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Clinical paper

Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children☆

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ABSTRACT

Purpose: Arterial hyperoxia after resuscitation has been associated with increased mortality in adults. The aim of this study was to test the hypothesis that post-resuscitation hyperoxia and hypocapnia are associated with increased mortality after resuscitation in pediatric patients.
Methods: We performed a prospective observational multicenter hospital-based study including 223 children aged between 1 month and 18 years who achieved return of spontaneous circulation after in-hospital cardiac arrest and for whom arterial blood gas analysis data were available.
Results: After return of spontaneous circulation, 8.5% of patients had hyperoxia (defined as $PaO_2 > 300$ mmHg) and 26.5% hypoxia (defined as $PaO_2 < 60$ mmHg). No statistical differences in mortality were observed when patients with hyperoxia (52.6%), hypoxia (42.4%), or normoxia (40.7%) ($p = 0.61$). Hypocapnia (defined as $PaCO_2 < 30$ mmHg) was observed in 13.5% of patients and hypercapnia (defined as $PaCO_2 > 50$ mmHg) in 27.6%. Patients with hypercapnia or hypocapnia had significantly higher mortality (59.0% and 50.0%, respectively) than patients with normocapnia (33.1%) ($p = 0.002$). At 24 h after return of spontaneous circulation, neither PaO_2 nor $PaCO_2$ values were associated with mortality. Multiple logistic regression analysis showed that hypercapnia (OR, 3.27; 95% CI, 1.62–6.61; $p = 0.001$) and hypocapnia (OR, 2.71; 95% CI, 1.04–7.05; $p = 0.04$) after return of spontaneous circulation were significant mortality factors.
Conclusions: In children resuscitated from cardiac arrest, hyperoxemia after return of spontaneous circulation or 24 h later was not associated with mortality. On the other hand, hypercapnia and hypocapnia were associated with higher mortality than normocapnia.
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1. Introduction

Current rates of return of spontaneous circulation (ROSC) after in-hospital cardiac arrest (CA) range from 50% to 73%; however, final survival is significantly lower.[1–7] Consequently, stabilisation interventions after initially successful resuscitation must be improved in order to reverse post-CA syndrome.

Post-CA syndrome is the result of the prolonged period of systemic ischaemia during CA and the subsequent reperfusion response that occurs after resuscitation and ROSC.[8,9]

Previous studies in animals have shown that excessive oxygen during the reperfusion period increases neuronal damage through production of free radicals and mitochondrial injury.[10] Once ROSC is achieved, ventilation with the minimum fraction of inspired oxygen (FiO_2) required to maintain adequate oxygen saturation of arterial blood (around 94%) may facilitate survival and favourable neurological outcome.[11–16] Several clinical studies of adult patients admitted to the intensive care unit after CA have analysed the

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influence of arterial hyperoxia on mortality and suggest that it significantly increases the mortality.[17–19] However, data on the potential influence of hyperoxia on the outcome of CA and resuscitation in children are lacking.

Conversely, hyperventilation is thought to worsen outcome after ROSC, because it diminishes cerebral blood flow and increases brain ischaemia[20–22]; nevertheless, no clinical data have been published regarding the eventual influence of hypocapnia or hypercapnia on survival after CA.

We describe the incidence of hyperoxia, hypocapnia, and hypercapnia after ROSC and the outcome of children who suffered in-hospital CA. Our main objective was to test the hypothesis that hyperoxia and hypocapnia after ROSC are associated with increased mortality in paediatric in-hospital CA.

2. Methods

The study population comprised patients from an ongoing multicentre study aged 1 month to 18 years who suffered in-hospital CA and achieved ROSC between December 2007 and 2009. The inclusion criterion was to have had at least an arterial blood gas analysis performed at ROSC and 24 h after CA. The study was approved by the local institutional review boards. CA was defined as the absence of a palpable central pulse, unresponsiveness, apnoea and severe bradycardia of less than 60 bpm with poor perfusion in infants requiring external cardiac compression and assisted ventilation.

The case report form included the following: patient-related variables (age, sex and weight), cause of CA, personal background characteristics of CA and resuscitation (type of CA, variables monitored, assisted ventilation or vasoactive drugs administered before the CA and staff who performed the resuscitation manoeuvres and procedures), first recorded electrocardiogram (ECG) rhythm, total duration of cardiopulmonary resuscitation (CPR) and first arterial blood gas analysis immediately after ROSC and 24 h after. The outcome-related variable was clinical status at hospital discharge (alive or dead).

Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) software version 15.0.1 (SPSS Inc, Chicago, IL, USA). Continuous data are presented as either mean and standard deviation or median and interquartile range as appropriate, based on the distribution of data; categorical data are reported as proportions and 95% confidence intervals (CIs).

For the purposes of this analysis, the cohort was divided into three exposure groups defined a priori based on PaO_2 in the first arterial blood gas values obtained. Hyperoxia was defined as a PaO_2 of 300 mmHg or greater (or a ratio of PaO_2 to FiO_2 (PaO_2/FiO_2) >300); hypoxia was defined as a PaO_2 of less than 60 mmHg or a PaO_2/FiO_2 <200.

Hypercapnia was defined as a $PaCO_2$ of less than 30 mmHg, hypocapnia, as a $PaCO_2$ of 50 mmHg or greater.

The primary outcome measure was in-hospital mortality, which was compared between groups using the chi-squared test; the Bonferroni correction was applied when groups were compared in pairs.

A scheduled secondary analysis of the results was performed in order to detect patients at risk of hyperoxia, who might have been undervalued using the limits presented above. For this purpose, a lower PaO_2 cut-off was considered to define hyperoxia: 200 mmHg rather than 300 mmHg in a first approximation, and 100 mmHg rather than 200 mmHg in a final step.

Multivariate logistic regression was performed to assess the potential influence of each of the factors on mortality. All the individual factors with statistical significance in the univariate analysis were included in the multivariate analysis. The results are expressed as odds ratio and 95% CIs. A p value <0.05 was considered significant.

3. Results

Of a total of 543 in-hospital CA episodes registered, 386 (71%) achieved ROSC. The study sample comprised the 223 patients in whom arterial blood gas data after ROSC were available. The baseline characteristics of patients are described in Table 1. We found that 46.5% of patients were younger than 1 year and 59% weighed less than 10 kg. CA occurred in the paediatric intensive care unit in 64% of cases. Out of the 223 patients, 19 were classified as hyperoxic (8.5%) and 59 as hypoxic (26.5%) (Table 1 and Fig. 1). Arterial blood gases were also recorded 24 h after CA in 173 patients.

In-hospital mortality was 40%. Patients with hyperoxia immediately after ROSC (PaO_2 criteria) had higher mortality (52.6%) than patients with hypoxia (42.4%) and than those with normoxia (40.7%), although the differences were not statistically significant ($p = 0.61$).

No significant differences in mortality were observed (PaO_2 criteria) in the arterial blood gas analysis 24 h after CA – hyperoxia 33%, hypoxia 29.8% and normoxia 35.8% – although there were only three patients in the hyperoxia group (Table 2).

In the secondary analysis, using a $PaO_2 > 200$ mmHg as the hyperoxia limit, no significant differences were recorded in mortality between patients with hyperoxia immediately after ROSC (39%), those with hypoxia (42.4%) and those with normoxia (43.1%) ($p = 0.9$). Likewise, although patients with hyperoxia 24 h after CA had higher mortality rates (57.1%) than those with hypoxia (31.6%) or normoxia (35.3%), the differences did not reach statistical significance ($p = 0.16$).

The results for mortality were similar when the hyperoxia limit was placed at 100 mmHg: hyperoxia 41.8%, hypoxia 42.4% and normoxia 42.4% ($p = 0.99$).

In 203 of the 223 patients, FiO_2 was registered simultaneously with the arterial blood gas analysis when performed immediately after ROSC, and in 152 when performed 24 h later. When groups were compared according to PaO_2/FiO_2 criteria, patients with a ratio above 300 had higher mortality (51.2%) than those with ratios between 200 and 300 (32%) or below 200 (42.2%); however, once again, the differences did not reach statistical significance ($p = 0.29$) (Table 2).

Considering the results 24 h after the CA assay, the PaO_2/FiO_2 hypoxia group had higher mortality (41.8%) than the hyperoxia group (24.2%) and the normoxia group (28.6%), although the difference was not significant ($p = 0.14$) (Table 2).

Arterial CO_2 measurements were available immediately and 24 h after ROSC for 221 and 152 patients, respectively. Patients with arterial hypercapnia or hypocapnia immediately after ROSC had significantly higher mortality than patients with normal arterial CO_2 values ($p = 0.002$).

No statistically significant differences in mortality were found between patients with hypercapnia and patients with hypocapnia (59.0% vs. 50.0%; $p = 1$) or between those with hypocapnia and those with normocapnia (50.0% vs. 33.1%; $p = 0.371$). However, mortality was significantly higher in the hypercapnia group than in the normocapnia group (59.0% vs. 33.1%; $p = 0.003$).

In the assay 24 h after CA, the hypocapnia group had higher mortality rates (44.4%) than the normocapnia group (33.1%), although the differences were not significant ($p = 0.37$) (Table 3).

The mortality of patients who presented hypercapnia and hypoxia immediately after ROSC was 47.8% in comparison with the rest of patients 36.8% ($p = 0.29$).

Table 1
Characteristics of patients.

Patient characteristics	All patients (N = 223)	Hyperoxia (N = 19)	Normoxia (N = 145)	Hypoxia (N = 59)
Age, median (IQR) (months)	14 (5–60)	41 (7–144)	15 (6–60)	8 (2–37)
Weight, median (IQR) (kg)	9 (5–17.5)	12 (6–38)	10 (6–19.5)	7 (4–13)
Female sex (%)	42.6	21.1	40	50.8
Initial type of arrest (cardiac) (%) (p = 0.03)	57.8	84.2	53.5	61.4
Etiology of arrest (%)				
Cardiac illness	33.3	52.6	30.6	36.2
Respiratory illness	35.5	15.8	38.9	32.8
Sepsis and infections	12.7	5.3	13.9	10.3
Others (p = 0.27)	18.5	26.4	16.6	20.7
Location of arrest (%)				
PICU	64.0	68.4	62.7	68.4
Emergency department [a]	20.4	15.8	23.2	12.3
Wards	6.2	0	4.9	10.5
Others (p = 0.68)	9.3	15.8	9.2	8.8
Initial cardiac rhythm (%)				
Asystole	37.9	31.6	39.0	34
Pulseless electric activity	54.6	52.6	52.9	62
Ventricular fibrillation or pulseless ventricular tachycardia (p = 0.52)	7.5	15.8	8.1	4
Time to initiation of resuscitation (<5 min) (%) (p = 0.39)	89.3	94.7	88.7	89.5
Resuscitation time (<20 min) (%) (p = 0.94)	83.5	78.9	85.5	79.7

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit.
[a] Patients suffered the CA in the Emergency department.

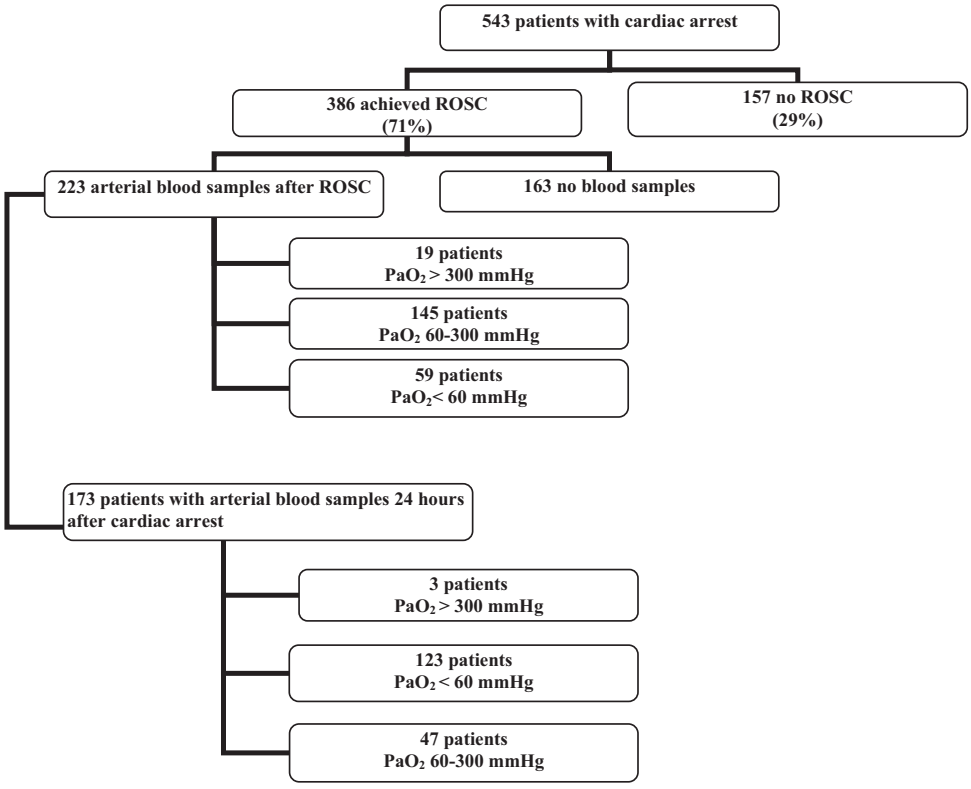

Fig. 1. Flowchart of patient distribution. ROSC (return of spontaneous circulation).

Table 2
In-hospital mortality according to partial arterial oxygen pressure (PaO_2) and PaO_2 to fraction of inspired oxygen ratio (PaO_2/FiO_2) groups.

In-hospital mortality (%)						
After ROSC	PaO_2 <60 mmHg (n = 59)	PaO_2 60–300 mmHg (n = 145)	PaO_2>300 mmHg (n = 19)	PaO_2/FiO_2 >300 (n = 43)	PaO_2/FiO_2 200–300 (n = 25)	PaO_2/FiO_2<200 (n = 135)
	42.4 p = 0.61	40.7	52.6	51.2 p = 0.29	32.0	42.2
24 h after CA	PaO_2 < 60 mmHg (n = 47)	PaO_2 60–300 mmHg (n = 123)	PaO_2 > 300 mmHg (n = 3)	PaO_2/FiO_2 > 300 (n = 33)	PaO_2/FiO_2 200–300 (n = 28)	PaO_2/FiO_2 < 200 (n = 91)
	29.8 p = 0.76	35.8	33.3	24.2 p = 0.14	28.6	41.8

Abbreviations: CA, cardiac arrest; ROSC, return of spontaneous circulation.

Table 3
In-hospital mortality according to $PaCO_2$.

In-hospital mortality (%)			
After ROSC	$PaCO_2$<30 mmHg (n = 30) 50.0 p = 0.02	$PaCO_2$ 30–50 mmHg (n = 130) 33.1	$PaCO_2$>50 mmHg (n = 61) 59.0
24 h after CA	$PaCO_2$ < 30 mmHg (n = 9) 44.4 p = 0.37	$PaCO_2$ 30–50 mmHg (n = 118) 33.1	$PaCO_2$ > 50 mmHg (n = 25) 32.0

Abbreviations: CA, cardiac arrest; ROSC, return of spontaneous circulation.

After adjusting for other factors in the multivariate analysis, both hypercapnia and hypocapnia immediately after ROSC were associated with mortality (Table 4).

Neither hyperoxia nor hypoxia was found to be a significant predictor of in-hospital mortality; when entered in the multivariate model, they did not modify the regression coefficient.

In contrast, other risk factors that proved to be significantly associated with a lower in-hospital death rate in multivariate logistic regression analysis were respiratory illness as cause of CA and initial shockable rhythm.

4. Discussion

Resuscitation from CA does not end after ROSC. Post-ROSC care has significant potential to prevent the early mortality caused by haemodynamic instability and further injury at the cellular level. The objectives of resuscitation include optimisation of cardiopulmonary function and systemic perfusion, identification of the precipitating causes of the arrest, institution of measures to prevent recurrence of CA and administration of therapies that might facilitate long-term survival.

4.1. Oxygenation after CA and outcome

The present study assessed the incidence of hyperoxia after paediatric in-hospital CA and its potential impact on mortality.

Arterial blood gas analysis performed immediately after ROSC revealed considerable variation in oxygenation, even if parameters were extended to PaO_2 values of 200 and 100 mmHg.Post-ROSC exposure to hyperoxia amongst our paediatric cohort was an uncommon occurrence. Aetiology of in-hospital CA in our population was mostly due to respiratory, which could partly justify the fact that hyperoxia was barely detected and lower than in adult studies.[17–19]

Most patients were normoxaemic 24 h after CA; moreover, analysis of PaO_2/FiO_2 ratios showed that, at the time, most patients needed high FiO_2 administration to reach normal PaO_2 values, thus implying some kind of underlying pulmonary damage or an alteration of the ventilation to perfusion relationship. Pulmonary circulatory dysfunction can induce low arterial oxygen saturation after ROSC. However, PaO_2/FiO_2 ratio values had no statistically significant impact on survival immediately after ROSC or 24 h later. A decrease in the PaO_2/FiO_2 ratio at 24 h showed a trend towards increased mortality rates, although this difference did not achieve statistical significance.

Table 4
Multiple logistic regression model with mortality as dependent variable.

Variable	OR	95% CI	p Value
Cause of arrest: respiratory illness	0.28	0.11–0.70	0.007
Initial type of arrest: cardiac	0.63	0.25–1.61	0.33
Place of arrest: PICU	1.45	0.72–2.92	0.30
Initial rhythm: VF or PVT	0.05	0.005–0.399	0.005
Duration of CPR > 20 min	1.88	0.71–5.01	0.21
$PaCO_2$ > 50 mmHg after ROSC	3.27	1.62–6.61	0.001
$PaCO_2$ < 30 mmHg after ROSC	2.71	1.04–7.05	0.04

Abbreviations: CI, confidence interval; OR, odds ratio; $PaCO_2$, arterial partial carbon dioxide pressure; PICU, pediatric intensive care unit; PVT, pulseless ventricular tachycardia; VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation.

Post-CA syndrome is a complex clinical condition that compromises survival after resuscitation and comprises potential brain injury, myocardial dysfunction and systemic ischaemia/reperfusion response.[8,9] Thus, after ROSC, goal-directed interventions are required in order to improve outcome. Variations in oxygenation and ventilation during CPR and after ROSC may trigger the cascade of events that contributes to tissue re-perfusion damage.[8,9] Oxidative stress is believed to result from a surge of reactive oxygen species, which could be favoured by a persistently hyperoxic environment.[10–15] Kilgannon et al.[17,19] found that, in an adult in-hospital CA sample, mortality was significantly higher in patients with hyperoxia after resuscitation. However, in contrast with our findings, most patients in that study were hypoxic, and no data were reported on the temporal relationship between blood gas analysis and ROSC.[17,19] Our results suggest that, in children, even after conducting CPR with 100% oxygen, the incidence of hyperoxia immediately after ROSC is low and becomes very rare 24 h after CA. These results are consistent with those of Bellomo et al.,[18] whose study of adults who had suffered non-traumatic CA showed hyperoxia as a rare event, occurring in 10.6% of their sample.

Kilgannon et al. established the hyperoxia limit at PaO_2 > 300 mmHg and concluded that hyperoxia in intensive care patients after CA was independently associated with increased in-hospital mortality, which worsened in cases with PaO_2 > 400 mmHg.

On the other hand, Bellomo et al.[18] did not observe a robust relationship between hyperoxia and mortality with the 300 or 400 mmHg limits. PaO_2 values did not remain associated with hospital mortality when the data were adjusted for relevant covariates such as concomitant illnesses and Acute Physiology and Chronic Health Evaluation (APACHE) scores.

In our study, arterial hyperoxia following CA was not associated with increased hospital mortality in children; furthermore, after adjustments for covariates, neither PaO_2 values nor PaO_2/FiO_2 ratios influenced the odds ratio for mortality.

We found that paediatric patients were more likely to be normoxic after ROSC and remain as such during the first 24 h after CA. This finding contrasts with the observations in adults made by Kilgannon et al.[17] and Bellomo et al.,[18] who found that 73.5% and 63% of patients, respectively, were hypoxaemic at the time.

Paediatric CA aetiology is different from adult CA. It is known that after acute coronary syndrome or acute myocardial infarction, hyperoxia causes coronary vasoconstriction, decreased myocardial blood flow and decreased myocardial oxygen consumption.[11,12] Therefore, the co-morbidity of acute coronary syndrome could be a

mechanism by which post-CA hyperoxia could worsen survival in adults when compared to children.

4.2. Ventilation after CA and outcome

Studies in pigs demonstrated that excessive ventilation rates significantly decreased coronary perfusion pressures and survival rates when CPR was conducted after inducing ventricular fibrillation in an adult CA model.[20–22] Increased ventilation rates and increased duration of ventilation are believed to impede venous blood return to the heart, thus decreasing coronary perfusion pressure during CPR. Furthermore, a direct and immediate transfer of the increase in intra-thoracic pressure to the cranial cavity with positive pressure ventilation reduces cerebral perfusion pressure. However, the results of these CA adult model studies should be interpreted with caution, as they focus on the influence of ventilation on the interruption of chest compression rather than on the impact of ventilation status according to arterial CO_2 values.

As shown in our sample, respiratory illnesses are one of the main causes of CA in children. Given the high incidence of underlying respiratory diseases and respiratory arrest before CA, children might develop hypercapnia more frequently than adults. This could also explain, at least in part, the low incidence of hypocapnia immediately after ROSC in our sample.

Recently published studies based on a paediatric animal model of CA with asphyxia also found the incidence of hypocapnia to be very low. Moreover, the animals barely achieved normal ventilation parameters and presented hypercapnia despite being ventilated at rates higher than those recommended by guidelines.[23–27]

Therefore, the optimal ventilation rate for resuscitation of CA and after ROSC in paediatric patients has yet to be defined.[27] Our study, which is the first to assess $PaCO_2$ values after ROSC in children, suggests that ventilation following current International Liaison Committee on Resuscitation (ILCOR) guidelines generally results in normocarbia or hypercapnia. It is noteworthy that excessive ventilation is a rare event in paediatric resuscitation (detected in <15% of our patients).

Children with normocapnia showed lower mortality than those with hypercapnia or hypocapnia in the univariate analysis. Furthermore, after adjusting for other significant variables in the multiple logistic regression analysis, hypocapnia and hypercapnia were associated with higher mortality.

Patients with hypoxia and hypercapnia presented non-significant higher mortality than the rest of patients, although only 23 patients presented hypoxia and hypercapnia.

On the other hand our data showed that patients with CA secondary to respiratory illness and initial defibrillation rhythms have better survival. These factors have been previously described in other studies.[1–7]

Our study has several limitations. First, it is an observational study with no planned intervention; therefore, no causal relationship could be inferred from the results. Second, the exact limits for defining excessive oxygen exposure are unknown; based on previous studies, we defined hyperoxia as a PaO_2 of 300 mmHg or greater,[17–19] and, although other PaO_2 values were considered in the secondary analysis, their possible influence on our results remains uncertain. Third, the number of children with hyperoxia was low, a finding that could account for the absence of significant differences in outcome. In addition, measurement of arterial blood gases cannot be considered a reliable marker of interstitial or cellular oxygen tension. Further studies are needed to determine the extent of tissue and cellular hypoxia and the associated oxygen requirements during and after resuscitation.

Although characteristics of our patients, including prior heart disease, were taken into consideration, those with congenital intracardiac shunt were not stratified, and this could have biased our results. The influence of temperature was not taken into consideration either, as hypothermia was an uncommon practice in paediatric post-ROSC care during the recruitment period and therapeutic hypothermia was not intended in most of our patients.

Another noteworthy limitation is that long-term outcome has not yet been assessed. We acknowledge that hyperoxia could be associated with brain injury and neurological impairment, as well as with extracerebral deleterious consequences not analysed in our study.

5. Conclusions

Most children who suffer in-hospital CA, although resuscitated with 100% FiO_2, are not exposed to arterial hyperoxia immediately after ROSC or 24 h later. Arterial hyperoxia at these time points was not associated with mortality in children. Ventilation during CPR and after ROSC achieves normal $PaCO_2$ values in most paediatric patients. Hypercapnia after ROSC is more frequent than hypocapnia and both could be associated with higher mortality.

Although targeting normal PaO_2 and $PaCO_2$ could be important for preventing further damage by post-CA syndrome in children, definitive clinical trials are needed to determine the impact of these strategies on survival and outcome in children who suffer CA.

Conflicts of interest statement

None of the authors has declared a conflict of interest.

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Appendix A.

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