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Retrospective Analysis of the Hemodynamic Consequences of Prehospital Supplemental Oxygen in Acute Stroke

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Abstract

Objective: Hyperoxia, the delivery of high levels of supplemental oxygen (sO₂) despite normoxia, may increase cerebral oxygenation to penumbral tissue and improve stroke outcomes. However, it may also alter peripheral hemodynamic profiles with potential negative effects on cerebral blood flow (CBF). This study examines the hemodynamic consequences of prehospital sO₂ in stroke.

Methods: A retrospective analysis of adult acute stroke patients (aged ≥18 years) presenting via EMS to an academic Comprehensive Stroke Center between January 1, 2013 and December 31, 2017 was conducted using demographic and clinical characteristics obtained from Get with the Guidelines-Stroke registry and subjects' medical records. Outcomes were compared across three groups based on prehospital oxygen saturation and sO₂ administration. Chi-square, ANOVA, and multivariable linear regression were used to determine if sO₂ was associated with differences in peripheral hemodynamic profiles.

Results: All subjects had similar initial EMS vitals except for oxygen saturation. However, both univariate and multivariable analysis revealed that hyperoxia subjects had slightly lower average ED mean arterial pressures (MAP) compared to normoxia (Cohen's *d* = 0.313).

Conclusions: Prehospital-initiated hyperoxia for acute stroke is associated with a small, but significant decrease in average ED MAP, without changes in heart rate, compared to normoxia. While limited by the inability to link changes in peripheral hemodynamical profiles directly to changes in CBF, this study suggests that hyperoxia may result in a relative hypotension. Further

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studies are needed to determine if this small change in peripheral vascular resistance translates into a clinically significant reduced CBF.

Keywords

Acute Ischemic Stroke; Prehospital; Hyperoxia

1. Introduction:

Stroke is a leading cause of morbidity and mortality worldwide.¹ Unlike other organ systems, the brain is highly dependent on a constant blood supply to provide glucose for its high metabolic demands. In acute ischemic stroke (AIS), disruption of this cerebral blood flow (CBF) and the resultant hypoxia leads to an infarct core and surrounding penumbral zone that may recover should it be provided sufficient oxygen and metabolic substrates in a timely fashion.^{2,3} Hyperoxia, the provision of high levels of oxygen, in preclinical models of AIS resulted in improved stroke outcomes.^{4,5} However, concerns regarding hyperoxia in humans are drawn in part from the known role of oxygen in vasoconstriction and potential for reduced CBF.

Several factors influence CBF, including cerebrovascular resistance, arterial blood gas composition, cerebral autoregulation, and metabolic demand. A key driver of CBF is cerebral perfusion pressure (CPP), which is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP).⁶ CPP reflects the pressure gradient across the cerebrovasculature that drives CBF and the exchange of oxygen and metabolites. With elevated arterial perfusion pressure (i.e. higher MAP), the healthy brain limits the development of cerebral edema secondary to increase CBF through tight autoregulation. In stroke, this normal protective mechanism is often impaired, leaving patients more susceptible to both cerebral edema with high MAPs and hypoperfusion with low MAPs. Changes in oxygenation can also more directly influence CBF, with hypoxia resulting in a cascade of events including activation of prostaglandins and nitric oxide that leads to vasodilation.⁷

Thus, the effects of hyperoxia in stroke may be mixed: the partial arterial pressure of oxygen (PaO₂) may increase resulting in more oxygen available for extraction; alternatively, hyperoxia may also cause vasoconstriction and decreased CBF. In rodent stroke models increased penumbral CBF and oxygenation dominates with hyperoxia treatment.^{5,8} However, the net effect in humans is less clear and has not been specifically studied in stroke. In other healthy and disease states, hyperoxia causes various effects on peripheral hemodynamical parameters such as heart rate and MAP.⁹ This study examines the relationship of the prehospital delivery of hyperoxia, defined here as the administration of supplemental oxygen despite a room air initial pulse oximetry >94%, in stroke on peripheral hemodynamic parameters that may contribute to changes in CBF.

2. Methods:

2.1 Study population and data abstraction:

This is a retrospective analysis of adult (aged ≥18 years) patients presenting via EMS with a suspected stroke to an academic Comprehensive Stroke Center between January 1, 2013 and December 31, 2017 who were subsequently confirmed to have had a stroke. Demographic and key clinical characteristics were obtained from Get with the Guidelines-Stroke (GWTG-S) registry and extracted from subjects' medical records into a REDCap database (Vanderbilt University). The first documented EMS vital signs and vital signs at ED arrival, 1 hour after arrival and 2 hours after arrival were extracted. Values were considered missing if not within 30 minutes of each time point. The mean arterial pressure (MAP) was calculated according to the formula $MAP = (1/3 \times SBP) + (2/3 \times DBP)$.¹⁰ This study was reviewed by the Research Subjects Review Board and approved under expedited status.

2.2 Data analysis:

Variables were compared across the three groups using SAS 9.4 software (SAS Institute, Cary, NC) based on prehospital oxygen level: those who received sO₂ despite normoxia (pulse oximetry >94%) ("hyperoxia"), those who received sO₂ for hypoxia ("hypoxia") and those who did not receive sO₂ ("normoxia") using chi-square tests for independence and ANOVA. Tukey post-hoc analysis was performed for pairwise comparisons when the ANOVA was significant. Missing data for analysis was less than 3% in all cases. Multivariate linear regression was used to compare the effects of hyperoxia in all types of stroke and subgroups of ischemic and hemorrhagic strokes on heart rate and MAP while controlling for baseline confounders. Potential confounders were chosen based on univariate analysis with p-values less than 0.10 (i.e. age, gender, stroke type, being of white race, history of any respiratory comorbidities, history of smoking, history of atrial fibrillation, history of coronary artery disease) and a likely confounding factor – a history of hypertension and baseline EMS vitals despite not having a chi-squared p-value that met this requirement. All models were assessed for multi-collinearity, with minimal concerns present as indicated by a maximum Variance Inflation Factor of 1.46. A student's t-test was used to compare average ED MAP between the hyperoxia and normoxia groups for the unadjusted analysis. The effect size of hyperoxia compared to control was described using a Cohen's *d*.

3. Results:

Of 1,352 patients with complete prehospital records identified from the GWTG-S registry, 848 patients (62.7%) did not receive sO₂ ("normoxia"), 144 patients (10.7%) received sO₂ for hypoxia ("hypoxia"), and 360 patients (26.6%) received sO₂ despite being normoxic ("hyperoxia"). Demographic and baseline comorbidities are shown in Table 1. Univariate analysis of patient's vitals are shown in Table 2. Hyperoxia subjects did not significantly differ from either normoxia or hypoxia subjects in terms of their initial EMS vital signs with exception of the lowest documented pulse oximetry. However, univariate analysis demonstrated that hyperoxia subjects had significantly lower systolic and diastolic blood pressure and MAP compared to normoxic subjects, but not compared to hypoxia subjects; hypoxia subjects did not significantly differ in terms of heart rate or blood pressure from

normoxic subjects. Additionally, the percent change in blood pressure over time compared to baseline EMS blood pressure did not significantly change with exception of the 2hour ED SBP in the hyperoxia group compared to normoxia group. After controlling for potential confounders using multivariate linear regression, hyperoxia subjects still had a significantly lower average ED MAP (100.3mmHg vs 105.3mmHg, $p<0.0001$) with a small to moderate effect size (Cohen's $d=0.313$). A similar pattern was seen on subgroup analysis (Table 3) with both ischemic and hemorrhage subgroups showing a significantly lower average ED MAP in the hyperoxia groups compared to normoxia.

4. Discussion:

This retrospective analysis observed a nearly 5% decrease in MAP in those receiving supplemental oxygen without initial hypoxia compared to normoxia. In a metanalysis of the hemodynamic effects of hyperoxia in various disease states and healthy volunteers, high levels of oxygen had variable effects on hemodynamic profiles.⁹ Healthy volunteers and subjects with coronary artery disease exposed to hyperoxia had significant changes in their heart rate (~5–7% decrease), cardiac output (~10% decrease), MAP (2–3% increase), and systemic vascular resistance (~11–12% increase). In contrast, patients admitted for heart failure who were treated with hyperoxia had no significant change in heart rate or MAP from baseline. Patients who were post-coronary artery bypass grafting also has an approximately 3% decrease in heart rate and 16% increase in systemic vascular resistance from baseline, but no significant change in cardiac output or MAP. The data presented here for stroke showed no significant effect on heart rate, but an approximately 5% decrease in MAP in hyperoxia subjects compared to normoxic subjects. While those receiving sO_2 for any reason are more likely to appear and/or be more ill compared to normoxic subjects and thereby more likely to have a lower blood pressure, the fact that those in the hyperoxic group had a lower MAP than even the hypoxic group make this explanation of underlying illness severity less likely.

Our findings identified an association between hyperoxia and a reduced MAP, however whether this is a clinically significant reduction requires further inquiry. In rodent and human pilot studies of hyperoxia, hyperoxia selectively increased cerebral blood flow and oxygenation to ischemic tissue, with the expected vasoconstriction in the contralateral hemisphere.^{4,5,11,12} Given the retrospective nature of the data presented here, we were unable to determine the effects of hyperoxia directly on CBF. Thus, it is possible that the effects of hyperoxia may not just be limited to disease state, but may also have tissue-specific effects that could allow for increased CBF despite a small decrease in MAP and CPP.

In ICU studies of acute stroke patients, hyperoxia was associated with increase mortality, specifically in the hemorrhagic stroke subtypes.¹³ While the data presented here does not show a significant difference in effects upon subgroup analysis of stroke subtypes, a relative hypotension and hypoperfusion could contribute to increased mortality. Another study of AIS patients failed to correlate PaO_2 with mortality.¹⁴ While the results presented here are unexpected, if the decrease in MAP and potentially decreased CPP were clinically significant, it could contribute to the possible increased mortality that has been seen in other

studies. However, the data here showed similar discharge modified Rankin scores in all groups which would might counter that hypothesis.

This study is limited by the retrospective nature from a single large academic center. It was not possible to correlate unindicated prehospital sO₂ use with an arterial blood gas to confirm hyperoxia (typically defined as a PaO₂>200mmHg). Additionally, imaging results were not available to directly measure CBF.

5. Conclusions:

In summary, despite the inability to link changes in peripheral hemodynamical profiles directly to changes in CBF, this study suggests that hyperoxia may result in a relative hypotension (~5% decrease in MAP) without a change in heart rate compared to normoxic subjects. Further studies are needed to determine if this small change in peripheral vascular resistance translates into a clinically significant reduced CBF.

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List of abbreviations:

AIS	acute ischemic stroke
bpm	beats per minute
CBF	cerebral blood flow
CPP	cerebral perfusion pressure
CVA	cerebrovascular accident
COPD	chronic obstructive pulmonary disorder
CAD	coronary artery disease
DBP	diastolic blood pressure
ED	emergency department
EMS	emergency medical services
GWTG-S	Get with the Guidelines-Stroke
HR	heart rate
MAP	mean arterial pressure
MV	mechanical ventilation
mRS	modified Rankin Scale
NRBM	non-rebreather mask

NIPPV	non-invasive positive pressure ventilation
PaO₂	partial arterial pressure of oxygen
PVD	peripheral vascular disease
SD	standard deviation
sO₂	supplemental oxygen
SBP	systolic blood pressure
TIA	transient ischemic attack

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Table 1:

Patient demographics and baseline comorbidities

Patient Characteristic		Hyperoxia (n=360)	Hypoxia (n=144)	Control (n=848)
Age (Mean, SD) *		70.1 (15.5) ‡	75.8 (13.9) †	69.1 (16.3)
Gender (n, %)	Female §	188 (53%)	74 (54%)	374 (45%)
	Ischemic	262 (74%)	100 (73%)	673 (82%)
Stroke Type (n, %)	Hemorrhagic	94 (26%)	38 (28%)	152 (18%)
	Hispanic	4 (1%)	3 (2%)	17 (2%)
Ethnicity (n, %)	White §	311 (87%)	119 (86%)	673 (82%)
	African American	34 (10%)	17 (12%)	120 (15%)
	Other	6(2%)	1 (1%)	26 (3%)
Respiratory Comorbidities (n, %)	Smoking §	62 (17%)	12 (9%)	142 (17%)
	COPD §	38 (11%)	18 (13%)	56 (7% %)
	Asthma	18 (5%)	8 (6%)	39 (5%)
	Sleep Apnea §	17 (5%)	11 (8%)	27 (3%)
Past Medical History (n, %)	Prior TIA and/or CVA	90 (25%)	48 (35%)	217 (26%)
	Dyslipidemia	181 (50%)	73 (53%)	436 (53%)
	Hypertension	271 (76%)	115 (83%)	619 (75%)
	Atrial Fibrillation §	108 (30%)	43 (31%)	183 (22%)
	Diabetes Mellitus	90 (25%)	41 (30%)	214 (26%)
	Obesity	28 (8%)	14 (10%)	51 (6%)
	CAD §	116 (33%)	54 (39%)	231 (28%)
	PVD	6 (2%)	4 (3%)	26 (3%)
	Carotid Stenosis	22 (6%)	9 (7%)	39 (5%)

* ANOVA p<0.05; tukey post-hoc analysis p<0.05 compared to control (†), to hypoxia(‡)

§ chi-square p<0.05

Abbreviations: SD – standard deviation, COPD – Chronic Obstructive Pulmonary Disorder; TIA Transient Ischemic Attack, CVA – Cerebrovascular Accident, CAD – Coronary Artery Disease, PVD – Peripheral Vascular Disease

Table 2:

Patient EMS and ED clinical, hemodynamic, and respiratory profiles

Clinical and Hemodynamic Parameters		Hyperoxia (n=360)	Hypoxia (n=144)	Normoxia (n=848)
EMS First Documented Vital Signs (mean, SD)	Heart Rate (bpm)	79.6 (19.5)	82.2 (20.1)	82.0 (18.3)
	Systolic Blood Pressure (mmHg)	153.5 (32.7)	155.8 (37.3)	160.5 (70.6)
	Diastolic Blood Pressure (mmHg)	87.1 (19.5)	89.7 (23.1)	89.2 (21.6)
	Mean Arterial Pressure (mmHg)	109.1 (21.9)	111.3 (25.0)	112.0 (21.5)
	Respiratory Rate (breaths/min)	17.8 (3.7)	18.2 (4.6)	17.6 (3.1)
	Lowest Pulse Oximetry (%) [*]	95.8% (6.0%) ^{‡,‡}	89.9% (4.6%) [‡]	94.7% (6.6%)
Type of sO ₂ provided by EMS (n, %)	Nasal Canula	275 (77%)	108 (76%)	n/a
	NRBM	46 (13%)	23 (16%)	n/a
	NIPPV	5 (1%)	5 (3%)	n/a
	MV	32 (9%)	7 (5%)	n/a
EMS sO ₂ in LPM excluding intubated patients (mean, SD) [^]		4.5 (4.2)	5.4 (4.7)	n/a
ED Vital Signs (mean, SEM)	Heart Rate (bpm)	78.8 (0.8)	80.3 (1.5)	79.1 (0.5)
	Systolic Blood Pressure (mmHg) [*]	142.9 (14.2) [‡]	146.0 (2.0)	148.9 (0.8)
	Diastolic Blood Pressure (mmHg) [*]	78.9 (0.9) [‡]	82.2 (1.6)	85.2 (1.4)
	MAP (mmHg) [*]	100.3 (0.9) [‡]	103.5 (1.5)	105.3 (0.5)
	Respiratory Rate (breaths/min) [*]	18.5 (0.2) [‡]	19.1 (0.3) [‡]	18.0 (0.1)
	Lowest Pulse Oximetry (%) [*]	97.9 (0.3) [‡]	96.8 (0.3) [‡]	97.7 (0.1)
% Change from baseline EMS (mean, SD)	0hr ED SBP	-2.1% (16.9%)	-1.6% (19.3%)	-1.3% (14.8%)
	1hr ED SBP	-6.2% (18.9%)	-3.9% (22.0%)	-5.7% (17.6%)
	2hr ED SBP [‡]	-6.0% (20.4%)	-0.5% (64.2%)	-8.2% (18.9%)
	0hr ED DBP	-1.1% (24.1%)	3.2% (29.2%)	4.6% (63.8%)
	1hr ED DBP	-7.2% (23.7%)	-8.8% (22.9%)	-1.9% (54.3%)
	2hr ED DBP	-8.6% (26.6%)	-6.1% (28.5%)	-4.0% (60.1%)
	0hr ED MAP	-1.5% (17.1%)	0.5% (20.2%)	-0.4% (15.4%)
	1hr ED MAP	-6.5% (18.1%)	-6.0% (19.4%)	-5.0% (16.9%)
	2hr ED MAP	-7.4% (20.8%)	-5.1% (24.0%)	-7.2% (17.8%)
Discharge mRS (mean, SD)		3 (2)	3 (2)	3 (2)

^{*} ANOVA p<0.05; Tukey post-hoc analysis p<0.05 compared to normoxia ([‡]), to hypoxia ([‡])

[^] Student's t-test p<0.05

Abbreviations: bpm – beats per minute, SD – standard deviation, SEM – standard error of the mean, mRS – modified Rankin Scale, NRBM – Non-Rebreather Mask, NIPPV – Non-invasive Positive Pressure Ventilation, MV – Mechanical Ventilation

Table 3a:

Effects of Hyperoxia compared to Normoxia on SBP

Stroke Type	SBP– mmHg (mean, SD)		Cohen's D	Unadjusted p-value [^]	Parameter Estimate for hyperoxia vs normoxia (95%CI)	Adjusted p-value
	Hyperoxia	Normoxia				
All Stroke Types	142.9 (22.3)	148.9 (23.0)	0.265	<0.001	–3.1 (–5.4 to –0.9)	0.007
Ischemic Strokes	142.3 (20.6)	148.4 (22.8)	0.281	<0.001	–5.3 (–8.5 to –2.2)	0.001
Hemorrhagic Stroke	145.0 (26.5)	151.2 (24.5)	0.243	0.057	–5.6 (–10.6 to –0.7)	0.022

Table 3b:

Effects of Hyperoxia compared to Normoxia on DBP

Stroke Type	DBP – mmHg (mean, SD)		Cohen's D	Unadjusted p-value [^]	Parameter Estimate for hyperoxia vs normoxia (95%CI)	Adjusted p-value
	Hyperoxia	Normoxia				
All Stroke Types	78.9 (17.2)	85.2 (15.0)	0.390	<0.001	–3.6 (–5.4 to –1.8)	<0.001
Ischemic Strokes	79.2 (17.0)	83.1 (15.0)	0.243	0.001	–3.3 (–5.3 to –1.2)	0.002
Hemorrhagic Stroke	78.9 (19.1)	84.4 (15.2)	0.319	0.017	–4.6 (–8.7 to –0.5)	0.029

Table 3c:

Effects of Hyperoxia compared to Normoxia on MAP

Stroke Type	MAP – mmHg (mean, SD)		Cohen's D	Unadjusted p-value [^]	Parameter Estimate for hyperoxia vs normoxia (95%CI)	Adjusted p-value
	Hyperoxia	Normoxia				
All Stroke Types	100.3 (16.4)	105.3 (15.5)	0.313	<0.001	–3.4 (–5.4 to –1.8)	<0.001
Ischemic Strokes	100.3 (15.2)	104.9 (15.3)	0.302	<0.001	–4.5 (–6.8 to –2.3)	0.001
Hemorrhagic Stroke	100.9 (19.6)	106.7 (16.0)	0.324	0.016	–4.8 (–8.7 to –0.9)	0.017

[^] student's t-test; satterthwaite p-value used for hemorrhagic strokes given Pr(F)<0.05; pooled p-value used for all stroke types and ischemic strokes given Pr(F)>0.05

multivariate linear regression adjusting for stroke type (only in all strokes), history of any respiratory comorbidity, gender, age, race, history of smoking, history of coronary artery disease, history of hypertension, history of atrial fibrillation, baseline EMS MAP.

Abbreviations: MAP – mean arterial pressure, SD – standard deviation