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ORIGINAL

Hyperoxia during cardiopulmonary bypass does not decrease cardiovascular complications following cardiac surgery: the CARDIOX randomized clinical trial

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Abstract

Purpose: Data on the benefit or or harmful effects of oxygen level on ischemic reperfusion injuries in cardiac surgery are insufficient. We hypothesized that hyperoxia during cardiopulmonary bypass decreases the incidence of postoperative atrial fibrillation (POAF) and ventricular fibrillation, and therefore decreases cardiovascular morbidity (CARDIOX study).

Methods: An open-label, randomized clinical trial including adults undergoing elective cardiac surgery, i.e. cardiopulmonary bypass (CPB) randomized 1:1 to an intervention group or standard group at two French University Hospitals from June 2016 to October 2018. The intervention consisted in delivering of an inspired fraction of oxygen of one to one during CPB. The standard care consisted in delivering oxygen to achieve a partial arterial blood pressure less than 150 mmHg. The primary endpoint was the occurrence of POAF and/or ventricular tachycardia/ventricular fibrillation (VT/VF) within the 15 days following cardiac surgery. The secondary endpoint was the occurrence of major adverse cardiovascular events (MACCE: in-hospital mortality, stroke, cardiac arrest, acute kidney injury, and mesenteric ischemia).

Results: 330 patients were randomly assigned to either the intervention group ($n = 161$) or the standard group ($n = 163$). Mean PaO_2 was 447 ± 98 mmHg and 161 ± 60 mmHg during CPB, for the intervention and standard group ($p < 0.0001$) respectively. The incidence of POAF or VT/VF were similar in the intervention group and the standard group (30% [49 of 161 patients] and 30% [49 of 163 patients], absolute risk reduction 0.4%; 95% CI, − 9.6–10.4; $p = 0.94$). MACCE was similar between groups with, an occurrence of 24% and 21% for the intervention group and the standard groups (absolute risk reduction 3.4%; 95% CI, − 5.7–12.5; $p = 0.47$) respectively. After adjustment, the primary and secondary endpoints remained similar for both groups.

Conclusion: Hyperoxia did not decrease POAF and cardiovascular morbidity following cardiac surgery with CPB.

Clinicaltrial.gov identifier: NCT02819739.

Keywords: Cardiac surgery, Hyperoxia, Outcomes, Postoperative atrial fibrillation

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Introduction

Cardiac surgery still has a high rate of postoperative morbidity and mortality [1]. To proceed with surgery, cardiopulmonary bypass (CPB) using a heart lung machine it is required to assure organ perfusion and oxygen delivery to tissues while the aorta is clamped. Although improvements have been made, few data are available on oxygen management during CPB [2]. The benefit/risk of hyperoxia use in critically ill and cardiac surgery patients is controversial [3]. The most common argument is the potential harmful effect of increased ischemic reperfusion lesions following cardiac surgery, which is due to increased tissue injury in organs through oxidative stress and free radical species. Thus, hyperoxia is often avoided as a safety precaution. In addition, hyperoxia may affect cardiovascular efficiency, with vascular vasoconstriction, heart rate decrease, and impaired cardiac function with coronary blood flow alterations [4, 5]. A recent meta-analysis is favorable to a more conservative oxygen therapy in critically ill patients and is supported by data on higher mortality without effect on mortality with a liberal oxygen therapy [6].

However, hyperoxia might have an ischemic preconditioning effect. In experimental studies, rats pre-exposed to hyperoxia have better tolerance to ischemic events. Beneficial effects on the myocardium were also reported. In an animal model, exposure to hyperoxia (over 95% of inspired fraction) showed myocardial protection after ischemic events [7–9]. Ischemic reperfusion lesions were attenuated with a decrease in transcription of NFkB. The size of myocardial infarctions and reperfusion arrhythmias were also decreased. Additionally, CPB can induce microcirculation disturbances with heterogeneity in organ perfusions. Based on this reasoning, arrhythmias and cardiovascular events might be prevented by avoiding ischemia through the use of a high oxygen target. There is insufficient evidence to recommend a partial oxygen blood pressure to be delivered during CPB. A recent meta-analysis highlighted the heterogeneity of confident conclusions in studies [10].

The objective of this study was to evaluate the association between exposure to hyperoxia during CPB and postoperative cardiac surgery morbidity and mortality. We hypothesize that hyperoxia during cardiopulmonary bypass decreases the incidence of postoperative atrial fibrillation (POAF) and ventricular fibrillation, and therefore decreases cardiovascular morbidity.

Take-home message

Oxygen target in cardiac surgery remains unknown with controversial data on benefit or harmful effects of hyperoxia. Hyperoxia during cardiopulmonary bypass does not decrease cardiovascular complications following cardiac surgery.

Methods

Trial design

The study was approved by the institutional review board at each participating site, and each participant provided written informed consent (CPP Nord Ouest II, Amiens, France; ref 2014-001403-44, clinicaltrials.gov registration NCT02819739) in line with the French law on clinical research [11]. We conducted a prospective, open-label, randomized, controlled, parallel-arm, bi center clinical trial at two tertiary university hospitals (Amiens and Dijon, France) to compare the cardiovascular effects of hyperoxia during CPB from June 2016 to March 2019.

Participants

Participants were aged 18 years or older and were scheduled for elective cardiac surgery with CPB. The exclusion criteria were: permanent atrial fibrillation, amiodarone therapy, presence of an internal pacemaker, hypothermia with cardiac arrest, off-pump cardiac surgery, and concurrent participation in another study.

Intervention

The intervention group was monitored to receive arterial oxygenation at FiO_2 of 1.0 during CPB, according to protocol. The standard group was monitored, according to protocol, to receive arterial oxygenation to obtain an arterial blood pressure measurement of under 150 mmHg during CPB. If venous oxygen saturation fell below 60% the perfusionist was allowed to increase FiO_2 until venous oxygen saturation was corrected to over 70%. During CPB, PaO_2 was continuously monitored with a Terumo CDI 500 (Terumo Europe, Leuven, Belgium). Anesthesia and cardiopulmonary bypass procedures were standardized for all patients. Postoperative hemodynamics objectives were as follows: diuresis over 0.5 mL kg^{-1} h^{-1}, mean arterial pressure over 65 mmHg and cardiac index over 2.2 mL min^{-1} m^{-2}. No prophylactic protocol of arrhythmia was planned. After CPB weaning, minimal FiO_2 was delivered to obtain SpO_2 over 95%. Anesthesia and postoperative care were in accordance with local practice.

Cardiopulmonary bypass management

CPB with a heart–lung machine (Stockert Sorin S5 Heart Lung, Milan, Italy) was performed at a target blood flow of 2.4 L min^{-1} m^{-2}. The mean arterial blood pressure was maintained at more than 65 mmHg by increasing the pump flow rate or, if then required, by administering

a bolus of phenylephrine or norepinephrine. During cardiopulmonary bypass, normothermia (bladder temperature > 36 °C) was maintained with a venous perfusion temperature of 37 °C. During CPB, homologous red blood cell transfusions were given to patients with a haemoglobin value below 8 g dL^{-1}. All patients received 2 g of tranexamic acid at the start of CPB. All patients had myocardial protection with cardioplegia. Depending on the surgical procedure, myocardial protection was ensured with antegrade cardioplegia (via the aortic root or the coronary ostia) and/or retrograde cardioplegia (via the coronary sinus). None of patients was treated with corticosteroids or serine protease inhibitors.

Endpoints

Primary endpoint

The main endpoint was the occurrence of POAF and/or ventricular fibrillation/tachycardia within the 15 days following cardiac surgery.

Secondary endpoint

The secondary endpoint was the occurrence of major adverse cardiovascular events (MACCE) within the 15 days following cardiac surgery. The criteria for an MACCE required the occurrence at least one outcome among the following: in-hospital mortality, successful resuscitated cardiac arrest, stroke, acute kidney injury, mesenteric ischemia. Other outcomes were myocardial injury biomarker at 6 h, day 1, and day 2, norepinephrine use, dobutamine use, intensive care unit stay (ICU) (days), and hospital stay (days) and out-of-hospital mortality.

Data collection and outcome definitions

Standard definitions of postoperative outcomes established by the European Society of Anesthesia were used [12]. Cardiac arrest was defined as the cessation of cardiac mechanical activity, as confirmed by the absence of circulation signs. Continuous ECG monitoring was performed during 48 h following the operation to detect a new onset of atrial fibrillation. Subsequently, a 12-lead ECG was performed every 24 h or whenever arrhythmia symptoms occurred. The presence of ECG-documented atrial fibrillation for at least 1 min was recorded, analyzed, and defined as "postoperative atrial fibrillation." Ventricular tachycardia (VT) and ventricular fibrillation (VF) were recorded by continuous ECG monitoring during the intensive care stay. Stroke was defined as an embolic, thrombotic, or hemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed on a cerebral scanner. Acute kidney injury was defined according to kidney disease: improving global outcomes (KDIGO) criteria as an increase in serum creatinine of over 27 µmol/L within 48 h or diuresis lower than 0.5 mL/kg/h. Myocardial injury was assessed by measuring peak value and kinetic of cardiac troponin during the postoperative course [13]. Cardiac troponin (ng/mL) was collected 6 h after ending CPB, then at day 1 and day 2 after CPB.

The following data were collected during patient inclusion: age, body mass index, gender, medical history (diabetes, dyslipidemia, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, sleep apnea syndrome, stroke, chronic kidney disease defined as a baseline glomerular filtration of under 60 mL/min), medications (beta blockers, calcium channel blockers, angiotensin enzyme converting inhibitors, aspirin, statins, diuretics), baseline left ventricular ejection, creatinine (µmol/L), surgical procedures (coronary artery bypass graft, valve replacement or combined surgery), and logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) to estimate the cardiac surgical risk [14].

The following operative data were collected: mean PaO_2 (mmHg) during CPB (calculated as the average of the value collected each 10 min), CPB and aortic clamp duration (min), cardioplegia type, rate of red blood cell transfusion, norepinephrine and dobutamine use, and PaO_2 (mmHg) at ICU admission.

Randomization

Prior to undergoing cardiac surgery, study participants were randomly assigned to one of two groups using a computer-generated randomization code (Clinsight® software). To ensure balance between each group, random block size of ten were generated. The randomization procedure was stratified by site, in a 1:1 ratio. Although the research staff members who collected data during surgery could not be blinded to group assignments, much attention was given to ensuring strict blinding during the surgery, the follow-up period and data collection. The list of randomized patients was generated by the Clinical Research Division of Amiens Hospital University and was transmitted to perfusionist. The randomization was performed on the day of the surgery just before the surgery. The anesthetist, nurse anesthetist, the surgeon and the intensive care clinician were blind to allocation treatment.

Safety assessment and adverse events

Outcomes and adverse events were recorded by physicians affiliated with Amiens and Dijon clinical research divisions who were blind to group assignments during hospitalization and follow-up at month 6 (supplementary file).

Statistical analysis

Sample size calculation was based on a previous analysis of a hospital database that demonstrated an absolute risk reduction for POAF and/or ventricular tachycardia/fibrillation of 15% with hyperoxia use. Assuming a prevalence of 45% of POAF/VF/VT based on our institution data and on reported series [15], we expected to demonstrate an absolute reduction of 15% with hyperoxia with a power of 80% and a two-tailed p value of 0.05. With an expected follow-up loss or missing data of 10%, the final sample size was 330 patients. A modified intention-to-treat protocol was implemented with the exclusion of patients who underwent heart beating surgery. The normality of the data distribution was assessed using the Shapiro–Wilk test. Quantitative data were expressed as mean ± standard deviation or median [interquartile range], as appropriate and qualitative data were expressed as numbers (percentage) without imputing missing data. The primary endpoint was evaluated by using a Chi square test. The secondary endpoints were evaluated by using a Chi square test. The absolute risk difference was expressed as the difference in endpoints between intervention and standard group. Adjusted analyses for the primary and secondary endpoints were performed after multiple imputations of missing data for the co-variables (ten replications) with a robust Poisson model. Repeated measures per-CPB were compared by using a mixed ANOVA model. Continuous variables were compared using a Student test. All hypothesis tests were two-sided and the threshold for statistical significance was set at $p < 0.05$ for primary and secondary endpoints. All analyses were performed using SAS version 9.4 (SAS Institute Inc) by a statistician (Momar Diouf).

Results

Participant flow

440 patients were screened from June 2016 to October 2018. 330 were randomized: 163 were allocated to the intervention group and 167 were allocated to the standard group. Two of 163 patients and four of 167 patients for respectively the intervention and the standard groups were excluded because of a change of cardiac surgery indication (off-pump coronary artery bypass graft) after the randomization. All patients were followed up until month 6 after the surgery (Fig. 1).

Baseline and cardiopulmonary data

The mean age was 67 ± 11 years and 66 ± 9 years for the intervention group and the standard group, respectively. Patients did not differ in terms of baseline characteristic data and cardiac surgical indications. The mean CPB duration was 100 ± 43 min and 103 ± 56 min for the intervention and standard the groups ($p = 0.59$). CPB parameters were similar between groups for mean CPB blood output, mean arterial pressure, hemoglobin, and hematocrit. All CPB parameters are reported in supplementary file. According to the treatment allocation, PaO_2 was significantly higher in the intervention group ($p < 0.0001$) (Tables 1 and 2; Fig. 2 and supplementary file).

Primary endpoint

The occurrence of POAF or VT/VF within the 15 days following surgery did not differ between the two groups (30% for the intervention and the standard groups, absolute risk reduction 0.4%; 95% CI, − 9.6–10.4; $p = 0.94$). After adjustment on age, LVEF, logistic Euroscore, duration of CPB, duration of aortic clamp and type of surgery, the primary endpoint did not differ between the two groups (relative risk = 1.00 [0.67; 1.49], $p = 0.99$) (Table 3, Supplementary File).

Secondary endpoints

The occurrence of MACCE was similar between groups with, an occurrence of 24% and 21% for the intervention group and the standard groups (absolute risk reduction 3.4%; 95% CI, − 5.7–12.5; $p = 0.47$) respectively. Four of 161 patients (2%) in the intervention group died during their hospital stay following cardiac surgery, whereas no patients died in the standard group (absolute risk reduction 2.5%; CI 95%, 0.08–6.3, $p = 0.06$). After adjustment, the MACCE remained similar for the intervention and standard groups (relative risk = 1.16 [0.73; 1.84], $p = 0.54$). At 6 months, none died in the intervention group whereas three of 163 patients (2%) died in the standard group ($p = 0.08$) (Table 3, Supplementary File).

Discussion

The main result of the present study is that hyperoxia during CPB did not decrease arrhythmia rates, or MACCE. The length of ICU and hospital stays were similar for both groups. Hyperoxia did not decrease myocardial injury as shown by kinetics of cardiac biomarkers.

Considering the lack of convincing studies and the ongoing debate on the effects of hyperoxia, we conducted a randomized study evaluating the cardiovascular effect of hyperoxia. We focused on arrhythmia because it remains an important complication associated with increased short-term hospitalization costs and decreased long-term survival [16]. Hyperoxia did not decrease POAF, moreover, it did not affect major cardiovascular morbidity. The rate of occurrence of POAF and MACCE are in accordance with those reported in the literature [17]. The MACCE rate was also in line with the STS database. Arrhythmia physiopathology is multifactorial. In our study, we postulated that hyperoxia, by preventing

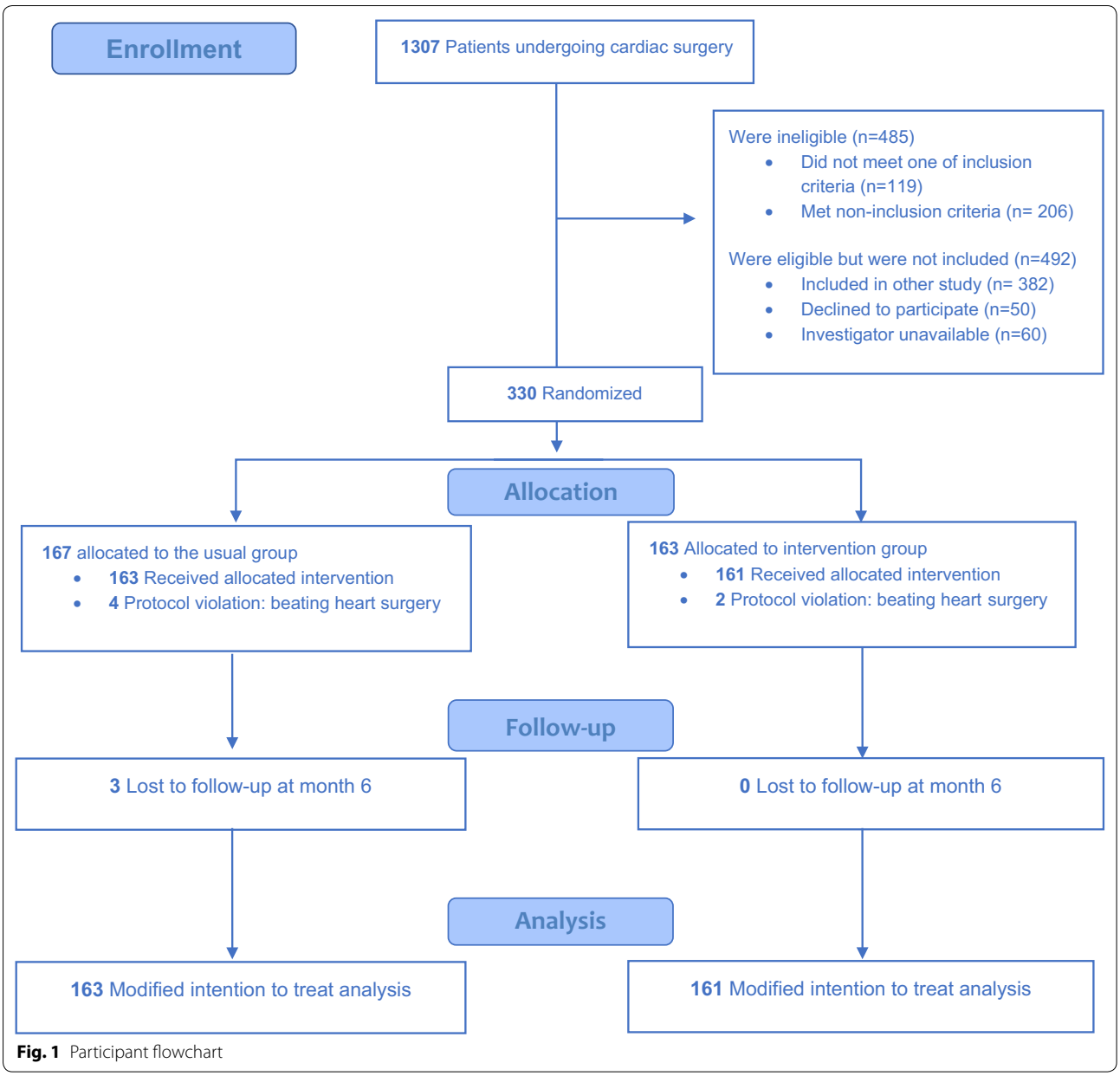

Fig. 1 Participant flowchart

ischemic injury, could reduce arrhythmia. This hypothesis is supported by studies on mitochondrial dysfunction associated with ischemia with calcium dysregulation [18]. It has been demonstrated that patients with POAF had more pronounced markers of atrial cell apoptosis [19].

We also did not show differences in MACCE outcomes. Few studies have correctly assessed the oxygen effect on cardiovascular clinical outcomes. Two recent randomized studies did not reveal differences in mortality or morbidity in cardiologic and neurologic areas [20, 21]. When considering acute myocardial infarction and acute stroke, the use of hyperoxia through a facial mask did not improve medical outcomes and mortality. In cardiac surgery, few data assessing clinical outcomes are found. On the same topic, a recent systematic review, highlighted the heterogeneity in endpoints and sample sizes of 12 identified randomized studied, making comparisons difficult. Another recent study failed to demonstrate that avoiding hyperoxia was beneficial for outcomes by reducing ischemic reperfusions [22].

As mentioned before, comparisons of outcomes in previous studies is difficult, mainly because of various definitions of hyperoxia [10]. Inoue et al. defined normoxia

Table 1 Baseline characteristics of the study population before surgery

Variables	Standard group ($n=163$)	Intervention group ($n=161$)
Age (years)	66 ± 9	67 ± 11
Male gender (*n*, %)	122 (75)	123 (76)
BMI (kg/m^2)	29.2 ± 14.3	28.9 ± 17.1
Medical history (*n*, %)		
Chronic kidney disease (creatinine clearance under 60 mL/min)	10 (6)	20 (12)
Dyslipidemia	72 (45)	71 (44)
Diabetes	41 (26)	42 (26)
Hypertension	87 (55)	100 (62)
Peripheral vascular disease	16 (10)	26 (16)
Stroke	11 (7)	11 (7)
Sleep apnea syndrome	16 (10)	15 (9)
COPD	10 (6)	9 (6)
Chronic treatment (*n*, %)		
Beta-blocker	76 (47)	73 (46)
Calcium channel blocker	26 (16)	34 (21)
Angiotensin enzyme converting inhibitor	86 (54)	86 (54)
Aspirin	70 (44)	86 (54)
Statin	83 (52)	87 (55)
Furosemide	22 (14)	33 (21)
Baseline echocardiographic LVEF (%)	60 ± 11	59 ± 11
Baseline creatinine (μmol L^{-1})	86 ± 30	92 ± 59
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)
Logistic Euroscore (%)	3.3 [2.1–6.3]	4.0 [2.3–8.4]

Data were expressed as mean ± standard deviation, as median [interquartile range], or as numbers (percentage)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction, *CABG* coronary artery bypass graft

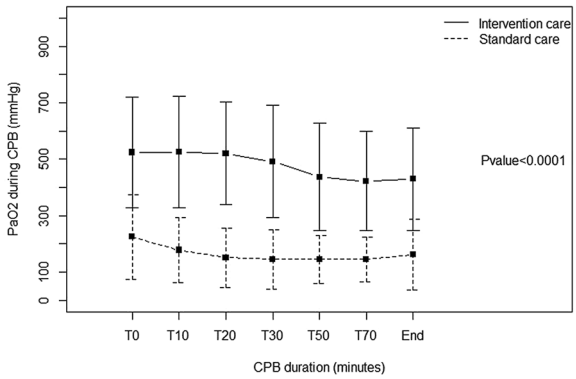

Fig. 2 PaO_2 during cardiopulmonary bypass (CPB) between intervention and standard groups. Data were reported from CPB starting (T0), every 10 min, every 20 min after 50 min and at CPB weaning (end). Data are presented mean (error bar: standard deviation)

Table 2 Characteristics of the study population during the surgical procedure

Variables	Standard group ($n=163$)	Intervention group ($n=161$)
Duration of CPB (min)	103 ± 56	100 ± 43
Duration of aortic clamp (min)	77 ± 42	72 ± 32
Mean PaO_2 during CPB (mmHg)	161 ± 60	447 ± 98
Cardioplegia (*n*, %)		
Blood	138 (84)	131 (87)
Delnido	16 (10)	12 (8)
Custodiol	9 (6)	8 (5)
RBC transfusion (*n*, %)	19 (12)	23 (14)
Vasoactive medication use (*n*, %)		
Norepinephrine	48 (29)	46 (29)
Phenylephrine	68 (43)	55 (35)
Ephedrine	20 (13)	14 (9)
Dobutamine	7 (4)	8 (5)
Epinephrine	3 (2)	3 (2)

Data were expressed as mean ± standard deviation or as number (percentage)

CPB cardiopulmonary bypass, *RBC* red blood cell transfusion, *ICU* intensive care unit

as a PaO_2 at 250 mmHg, which had already been considered as hyperoxia compared to McGuinness and Smit B's studies [23, 24]. Regarding the definition of hyperoxia, authors had a wide range of PaO_2 values, varying from 250 to over 500 mmHg, which represents a varied hyperoxia grade [23]. Currently, there is no standard definition of normoxia and hyperoxia. From a physiologic point of view, hyperoxia is used to describe an oxygen fraction of over 21% and normoxia to describe an oxygen fraction between 10 and 21%. Nevertheless, PaO_2 depends on various parameters including temperature, altitude, and alveolar ventilation. At an atmospheric pressure of 760 mmHg, the mean PaO_2 in blood is 90 mmHg supposing the absence of alveolar capillary diffusion. However, the oxygen target to achieve in an organ is unknown as there is a change in regional perfusion and oxygenation during cardiac surgery and CPB [22, 25–27]. In our study, we aimed to target a PaO_2 of 150 mmHg in the standard group to be at physiological level. However, we targeted a central venous oxygen saturation of over 65% during CPB as routine in our practice to have an oxygen delivery adapted to each patient's oxygen demand.

Table 3 Primary and secondary outcomes within the 15 days following cardiac surgery

Type of event	Standard group ($n = 163$)	Intervention group ($n = 161$)	Absolute risk difference (intervention-standard)	*p* value
Primary endpoint				
PAOF or VT/VF (*n*, %)	49 (30)	49 (30)	0.4% [− 9.6–10.4]	0.94
POAF (*n*, %)	48 (29)	47 (29)	0.0% [− 9.5–10.2]	0.94
VT/VF (*n*, %)	4 (2)	4 (2)	0.0% [− 3.3–3.4]	0.99
Secondary endpoints				
MACCE (*n*, %)	34 (21)	39 (24)	3.4% [− 5.7–12.5]	0.47
Outcomes (*n*, %)				
Cardiac arrest	2 (1)	3 (2)	0.6% [− 2.0–3.3]	0.64
In-hospital mortality	0 (0)	4 (2)	2.5% [0.08–6.3]	0.06
Acute kidney injury	30 (18)	35 (22)	3.3% [− 5.4–12.0]	0.45
Stroke	2 (1)	1 (1)	− 0.6% [− 2.7–1.5]	0.57
Mesenteric ischemia	0 (0)	2 (1)	1.2% [− 0.5–2.9]	0.25
Cardiac troponin (ng/L)				
6 h post CPB	7.4 [4.3–14.4]	8.0 [4.3–15.4]	–	0.79
Day 1 post CPB	4.3 [2.5–8.0]	4.6 [2.8–8.4]	–	0.53
Day 2 post CPB	1.9 [1.0–3.9]	2.0 [1.0–3.7]	–	0.80
Norepinephrine (*n*, %)	60 of 153 (39)	47 of 156 (30)	− 9.1% [− 19.7–1.5]	0.10
Dobutamine (*n*, %)	11 of 153 (7)	10 of 156 (6)	− 0.7% [− 6.3–4.9]	0.81
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 month 6	3 (2)	0 (0)	–	0.08

Data were expressed as median [interquartile range] or as number (percentage). Absolute difference was expressed as a percentage with the 95% CI range. Comparisons were performed using Student's *t* test, Wilcoxon–Man–Whitney, Chi square, or Fischer's exact as appropriate

POAF postoperative atrial fibrillation, *VT* ventricular tachycardia, *VF* ventricular fibrillation, *MACCE* major adverse cardiovascular and cerebral events, *CPB* cardiopulmonary bypass, *ICU* intensive care unit

Our study presents some limitations. First, the monitoring and screening of arrhythmias may not have been rigorous enough and diagnoses could have been missed. Indeed, during ICU management, patients were continuously monitored with a 3-lead ECG, and a 12-lead ECG was performed when a screen monitor revealed arrhythmia. Some patient may have had a transient new undiagnosed onset POAF. Nevertheless, the observed incidence of POAF is closed to those described in the literature. Moreover, because both group treatments had similar monitoring of POAF we believe this bias as negligible. Concerning hyperoxia, we can discuss the exposition time and the value of hyperoxia used in the present study. Even hyperoxia has more pronounced effects after long exposure time, a short time exposure was demonstrated to be sufficient to increase reactive oxygen species and enhance inflammatory response [28, 29]. Hyperoxia is demonstrated to have time- and dose-dependent effects. In this regard the difference between the two groups was sufficiently clinical relevant to demonstrate any clinical effects [28, 29]. Concerning our oxygen target, the PaO_2 value tends to decrease, whereas heart lung machine oxygen delivery was set at an oxygen fraction of one in the intervention group and 0.4–0.5 in the standard group. In both investigation centers, the same in-line blood gas analyzer (CDI 550 in line gas blood monitoring system, Terumo) was used as described in the methodology paragraph. We believe that the trend is related to the need to recalibrate the device. Because four patients died before the end time point, we can discuss a competing risk analysis. Two of these patients had arrythmia before death. The other two patients may have no impact on statistical result. As for the methodology, no blinding was applied for assessment of medical events. However, all endpoints and follow-up data were collected by a clinical research assistant independent of the medical practitioner and the ICU clinician was blind to the allocation of group. Mechanical ventilation was standardized in all groups. No per CPB lung ventilation was initiated to avoid supplementary oxygen delivery. Thus, to demonstrate the benefits of hyperoxia, our results did not suggest side effects on outcomes. Moreover, reported adverse events were mainly related to cardiac surgery complications. Our results did not resolve the question of oxygen target during CPB.

Conclusion

Based on our results, hyperoxia during cardiopulmonary bypass surgery did not decrease the occurrence of postoperative morbidity assessed by POAF, ventricular fibrillation/tachycardia, or MACCE. The results do not support the use of hyperoxia to decrease postoperative complication. Similarly, hyperoxia did not increase postoperative morbidity.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05761-4) contains supplementary material, which is available to authorized users.

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Author contributions
OAA: study design, performing the procedure, writing the first manuscript and revising the manuscript; PH: study design, performing the procedure and revising the manuscript; PGG: study design, performing the procedure, and revising the manuscript; MD: statistical analysis; EL: study design and revising the manuscript; CB: performing the procedure; EJ: data collection; CB: performing the procedure; all the authors: revision and final approval of the version to be submitted.

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Compliance with ethics standards

Conflicts of interest
All authors report no conflict of interest.

Ethical approval
This study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee.

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