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Clinical paper

Increasing arterial oxygen partial pressure during cardiopulmonary resuscitation is associated with improved rates of hospital admission☆

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ABSTRACT

Aim: As recent clinical data suggest a harmful effect of arterial hyperoxia on patients after resuscitation from cardiac arrest (CA), we aimed to investigate this association during cardiopulmonary resuscitation (CPR), the earliest and one of the most crucial phases of recirculation.
Methods: We analysed 1015 patients who from 2003 to 2010 underwent out-of-hospital CPR administered by emergency medical services serving 300,000 inhabitants. Inclusion criteria for further analysis were nontraumatic background of CA and patients >18 years of age. One hundred and forty-five arterial blood gas analyses including oxygen partial pressure (paO2) measurement were obtained during CPR.
Results: We observed a highly significant increase in hospital admission rates associated with increases in paO2 in steps of 100 mmHg (13.3 kPa).

Subsequently, data were clustered according to previously described cutoffs (≤60 mmHg [8 kPa]], 61–300 mmHg [8.1–40 kPa], >300 mmHg [>40 kPa]). Baseline variables (age, sex, initial rhythm, rate of bystander CPR and collapse-to-CPR time) of the three compared groups did not differ significantly. Rates of hospital admission after CA were 18.8%, 50.6% and 83.3%, respectively. In a multivariate analysis, logistic regression revealed significant prognostic value for paO2 and the duration of CPR.
Conclusion: This study presents novel human data on the arterial paO2 during CPR in conjunction with the rate of hospital admission. We describe a significantly increased rate of hospital admission associated with increasing paO2. We found that the previously described potentially harmful effects of hyperoxia after return of spontaneous circulation were not reproduced for paO2 measured during CPR.

Clinical trial registration: n/a.

1. Introduction

In recent years, several studies have highlighted potential detrimental effects of hyperoxia in the context of cardiopulmonary resuscitation (CPR) and other ischemia-reperfusion situations. Most of the data derive from controlled animal and laboratory studies[1–3] and point at poorer neurological outcome following hyperoxia after return of spontaneous circulation (ROSC).[4]

The only randomized controlled human study compared inspiratory oxygen concentrations of 30% and 100% after ROSC as a feasibility study and evaluated surrogate markers for brain injury. No difference in survival was observed, and the study was not powered to reveal differences in overall or neurologic outcome.[5]

Two large observational studies have been published that elucidate the impact of hypoxia, normoxia and hyperoxia after ROSC on survival and functional status of patients resuscitated from cardiac arrest (CA). Although some of the data suggest a detrimental effect of hyperoxia comparable to that of hypoxia on survival when applied after CPR,[6,7] this effect has not been convincingly reproduced.[8] Also in neonatal resuscitation, a field where the use of oxygen has also been investigated experimentally, results regarding a possible survival benefit of any oxygen regimen are conflicting.[9,10] The exact mechanisms behind an adverse effect of oxygen are unclear, but undesirable influences of hyperoxia and

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oxygen toxicity on coronary blood flow, brain injury and tissue oxygenation are currenty debated.[11–13] Beyond that, there is scarce evidence in humans for a clinical impact of reoxygenation injury in an emergency setting. Current European Resuscitation Council Guidelines for CPR recommend titration of oxygen during and after CPR to achieve a peripheral oxygen saturation of 94–98%,[14] whereas the American Heart Association recommends the empirical use of 100% oxygen during CPR and its titration after ROSC.[15] Still, there are no human outcome studies on the influence of the arterial oxygen partial pressure (paO2) during CPR.[16] As CPR is the earliest phase of recirculation and reperfusion in any victim of CA, the potential (re)oxygenation injury in this phase must be of utmost interest.

In view of this unclear situation, we aimed to investigate the impact of paO2 measured by point-of-care-testing (POCT) during out-of-hospital CPR on the rate of survival to hospital admission (HA) to test the hypothesis that supranormal paO2 has a detrimental effect on this endpoint.

2. Methods

We extracted data on patients treated by the local EMS from January 1, 2003 to December 31, 2010. Inclusion criteria were: age >18 years, nontraumatic CA, duration of CPR >5 min and arterial blood gas analysis including paO2 measurement during CPR.

All patients were treated by a physician staffed EMS serving about 300,000 inhabitants in a metropolitan and suburban area. The EMS comprises two emergency response cars and two mobile intensive care units with a minimum of four persons on site. The crews (at least one emergency physician and two paramedics on site) are specially trained in both the administration of advanced cardiac life support including endotracheal intubation and the use of point-of-care arterial blood gas testing.

Included patients were treated in accordance with the respective guidelines for CPR concerning medications and defibrillation. Before arterial blood gas samples were drawn, advanced cardiac life support measures had been implemented. Chest compressions were performed manually. A peripheral (or the external jugular) vein was cannulated for drug administration and all patients underwent endotracheal intubation within the first minutes of ACLS. Tube position was checked and cases of oesophageal misplacement were recognized by capnometry or a calorimetric device. In such cases patients were intermittently ventilated by bag mask and reintubated endotracheally. No cases of persistent tube misplacement were reported. Patients were ventilated during CPR with 100% inspiratory oxygen, either by bag ventilation with oxygen reservoir (Ambu® Mark III) or by volume controlled ventilation with an emergency respirator (Draeger® Oxylog® 2000 or 3000).

As soon as feasible, but no later than 60 min after the commencement of chest compressions, an arterial blood gas sample was obtained either with an indwelling arterial catheter or single arterial puncture with a microsampler during CPR. At the time of sampling, all patients were intubated and ventilated with 100% oxygen and were receiving manual chest compressions. In cases of repeated ABG measurements, the first sample was used for analysis. Samples were processed immediately by a portable POCT analyser as described earlier.[17]

2.1. Data

Data were obtained by two independent reviewers (GG, FH); inconsistencies were resolved by discussion. We recorded the following variables using the Utstein style (uniform reporting of data from out-of-hospital arrest).[18] Age, sex, witnessed CA, bystander resuscitation, collapse-to-CPR start interval (time between CA and initiation of sufficient CPR), presumed etiology, initial ECG rhythm, duration of CPR, medications administered (adrenaline, atropine, amiodarone, sodium bicarbonate, systemic thrombolysis), shocks delivered.

For comparability with regard to different durations of CPR, repeated measures (adrenaline, shocks) were normalized to 10 minutes of CPR time.

2.2. Survival data

Patients were admitted to one of two ICUs (intensive care units), one located at an academic referral center with a total capacity of 15 medical ICU beds (in the following referred to as hospital 1), the other at a general hospital with a total capacity of nine medical ICU beds (hospital 2). Both hospitals provided facilities for coronary intervention.

Spontaneous circulation upon HA leading to inhospital stay at an ICU for at least one hour was chosen as the main outcome parameter to evaluate immediate effects of prehospital treatment. Transport to hospital mandated sustainable ROSC on site; otherwise, patients were declared dead by the emergency physician.

Overall ROSC rates (including patients who achieved ROSC at any timepoint but deceased in the field) were also recorded.

Secondary survival (defined cerebral performance category [CPC] 1 or 2[19] at day 28 or at discharge) were also recorded. Differences in ICU treatment were not the aim of the study and thus not evaluated.

2.3. Oxygen subgrouping

Initially, rates of HA were calculated for groups of patients in steps of 100 mmHg (13.3 kPa) paO2. For further analyses consistent with previous findings,[6–8] patients were allocated to groups as follows: low oxygen ($\leq$60 mmHg [$\leq$8 kPa]), intermediate oxygen (61–300 mmHg [8.1–40 kPa]) and high oxygen (>300 mmHg [>40 kPa]).

2.4. Statistical analyses

Data were analysed using SPSS Statistics 17 software (IBM® Corporation, USA). The Kolmogorov–Smirnov test was used to test for Gaussian distribution of continuous variables. Descriptives are given as mean $\pm$ standard deviation.

Student's *t*-test, one-way-ANOVA, Kruskal–Wallis test, Mann–Whitney tests, Chi-squared test or Fisher's exact test were used as appropriate. Odds ratios were calculated by logistic regression analysis. Significance was assumed when p values were $\leq$0.05. Intervariable correlations were calculated using the contingency coefficient or Pearson's correlation as appropriate.

For multivariate analysis, logistic regression with backward elimination of variables was used. The significance level was set to 0.05, probability for removal of variables was 0.07; a maximum of 20 iterations was permitted. HA was used as dependent variable.

2.5. Ethical considerations

The study protocol was approved by the local ethics committee (IORG0002039), number 24-398 ex 11/12.

3. Results

During the study period, 43,569 protocols of emergency responses (i.e. total activations of the emergency medical system) were documented and resuscitation was attempted in 1015 persons, 1005 of whom had nontraumatic CA. After selection of adult patients who had had an arterial blood gas analysis during CPR

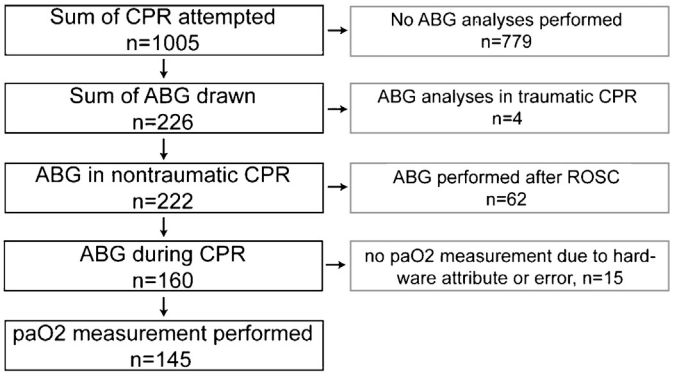


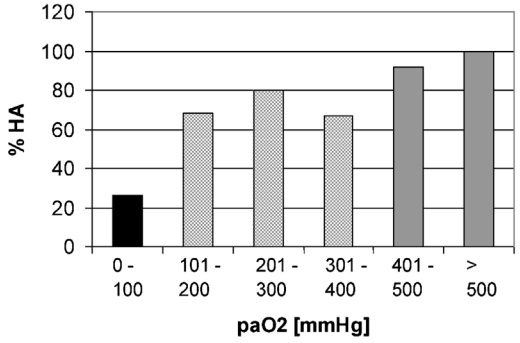
Fig. 1. Arterial blood gas analyses eligible for the study. In the study period, resuscitation according to guidelines was attempted in 1005 nontraumatic cardiac arrests. For analysis of paO2 during CPR, 145 arterial blood gas analyses could be used. CPR: cardiopulmonary resuscitation; ABG: arterial blood gas analysis; ROSC: return of spontaneous circulation; paO2: arterial oxygen partial pressure.

(ABG cohort), 145 patients remained for further analysis (Fig. 1). The exact timepoint of the ABG was documented in 55 patients; the median collapse to ABG interval was 27 min (range 5–60 min).

Fig. 2 displays a nearly linear increase of the rate of HA for groups of patients categorized by their paO2 in steps of 100 mmHg each, whereas data for the subsequently used oxygen subgroups are presented in Table 1.

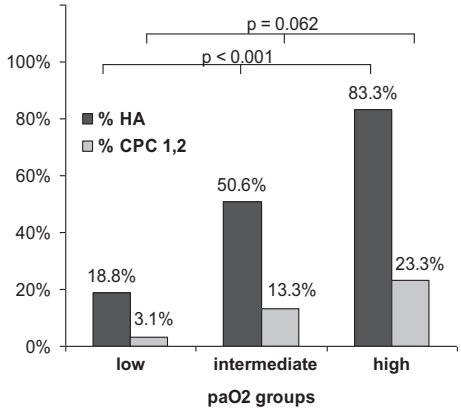
There were no significant differences in patient baseline characteristics and factors determining resuscitation outcome *a priori*[20] between the three compared oxygen groups (Table 1A).

Interventions during CPR were also comparable between the groups. There were no significant differences regarding the doses of adrenaline, amiodarone, sodium bicarbonate and the number of defibrillations administered. Notably, the rate of systemic



paO2 (mmHg)	paO2 (kPa)	n	Died in the field	Any ROSC	Survived to HA	Survived with CPC 1 or 2
0-100	0 - 13.3	76	56	26	20	4
101-200	13.4-26.7	25	8	17	17	6
201-300	26.8-40.0	14	3	11	11	2
301-400	40.1-53.3	13	4	9	9	5
401-500	53.4-66.7	12	1	11	11	1
>500	>66.7	5	0	5	5	1

Fig. 2. Rates and numbers of HA, any ROSC and neurologically intact survival (CPC) according to paO2 (in steps of 100 mmHg). A highly significant ($p < 0.001$) rise in HA with increasing levels of paO2 could be found among the six displayed groups of 100 mmHg paO2 each. paO2: arterial oxygen partial pressure; HA: hospital admission; mmHg: millimetres of mercury; kPa: kilopascal; ROSC: return of spontaneous circulation; CPC: cerebral performance category.



Oxygen Group	paO2 (mmHg)	paO2 (kPa)	n	Died in the field	Any ROSC	Survived to HA	Survived with CPC 1 or 2
Low	0-60	0-8	32	26	7	6	1
Intermediate	61-300	8.1-40	83	41	47	42	11
High	>300	>40	30	5	25	25	7

Cerebral performance category

Fig. 3. Rates and numbers of HA, ROSC and neurologically intact survival (CPC) in the low (paO2 0–60 mmHg), intermediate (paO2 61–300 mmHg) and high (paO2 > 300 mmHg) groups. Rates of HA (18.8%, 50.6% and 83.3%, respectively) increased significantly ($p < 0.001$) with increasing paO2. This could not be displayed for neurologically intact survival ($p = 0.062$). paO2: arterial oxygen partial pressure; HA: hospital admission; mmHg: millimetres of mercury; kPa: kilopascal; ROSC: return of spontaneous circulation; CPC: cerebral performance category.

thrombolysis was relatively high, but not different between groups (Table 1B), and the same applied for presumed thrombembolic causes for CPR (p = ns).

Durations of CPR were: low O2: 39.8 ± 15 min, intermediate O2: 34.9 ± 22.9 min and high O2: 28.4 ± 18.9 min ($p = 0.006$ versus low). Moreover, Table 1 reports baseline characteristics and interventions in patients not subgrouped according to their paO2 during CPR as comparative data for patients without available oxygen data.

3.1. Survival to HA

Of all patients in the ABG cohort ($n = 145$), 50.3% achieved a sustainable ROSC and were subsequently admitted to hospital (in comparison, 29.4% of the non-ABG cohort [$n = 860$] achieved HA; overall HA rate [$n = 1005$]: 32.4%). Of all admitted patients, 64% were admitted to hospital 1, 36% to hospital 2. The majority of high-oxygen patients (83.3%) reached the endpoint hospital admission, whereas this was possible in 50.6% of intermediate and only for 18.8% of low oxygen patients (Fig. 3). There was no impact of either the presumed aetiology (cardiac versus noncardiac) on this effect, or the resuscitation guideline iteration in the year 2005. Fig. 4 shows the odds ratios for HAs.

After multivariate logistic regression (potential predictive variables entered at the first step, Table 2A), only the duration of CPR and the arterial pO2 remained as significant contributors to survival (Table 2B).

3.2. ROSC at any stage

In six patients, ROSC at any stage and HA differed (low and intermediate groups, p = ns, see Fig. 3).

Table 1
(A) Baseline characteristics of CPR for oxygen subgroups (columns low-high) and patients not included in the oxygen analysis (Comparison). (B) Interventions during CPR (in alphabetical order) paO2: arterial oxygen partial pressure; mmHg: millimetres of mercury; kPa: kilopascal; CPR: cardiopulmonary resuscitation; VF/VT: ventricular fibrillation/ventricular tachycardia; SD: standard deviation.

Oxygen group (paO2, mmHg) (paO2, kPa)		Low (<60) (<8)	Intermediate (61–300) (8.1–40)	High (>300) (>40)	*p*	Comparison[†]
n		32	83	30		
(A)						
Age (years)	Mean (SD)	62.7 (15.9)	66.9 (15.5)	65.3 (12.1)	0.262	66.4 (17.4)
Sex: female	%	9.4	28.9	23.2	0.099	40.4[*]
Collapse to CPR interval (min)	Mean (SD)	5.0 (6.8)	5.3 (5.8)	5.0 (5.5)	0.747	5.8 (5.7)
Bystander CPR	%	59.4	41.5	37.9	0.159	35.5[*]
Initial rhythm VF/VT	%	40.6	43.4	46.7	0.891	48.1
(B)						
Adrenaline/10 min CPR (mg)	Mean (SD)	1.34 (0.52)	1.50 (1.08)	1.21 (0.89)	0.348	1.50 (2.2)
Amiodarone	%	34.4	28.9	23.3	0.455	11.5[*]
Atropine	%	68.8	59.0	36.7	0.045	46.7[*]
Shocks/10 min CPR	Mean (SD)	0.97 (1.06)	0.94 (1.47)	0.70 (0.84)	0.544	0.72[*] (1.30)
Sodium bicarbonate 8.4% (ml)	Mean (SD)	66.7 (62.0)	67.3 (73.5)	73.5 (73.5)	0.900	41.6[*] (66.2)
Thrombolysis	%	31.3	22.9	13.3	0.134	9.9[*]

[†] Patients with nontraumatic CPR not subgrouped according to paO2.
[*] $p < 0.05$ versus the cumulative ABG group.

3.3. Secondary survival

CPC 1 and 2 rates at 28 days or discharge were positively correlated with higher pO2 during CPR however did not reach significance ($p = 0.06$).

4. Discussion

As oxygenation and reperfusion, together with defibrillation if necessary, are the hallmarks of CPR, the administration of maximum doses of oxygen during CPR is an essential item in resuscitation guidelines despite the lack of evidence for this measure.[11,12] The need for such evidence was underlined by the International Liaison Committee on Resuscitation in 2010 when the use of supplementary oxygen during CPR was defined as a question for future research.[21] This study provides novel information on that issue and is the first study to investigate an ABG dataset obtained in humans undergoing prehospital CPR.

We investigated a cohort of 145 patients in an 8-year period who underwent CPR administered according to the guidelines of the European Resuscitation Council (ERC) by a physician-staffed metropolitan emergency medical system. Our aim was to assess whether paO2 measured by ABG during CPR had a relevant impact on the rate of HA. We first divided our cohort into groups according to steps of 100 mmHg oxygen to show a consistent increase of primary survival according to paO2. At present there are no universally accepted definitions of hyp-, norm- and hyperoxic in this context; thus oxygen cutoffs previously postulated[6,7] were used for comparability and are desciptively referred to as low, intermediate and high oxygen groups rather than hyp-, norm- and hyperoxic with their physiologic implications.

The rate of HA differed significantly ($p < 0.001$) between the above-mentioned oxygen groups in univariate analysis. This effect was also reproducible when groups of comparable outcome (similarly shaded in Fig. 2) were clustered (see Supplementary Table S1). As evidence for an independent predictive character of paO2, it was the only factor besides duration of CPR that remained in a multivariate analysis investigating the respective endpoint. Notably, neither previously confirmed factors of survival as the rate of bystander CPR or the initial rhythm, nor the pCO2, base excess or pH provided any significant additional information.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2013.01.012.

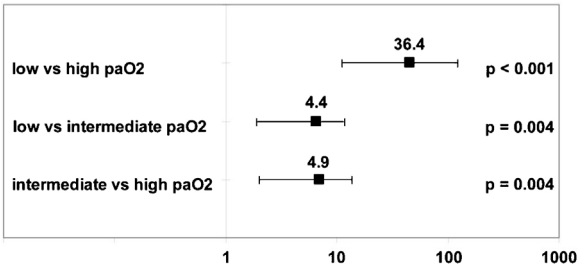


Fig. 4. Odds ratios and confidence intervals for HA according to paO2 groups during cardiopulmonary resuscitation. Significant odds ratios for survival to HA between the low and high oxygen groups (36.4 [95% confidence interval, 10.1–131.4]) as well as between the low and intermediate (4.4 [95% confidence interval, 1.7–11.9]) and between the intermediate and high oxygen groups (4.9 [95% confidence interval, 1.7–14.0]) are displayed. paO2: arterial oxygen partial pressure; HA: hospital admission.

Table 2
Variables in a univariate (A) and multivariate (B), after stepwise backward elimination of variables) logistic regression model. Endpoint: hospital admission.

Variable	*p*	$e(\beta)$
(A)		
Sex	0.109	3.551
Age	0.724	0.993
Bystander CPR	0.420	1.769
Collapse to CPR interval	0.427	0.955
Initial rhythm VF/VT	0.894	0.906
Adrenaline	0.793	0.961
Amiodarone	0.865	0.887
Atropine	0.165	2.467
Thrombolysis	0.072	0.238
Total shocks	0.767	1.032
Duration of CPR	0.000	0.923
paO2	0.020	1.006
paCO2	0.884	0.996
pH	0.885	2.634
BE	0.744	0.960
(B)		
Duration of CPR	0.000	0.926
paO2	0.001	1.007

CPR: cardiopulmonary resuscitation; VF/VT: ventricular fibrillation/ventricular tachycardia; paO2: arterial oxygen partial pressure; paCO2: arterial carbon dioxide partial pressure; BE: base excess.

Since hypercapnia exacerbates acidosis and CO2 excretion is impaired during states of reduced lung perfusion, an effect of pCO2 on primary survival may be expected, which we did not observe. This investigation was directed at examining the effects of pO2, but not the effects of acid–base status. Thus, we did not exclude patients who had received sodium bicarbonate before obtainment of the ABG, which may cause falsely high pCO2 or base excess measurements. Moreover, hypercapnia may have been corrected rapidly, as all patients were intubated at the time the sample was obtained and lung perfusion may have been sufficient, as this group represents a positively selected sample, as discussed below.

The increased rates of HA with increased paO2 and the significant odds ratios for HA between the oxygen groups (Fig. 4) may underline a clinical importance of this association. Secondary (favourable neurological) outcome has to interpreted with utmost caution in this dataset with respect to the small number of events. Data show a trend similar to primary survival data, but statistical significance was not reached.

Interestingly, the HA rate in tha ABG cohort was 50%. In historic cohorts, HA was reported in 10–15%[22,23]; in this study, patients in whom no ABG was performed, achieved HA in 29%, which is in line with data from a recently published large registry of CA victims.[24] However, a 50% HA rate is highly likely to represent a positive selection of patients. First, patients from whom an ABG during CPR can be obtained are positively selected owing to their hemodynamic situation, as ABG samples can only be obtained during CPR when sufficient peripheral circulation is generated by the chest compressions. Second, in comparison to patients without ABG during CPR, ABG patients were more often resuscitated by bystanders and interventions during CPR were more intense (higher rates and numbers of interventions). Interestingly, ABG was performed significantly less often during CPR in women. So, an effect in comparison to the non-ABG group is not surprising, but when investigating the effects of paO2 during CPR, a bias against an unselected cohort has to be taken into account. The results could certainly not be applied to a general population but may serve as a proof-of-principle.

In contrast, there is no evidence that the observed differences in the rates of HA between the compared oxygen groups could be due to baseline factors. The relevant treatments during CPR were also comparable. Administration rates of amiodarone or sodium bicarbonate were comparable in all groups and no differences in the use of repetitive interventions like adrenaline or defibrillation (adjusted to the total CPR time) could be found. The only significant difference in treatment during CPR was the administration rate of atropine.

As the observed benefit in the HA rate with increasing oxygen tension may be due to differences in the pulmonary and circulatory situation, it may be a surrogate for the severity of the underlying disease and thus predictive of outcome. Alternatively high paO2 during CPR may be seen as a surrogate marker for sufficient circulation and adequate ventilation. In either case it is clear why patients with higher paO2 achieve higher incidence of ROSC and HA. The question of which explanation is correct cannot be addressed by the present retrospective data due to the fact that neither quality of CPR nor the severity of patient's illness was standardized. This point may deserve further investigation in experimental models. However, paO2 obtained during CPR could be of prognostic value.

Reasons for the benefit of higher oxygen tensions during CPR can more easily be hypothesized than explained. There is evidence demonstrating important pathophysiologic effects of hyperoxia on the circulatory system such as decreased coronary blood flow or an increase in coronary vascular resistance.[9] Assuming a similar effect for patients during CPR, it is interesting that our data show an increased rate of HA. Animal experiments have provided important insights into the pathophysiology of oxygen delivery to tissues during extremely low flow conditions such as CPR. Specifically, tissue oxygen partial pressure declines during experimental CA but can be restored by CPR. However, tissue oxygen partial pressure stays in the normal range during CPR despite arterial hyperoxia, but greatly increases after ROSC without any considerable change in inspiratory oxygen fraction or arterial paO2.[25] Also, in a model of severe cerebral blood flow reduction, arterial hyperoxia did not increase oxygen delivery to the brain tissue.[26]

In analogy to these findings it can be hypothesized that arterial hyperoxia during CPR does not involve the same degree of tissue hyperoxia and therefore high doses of inspiratory and arterial oxygen may not adversely affect resuscitation outcome in this phase. We could not address this question in our study, but our data may indicate a promising direction for further research. Future prospective studies should address controlled reoxygenation regimens during CPR and their impact on arterial oxygen and survival.

4.1. Limitations

Several limitations have to be considered in this study.

POC testing is standard of care in our emergency medical system and is used at the discretion of the attending staff. Thus, this is not an interventional study in which groups of patients would have been treated with different paO2 targets to prove the impact of hyperoxia on survival, and we do not report the administration of different FiO2 fractions to address their impact on patient outcome experimentally. Due to the retrospective case-control character we are limited to reporting an association rather than causation.

Second, the investigated group naturally is subject to the selection bias mentioned above, being an inherent problem when investigating ABGs during CPR. To convincingly evaluate the circulatory situation during CPR, continuous arterial blood pressure monitoring would have been desirable, but we cannot provide these data for the majority of patients.

Third, owing to the limited sample size of 145 patients, analyses of neurologically intact survival are not be sufficiently powered.[27] With respect to the aim of CPR to restore the patient's physiological function and considering the potentially harmful effects of oxygen on neurologic outcome that have been addressed experimentally,[28] this important question will have to be clarified by large, prospective and randomized trials.

5. Conclusions

This is the first study to report an association between arterial oxygen tension measured during CPR and outcome rates after out of hospital cardiac arrest. We found a significantly increased rate of HA, but not neurologic outcome, to be associated with increasing paO2. Pertaining to the limited sample size, larger, prospective and randomized studies will have to reassess this observations.

Conflict of Interest Statement

None declared.

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