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Clinical paper

Early hyperoxemia is not associated with cardiac arrest outcome

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Abstract

Aim: Studies suggest that hyperoxemia increases short-term mortality after cardiopulmonary resuscitation (CPR), but the effect of hyperoxemia on long-term outcomes is unclear. We determined the prevalence of early hyperoxemia after CPR and its association with long-term neurological outcome and mortality.

Methods: We analysed data from adult cardiac arrest patients treated after CPR in tertiary ICUs during 2005–2013. We retrieved data from the resuscitation and the first arterial blood sample collected after return of spontaneous circulation (ROSC) (severe hyperoxemia defined as $PaO_2 > 40$ kPa and moderate as PaO_2 16–40 kPa). We inspected two outcomes, neurological performance at one year after resuscitation according to the Cerebral Performance Category and one-year mortality. We used logistic regression to test associations between hyperoxemia and the outcome and interaction analyses to test the effect of hyperoxemia exposure on the outcomes in smaller subgroups.

Results: Of 1110 patients 11% had severe hyperoxemia, prevalence was 10% for out-of-hospital arrests, 13% for in-hospital arrests and 9% for in-ICU arrests. In total 585(53%) patients had an unfavourable neurological outcome. Compared to normoxemia, severe (Odds ratio [OR] 0.81, 95% confidence interval [CI] 0.50–1.30) and moderate hyperoxemia (OR 0.94 95%CI 0.69–1.27) did not associate with neurological outcome. Additionally, hyperoxemia had no association with mortality. In subgroup analyses there were no significant associations between severe hyperoxemia and outcomes regardless of cardiac arrest location, initial rhythm or time-to-ROSC.

Conclusion: We found no association between early post-arrest hyperoxemia and unfavourable outcome. Subgroup analysis found no differential effect depending on arrest location, initial rhythm or time-to-ROSC.

Keywords: Cardiac arrest, Post cardiac arrest care, Hyperoxia, Hyperoxemia, Post resuscitation care, Neurological outcome, Cardiac arrest outcome, Intensive care after cardiac arrest, Out of hospital cardiac, arrest, In hospital cardiac arrest, Intensive care unit cardiac arrest

Introduction

Anoxic brain injury is the major cause of disability and death after cardiac arrest (CA), thus any effort aiming to alleviate intra-arrest hypoxemia appear intuitively well founded.[1,2] The latest European Resuscitation Council guidelines advocate using 100% fraction of inspired oxygen (FiO_2) during cardiopulmonary resuscitation (CPR) and targeting an oxygen saturation level of 94–98% during the post-resuscitation period.[3] Cerebral blood flow and oxygen supply are compromised during cardiac arrest but may change rapidly after the return of spontaneous circulation (ROSC). Experimental evidence

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suggests that extreme hyperoxemia after CA and ROSC may exacerbate reperfusion injury.[1,4,5] Harmful effects of hyperoxemia are related to increased oxidative stress which is especially critical for the brain and myocardium.[1,6,7] Animal models have suggested that avoiding hyperoxemia after resuscitation might reduce the neurological injury.[8,9] Retrospective studies in selected and smaller samples showed that hyperoxemia in cardiac arrest may influence short-term outcome.[10,11] The effect of hyperoxemia on long-term neurological outcome is less clear. In addition, most of the previous studies have focused only on out-of-hospital cardiac arrest (OHCA) patients and studied oxygenation mainly during intensive care. Given the differences in the cardiac arrest aetiology, management, and delay to treatment the possible harmful effect of hyperoxemia and the severity of the ischaemic insult may vary between arrest locations. Inspecting CA occurring in different locations can help to understand if certain patient groups are more susceptible to be harmed from severe hyperoxemia exposure than others. The design of future interventional trials would benefit from more epidemiological data on the prevalence and outcome of hyperoxemia in different settings. If early post-arrest hyperoxemia is found to associated with poor neurological outcome, one option would be to limit FiO_2 already during CPR.[12] On the other hand, some studies have suggested improved outcome with intra-arrest hyperoxemia.[13] Thus, previous research is unclear on whether hyperoxemia is harmful when exceeding some threshold or if it is a matter of time- and dose-dependent exposure, and further if there is some certain time-point during or after resuscitation when exposure is most critical.

We aimed to study the impact of early post-ROSC hyperoxemia, as indicated by the first arterial blood gas sample obtained within two hours after ROSC, on long-term outcome in a sample of patients treated after CA occurring at different locations. We hypothesized that hyperoxemia exposure would be significantly associated with poor neurological outcome and higher mortality and that the prevalence of hyperoxemia would vary according to CA-location. In addition, we wanted to study if any possible association between hyperoxemia and outcome would be different depending on arrest location, initial rhythm or time-to-ROSC.

Material & methods

Study setting

We conducted a retrospective cohort study of adult (age ≥18) CA patients treated in the tertiary intensive care units (ICUs) of Helsinki University Hospital between 2005–2013. All participating ICUs followed the same treatment protocols which did not change significantly during the study period.[14,15] The ethics committee of the Operative Division of Helsinki University Hospital (June 2014:194/13/03/02/2014 TMK02§97) and the Finnish National Institute for Health and Welfare (May 2014:THL/713/5.05.01/2014) approved of the study. We included only patients with their first CA event. All patients received CPR either prior to the ICU admission or during the ICU stay depending on the arrest location. We included OHCA and in-hospital cardiac arrest (IHCA) patients in this study, and we used a separate category for cardiac arrests located in the intensive care unit (ICUCA) in which ROSC was achieved. We excluded patients lacking information about the neurological outcome and an applicable arterial blood gas sample (Fig. 1).

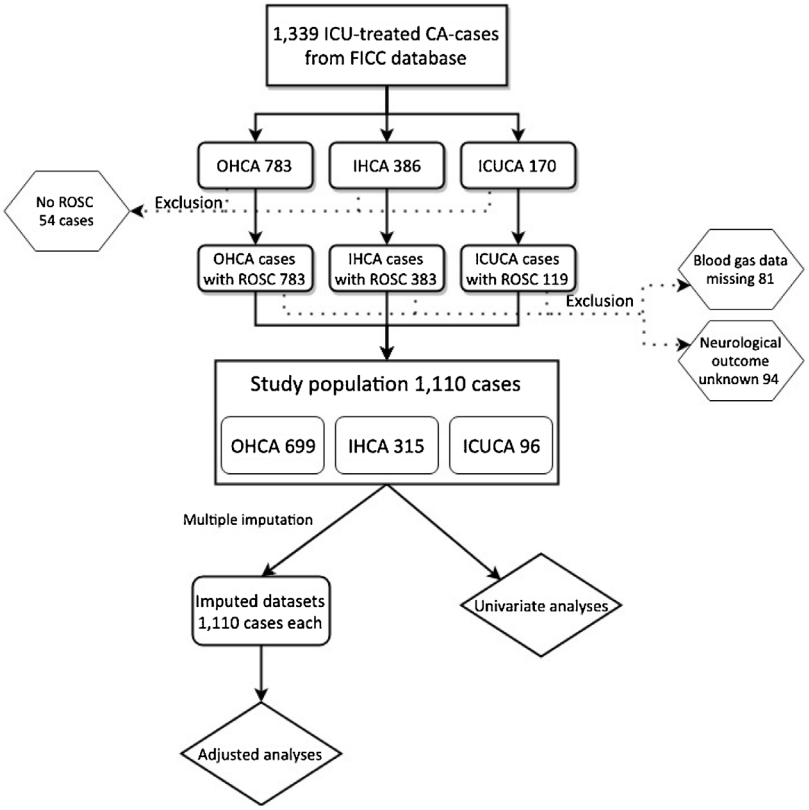

Fig. 1 – Flowchart of patient inclusion and exclusion, (FICC = Finnish Intensive Care Consortium).

Data sources and study variables

We used the Finnish Intensive Care Consortium (FICC) database to retrospectively identify all adult CA patients treated in the ICUs of Helsinki University Hospital 2005–2013. FICC is coordinating a national intensive care benchmarking programme.[16] We collected data on hospital survival, APACHE II (Acute Physiology and Chronic Health Evaluation II) and SAPS II (Simplified Acute Physiology Score II) components and scores from the FICC database.[17,18] We collected information regarding time-to-ROSC, initial cardiac rhythm, cardiac arrest location, and neurological outcome for survivors one year after the arrest from the hospital electronic health records and the date of deaths from Finnish Population Register Centre database. Our data collection and combination of databases are in accordance with our previous study.[19]

The primary outcome measure was neurological outcome according to the Pittsburgh Cerebral Performance Category (CPC), (CPC 1–2 considered as favourable and CPC 3–5 as unfavourable outcome).[20] We evaluated neurological status based on the electronic health records closest to one year after CA. As a secondary outcome we inspected overall mortality at 365 days after CA. Our primary exposure of interest was arterial PaO_2 early on post-resuscitation period. We determined PaO_2 from the first available arterial blood gas (ABG) sample collected up to two hours after ROSC. We used samples collected in hospital and in the pre-hospital setting before hospital admission. We defined severe hyperoxemia as $PaO_2 > 40$ kPa, moderate hyperoxemia as PaO_2 16–40 kPa, normoxemia as PaO_2 8–16 kPa and hypoxemia as $PaO_2 < 8$ kPa, the definition follows thresholds used in previous studies.[21–24]

Statistical analyses

We compared categorical data using a two-sided chi-squared test. We analysed continuous data using non-parametric Mann–Whitney U test (data presented as medians with interquartile ranges [IQR]). We considered p-values <0.05 as statistically significant. All continuous variables tested were skewed. We used significant variables from the univariate analyses (Table 1) to select variables for the multivariable models and tested the variables to avoid multicollinearity. A description of the covariate selection for the multivariable model is found in the electronic Supplemental material. Before conducting the multivariable analysis we applied multiple imputation to estimate missing covariate values in the dataset. In process of multiple imputation statistical analysis software made five parallel datasets with missing values estimated based on the original values' minimum, maximum and value distribution. There were missing variables with following parameters: initial rhythm, time-to-ROSC, APACHE II score, haemoglobin, creatinine, lactate, mean arterial pressure, and glucose. The amount of missing data with each variable was low (<5%). Baseline characteristics of complete cases and cases with missing values is presented in electronic Supplemental material (ESM Table 1). Analyses with the imputed data produces results from the original and parallel datasets and finally pooled results combining all the previous.

We conducted multivariable analyses by using logistic regression. Values are presented as odds ratios (OR) with 95% confidence intervals (CI). Only pooled values are reported and values from the not imputed original data are presented in the supplemental tables. Additionally, we used logistic regression in subanalyses to test interactions between covariates and their effect on outcome. All statistical analyses were performed with SPSS statistics 25.0 for mac OS (Armonk, NY: IBM Corp).

Results

We identified 1339 patients who were treated after cardiac arrest in the ICU between years 2005–2013. Fifty-four patients who did not achieve ROSC, 94 who lacked information about neurological outcome and 81 with missed relevant blood gas data were excluded (Fig. 1). The remaining 1110 cases formed the study population. Before imputation there were 941 complete cases without missing data. Unadjusted analyses were conducted before imputation. Results and the number of missing cases are presented in Tables 1 and 2 showing patient characteristics by neurological outcome and unadjusted comparison between the outcome and different predictors.

Hyperoxemia prevalence & effect on neurological outcome

Of the 1110 patients in the study sample 11% had severe hyperoxemia and 37% had moderate hyperoxemia. According to the first ABG sample 9% of patients were hypoxemic. The overall hyperoxemia prevalence and prevalence by CA-location is presented in Table 3. Prevalence of severe hyperoxemia varied between different arrest locations being 10% for OHCA, 13% for IHCA and 9% for ICUCA patients. Hypoxemia was most common in ICUCA (15%) and least common in OHCA (7%). There was a statistically significant difference in the occurrence of hyperoxemia between CA-locations ($p = 0.024$).

In the study population 585(53%) had a poor neurological outcome (CPC scores 3–5). Factors related to neurological outcome are presented in detail in Table 2. In all oxygen-groups the proportion of poor outcomes was similar (52–54%) with no statistically significant differences. In unadjusted regression analyses and after adjusting for confounding factors there were no associations between neurological outcome and oxygen groups. In unadjusted analyses comparing to the normoxemia the ORs for poor neurological outcome in severe hyperoxemia was 1.05 (95% CI 0.71–1.57) and 1.07 (95% CI 0.82–1.39) in moderate hyperoxemia. Additionally, in adjusted analyses the difference between oxygen groups was not significant, ORs in patients with severe hyperoxemia was 0.89 (95% CI 0.56–1.42) and with moderate hyperoxemia 1.07 (95% 0.80–1.45). The adjusted analysis with pooled and original results is presented in Table 4. Additionally, we conducted a sensitivity analysis excluding cases with CPC score 5 from the analysis. In this subpopulation severe hyperoxemia was not an independent predictor of poor neurological outcome (CPC scores 3–4), (OR 1.61 [95% CI 0.51–5.12]), see results ESM Table 2.

Mortality

As a secondary outcome we analysed mortality one year after CA. One-year survival after CA between oxygen groups is presented on Kaplan–Meier analysis in Fig. 2, no significant differences were detected between groups. We also compared survival between oxygen groups in different arrest locations, Kaplan–Meier analyses are presented in Supplemental material in ESM Fig. 1, no significant differences in survival were found between CA locations. Severe (0.76 95% CI 0.45–1.24) or moderate hyperoxemia (0.94 95% CI 0.69–1.27) was not associated with higher one-year mortality compared with normoxemia. Results for mortality are presented in Supplemental material ESM Table 3.

Table 1 – Unadjusted association between neurological outcome and independent predictors, odds are presented as a probability of poor outcome (CPC 3-5).

Predictor (reference cat.)	OR for poor outcome (95% CI)	p-Value	Missing cases
PaO_2 (normoxemia)			
Hypoxemia (<8 kPa)	1.04 (0.68–1.60)	0.85	
Mod. hyperoxemia (16–40 kPa)	1.07 (0.82–1.39)	0.64	
Severe hyperoxemia (>40 kPa)	1.05 (0.71–1.57)	0.80	
$PaCO_2$ (normocapnia)			
Hypocapnia (<4,5 kPa)	1.17 (0.83–1.66)	0.37	
Hypercapnia (>6 kPa)	1.17 (0.91–1.52)	0.22	
Age (years)	1.03 (1.02–1.04)	<0.001	
Male gender	1.08 (0.83–1.39)	0.57	
Time-to-ROSC (min)	1.01 (1.00–1.03)	0.02	93
Initial rhythm (VT/VF)			50
PEA	2.94 (2.21–3.91)	<0.001	
Asystole	3.78 (2.54–5.63)	<0.001	
Other	2.53 (0.84–7.62)	0.1	
CA Location (OHCA)			
IHCA	1.78 (1.37–2.30)	<0.001	
ICUCA	2.24 (1.47–3.41)	<0.001	
Comorbidities (yes)			
Chronic renal disease	1.24 (0.67–2.31)	0.5	192
Lung disease	1.44 (0.90–2.29)	0.13	152
Liver disease	3.30 (0.99–9.28)	0.05	
NYHA-class prior CA (NYHA I)			100
NYHA II	0.96 (0.68–1.36)	0.82	
NYHA III	1.32 (0.86–2.12)	0.19	
NYHA IV	1.02 (0.69–1.51)	0.91	
Modified APACHE score (excluding points for PaO_2)	1.12 (1.09–1.13)	<0.001	5
Vital signs			
Central temperature (C°)	1.17 (1.11–1.23)	<0.001	33
MAP (worst during 24 h) (mmHg)	0.97 (0.96–0.98)	<0.001	12
Heart rate (bpm)	1.01 (1.005–1.011)	<0.001	4
Respiratory rate	1.04 (1.03–1.06)	<0.001	9
GCS	0.96 (0.94–0.98)	<0.001	14
Laboratory parameters			
Arterial pH	0.07 (0.03–0.16)	<0.001	4
Plasma glucose (mmol/l)	1.03 (1.01–1.06)	0.005	50
Lactate (mmol/l)	1.14 (1.10–1.18)	<0.001	42
Haemoglobin (g/l)	0.99 (0.98–0.99)	<0.001	23
Creatinine (μmol/l)	1.003 (1.001–1.004)	<0.001	42
Witnessed by anyone (yes)	0.55 (0.37–0.83)	0.004	19
Admission type			
Emergency	2.97 (1.03–7.06)	0.04	4
Operative	0.76 (0.49–1.16)	0.2	

Effect of hyperoxemia exposure on outcome in different subgroups

We tested interactions between oxygen level and different covariates to see if oxygen would be a significant predictor of the neurological outcome or mortality in different subgroups. We tested the following interactions; initial rhythm*PaO_2, CA-location*PaO_2, and time-to-ROSC*PaO_2. PaO_2 was tested separately as continuous variable and categorical variable. No interactions associated with neurological outcome were found. With mortality significant interactions were found between PaO_2 and PEA as an initial rhythm. Additionally, significant interaction was found between severe hyperoxemia and time-to-ROSC. The significance level of different interactions is found from ESM Table 4 in Supplemental material.

Multivariable model accuracy

The area under the receiving operating characteristic (ROC) curve was 0.73 for model predicting neurological outcome and 0.75 for model predicting one-year mortality. Hosmer–Lemeshow test indicated fit models (p-value >0.05).

Discussion

In this retrospective large single-centre study with CA-patients treated in ICU we found no association between early exposure to hyperoxemia and long-term neurologic outcome or mortality. These findings suggest the lack of clear association between short-term initial

Table 2 – Baseline characteristics of study population by CPC-score one year after cardiac arrest.

Patient characteristics	All patients in group No. of patients (%)/median (IQR)	Good outcome (CPC-scores 1–2)	Poor outcome (CPC-scores 3–5)	p-Value*	Cases missing
	1110	525 (47%)	585 (53%)		
PaO_2 (kPa)	15.3 (10.5–25.7)	15.2 (10.4–24.6)	15.5 (10.7–26.4)	0.36	
PaO_2 (No. of patients (%))				0.97	
Hypoxemia (<8 kPa)	98 (9%)	47 (48%)	51 (52%)		
Normoxemia (8–16 kPa)	483 (43%)	232 (48%)	251 (52%)		
Moderate hyperoxemia (16–40 kPa)	407 (37%)	189 (46%)	218 (54%)		
Severe hyperoxemia (>40 kPa)	122 (11%)	57(47%)	65 (53%)		
Gender				0.67	
Female	309 (28%)	143 (46%)	166 (54%)		
Male	801 (72%)	382 (48%)	419 (52%)		
Age (years)	63 (54–71)	60 (50.5–68)	65(56–74)	<0.001	
ROSC (min)	16 (10–22)	15 (9–21)	18 (10–24)	0.004	93
PCO_2 (kPa)	5.6 (4.8–6.7)	5.6 (4.8–6.5)	5.6 (4.8–6.7)	0.39	
PCO_2 (No. of patients (%))				0.53	
Hypocapnia (<4,5 kPa)	212 (19%)	97 (46%)	115 (54%)		
Normocapnia (4,5–6 kPa)	473 (43%)	233 (49%)	240 (51%)		
Hypercapnia (>6 kPa)	425 (38%)	195 (46%)	230 (54%)		
Initial rhythm				<0.001	50
VT/VF	643 (61%)	377 (59%)	266 (41%)		
PEA	274 (26%)	89 (33%)	185 (68%)		
Asystole	132 (12%)	35 (27%)	97 (73%)		
Other	11 (1%)	4 (36%)	7 (64%)		
CA location				<0.001	
OHCA	699 (63%)	370 (53%)	329 (47%)		
IHCA	315 (28%)	121 (38%)	194 (62%)		
ICUCA	96 (9%)	34 (35%)	62 (65%)		
Comorbidity (yes)					
Liver disease	18 (2%)	4 (22%)	14 (78%)	0.04	
Lung disease	71 (7%)	30 (42%)	41 (58%)	0.45	152
Renal disease	37 (4%)	16 (43%)	21 (57%)	0.59	192
NYHA-classification (prior CA)				0.32	100
I	680 (67%)	342 (50%)	338 (50%)		
II	141 (14%)	72 /51%)	69 (49%)		
III	86 (8%)	33 (40%)	50 (60%)		
IV	106 (11%)	51 (48%)	55 (52%)		
Modified APACHE II score (points for PaO_2 excluded)	23 (17–29)	19 (15–25)	27 (20–31.25)	<0.001	5
Vital signs					
Central temperature (C°)	36.6 (34.8–37.7)	36.1 (34.4–37.6)	37 (35.2–37.8)	<0.001	33
MAP worst during 24 h (mmHg)	68 (58–131)	102 (61–119)	65 (54–115)	<0.001	12
Heart rate	55 (44–135)	52 (43–69)	61 (45–120)	<0.001	4
Respiratory rate	14 (10–23)	11 (9–18)	17 (10–26)	<0.001	9
GCS (worst during 24 h)	15 (3–15)	15 (8–15)	8 (3–15)	<0.001	14
Laboratory parameters					
Arterial pH	7.29 (7.22–7.44)	7.31 (7.25–7.46)	7.28 (7.18–7.41)	<0.001	4
Creatinine (μmol/l)	86 (67–121)	79 (64–99)	98 (71–139)	<0.001	42
P-Glucose (mmol/l)	10.6 (8.2–13.9)	9.9 (7.9–13)	11.2 (8.6–14.4)	<0.001	50
P-Lactate (mmol/l)	4.3 (2.1–7.5)	3.3 (1.8–5.9)	5.5 (3.0–8.9)	<0.001	42
Haemoglobin (g/l)	127 (105–141)	130 (115–143)	121 (100–138)	<0.001	23
Admission Type					
Operative (yes)	91 (8%)	48 (53%)	43 (47%)	0.28	
Emergency (yes)	1087 (98%)	510 (47%)	577 (53%)	0.063	4
Witnessed by anyone (yes)	977 (90%)	480 (49%)	497 (51%)	0.001	19

* p-Value conducted with chi-squared test with categorical and with Mann–Whitney U test with continuous variable.

Table 3 – Overall hyperoxemia prevalence and prevalence by cardiac arrest location.

	Total No. of (% of total patients)	Hypoxemia (PaO_2 <8 kPa) No. of patients (%)	Normoxemia (PaO_2 8–16 kPa)	Moderate hyperoxemia (PaO_2 16–40 kPa)	Severe hyperoxemia (PaO_2 >40 kPa)	p-Value*
All patients	1110	98 (9%)	483 (43%)	407 (37%)	122 (11%)	
				All with oxygen >16 kPa 529 (48%)		
CA-location						0.024
OHCA	699 (63%)	47 (7%)	307 (44%)	272 (39%)	73 (10%)	
IHCA	315 (28%)	37 (12%)	132 (42%)	106 (33%)	40 (13%)	
ICUCA	96 (9%)	14 (15%)	44 (46%)	29 (30%)	9 (9%)	

* p-Value calculated using Chi-Square method.

Table 4 – Adjusted analysis of the neurological outcome, odds are presented as a probability of poor outcome (CPC 3-5).

Predictor (ref. category)	Pooled OR for poor outcome (95% CI)[a]	p-Value	Original OR for poor outcome (95% CI)[b]	p-Value
PaO_2-group (normoxemia)				
Hypoxemia (<8 kPa)	0.78 (0.48–1.27)	0.31	0.76 (0.45–1.30)	0.32
Moderate hyperoxemia (16–40 kPa)	1.07 (0.80–1.45)	0.64	1.02 (0.74–1.41)	0.90
Severe Hyperoxemia (>40 kPa)	0.89 (0.56–1.42)	0.62	0.83 (0.50–1.37)	0.54
$PaCO_2$-group (normocapnia)				
Hypocapnia (<4,5 kPa)	0.88 (0.61–1.28)	0.5	0.84 (0.56–1.25)	0.38
Hypercapnia (>6 kPa)	0.93 (0.69–1.26)	0.65	0.84 (0.61–1.16)	0.28
Initial rhythm (VT/VF)				
PEA	1.86 (1.31–2.64)	<0.001	1.73 (1.19–2.52)	0.004
Asystole	2.40 (1.50–3.85)	<0.001	2.38 (1.43–3.95)	0.001
Other	2.23 (0.51–9.73)	0.28	2.02 (0.55–7.50)	0.29
CA-location (OHCA)				
IHCA	0.99 (0.69–1.43)	0.97	0.93 (0.62–1.38)	0.55
ICUCA	1.40 (0.82–2.39)	0.22	1.15 (0.64–2.14)	0.61
Modified APACHE II score[c]	1.08 (1.06–1.10)	<0.001	1.08 (1.05–1.10)	<0.001
MAP	1.00 (0.99–1.001)	0.11	1.00 (0.99–1.001)	0.13
Creatinine (μmol/l)	1.00 (0.998–1.001)	0.08	1.00 (0.997–1.001)	0.22
Hb (g/l)	1.00 (0.99–1.003)	0.24	1.00 (0.99–1.004)	0.38
P-Lactate (mmol/l)	1.06 (1.02–1.10)	0.006	1.06 (1.02–1.11)	0.005
P-Glucose (mmol/l)	1.01 (0.99–1.04)	0.38	1.01 (0.99–1.04)	0.43

Hosmer–Lemeshow goodness of fit test for the model conducted with original values p = 0.141.
[a] Pooled odd ratios are conducted with database in which missing values has been estimated with multiple imputation.
[b] Original odd ratios are conducted with database in which all cases with missing values excluded.
[c] APACHE II score excluding points for oxygenation.

hyperoxemia and long-term outcome after CA and successful resuscitation. Short-term exposure to hyperoxemia may be common and difficult to avoid given the recommend use of 100% oxygen during CPR. As the injury mechanisms may differ both based on severity of the ischemic insults as well as the cause of the arrest we conducted a set of interaction analyses and found no clear subgroup differences between early hyperoxemia and neurological outcome.

Hyperoxemia prevalence

Many previous studies define extreme hyperoxemia as 300 mmHg (≈40 kPa) or higher. These studies have used varying settings and the overall prevalence for hyperoxemia have varied between 6–41%.[13,21,23,25–28] We used the same threshold for hyperoxemia as these previous studies and found that the prevalence for severe hyperoxemia measured from the first available arterial sample within two hours after ROSC was 11%. However, almost 40% were exposed to a moderate level of hyperoxemia (PaO_2 > 16 kPa/120 mmHg) according to the first available sample. Previously the highest values for hyperoxemia prevalence have been detected when including samples collected prior to hospital admission, suggesting the oxygen titration is easier in the hospital.[13,25] Two studies conducted in the United States observed a severe hyperoxemia prevalence of 18% and 24% during the ICU stay after CA.[21,28] In a general ICU population a

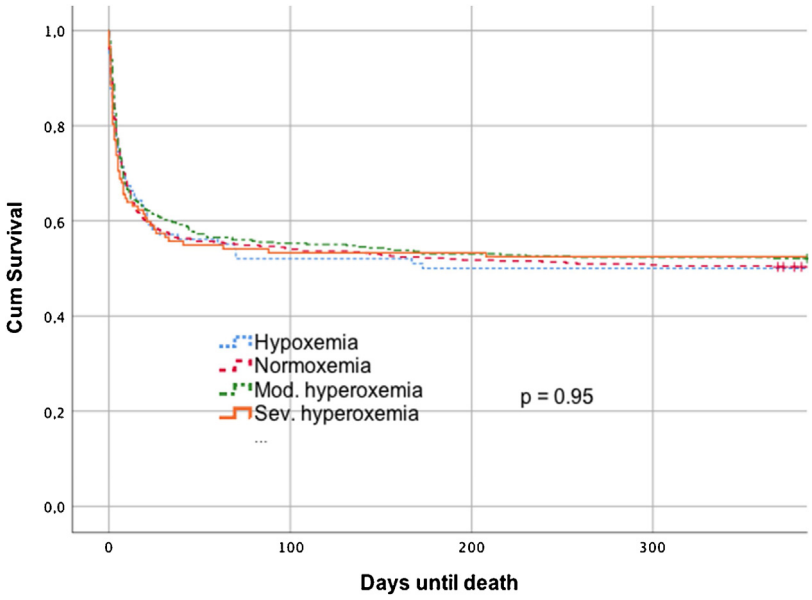

Fig. 2 – Kaplan Meier analysis of one-year survival between oxygen groups. Groups are defined as following: hypoxemia PaO_2 <8 kPa, normoxemia PaO_2 8–16 kPa, moderate hyperoxemia PaO_2 16–40 kPa and severe hyperoxemia PaO_2 > 40 kPa.

prevalence of 11% for hyperoxemia and 29% for moderate hyperoxemia has been observed.[26] Slightly higher oxygen values have been detected in studies conducted in the United States compared to European studies which may be related to the subtle differences in resuscitation guidelines between continents.[3,10,21,26–29] European resuscitation guidelines emphasize targeting a peripheral oxygen saturation of 94–98% after ROSC, while the American Heart Association guidelines emphasize the avoidance of hypoxemia.[3,29] Our study revealed slight differences between hyperoxemia prevalence in different arrest locations, with the highest prevalence occurring in IHCA patients. Two other studies reported the prevalence by CA location and their results differ from ours. In a study conducted by Bellomo et al. the prevalence was slightly higher with OHCA and in another study conducted by Nelskylä et at. OHCA patients were notably more often hyperoxemic compared to IHCA or ICUCA patients (65% vs. 21% and 30%).[23,25]

Effect of hyperoxemia on outcomes

The major factor in tissue damage and organ dysfunction after ischemia-reperfusion is the formation of reactive oxygen species, the amount of which increases with increasing PaO_2.[1,4,5,30] The severity of cerebral reperfusion injury is not only defined by arterial PaO_2, as cerebral circulatory autoregulation is affected by many mediators, making the understanding of CNS reperfusion pathophysiology challenging.[31] Furthermore, the optimal level of oxygenation during resuscitation is not known. There is evidence suggesting ROSC is more likely achieved with higher intra-arrest arterial PaO_2.[13,32] One animal study suggested early hyperoxemia exposure after ROSC is harmful for neuronal tissue but later exposure is not.[9] The arterial PaO_2 measured soon after ROSC is, after intra-arrest PaO_2, the second best indicator of oxygenation achieved during resuscitation. As our results indicate no clear association of early hyperoxemia, it seems that hyperoxemia exposure during resuscitation and early after ROSC may not compromise outcome and would thus not be necessary to avoid. Nonetheless, it may be necessary to decrease FiO_2 soon after ROSC when arterial oxygenation can be monitored appropriately in order to avoid harmful effects of later and prolonged hyperoxemia exposure.

Randomised data on oxygen use after CA are limited. A randomized human pilot study conducted by Kuisma et al. studied effect of 100% and 30% FiO_2 for one hour immediately after ROSC and found no differencies in oxygenation or levels of neurone spesific enolase (NSE), a marker of brain injury.[33] Jakkula et al., compared the effect of targeting normoxemia (10–15 kPa) or moderate hyperoxemia (20–25 kPa) during the first 36 h of intensive care and no differences in NSE levels over time, additionally there was no difference in neurological outcome.[34] Cerebral oxygen saturation was significantly higher in the moderate hyperoxemia group but the clinical implication of this is unclear. All randomised studies have focused on OHCA-patients. One may assume that the pathophysiological processes and the severity of hypoxic brain injury and cardiac failure vary slightly depending on the arrest location.[35] In our study early hyperoxemia exposure was not associated with neurological outcome or mortality and in sensitivity analyses the association did not change by CA-location. Further on, we found no difference in the association between hyperoxemia and outcome indexed by several factors influencing the severity of hypoxic-ischaemic brain injury i.e. initial rhythm and duration of the arrest.

Strengths and limitations

Our study presents a large sample of patients with detailed data on factors at CA, ICU care and long-term outcomes. A difference from previous studies is that we used the first available ABG samples, including pre-hospital samples, after ROSC to determine hyperoxemia exposure rather than samples collected not until in ICU. Additionally, our data consists of patients with CA occurring in different

locations. The possible differences between the cardiac arrest aetiology and delay to treatment were recognized from the beginning and managed in the statistical analysis design. We performed retrospective sensitivity analysis to detect the minimum detectable difference in outcomes between hyperoxemia and non-hyperoxemia groups with our sample size. With 95% likelihood we can detect an effect greater than 0.10/10% in outcomes between the groups. Other studies have shown effects at least 0.12/12%, therefore a Type II error seems unlikely.[10,21]

However our study has some limitations. The retrospective method can only point out association and not causality. In our dataset ABG samples are not time-stamped, making it uncertain exactly how long after ROSC they were collected. However, we excluded samples collected more than two hours after ROSC. As we only used one ABG sample to determine PaO_2, and are thus unable to determine duration of hyperoxemia, it is likely that the exposure in some cases may have been more of an early pulse than prolonged exposure. The majority of our cases were OHCAs but for those cases we lack the information whether the inspected ABG sample was collected before or after hospital admission. Thus, it is possible that oxygen therapy had already been titrated reducing the prevalence of hyperoxemia. In addition, we studied long-term outcome, which may be influenced by many other factors as well during the follow up period. Lastly, due to missing data, we could not use all included patients in all analyses. However, additional analyses with imputed data showed comparable results.

Conclusions

In this study we found no association between early post-ROSC hyperoxemia and outcomes after cardiac arrest and successful CPR. Extreme hyperoxemia was fairly uncommon in our study sample including the first available arterial blood gas measurement within 2 h after ROSC. Further, we were unable to detect neither harm nor benefit from early hyperoxemia regardless of arrest location, initial rhythm or delay to ROSC, suggesting that there is no association between hyperoxemia during and soon after CPR and long-term outcome.

Conflicts of interests

Authors have no conflicts of interests regarding this study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.035.

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