Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: A prospective multi-center protocol-directed cohort study

Supplemental Material

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Methods

We used multivariable logistic regression analysis to identify what patient and management characteristics were associated with hyperoxia on the one or six hour arterial blood gas analyses. We entered into the model ventilator settings (i.e. FiO_2, PEEP, tidal volume, and respiratory rate) corresponding to the one and six hour PaO_2, as well as any patient characteristics found to be statistically different at a conservative $p < 0.1$ between the no hyperoxia and hyperoxia cohorts.

Sensitivity analyses: First, in order to test if hyperoxia remained independently associated with poor neurological outcome, after adjusting for additional candidate variables, we performed a multivariable generalized linear regression model with a log link entering candidate variables into the model if statistically different at $p < 0.10$ between PaO_2 groups. Backward elimination with a criterion of $p < 0.05$ for retention in the model was used. Second, given both out-of-hospital and in-hospital cardiac arrest patients were included in this cohort, we performed a test of interaction in our original generalized linear regression model to assess whether the effect of treatment differed between the two subgroups. Unless there was evidence against the null hypothesis of homogeneity of effects (i.e., $p < 0.05$), the overall relative risk was regarded as the most reliable guide to the approximate relative risk for both subgroups. Finally, to test if hyperoxia was associated with poor neurological outcome among survivors, we performed a generalized linear regression analysis with a log link, adjusting for the candidate variables retained in the original model and limited to patients who survived to hospital discharge.

Results

Supplemental Table 1: Multivariable logistic regression model with hyperoxia (defined as partial pressure of arterial oxygen > 300 mmHg) as the dependent variable.

Variables	Odds Ratio	95% CI	p-value
FiO_2	1.08	1.05 - 1.11	<0.001
PEEP (cmH_2O)	0.83	0.70 - 0.97	0.020
Tidal volume (cc/kg PBW)	1.10	0.83 - 1.45	0.519
Respiratory rate (breaths/min)	0.94	0.88 - 1.01	0.082
Plateau pressure > 30 cmH_2O	0.37	0.14 - 1.01	0.052
$PaCO_2$ (mmHg)	0.99	0.98 - 1.01	0.484
Female	0.65	0.33 - 1.30	0.224

FiO_2, fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end expiratory pressure; $PaCO_2$, partial pressure of arterial carbon dioxide

Full multivariable generalized linear models for the primary and secondary outcomes.

Supplemental Table 2: Multivariable generalized linear model (log link) with poor neurological outcome [defined as modified Rankin Scale (mRS) > 3 at hospital discharge] as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level (Listwise deletion).

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.23	1.11 - 1.35	<0.001
VT/VF	0.66	0.55 - 0.80	<0.001
Age	1.06	1.02 - 1.11	0.004
Metabolic acidosis†	1.45	1.24 - 1.69	<0.001
Arterial hypotension‡	1.33	1.20 - 1.47	<0.001
Charlson co-morbidity index	1.06	1.02 - 1.09	0.001

Removed for non-significance: In-hospital cardiac arrest (p = 0.833); cardiopulmonary resuscitation > 20 min (p = 0.057).

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; VT/VF, ventricular tachycardia/ventricular fibrillation.

Model has good fit: Deviation test p = 1.0

Supplemental Table 3: Multivariable generalized linear model (log link) with poor neurological outcome [defined as modified Rankin Scale (mRS) > 3 at hospital discharge] as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level [Multiple imputation. ventricular tachycardia/ventricular fibrillation (VT/VF), 23 observation imputed; cardiopulmonary resuscitation (CPR) > 20 min, 5 observations imputed].

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.24	1.13 - 1.35	<0.001
VT/VF	0.65	0.55 - 0.77	<0.001
Age	1.07	1.03 - 1.11	0.001
Metabolic acidosis†	1.39	1.23 - 1.57	<0.001
Arterial hypotension‡	1.29	1.14 - 1.47	<0.001
Charlson co-morbidity index	1.04	1.01 - 1.07	0.019
CPR > 20 min	1.19	1.02 - 1.39	0.026

Removed for non-significance: In-hospital cardiac arrest (p = 0.654)

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval.

Supplemental Table 4: Multivariable generalized linear model (log link) with in-hospital mortality as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level (Listwise deletion).

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.24	0.99 - 1.55	0.060
VT/VF	0.70	0.57 - 0.86	0.001
Age	1.07	1.00 - 1.15	0.044
Metabolic acidosis†	2.02	1.22 - 3.33	0.006
Arterial hypotension‡	1.46	1.23 - 1.74	<0.001
Charlson co-morbitiy index	1.11	1.07 - 1.16	<0.001
CPR > 20min	1.48	1.28 - 1.71	<0.001

Removed for non-significance: In-hospital cardiac arrest (p = 0.130)

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; CPR, cardiopulmonary resuscitation; VT/VF, ventricular tachycardia/ventricular fibrillation.

Model has good fit: Deviance test p = 1.0

Supplemental Table 5: Multivariable generalized linear model (log link) with in-hospital mortality as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level [Multiple imputation. ventricular tachycardia/ventricular fibrillation (VT/VF), 23 observation imputed; cardiopulmonary resuscitation (CPR) > 20 min, 5 observations imputed].

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.25	1.01 - 1.54	0.040
VT/VF	0.66	0.54 - 0.81	0.001
Age	1.08	1.02 - 1.14	0.007
Metabolic acidosis†	1.96	1.28 - 3.00	0.002
Arterial hypotension‡	1.43	1.26 - 1.64	<0.001
Charlson co-morbitiy index	1.12	1.08 - 1.17	<0.001
CPR > 20min	1.46	1.32 - 1.62	<0.001
In-hospital cardiac arrest	0.79	0.64 - 0.98	0.031

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval.

Supplemental Table 6: Multivariable generalized linear regression model (log link) with the Full Outline of UnResponsiveness (FOUR) score at 72 hours after ROSC as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level (Listwise deletion).

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.32	1.03 - 1.69	0.026
VT/VF	0.48	0.42 - 0.54	<0.001
In-hospital cardiac arrest	0.55	0.37 - 0.82	0.003
Metabolic acidosis†	1.85	1.30 - 2.61	0.001
Arterial hypotension‡	1.55	1.08 - 2.21	0.016

Removed for non-significance: Age (p = 0.770); Charlson comorbidity index (p = 0.839); cardiopulmonary resuscitation > 20min (p = 0.204).

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; VT/VF, ventricular tachycardia/ventricular fibrillation.

Model has good fit: Deviance test p = 1

Supplemental Table 7: Multivariable generalized linear regression model (log link) with the Full Outline of UnResponsiveness (FOUR) score at 72 hours after ROSC as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level (Multiple imputation. ventricular tachycardia/ventricular fibrillation (VT/VF), 23 observation imputed; cardiopulmonary resuscitation (CPR) > 20 min, 5 observations imputed).

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.39	1.11 - 1.74	0.004
VT/VF	0.44	0.36 - 0.55	<0.001
In-hospital cardiac arrest	0.54	0.36 - 0.81	0.003
Metabolic acidosis†	1.93	1.34 - 2.77	<0.001
Arterial hypotension‡	1.44	1.08 - 1.91	0.013

Removed for non-significance: Charlson comorbidity index (p = 0.504); Age (p = 0.426); CPR > 20 min (p = 0.081).

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; VT/VF, ventricular tachycardia/ventricular fibrillation.

CI, confidence interval.

Sensitivity analyses for the primary outcome

Supplemental Table 8: Results of sensitivity analysis: Multivariable generalized linear regression model (log link) with poor neurological outcome [defined as modified Rankin Scale (mRS) > 3 at hospital discharge] as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level.

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.23	1.05 - 1.44	0.010
Plateau pressure > 30 (cmH_2O)	1.41	1.15 - 1.72	0.001
Time to first ABG (min)	1.00	1.00 - 1.00	0.015

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation.

ABG, arterial blood gas; CI, confidence interval

Removed for non-significance: time-weighted average saturation of arterial oxygen (p = 0.974); mean partial pressure of arterial carbon dioxide (p = 0.730); mean peak end expiratory pressure (p = 0.315); gender (p = 0.114).

Supplemental Table 9: Results of sensitivity analysis: Multivariate generalized linear regression model (log link) with poor neurological outcome [defined as modified Rankin Scale (mRS) > 3 at hospital discharge] as the dependent variable, entering interaction term between hyperoxia and location of cardiac arrest.

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.30	1.11 - 1.51	0.001
In-hospital cardiac arrest	1.11	0.88 - 1.40	0.391
Interaction: Hyperoxia and In-hospital cardiac arrest	0.80	0.56 - 1.15	0.233
VT/VF	0.66	0.55 - 0.79	<0.001
Age	1.07	1.01 - 1.12	0.014
Metabolic acidosis†	1.43	1.15 - 1.78	0.001
Arterial hypotension‡	1.31	1.13 - 1.53	<0.001
Charlson co-morbitiy index	1.05	0.99 - 1.13	0.122

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CPR, cardiopulmonary resuscitation; LCI, lower confidence interval; UCI, upper confidence interval; VT/VF, ventricular tachycardia/ventricular fibrillation.

Supplemental Table 10: Results of sensitivity analysis: Multivariable generalized linear regression model (log link) with poor neurological outcome [defined as modified Rankin Scale (mRS) > 3 at hospital discharge] as the dependent variable among patients who survived to hospital discharge (n = 127), taking into account the random effects at the institution (i.e. site of enrollment) level.

Variables	Relative Risk	95% CI	p-value
Hyperoxia*	1.42	1.09 - 1.87	0.011
VT/VF	0.43	0.27 - 0.67	<0.001
Age	1.14	0.98 - 1.32	0.090
Metabolic acidosis†	1.36	0.71 - 2.60	0.356
Arterial hypotension‡	1.37	0.80 - 2.35	0.257
Charlson co-morbidity index	1.05	0.84 - 1.32	0.663

*Defined as exposure to a partial pressure of arterial oxygen > 300 mmHg during the first 6 hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

CI, confidence interval; CPR, cardiopulmonary resuscitation; VT/VF, ventricular tachycardia/ventricular fibrillation.

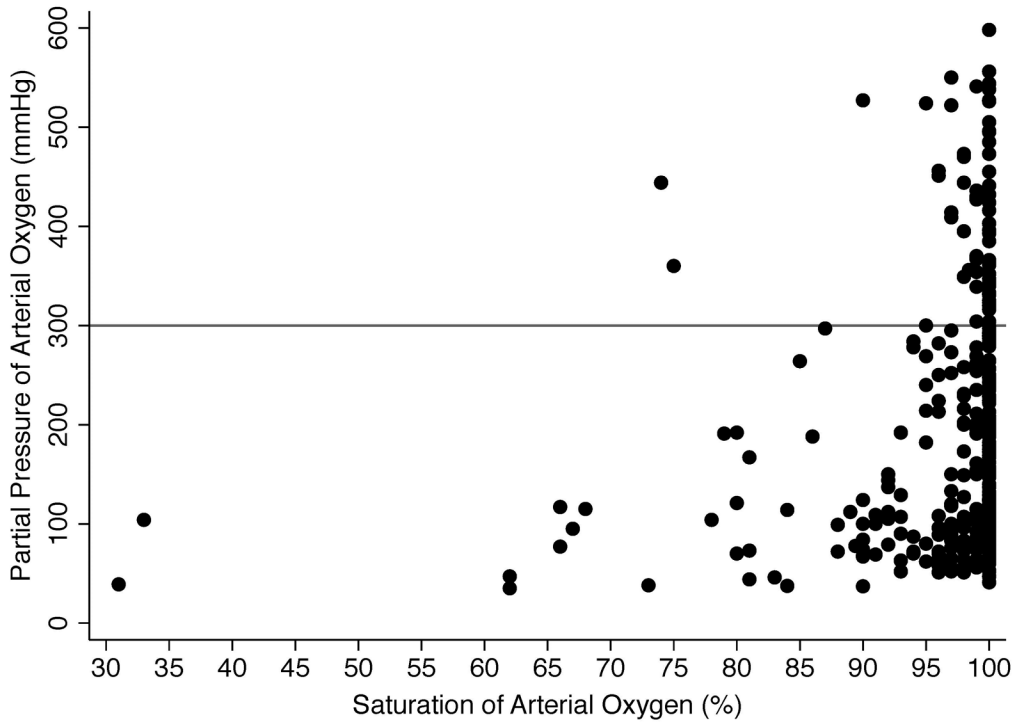
Supplemental Table 11: Multivariable generalized linear regression model (log link) with duration of hyperoxia exposure as an independent variable and poor neurological outcome [defined as modified Rankin Scale (mRS) > 3 at hospital discharge] as the dependent variable, taking into account the random effects at the institution (i.e. site of enrollment) level.

Variables	Odds Ratio	95% CI	p-value
Duration of hyperoxia exposure*	1.03	1.02 - 1.05	<0.001
VT/VF	0.66	0.54 - 0.80	<0.001
Age	1.07	1.02 - 1.12	0.006
Metabolic acidosis†	1.42	1.19 - 1.70	<0.001
Arterial hypotension‡	1.29	1.17 - 1.42	<0.001
Charlson co-morbidity index	1.05	1.02 - 1.09	0.004
Number of ABGs	1.05	0.96 - 1.15	0.265
Time to first ABG	1.00	1.00 - 1.00	0.821

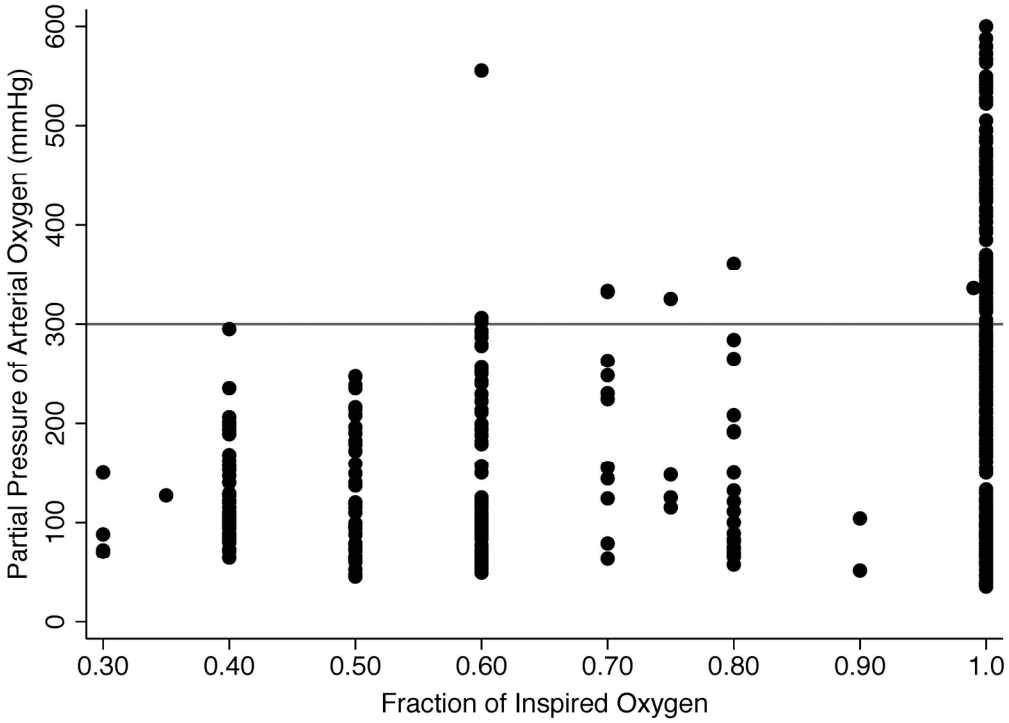
*Calibrated for one-hour increase in the duration of exposure to partial pressure of arterial oxygen > 300 mmHg during the initial six hours after return of spontaneous circulation. †Defined as a base deficit ≤ -6 during the first 6 hours after return of spontaneous circulation. ‡Defined as mean arterial pressure < 70 mmHg during the first 6 hours after return of spontaneous circulation.

ABG, arterial blood gas; CI, confidence interval; CPR, cardiopulmonary resuscitation; VT/VF, ventricular tachycardia/ventricular fibrillation.

Supplemental figure 1: Scatterplot of partial pressure of arterial oxygen (PaO_2) and corresponding saturation of arterial oxygen [PaO_2 = 300 mmHg (horizontal line)].



Supplemental figure 2: Scatterplot of partial pressure of arterial oxygen (PaO_2) and fraction of inspired oxygen [PaO_2 = 300 mmHg (horizontal line)].



Supplemental figure 3: Bland-Altman plot for relationship between saturation of arterial oxygen (SaO_2) and partial pressure of arterial oxygen (PaO_2). Dash line: mean difference. Solid lines: 95% confidence interval of mean difference.