Hyperoxia during cardiopulmonary bypass does not increase respiratory or neurological complications: a *post hoc* analysis of the CARDIOX study

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Editor—Despite advances in surgical techniques and anaesthetic management, morbidity after cardiac surgery with cardiopulmonary bypass (CPB) is still high.[1] Such morbidity includes cardiovascular, renal, pulmonary, and neurological complications. One of the mechanisms linked to such complications is oxidative stress and the formation of reactive oxygen species (ROS) associated with ischaemia–reperfusion.[2] Hyperoxia has thus been suggested to be associated with the enhancement of ischaemia–reperfusion injuries and increased ROS generation.[2] In the operating theatre, hyperoxia is generally avoided as a safety precaution, as it has been associated with worse outcomes for critically ill adult patients and is not recommended.[3] However, hyperoxia during CPB has a preconditioning effect on the heart and brain, and can decrease gas microemboli.[4] A recent randomised study showed no increase in the cardiovascular complication rate with the use of hyperoxia during CPB.[5]

In cardiac surgery, pulmonary complications manifest early as hypoxaemia, pneumonia, acute respiratory distress syndrome, and tracheal re-intubation.[6] Adverse neurological outcomes, such as delirium, stroke, and seizure, are frequent as well.[7] There is current debate concerning the link between hyperoxia during cardiac surgery and non-cardiovascular outcomes. Current guidelines suggest that hyperoxia is associated with postoperative pulmonary complications.[8] Because of significant clinical heterogeneity between available trials, Heinrichs and colleagues[9] were unable to perform a meta-analysis of the impact of hyperoxia on outcomes. Data are lacking regarding the association between hyperoxia and non-cardiovascular outcomes after cardiac surgery.

We performed a *post hoc* analysis of the Impact of Hyperoxia During Cardiopulmonary Bypass in the Occurrence of Cardiovascular Complications After Cardiac Surgery (CARDIOX) study to assess postoperative pulmonary and neurological outcomes during the first 15 postoperative days. The CARDIOX study was a bicentric randomised study assessing two levels of oxygenation (standard care with Pa_{O_2} <150 mm Hg *vs* interventional care with F_{IO_2} set to 1) during CPB (NCT02819739).[5] The ventilation strategy was standardised for all patients, consisting of a lung protective strategy (tidal volume of 6–8 ml kg^{-1} ideal body weight, PEEP 5–10 cm H_2O, and recruitment manoeuvres) before and after CPB and in the ICU; F_{IO_2} set to obtain Sp_{O_2} of 95–99%; and no lung ventilation during CPB, with tracheal extubation following established guidelines.[10] Neurological outcomes were defined as occurrence of delirium (assessed using the Confusion Assessment Method for the ICU scale), seizure, or stroke. Stroke was defined as an embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, and impaired memory). Postoperative pulmonary complications were defined as postoperative pneumonia or tracheal re-intubation.[11]

The population studied consisted of valvular and coronary artery bypass grafting patients. Mean Pa_{O_2} was significantly higher in the interventional care than the standard care group (447 [98] *vs* 161 [60] mm Hg; $P<0.0001$). Amongst the 324 patients included, 25 had pneumonia (14 under standard care [9%] *vs* 11 [7%] under interventional care; $P=0.136$) and eight (3%) were re-intubated (three [2%] under standard care *vs* five [3%] under interventional care; $P=0.723$). Neurological outcomes did not differ between groups: 32 patients (10%) experienced delirium (20 [13%] under standard care and 12 [9%] under interventional care; $P=0.136$) and two (1% in each group) had a seizure. Two patients (1%) under standard care and one patient (1%) under interventional care had a stroke ($P=0.57$). The number of deaths and ICU and hospital length of stay did not differ between groups.

Our *post hoc* analysis of the CARDIOX study found no increase in the rate of pulmonary or neurological complications with the use of hyperoxia during CPB (Table 1). Several studies have shown that hyperoxia increases the pro-inflammatory state, suggesting a higher incidence of complications and death. Discrepancies between the results of these studies and our own can be explained by several factors. Hyperoxia was applied only during a limited time (i.e. the time necessary for CPB) and was generated by an artificial lung membrane, and then distributed in the blood to the lungs. Because the lungs are partially excluded during CPB, they may be protected from hyperoxia-induced injury. Aside from the effects of oxygen itself, lung-protective ventilation strategies may also play a role in the prevention of pulmonary complications. Most studies have been performed in animal models or included small patient cohorts with non-clinical outcomes. Our analysis suffers from the low number of events, because the study was not specifically designed to assess this point.

We do not suggest applying a high concentration of oxygen during CPB. However, because oxygen delivery during and after CPB is fundamental for positive clinical outcomes,

Table 1 Clinical characteristics and outcomes. Data are expressed as mean [standard deviation] or as number (%). CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass. Comparisons were performed using the χ^2 test.

Variable	Standard care (n=163)	Interventional care (n=161)	P-value
Baseline characteristics			
Age (yr)	66 [9]	67 [11]	
Male sex (n, %)	122 (75)	123 (76)	
BMI (kg m^{-2})	29.2 [14.3]	28.9 [17.1]	
Euroscore II (%)	5.0 [3.0−7.0]	5.0 [3.0−7.0]	
Surgery type (n, %)			
Isolated CABG	44 (29)	42 (27)	
Valve replacement	87 (55)	90 (57)	
CABG+valve	20 (13)	19 (12)	
Ascending aorta	5 (7)	7 (5)	
Intraoperative characteristics			
Mean Pao_2 during CPB (mm Hg)	161 [60]	447 [98]	<0.0001
Duration of CPB (min)	103 [56]	100 [43]	
Duration of aortic clamp (min)	77 [42]	72 [32]	
Red blood cell transfusion (n, %)	19 (12)	23 (14)	
Neurological complications (n, %)			
Delirium	20 (13)	12 (8)	0.136
Seizure	2 (1)	2 (1)	1.000
Stroke	2 (1)	1 (1)	0.57
Respiratory complications (n, %)			
Postoperative pneumonia	14 (9)	11 (7)	0.532
Tracheal re-intubation	3 (2)	5 (3)	0.723
ICU course			
ICU discharge (days)	2 [2−3]	2 [2−3]	0.94
Hospital discharge (days)	11 [9−14]	10 [9−12]	0.09
Out-of-hospital mortality at 30 days	3 (2)	0 (0)	0.08

physicians should not be afraid of using supraphysiological concentrations of oxygen to optimise oxygen delivery. Indeed, a recent study performed in the ICU found that a conservative oxygen strategy was associated with worse outcomes, reflecting organ ischaemia.[12] Based on this *post hoc* analysis of the CARDIOX study, hyperoxia during CPB did not increase neurological or pulmonary complications. Controlled studies with a larger sample size are required to better address this specific issue.

Declarations of interest

The authors have declare that they have no conflicts of interest.

References

1. D'Agostino RS, Jacobs JP, Badhwar V, et al. The society of thoracic surgeons adult cardiac surgery database: 2018 update on outcomes and quality. *Ann Thorac Surg* 2018; **105**: 15–23
2. Xia Z, Li H, Irwin MG. Myocardial ischaemia reperfusion injury: the challenge of translating ischaemic and anaesthetic protection from animal models to humans. *Br J Anaesth* 2016; **117**: ii44–62
3. Chu DK, Kim LH-Y, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; **391**: 1693–705
4. Liu W, Liu K, Tao H, Chen C, Zhang JH, Sun X. Hyperoxia preconditioning: the next frontier in neurology? *Neurol Res* 2012; **34**: 415–21
5. Abou-Arab O, Huette P, Martineau L, et al. Hyperoxia during cardiopulmonary bypass does not decrease cardiovascular complications following cardiac surgery: the CARDIOX randomized clinical trial. *Intensive Care Med* 2019; **45**: 1413–21
6. Zochios V, Collier T, Blaudszun G, et al. The effect of high-flow nasal oxygen on hospital length of stay in cardiac surgical patients at high risk for respiratory complications: a randomised controlled trial. *Anaesthesia* 2018; **73**: 1478–88
7. Giménez-Milà M, Vuylsteke A. Oxygen, cardiac surgery, and delirium. *J Cardiothorac Vasc Anesth* 2018; **32**: 691
8. Young CC, Harris EM, Vacchiano C, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. *Br J Anaesth* 2019; **123**: 898–913
9. Heinrichs J, Lodewyks C, Neilson C, Abou-Setta A, Grocott HP. The impact of hyperoxia on outcomes after cardiac surgery: a systematic review and narrative synthesis. *Can J Anaesth* 2018; **65**: 923–35
10. Langeron O, Bourgain J-L, Francon D, et al. Difficult intubation and extubation in adult anaesthesia. *Anaesth Crit Care Pain Med* 2018; **37**: 639–51
11. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *Br J Anaesth* 2018; **120**: 1066–79
12. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med* 2020; **382**: 989–98

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