbidity Associated with Cardiac Surgery

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Abstract

In a prospective randomized open study, 48 patients underwent coronary bypass operation using cardiopulmonary bypass (CPB), with the same type of membrane oxygenator. Twenty-four patients were oxygenated during CPB by high PO_2 level between 190 and 300 mmHg (H-PO_2) and in the remaining patients the PO_2 was maintained low between 75 and 112 mmHg (L-PO_2.) The groups were comparable regarding age, sex, perfusion time, aortic occlusion time and preoperative blood cell rheological status.

The effect of possible oxygen toxicity was assessed by monitoring blood cell rheology and analyzing the postoperative complications. Blood cell rheology was studied using standard microfiltration methods and samples were taken regularly during CPB.

There was a significant reduction in blood cell rheology in both groups during CPB in a time-dependent manner. The L-PO_2 group had significantly better rheology than the H-PO_2 group, which was first noted at 60 min for red cells ($p<0.01$).

Following operation, the time spent on the respirator was significantly lower in the L-PO_2 compared to the H-PO_2 (5.3 h ± 1.8 h vs. 7.2 h ± 2.5 h, $p<0.01$).

There was significantly more bleeding in the H-PO_2 group ($p<0.05$) and the use of blood products was significantly raised ($p<0.01$). The total number of complications requiring treatment (arrhythmias, myocardial infarction, cardiovascular accidents and respiratory insufficiency) showed a significantly higher frequency in the H-PO_2 (16/24 vs. 6/24; $p<0.01$) compared to the L-PO_2. There were three cases of mild renal failure in the H-PO_2 group which was managed with conservative treatment. A significantly higher liver enzymes ($p<0.01$) and creatinine levels ($p<0.05$) were seen in the H-PO_2 group.

This study suggests that the use of high PO_2 levels during CPB might lead to increased morbidity postoperatively and should be avoided.

Introduction

During cardiopulmonary bypass (CPB), blood oxygenation is of great importance for maintaining oxygen supply and tissue preservation. Arterialized blood, with oxygen partial pressures in excess of the normal range has been implicated in microaeroemboli[1] and organ ischemia[2]. Cardiac surgeons continue to be surprised by the unexpected appearance of air bubbles in the course of cardiac surgery. The true incidence of morbidity and mortality related to air embolism and high oxygen partial pressures is difficult to determine because of a wide spectrum of clinical manifestations. Arrhythmia and or reduced cardiac output are the manifestations of coronary air embolism[3]. A fundamental concept concerning gas phase separation from liquid is Henry's law, whereby at equilibrium the dissolved gas concentration is directly proportional to the partial pressure of the gas in the liquid[4]. The basic pathology associated with gas embolism is that of tissue ischemia or infarction

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due to the occlusion of nutrient blood vessels. The production of gaseous microemboli associated with bubble oxygenators during extracorporeal circulation (ECC) has prompted considerable attention regarding product design and arterial filtration needs.

The aim of this study was to investigate whether high oxygen partial pressure was associated with a relatively higher morbidity/mortality and to see if red cell filtrability was affected by the high PO_2 during CPB.

Patients and Methods

Forty-eight patients participated in this prospective randomized study. All patients underwent elective coronary artery bypass grafting (CABG). Patients were randomized into two groups of 24 patients each: Low (physiological) oxygen tension (L-PO_2) and high (non-physiological) oxygen tension (H-PO_2) with 75-112 mmHg and 190-300 mmHg respectively (Fig. 1). The general patient data is presented in Table 1. The same type of membrane oxygenator was used for all patients[a]. An arterial filter was not used in this study. The same standard technique for CPB was employed for all patients. The extracorporeal circuit (ECC) was primed with 7500IE heparin in two liters of Ringerdex[b]. After heparinization (3mg/kg), CPB was started. The activated coagulation time[c] was maintained around 450 seconds during CPB. The patient was maintained at 28-30°C for the cardiac procedure. To achieve cardioplegia, a modified St. Thomas solution at 4°C was used. Following this the patient was rewarmed to 34°C (rectal) and taken off bypass following which heparin was neutralized by protamine. The blood-gas flow ratio was 1:1. No drugs other than heparin were added to the prime or perfusion fluid. The hematocrit varied from 18 to 30 percent and was comparable for both groups. No patient received blood during the perfusion.

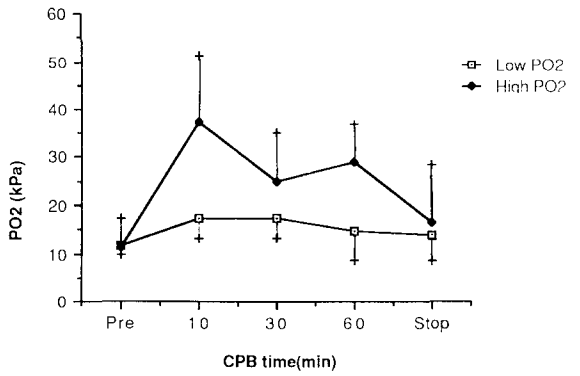
Blood Sampling

Total hemoglobin (HGB), red cell filtration rate (RFR), white cell count (WCC), platelet count (PC), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and creatinine (Krea) were done pre- and postoperatively. In addition, samples for RFR were done during the operation.

RFR Measurement Technique

Blood samples for the microfiltration studies were taken preoperatively and during the perfusion (10, 30 and 60 min. and at the end of CPB). The sampled blood (10 ml in EDTA test tubes) was immediately centrifuged at 4000 rpm for five minutes and the supernatant fluid, buffy coat and upper 5 mm of the red cell were discarded. The red cells were immediately washed twice in isotonic saline at room temperature (22°C) and resuspended in saline in an amount giving a 20 percent red cell suspension. Without further delay the red cell suspension (0.5 ml) was allowed to pass by gravity through a nucleopore polycarbonate filter with a 5 um pore size. The height of the suspension above the filter was allowed to fall from 11.5 to 8.5 cm and the time required for this fall was noted. Each filter was initially tested with saline solution and only filters with a mean flow time of 2.0 ± 0.2 sec were used. The red cell filtration rate (RFR) was calculated by the standard formula[5].

Figure 1



Changes in arterial PO_2 during cardiopulmonary bypass (CPB).

Table 1: Patient Data (SD±)

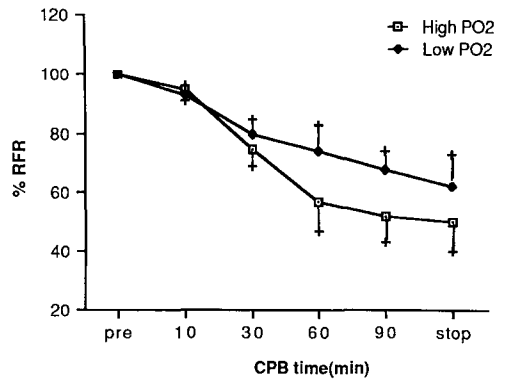
Patients	L-PO_2	H-PO_2
Age (years)	61±7	62±4
Sex		
Male	21	19
Female	3	5
E. Fraction	0.6±0.2	0.6±0.1

Postoperative Morbidity and Complications

The frequency of postoperative morbidity (postoperative bleeding, respirator usage, blood transfusion, rhythm disturbance, myocardial infarction, cerebrovascular accidents and infection) was also studied and compared between the two different groups (L-PO_2 and H-PO_2). Postoperative bleeding was defined as all fluid from mediastinal drains from the end of the operation for 24 hours. Time on the respirator was defined as the time from the end of the operation until the patient was permanently extubated. Blood transfusion was defined as the number of units of

a Maxima, Medtronic Cardiopulmonary Division, Anaheim, CA
b Pharmacia, Uppsala, Sweden
c International Technidyne Corp., Edison, NJ 08820

Figure 2



The red cell filtration rates (RFR) in both groups were significantly reduced during CPB but to significantly greater extent in the H-PO_2 group. The preoperative value (pre) was taken as 100%.

Table 2: Perfusion Data

	L-PO_2	H-PO_2
Oxygenator	MAXIMA	MAXIMA
ECC Time (min)	75.2±20	73.8±19
Aorta Occlusion (min)	42.6±12	43.4±12
CPB Flow (L/min)	4.2±0.4	4.2±0.5
Gas Flow (L/min)	4.4±0.5	4.5±0.4

blood (400 ml/U) or plasma (400ml/U) given from the end of the operation up to the end of the first week. Arrhythmias that needed treatment after the first 24 hours and up to 10 days postoperatively were included as a complication. If the same dysrhythmia occurred several times in the same patient it was then considered as one complication. The number of complications such as myocardial infarctions, cerebrovascular accidents and infections was also noted and compared between the two groups.

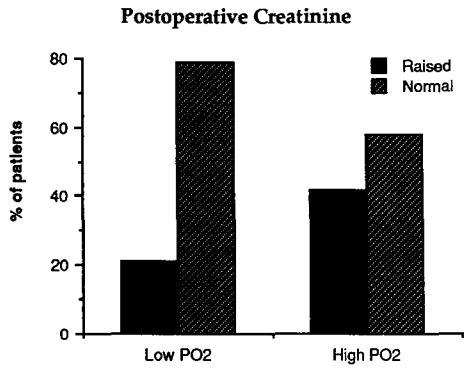
Statistical Methods

All means were expressed with one standard deviation (±SD). Inter-group comparisons were done using the appropriate students' t-test or by the modified t-test described by Swinscow[6]. Comparisons of proportions were carried out by the Chi-square test and percentages were compared by the method described by Swinscow[6].

Results

There were no significant differences in the mean values for perfusion time, duration of aortic occlusion, blood flow rates and other parameters during CPB for all groups (See Table 2).

Figure 3



The frequency of pathologically increased creatinine values was higher in the H-PO_2 group.

Table 3: Postoperative Morbidity (SD±)

	L-PO_2	H-PO_2	p
Respirator Time (hrs)	5.3±1.8	7.2±2	<0.01
24 hrs Bleeding (ml)	612±190	944±250	<0.05
Blood Transfusion			
Whole (u)	0.42±0.1	0.25±0.1	ns
Plasma (ml)	334±74	650±96	<0.05
Erythrocytes (u)	0.37±0.1	1.12±0.3	<0.05

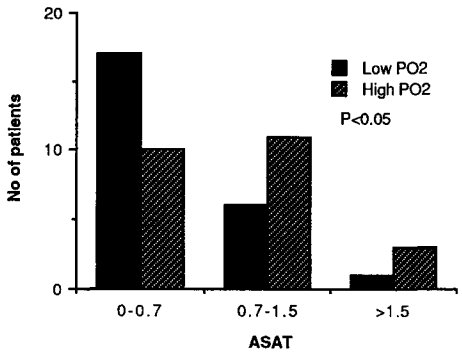
Red Cell Filtrability (See Figure 2)

The mean preoperative RFR values for the L-PO_2 and H-PO_2 groups were 45 and 43 ul/sec respectively. The mean RFR in both L-PO_2 and H-PO_2 groups showed reductions during CPB but was greater in the H-PO_2 group. The respective mean preoperative RFR values in both groups were reduced at the end of CPB to 60 percent and 50 percent of the outset values ($p<0.01$). In both groups the significance of change was first noted at 30 minutes. Following this, a significant difference when comparing L-PO_2 and H-PO_2 reductions was first seen after 60 minutes ($p<0.01$). The differences in RFR values remained statistically significant throughout the remaining CPB ($p<0.01$).

Renal Function (See Figure 3)

The mean serum creatinine (S-krea) increased postoperatively but to a significantly lesser extent in the L-PO_2 group ($p<0.05$). In the H-PO_2 group 42 percent of the patients had an increased serum creatinine postoperatively compared to 21 percent of the patients in the L-PO_2 group ($p<0.05$).

Figure 4



The distribution of pathologically high values of aspartate aminotransferase (ASAT) was significantly more intense in the H-PO_2 group. The frequency of normal values was however comparable.

Liver Function (See Figure 4)

The distribution of maximum S-ASAT postoperatively showed that 17 patients (71 percent) in the L-PO_2 group had normal values (0-0.7 ukat) compared to 10 patients (42 percent) in the H-PO_2 group.

In the S-ASAT range of 0.71-1.5 ukat, the L-PO_2 group had 6 patients (25 percent), compared to 11 (46 percent) in the H-PO_2 group. At S-ASAT of over 1.6 ukat, one patient (4 percent) in the L-PO_2 group was registered compared to 4 patients (12 percent) in the H-PO_2 group. The maximum S-ALAT level postoperatively showed that the frequency of normal values was comparable in both groups. However, the distribution of pathological S-ALAT values was qualitatively worse in the H-PO_2 group ($p<0.01$).

Postoperative Complications and Morbidity

The amount of postoperative bleeding, respirator usage, blood transfusion and the number of cardiac complications (arrhythmias and infarction) was found to be less in the L-PO_2 group than in the H-PO_2 group (See Tables 3 and 4).

The mean values of postoperative loss of blood via the mediastinal drains were lowest in the L-PO2 group ($p<0.05$). The mean number of plasma and erythrocyte units transfused in the two groups showed the same significant pattern ($p<0.05$) (See Table 3). The mean respiratory time showed the same pattern of significance ($p<0.01$); the H-PO2 group showed a 35 percent increase.

The frequency of cardiac complications was lower, 6/24 (25 percent) in the L-PO_2 group compared to the 13/24 (54 percent) in the H-PO_2 group. This was significantly different ($p<0.01$) (See Table 4).

Table 4: Cardiac Complications

	L-PO_2	H-PO_2	p
Arrhythmias			
Atrial Fib/Fla	6	10	
Ventr Fib	0	1	
Infarction	0	2	<0.01

Table 5: Extra-Cardiac Complications

	L-PO_2	H-PO_2
Cerebral	0	1
Respiratory	0	2
Renal	1	2

Regarding extra-cardiac complications, there was one cerebrovascular accident, two cases of respiratory and two cases of renal failure in the H-PO_2 group compared to one renal failure in the L-PO_2 group (See Table 5). There was no mortality in either group and all patients were discharged from the hospital.

Discussion

This study reveals that hyperoxia itself may be detrimental to red cell rheology during CPB and that the resulting increased blood trauma during the operation is probably damaging to organ function in the sensitive and demanding postoperative period that follows shortly. Hyperoxia during CPB increases blood trauma reflected by the poor rheological performance of RBCs in the H-PO_2 group. Further evidence is the increased use of blood products postoperatively to maintain adequate circulating volume and hemoglobin levels in the absence of significant differences in postoperative blood loss.

The first question that arises in one's mind is how does hyperoxia influence red cell rheology as well as lead to an apparent increase in organ dysfunction. For this to be answered, the effects of high oxygen tension during CPB have to be considered. It is known that gaseous microemboli (GMEs) are produced in various parts of the extracorporeal equipment[2,7-11] especially with the use of bubble oxygenators. The membrane oxygenator is known to produce fewer GMEs, and for this reason was used in the study. There was no difference in the mean CPB times of the two groups which suggests that rheological and morbidity developments might be due to hyperoxia.

Earlier studies showed that patients in whom the mean PaO_2 was below 150 mmHg during the period of CPB received a significantly lower number of GME than a similar group of patients in whom the mean PaO_2 was above 150 mmHg.[2] This might establish the close, direct relationship between PaO_2 and GME detected and confirm that the

GME load to the patient can be dramatically reduced by maintaining the PaO_2 closer to physiological levels as implied to this study.

Previous studies have shown that the microcirculation is disturbed and significantly reduced both in the myocardium and skin following CPB for several days and that this phenomenon was related to reduced blood rheology among other possible explanations[12]. The GME that might have been produced especially with hyperoxia would thus tend to disturb the microcirculation of vital organs leading to areas of ischemia and reperfusion. Reperfusion of the ischemic myocardium can reduce the extent of myocardial necrosis after acute coronary artery occlusion, but it is known that reperfusion can also cause further damage to jeopardized cells[13]. It has been suggested that the generation of oxygen derived free radicals at the time of reoxygenation may be responsible for this reperfusion injury and may be of importance in other complications of ischemia. Arrhythmias occur commonly during reperfusion after coronary occlusion. Furthermore, Hearse and associates demonstrated that a variety of agents that inhibit the production of or scavenge oxygen radicals significantly reduced arrhythmia[14,15]. Thus the reason for increased frequency of arrhythmias in the H-PO_2 group might be associated with oxygen derived free radicals.

Another mechanism through which hyperoxia acts is the direct production of oxygen free radicals which lead to the production of extremely toxic hydroxl radical. The radicals are cytotoxic and are involved in all forms of inflammation and lead to the lipid peroxidation of cell membranes and disturbances of mitochondrial functions.

The generation of free radicals is potentiated on the reperfusion of ischemic tissue. This has been seen during CPB and upon reperfusion of the myocardium that has previously had its blood supply stopped by acute coronary occlusion[13-15]. The hyperoxia group would thus appear to be more sensitive to reperfusion damage due to more oxygen delivered to the ischemic myocardium following aortic declamping or during the reperfusion of the body during rewarming in order to remove CO_2 adequately.

The effect of hypothermia would increase vasospasm and areas of ischemia in the microcirculation, which then have to be reperfused. Hyperoxic blood is probably not the ideal state of the blood to be in for this purpose. It is interesting to note that the use of free radical scavengers reduces the organ dysfunction following ischemic perfusion experimentally and this has been clinically tested during heart surgery with encouraging preliminary results. It is well known that myocardium, brain, liver, lung and kidney dysfunction occur as a result of using CPB as seen in this study. This organ dysfunction has been related to the toxic changes in blood as a result of using the extracorporeal system.

It is also known that free radicals can damage all these organs[16-19]. The results from this study suggest that hyperoxia appears to increase damage to red cell rheology and postoperative organ performance. The damage to organs and the resulting complications could be due to the combined effect of disturbed microcirculation caused by poor red cell rheology and GME. Although these findings are from a few patients, they should however point out the potential of oxygen toxicity when hyperoxia is used during CPB.

References

1. Kuntz, R.A. and Maurer, W.G: An Examination of Cavitation as it relates to the extracorporeal arterial infusion model. JECT 1982;14(2)345-354.
2. Taylor, K. M: Cardiopulmonary Bypass, Principles and management,London; Chapman and Hall; 1986: 313-354.
3. Geoghegan, T. and Lam, C. R.: The mechanism of death from intracardiac air and its reversibility. Ann. Surg. 1953; 138: 350-359.
4. Harvey, E., Newton, Barnes, D.K., Mc Elroy, W.E., Whiteley, A.H., Pease, D.C. and Cooper, R.W.: Bubble Formation in Animals, I. Physical Factors. J. Cell and comp. Physiol.1944; 24:1-22.
5. N. Hirayama T., Yamaguchi, H, Allers, M., Roberts, D., and William-Olsson, G.: Change in red cell deformability associated with anesthesia and cardiopulmonary bypass in open heart surgery. Scand. J. Thor. Cardiovasc. Surg. 19:257-262,1985.
6. Swinscow TDV. Statistics at Square One, 8th edn, London: British Medical Association, 1983.
7. Loop, F.D., Szabo, J., Rowlinson, R.D. and Urbanek, K.: Events Related to Microembolism During Extracorporeal Perfusion in Man: Effectiveness of in-line Filtration Recorded by Ultrasound. Ann Thor Surg:1976, 21: 412-420.
8. Kessler, J. and Patterson, R. H.: The production of microemboli by various blood oxygenators. Ann. Thor. Surg. 1970; 9:221-228.
9. Jordan, P., Tolstedt, G. E. and Beretta F. F.: Microbubble formation in artificial oxygenation. Surgery.1958; 43:266-269.
10. Kaplan, S., Clark, L. C., Fox, R. P., Daoud, G. and Shemtob, A: Oxygen embolization during deep hypothermia. Arch. Surg. 1962: 84:122-129.
11. Chan, K. S. and Yang, W. J.: Surgery of literature related to the problems of gas embolism in the human body. J. Biomech. 1969; 2:299-304
12. Al-Khaja, N., Belboul, A., Bergman, P., Roberts, D., and William-Olsson, G.: Cutaneous microcirculation and blood rheology following cardiopulmonary bypass. Laser dopler flowmetric and blood cell rheologic studies.Scand. J. Thor. Cardiovasc. Surg., 1988; 22:149-153.
13. Braunwald E, Kloner RA: Myocardial reperfusion: a double edged sword? J Clin Invest 1985;76: 1713.

14. Bernier M, Hearse DJ, Manning AS: Reperfusion-induced arrhythmias and oxygen-derived free radicals. Circ. Res 1986 58: 331.
15. Hears DJ, Tosaki A: Free radicals and reperfusion-induced arrhythmias: protection by spin trap agent PBN in the rat heart. Circ Res 1987, 60: 375.
16. Faedda, R., Satta, A., Brance, G.F. et al.: Superoxide radicals (SR) in the pathophysiology of ischemic acute renal failure (ARF). Adv Eyp Med Biol. 1987;212:69-74.
17. Brigham, K.L.: Role of free radicals in lung injury. Chest. 1986, 89: 859-863.
18. Royston, D., Fleming,J.S., Desai, J.B. et al.: Increased production of peroxidation products associated with cardiac operation. J Thorac Cardiovasc Surg. 1986; 91: 759-766.
19. Otani, H., Engelman, R.M., Rouson, J.A. et al.: Cardiac performance during reperfusion improved by pretreatment with oxygen free redical scavangers. J Thorac Cardiovasc Surg. 1986; 91: 290-295.