Hyperoxia and mortality in Conventional versus Extracorporeal Membrane Oxygenation Cardiopulmonary Resuscitation

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Research

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Abstract

Background

Hyperoxia has been associated with adverse outcomes in post cardiac arrest (CA) patients. However, little data are available from mixed cohorts, where extracorporeal membrane oxygenation cardiopulmonary resuscitation (ECPR) and conventional CPR (CCPR) were utilised. The independence of effect of hyperoxia in this setting is not clear. Study-objective was to examine the association between hyperoxia and 30-day mortality in a mixed cohort of ECPR and CCPR patients.

Methods and design

This was a retrospective cohort study of CA patients admitted to a tertiary level cardiac arrest centre in Australia from 1st January 2013 to 31st August 2018. Mean arterial oxygen levels (PaO_2) and episodes of extreme hyperoxia ($PaO_2 \geq 300$mmHg) were analysed over the first 8 days. The primary outcome was 30-day mortality.

Results

A total of 169 post CA patients were assessed over a 6.5-year time period: 79 patients undergoing ECPR vs 90 patients undergoing CCPR. The mean age of the cohort was 54 (± 17) years; 126/169 (74%) were male and 119/169 (70%) were treated for out of hospital cardiac arrest (OHCA). Compared to CCPR, ECPR patients were younger, had a longer low flow time and higher illness severity scores on admission. Mean PaO_2-levels were higher in patients in the ECPR vs CCPR group (211mmHg ± 58.4 vs 119mmHg ± 18.1; $p < 0.0001$) as was the proportion with at least one episode of extreme hyperoxia (58/79 (73%) vs 36/90 (40%), $p < 0.01$). ECPR patients presented with a higher mortality (54.4%) vs CCPR patients (34.4%). After adjusting for age, sex, BMI, highest lactate pre-treatment, use of ECMO, low flow time, pulse pressure on admission day, and severity of illness (APACHE III score), any episode of extreme hyperoxia was independently associated with a 2.57-fold increased risk of 30-day mortality (OR: 2.57, 95% CI: 1.09–6.06; $p = 0.031$) irrespective of the CPR-mode.

Conclusion

We found extreme hyperoxia (PaO_2-level ≥ 300mmHg) was more common in ECPR patients in the first 8 days post CA and was independently associated with higher 30-day mortality, irrespective of whether ECPR was employed. Prospective studies that compare different oxygen targets are needed to see if a strategy of lower oxygen exposure improves outcomes.

Introduction

The potential harm of hyperoxia in critically ill patients is being increasingly recognised. Multiple studies have demonstrated this association in patients with sepsis[1, 2], myocardial infarction[3], stroke[4],

traumatic brain injury[5–11] as well as in post cardiac arrest (CA) patients.[1, 12–16] Post CA patients may represent a particularly vulnerable group, as the damaging effects of ischemia-reperfusion injury may be worse in the brain. The recently published ICU ROX trial suggested potentially improved outcomes with conservative compared to liberal oxygen therapy in patients with hypoxic ischaemic encephalopathy post CA.[17]. The potential mechanisms of the injurious effects of oxygen include cerebral and coronary vasoconstriction[18] and the production of reactive oxygen species (ROS) which stimulate a proinflammatory response and cell damage.[19–21] In view of this, current recommendations by the American Heart Association suggest use of 100% oxygen during CPR and oxygen titration (targeting a peripheral capillary oxygen saturation (SpO_2) of 92–96%) after successful return of spontaneous circulation (ROSC).[22]

Over the last few years, the use of extracorporeal membrane oxygenation (ECMO) cardiopulmonary resuscitation (ECPR) has been growing, and may provide a significant survival benefit over conventional CPR (CCPR) in patients with refractory CA.[23, 24] However while ECPR provides both mechanical haemodynamic and oxygenation support, [25–27] ECPR may also be associated with significantly elevated arterial oxygen levels.[1, 12, 13] To date, little is known about the incidence of hyperoxia in patients treated with ECPR compared to CCPR, and whether there is an association between hyperoxia and poor outcomes, independent of the method of resuscitation.

The primary objective of this study was to explore the association between extreme hyperoxia (PaO_2-level ≥ 300mmHg) and 30-day mortality in a mixed cohort of ECPR and CCPR patients. Secondary objectives were to describe mean oxygen levels and the incidence of extreme hyperoxia post CA, in each sub-group.

Methods

Study design

This was a single centre, retrospective cohort study. The study was approved as low risk by the Alfred Hospital Human Ethics Committee (application: 28/20), with a waiver of individual patient informed consent.

Setting

The setting was a 50-bed, quaternary referral ICU in Melbourne, Australia that has almost 3000 admissions to ICU per year. It provides state services for burns, trauma, and hyperbaric medicine, heart and lung transplant, ventricular assist devices (VAD), and has had an ECMO-program since 1990, providing over 100 ECMO runs annually.

Participants

Adult patients (> 16 years old) admitted to the intensive care unit (ICU) following in-hospital or out of hospital CA of primary cardiac origin from 1st January 2013 to 31st August 2018 were included in this study. Patients were excluded if they had a non-cardiac cause of their CA (e.g. drug overdose, trauma, hypoxia), they were treated with veno-venous (VV) ECMO, or if they died < 24 hours after admission (as oxygen levels are unlikely to have impact on mortality in this group). Patients were either managed with ECPR or CCPR.

Data management and collection

We collected data concerning patient demographics (age, weight, height, gender), illness severity scores (APACHE Score II and III / SOFA score), the reason for CA, and the initial rhythm. We further extracted the two important CPR time variables: No-flow-time (period of CA where no CPR is performed) and low-flow-time (period of CA where CPR is performed but ROSC has not yet been established). The type of arrest (out of hospital or in hospital CA) was also recorded. Laboratory results, hemodynamic and ventilation-parameters, the need for renal replacement therapy and ECMO-parameters (site of cannulation, size of cannulas, mode, blood flow, fresh gas flow, ECMO complications and duration) were assessed on admission and daily from day 1 to day 8.

All arterial blood gas (ABG) samples in the ECPR group were taken from the right arm as per the institutional ECMO protocol due to the risk of differential arterial gas tensions during VA ECMO. Either arm could be used in the CCPR group. These were taken as per routine protocol (1–2 hourly) or more frequently following any change of condition. We assessed the highest, the mean, and lowest PaO_2-value over a timeframe of 8 consecutive days. Hyperoxia was defined as a PaO_2-level of 101–299 mmHg. Extreme hyperoxia was defined as any recorded PaO_2 -level ≥ 300 mmHg over the first 8-days, as per previous authors. [8, 12, 14, 28]. In case of non-availability of PaO_2-values these were classified as missing data. Additional data were retrieved from electronic database records. No assumptions were made regarding missing data. All proportions were calculated as percentages of the patients with available data.

CA management

CA management was standardized as per local hospital and ambulance service guidelines.[29–31] CPR was initially performed manually in all cases, but if prolonged > 10 minutes was switched to the Lucas® chest compression system (Physiocontrol, Redmond) to facilitate transportation.[25] Patients with CA were treated via two different pathways: CCPR was initiated in all patients, while ECPR with implementation of VA ECMO was initiated in refractory CA when there were no contraindications. ECPR inclusion and exclusion criteria for CA patients have been previously published.[25, 32] In the ECPR group hemodynamic support was maintained with either the Cardiohelp® (HLS, Maquet) or Rotaflow® (PLS, Getinge Group). The initial typical settings of the ECMO were a fresh gas flow oxygen fraction (FsO_2) of 1.0, 3l/min blood flow, 3l/min fresh gas (sweep) flow and ventilator settings of FiO_2 0.5, positive end expiratory pressure (PEEP) 10 cmH_2O and pressure control level above PEEP (PC) 10cmH_2O. These were

both adjusted to maintain mean arterial pressure of ≥ 65 mmHg, normalization of lactate, SpO_2 in the right arm of between 94–100% and normocapnia. Withdrawal of care occurred when clinical, radiological and biochemical information were consistent with a poor outcome.

Outcomes

The primary outcome was all cause 30-day mortality. Secondary outcomes included hospital and ICU length of stay, days of invasive ventilation and complications of treatment (infection, CNS complications, hepatic injury, renal failure, multiorgan failure, vascular injury) in each sub-group (ECPR and CCPR).

Statistical analysis

Continuous variables were summarised using means and standard deviation (SD) or medians and interquartile ranges (IQR) according to data type and distribution. Categorical variables were summarised using frequency counts and percentages. Comparisons between groups were made using Student's t-test or Mann-Whitney U test as appropriate for continuous variables and chi-square test with Yates correction for categorical variables. The relationship between oxygen levels over the eight-day period in the ECPR group and CCPR group were determined using linear mixed modelling fitting main effects for group, time, and an interaction between group and time. Results from the mixed effects models were reported as adjusted means and 95% CI. Univariate and multivariate analyses for 30-day mortality were performed using logistic regression with results reported as odds ratios (OR) and 95% confidence intervals (95% CI). Variables with a $p < 0.05$ on univariate analysis and those deemed to be clinically important (age, gender) were included in the multivariable logistic regression model. A two-sided p-value less than 0.05 was chosen to indicate statistical significance. Analyses were performed using SPSS Statistics version 25 (IBM 2017) or SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 204 patients were admitted to the ICU post CA between 1st January 2013 and 31st August 2018 (Fig. 1). 35 patients were excluded from the study as they died within the first 24 hours (23 in the ECPR and 12 in the CCPR group), leaving a total of 169 patients: 79 patients underwent ECPR and 90 patients underwent CCPR. Mean age was 54 (± 17) years old, 126/169 (74%) were male, and the mean APACHE III score was 104 (± 32). Table 1 outlines the characteristics of the ECPR and CCPR patient groups: ECPR patients were younger, had longer low flow times, were more likely to have had an in-hospital CA, had lower pulse pressure, had higher illness severity scores, troponin levels and lactate levels on admission.

Table 1
Characteristics of the ECPR and the CCPR group.

	Total CPR (N = 169)	ECPR (N = 79)	CCPR (N = 90)	p-value
Age (years)	54.25 ± 17.1	49.2 ± 15.5	58.6 ± 17.3	< 0.01
Sex, male	126 (74.6%)	57 (72.1%)	69 (76.7%)	0.50
BMI (kg/m2)	27.1 ± 5.1	26.6 ± 4.4	27.6 ± 5.7	0.21
APACHE III score	104.3 ± 31.7	108.9 ± 33.7	100.3 ± 29.4	0.08
No flow time (min)	5 (3–5)	3 (2–5)	5 (3–5)	< 0.01
Low flow time (min)	20 (10–45)	40 (10–60)	15 (9.5–22.5)	< 0.01
Cardiac arrest rhythm	13 (7.7%)	7 (8.9%)	6 (6.7%)	0.86
-Asystole	129 (76.3%)	59 (74.7%)	70 (77.8%)	
-VF	27 (16.0%)	13 (16.5%)	14 (15.6%)	
-PEA				
Arrest witnessed	169 (100%)	79 (100%)	90 (100%)	0.35
Cardiac arrest category	85 (50.3%)	45 (57.0%)	40 (44.4%)	< 0.01
-Acute myocardial infarction	13 (7.7%)	7 (8.9%)	6 (6.7%)	
-Decompensated Chronic CM	4 (2.4%)	3 (3.8%)	1 (1.1%)	
-Acute heart failure	2 (1.2%)	2 (2.5%)	0 (0%)	
-Myocarditis	5 (3.0%)	5 (6.3%)	0 (0%)	
-Perioperative decompensation	60 (35.5%)	17 (21.5%)	43 (47.8%)	
-No known disease				
Out of hospital CA	119 (70.4%)	42 (53.2%)	77 (85.6%)	< 0.01
In-hospital CA	50 (29.6%)	37 (46.8%)	13 (14.4%)	< 0.01
Pulse-Pressure (mmHg) on day of admission to ICU	47.6 ± 24.7	34.8 ± 18.6	58.9 ± 23.9	< 0.01
CRRT in ICU	84 (49.7%)	66 (83.5%)	18 (20%)	< 0.01

APACHE = Acute physiology and chronic health evaluation, BMI = Body mass index, CM = Cardiomyopathy, CRRT = Continuous renal replacement therapy, GFR = Glomerular filtration rate, N = number, LOS = length of stay, PEA = pulseless electrical activity, SOFA = Sequential organ failure assessment, VF = Ventricular fibrillation, data are presented as mean ± standard deviation (SD), median (IQR) or number (percentage).

	Total CPR (N = 169)	ECPR (N = 79)	CCPR (N = 90)	p-value
Peak troponin (ng/l)	2663 (224-44866)	4126 (89-149207)	2532 (371-21183)	0.02
Creatinine (umol/l) on admission to ICU	125.3 ± 67.9	124.3 ± 51.9	126.2 ± 79.6	0.86
Estimated GFR (ml/min/1,73m^2)	63.7 ± 28.7	64.5 ± 30.2	62.9 ± 27.4	0.71
Lactate (mmol/ l) on admission to ICU	6.6 (3.0-8.1)	8.7 (3.7–12.6)	4.7 (2.3–6.3)	< 0.01
pH on admission to ICU	7.19 ± 0.2	7.16 ± 0.3	7.21 ± 0.2	0.01
SOFA Score Day 1	9.6 ± 3.2	10.6 ± 2.8	8.7 ± 3.2	< 0.01
Highest FiO2 (%) on admission to ICU	76.4 ± 28.7	91.0 ± 20.8	63.5 ± 28.7	< 0.01
Highest paCO2 (mmHg) on admission to ICU	47.4 ± 17.2	46.5 ± 20.8	48.3 ± 13.3	0.51
Highest paO2 (mmHg) on admission to ICU	213.8 (88-293.5)	279.1 (91–482)	156.4 (87.8-175.8)	< 0.01
Mean paO2 (mmHg) adjusted over 8 observation days	165.2 ± 63.4	211.4 ± 58.4	119.0 ± 18.1	< 0.01
Cumulative extreme hyperoxia (paO2 ≥ 300mmHg)	107 (63,31%)	58 (73,41%)	36 (40%)	< 0.01

APACHE = Acute physiology and chronic health evaluation, BMI = Body mass index, CM = Cardiomyopathy, CRRT = Continuous renal replacement therapy, GFR = Glomerular filtration rate, N = number, LOS = length of stay, PEA = pulseless electrical activity, SOFA = Sequential organ failure assessment, VF = Ventricular fibrillation, data are presented as mean ± standard deviation (SD), median (IQR) or number (percentage).

Oxygen Levels in ECPR versus CCPR

More patients manifested extreme hyperoxia (at any point over the first 8-days) in the ECPR group (58/79 (73%), as compared to the CCPR group (36/90 (40%), p < 0.01). On the day of ICU admission, extreme hyperoxia was present in 34.3% in the ECPR group versus 10.1 % in the CCPR group (p < 0.001). Peak

oxygen levels and inspired fraction of oxygen (FiO_2) on admission to ICU were also higher in the ECPR group than in the ECPR group (Table 1). Peak, average, and lowest PaO_2-levels were also higher over the first 8 days in the ECPR group compared to the CCPR group (Table 1, Fig. 2). Oxygen levels were highest in both groups on the first day of admission, but then decreased over the subsequent seven days. The mean PaO_2-level (adjusted over the timeframe of the 8 monitored days using a mixed linear model) was 211.4 mmHg ± 58.4 in the ECPR group versus 119.0 mmHg ± 18.1 in the CCPR group ($p < 0.001$). This difference was most pronounced during the first 3 days after initiation of treatment but the difference remained until day 8. Over the 8-day period, all mean paO_2-levels were significantly higher ($p < 0.0001$) in the ECPR group than in the CCPR group.

Outcomes and processes of care

Overall hospital mortality was 74/169 (44%) (Table 2). Mortality was higher in the ECPR group compared to the CCPR group (43/79 (54%) vs 31/90 (34%), $p = 0.02$)).

Table 2
Comparison of outcome parameters in ECCPR versus CCPR

	Total CPR (N = 169)	ECPR (N = 79)	CCPR (N = 90)	p-value
Primary outcome	74 (43.79%)	43 (54.43%)	31 (34.4%)	0.02
30-day mortality				
Secondary Outcome				
ECMO duration (days)	0 (0-4.3)	4.3 (2.5–8.1)	0 (0–0)	N/A
Invasive ventilation (days)	4.3	6.6	3.01	< 0.001
	(1.9-8)	(3.1–11.9)	(1.5–6.4)	
ICU LOS (days)	6.9 (2.5–1.5)	9.6 (4.1–18.7)	4.7 (2.8–8.4)	< 0.001
Hospital LOS (days)	11.6	15.1	8.9	< 0.001
	(6.0-25.1)	(4.8–34.0)	(6.0-14.4)	
Hospital LOS (days)	10	15	8.0	< 0.001
start from ICU admission	(5-23.5)	(4–32)	(5–13)	
Infection	98 (57.99%)	43 (54.43%)	55 (61.11%)	< 0.001
No infection	17 (10.06%)	15 (18.99%)	2 (2.22%)	
Bloodstream infection	36 (21.30%)	11 (13.92%)	25 (27.78%)	
Pneumonia	3 (1.78%)	2 (2.53%)	1 (1.11%)	
Catheter related infection	1 (0.59%)	-	1 (1.11%)	
Abdominal infection	14 (8.28%)	7 (8.86%)	7 (7.78%)	
Multiple infection sites				
CNS complications	105 (62.13%)	51 (64.56%)	54 (60.00%)	0.06
No CNS complications	14 (8.28%)	2 (2.53%)	12 (13.33%)	
Delirium	2 (1.18%)	2 (2.53%)	-	
Intracranial haemorrhage	9 (5.33%)	6 (7.59%)	3 (3.33%)	
Stroke	38 (22.49%)	18 (22.78%)	20 (22.22%)	
Hypoxic brain injury	1 (0.59%)	-	1 (1.11%)	
Seizure				
Vascular injury	13 (7.69%)	12 (15.19%)	1 (1.11%)	0.001
Hepatic injury	19 (11.24%)	16 (20.25%)	3 (3.33%)	0.001

	Total CPR (N = 169)	ECPR (N = 79)	CCPR (N = 90)	p-value
Acute Renal failure	40 (23.67%)	33 (41.77%)	7 (7.78%)	< 0.001
Renal replacement therapy	84 (49.70%)	66 (83.54%)	18 (20.00%)	< 0.001
Multiorgan failure	19 (11.24%)	16 (20.25%)	3 (3.33%)	0.001

The ECPR group also had longer duration of invasive ventilation, and longer ICU and hospital length of stay,

Factors associated with 30-day mortality

Table 3 provides the unadjusted factors associated with 30-day mortality. A longer no flow time and low flow time, a higher APACHE II score and use of ECPR were all associated with a higher risk of death. Highest PaO_2-Levels and any episode of extreme hyperoxia (PaO_2-level ≥ 300mmHg) were also associated with increased mortality. After adjusting for age, sex, BMI, highest lactate level pre-treatment, ECMO therapy, low flow time, APACHE III score and highest pulse pressure on admission, low flow time and extreme hyperoxia (PaO_2-level ≥ 300mmhg) at any point in the first 8 days (OR 2.57; C1.09-6.06; p = 0.031) were independently associated with 30-day mortality (Table 4).

Table 3
Univariate analysis of factors associated with 30-day-mortality in CCPR and ECPR.

Variable	30-day mortality		Odds ratio (95% CI)	p-value
	Yes (N = 72)	No (N = 97)		
No flow time (min)	5 (3–5)	3 (3–5)	1.11 (1.00-1.23)	0.048
Low flow time (min)	30 (11–60)	15 (7–25)	1.03 (1.05–1.02)	< 0.0001
ECPR	41 (56.9%)	38 (39.1%)	2.05 (1.11–3.82)	0.02
Highest pulse pressure on admission (mmHg)	44.79 ± 23.22	50.52 ± 22.35	0.99 (0.98-1.00)	0.11
Age (years)	54.65 ± 17.36	53–96 ± 16.99	1.00 (0.98–1.02)	0.80
BMI (kg/m^2)	27.27 ± 5.66	27.00 ± 4.74	1.01 (0.95–1.07)	0.73
APACHE II	29.01 ± 6.97	25.41 ± 7.87	1.07 (1.02–1.12)	0.003
APACHE III	112.24 ± 30.18	98.41 ± 31.65	1.01 (1.00-1.03)	0.62
Sex, male	54 (75%)	72 (74.2%)	1.04 (0.52–2.10)	0.91
OHCA	49 (68%)	70 (72.1%)	0.82 (0.42–1.6)	0.56
Targeted temperature management (28 hours at 36°C)	38 (52.7%)	53 (54.6%)	0.93 (0.5–1.71)	0.81
Highest paO_2 (mmHg) of mean paO_2 (mmHg) day 1–8	347.15 ± 155.67	268.39 ± 145.38	1.00 (1.00-1.01)	0.001
Cumulative extreme hyperoxia (paO_2- Level ≥ 300mmHg)	42 (58.3%)	32 (32.9%)	2.84 (1.51–5.35)	0.001

Table 4
Multivariate analysis of factors associated with 30-day-mortality in CCPR and ECPR

Variable	OR (95% CI)	p-value
Age (years)	1.02 (1.00-1.04)	0.09
Sex (Male)	0.98 (0.44–2.19)	0.97
BMI	1.03 (0.97–1.11)	0.34
APACHE III	1.01 (0.99–1.02)	0.45
Highest lactate before treatment	1.01 (0.93–1.10)	0.82
ECMO-therapy	0.71 (0.27–1.88)	0.49
Low flow time (min)	1.03 (1.01–1.05)	0.001
Highest pulse pressure on admission day	1.00 (0.98–1.02)	0.79
Cumulative extreme hyperoxia (paO2- Level ≥ 300 mmHg)	2.57 (1.09–6.06)	0.031

Discussion

Key findings

In this study of post CA patients, we found any episode of extreme hyperoxia (PaO_2-level ≥ 300mmHg) in the first 8 days was significantly associated with higher 30-day mortality. We found that although extreme hyperoxia was more common in ECPR patients, the association between extreme hyperoxia and mortality was independent of the method of resuscitation (ECPR vs CCPR), age, sex, low flow time, highest pulse pressure on admission, and severity of illness.

Relationship to previous studies

Multiple previous studies have investigated the relationship between hyperoxia and outcomes post CA managed with CCPR. A study by Wang et al. analysed oxygen levels taken within 24 hours post CA in 9186 patients treated with CCPR. The data were extracted from the Resuscitation Outcomes Consortium (ROC) database. Wang et al. demonstrated that hyperoxia (arterial paO_2-levels ≥ 300mmHg monitored within the first 24 hours post ROSC) was associated with increased mortality.[33] A metanalysis by Patel et al. combining 16 observational studies with a total of 40,573 adult post CA patients also revealed that hyperoxia post CA was associated with higher mortality.[34] In patients managed with ECPR for CA, hyperoxia seems to be associated with a similar degree of worse outcomes; a large retrospective analysis of the Extracorporeal Life Support Organisation (ELSO) by Munshi et al. found that extreme hyperoxia (PaO_2 ≥ 300mmHg 24 hours post CA) occurred in 22% of the 1041 patients treated with ECPR,[12], and that moderate arterial hyperoxia (PaO_2-level 101-300mmHg) was associated with an increased risk of death. Halter et al. showed that hyperoxia was associated with 30-day mortality in patients with

refractory OHCA managed with ECMO[1] and a single centre French study of 66 patients treated with ECPR for OHCA showed that hyperoxia (detected 30 minutes post CA) occurred in 62% of the cases.[1]

These studies have been limited as they only assess oxygen levels very early post arrest (from 30 minutes to 24 hours).[1, 12] In our study, we assessed oxygen levels over the first 8 days, providing a more complete dose and impact of oxygen on the patient. In addition, the studies above have not directly compared CCPR and ECPR patients. In our study, extreme hyperoxia remained significantly associated with mortality, even when controlling for ECPR. This suggests the relationship remains independent of method of resuscitation. A further factor is that previous ECMO studies have failed to adequately control for low cardiac output which can occur post cardiac arrest and which may grossly elevate arterial oxygen levels measured from the right radial artery.[35] In our analysis, we adjusted for pulse pressure – a surrogate marker for native cardiac output – and still the relationship of extreme hyperoxia and mortality persisted.

Implications

This study suggests that higher levels of oxygen are independently associated with higher 30-day mortality in post CA patients, regardless of method of resuscitation. Prospective studies that compare different oxygen targets are needed to see if a strategy of lower oxygen improves outcomes.

Limitations

Our study had several limitations. First, it is a single-centre observational study which may limit generalisability to other centers. Second, all arterial blood gas samples were taken for routine practice (every 1–2 hours), and some changes in oxygen levels have been not recorded. Third, we excluded patients that died in the first 24 hours as oxygen levels are unlikely to have impact on mortality in this sub-group, however this resulted in a moderate number of patients being excluded. Although we measured pulse pressure as a surrogate for cardiac output, we did not directly measure this variable, and low cardiac output may have been an unmeasured confounder for our results.

Conclusions

We found extreme hyperoxia (PaO_2-levels ≥ 300mmHg) in the first 8 days post CA was independently associated with higher 30-day mortality. We found that although extreme hyperoxia was more common in ECPR patients, the association between extreme hyperoxia and mortality was independent of the method of resuscitation (ECPR vs CCPR). Further interventional studies are required to investigate if reducing PaO_2-levels by decreasing the amount of applied oxygen will improve patient outcomes post CA.

Abbreviations

ABG arterial blood gas analysis

APACHE acute physiology and chronic health evaluation

CA cardiac arrest

CCPR conventional cardiopulmonary resuscitation

CI confidence interval

CNS central nervous system

ECMO extracorporeal membrane oxygenation

ECPR ECMO-Cardiopulmonary resuscitation

FiO_2 Inspired oxygen fraction

FsO_2 fresh gas flow oxygen fraction

ICU intensive care unit

IQR interquartile range

OHCA out of hospital cardiac arrest

OR odds ratio

paO_2 partial pressure of oxygen

PEEP positive endexpiratory pressure

ROS reactive oxygen species

ROSC return of spontaneous circulation

SD standard deviation

SOFA sepsis related organ failure assessment

VA veno-arterial

VAD ventricular assist device

VS versus

VV veno-venous

Declarations

Authors´ Contributions

SES conducted the chart reviews of patients and checked for patient enrollment. SES, EP, AB analysed and interpreted the data. SES and AB wrote the first draft of the manuscript. SES, EP, AB, AU and DP critically revised the manuscript. AB organized the study as an overall supervisor. All the authors reviewed the final draft of the manuscript and agreed on submitting it to *Critical Care.*

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Ethics approval and consent to participate

Prior to the start of the study, approval was obtained by the Alfred Hospital Human Ethics Committee (application: 28/20). The study was approved as a low risk with a waiver of individual patient informed consent.

Consent for publication

Not applicable

Competing interests

All authors of this manuscript have no competing interests.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

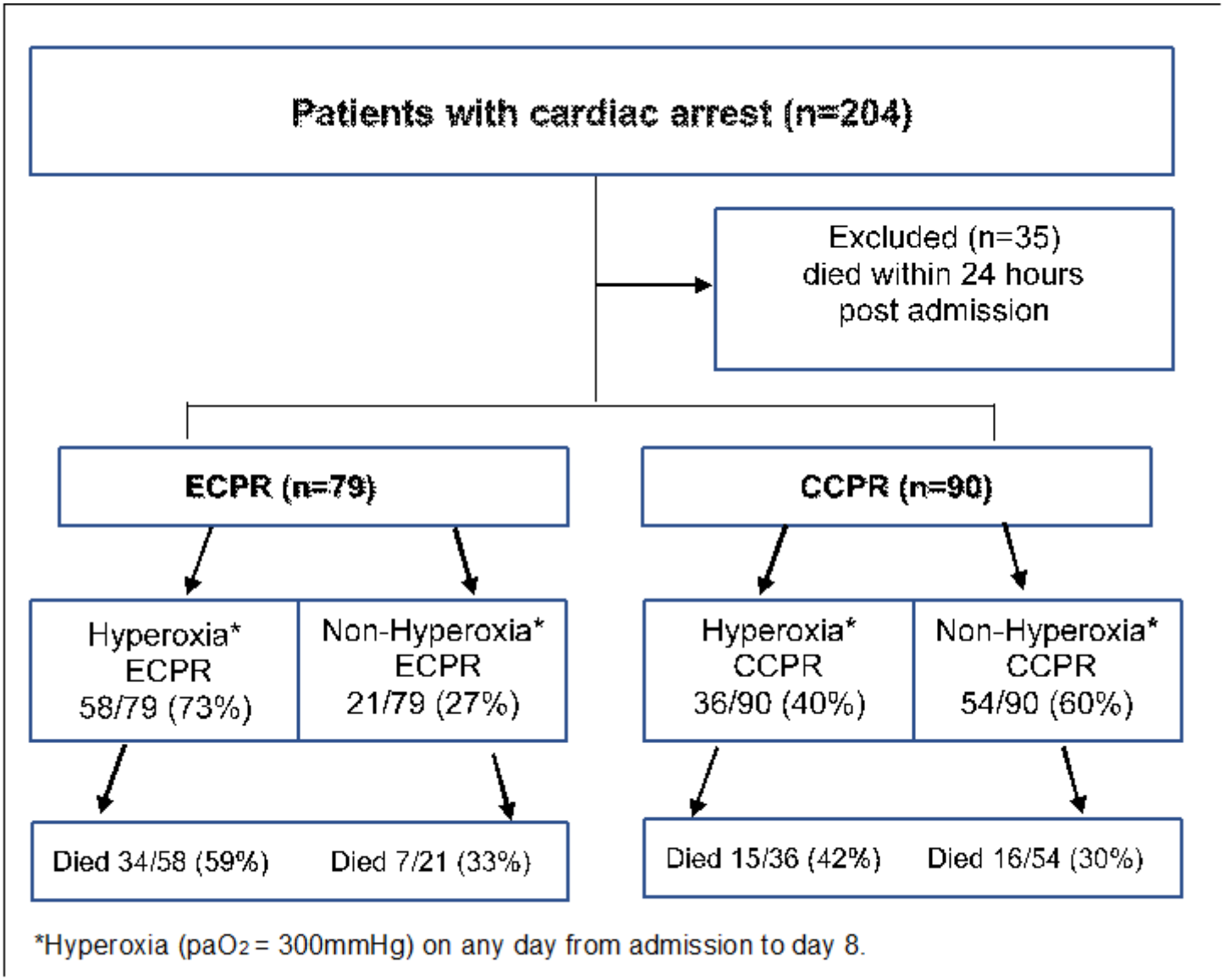

Figure 1

Study flow chart

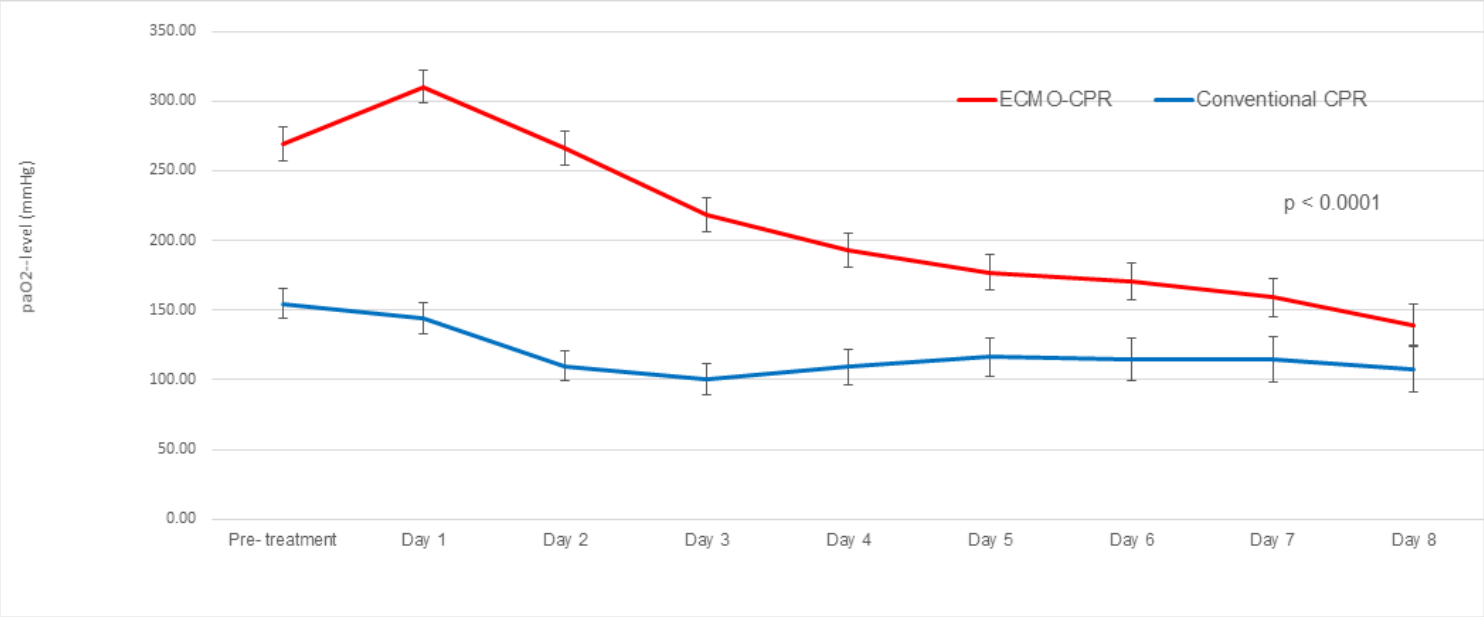

Figure 2

Mean (95% Confidence Interval) daily paO2–levels adjusted over time (8 days) in the ECPR group and the CCPR group.

Supplementary Files

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- Supplement.png