

WORKSHEET for Evidence-Based Review of Science for Veterinary CPR

1. Basic Demographics

Worksheet author(s)

Jennifer Kyes	Date Submitted for review:

2. Clinical question: PA08

In dogs and cats with ROSC after cardiac arrest (P), does the administration of 100% oxygen (I) compare to titration to normoxia (eg to SpO2>94%) (C), result in improved outcome (O) (survival to discharge neurological function)?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? NO

4. Search strategy (including electronic databases searched):

4a. Databases

-MEDLINE via PUBMED, CAB:

1. Hypoxia
2. normoxia
3. global ischemia and reperfusion
4. Cardiopulmonary resuscitation
5. oxygen utilization
6. cerebral ischemia
7. heart arrest
8. dogs

4b. Other sources

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

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Comment [1]: Please state the date of the search and the number of hits resulting from each search. Also, were these textword searches or MeSH searches. The idea to provide these details is that everyone can reproduce search and the selection of relevant articles.

Inclusion criteria

Original research manuscripts, human or whole animal studies or cardiac arrest or post-arrest or reperfusion

Exclusion criteria

Review articles, Hypothesis paper, abstracts only, non-peer reviewed publication, isolated organ studies, studies that do not address the stated question, case reports, conference proceedings. Hyperbaric oxygen

4d. Number of articles/sources meeting criteria for further review: 17 articles were reviewed and 4 were discarded; 2 that dealt with stroke events rather than CPA, 1 had too many confounding variables and 1 that was not relevant to the question.

5. Summary of evidence

Evidence Supporting Clinical Question – 100% O2 improves outcome

Good						
Fair						
Poor						
	1	2	3	4	5	6
Level of evidence (P)						

Italics : Non target species ie) humans, rats, gerbils, pigs.

- (A) Improved neurological outcome
- (B) Reduced biomarkers of oxidative stress or tissue peroxidation
- (C) Reduced mortality
- (D) Reduced neuronal cell death
- (E) Cardiac function/cardiac index

Evidence Neutral to Clinical question – 100% O2 vs 21% O2 are equal

Good			Zwemer 1995 B			<i>Smith 2006 B</i> <i>Kuisma 2006 D</i> <i>Lipinski 1999 A,C,D</i> <u><i>Kilgannon 2010</i></u> <u><i>Kilgannon 2011</i></u>
Fair						
Poor						
	1	2	3	4	5	6
Level of evidence (P)						

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Italics : Non target species ie)humans, rats, gerbils, pigs.

- (A) Improved neurological outcome
- (B) Reduced biomarkers of oxidative stress or tissue peroxidation
- (C) Reduced mortality
- (D) Reduced neuronal cell death
- (E) Cardiac function/cardiac index

Evidence Opposing Clinical Question – 100% O2 is detrimental to outcome

Good			Richards 2006 B Liu 1998 A,B Zwemer 1995 A,C Zwemer 1994 A Vereczki 2006 B,D Balan 2006 A,D Richards 2007 B,D Marsala 1992 D			Mickel 1986 B,C Adbel-Rahman 2009 E
Fair						
Poor						
	1	2	3	4	5	6
Level of evidence (P)						

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 Marsala 1992 D -

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- Italics : Non target species ie) humans, rats, gerbils, pigs,*
- (A) Improved neurological outcome
 - (B) Reduced biomarkers of oxidative stress or tissue peroxidation
 - (C) Reduced mortality
 - (D) Reduced neuronal cell death
 - (E) Cardiac function/cardiac index

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The American Heart Association recommends that 100% inspired oxygen be used during advanced life support. The concern regarding the administration of 100% oxygen is based on our current understanding of ischemia-reperfusion injury. Reperfusion injury occurs when previously hypoxic or ischemic tissues are exposed to high oxygen concentrations. Reperfusion and the administration of oxygen result in the formation of oxygen free radicals causing lipid peroxidation, neuronal injury and neuronal cell death. Reperfusion injury reduces neurological outcome and increases patient mortality. Many studies have evaluated the administration of 100% inspired oxygen (hyperoxic) versus 21-30% inspired oxygen (normoxic) therapy following cardiopulmonary-resuscitation. Studies have specifically evaluated neurological outcome, biomarkers of oxidative stress or tissue peroxidation, mortality, neuronal cell death and cardiac function.

All of these animal studies are not sufficiently powered which is a common problem in veterinary science.

Despite the few prospective, randomized, controlled clinical trials in target species there is sufficient evidence to support that 100% inspired oxygen after ischemic injury results in neuronal tissue injury via lipid peroxidation and oxidative injury, neuronal cell death, and reduced neurological outcome. It also suggests increased mortality although there is less evidence to support this as none of these studies follow long term (>24 hours) neurological deficits or survival.

7. Conclusion

Current recommendations should be modified to discourage the use of 100% inspired oxygen during advanced life support and to encourage 21-30% inspired oxygen to reduce reperfusion injury and the formation of radical oxygen species. Patients should be ventilated on room air (FiO₂ 0.21-0.3) and pulse oximetry values should be kept between 95% and 100%.

8. Acknowledgement

NIL

9. Citation list

Two more articles of interest:

[PMID- 21606393](#)

[OWN - NLM](#)

[STAT- Publisher](#)

[DA - 20110614](#)

[IS - 1524-4539 \(Electronic\)](#)

[IS - 0009-7322 \(Linking\)](#)

VI - 123
IP - 23
DP - 2011 Jun 14
TI - Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest.
PG - 2717-2722
AB - Background- Laboratory and recent clinical data suggest that hyperoxemia after resuscitation from cardiac arrest is harmful; however, it remains unclear if the risk of adverse outcome is a threshold effect at a specific supranormal oxygen tension, or is a dose-dependent association. We aimed to define the relationship between supranormal oxygen tension and outcome in postresuscitation patients. Methods and Results- This was a multicenter cohort study using the Project IMPACT database (intensive care units at 120 US hospitals). Inclusion criteria were age >17 years, nontrauma, cardiopulmonary resuscitation preceding intensive care unit arrival, and postresuscitation arterial blood gas obtained. We excluded patients with hypoxia or severe oxygenation impairment. We defined the exposure by the highest partial pressure of arterial oxygen (PaO₂) over the first 24 hours in the ICU. The primary outcome measure was in-hospital mortality. We tested the association between PaO₂ (continuous variable) and mortality using multivariable logistic regression adjusted for patient-oriented covariates and potential hospital effects. Of 4459 patients, 54% died. The median postresuscitation PaO₂ was 231 (interquartile range 149 to 349) mm Hg. Over ascending ranges of oxygen tension, we found significant linear trends of increasing in-hospital mortality and decreasing survival as functionally independent. On multivariable analysis, a 100 mm Hg increase in PaO₂ was associated with a 24% increase in mortality risk (odds ratio 1.24 [95% confidence interval 1.18 to 1.31]). We observed no evidence supporting a single threshold for harm from supranormal oxygen tension. Conclusion- In this large sample of postresuscitation patients, we found a dose-dependent association between supranormal oxygen tension and risk of in-hospital death.
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LA - ENG

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PT - [JOURNAL ARTICLE](#)
DEP - [20110523](#)
TA - [Circulation](#)
JT - [Circulation](#)
JID - [0147763](#)
EDAT- [2011/05/25 06:00](#)
MHDA- [2011/05/25 06:00](#)
CRDT- [2011/05/25 06:00](#)
PHST- [2011/05/23 \[aheadofprint\]](#)
AID - [CIRCULATIONAHA.110.001016 \[pii\]](#)
AID - [10.1161/CIRCULATIONAHA.110.001016 \[doi\]](#)
PST - [ppublish](#)
SO - [Circulation. 2011 Jun 14;123\(23\):2717-2722. Epub 2011 May 23.](#)

PMID- [20516417](#)
OWN - [NLM](#)
STAT- [MEDLINE](#)
DA - [20100602](#)
DCOM- [20100603](#)
LR - [20101006](#)
IS - [1538-3598 \(Electronic\)](#)
IS - [0098-7484 \(Linking\)](#)
VI - [303](#)
IP - [21](#)
DP - [2010 Jun 2](#)

TI - [Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality.](#)

PG - [2165-71](#)

AB - [CONTEXT: Laboratory investigations suggest that exposure to hyperoxia after resuscitation from cardiac arrest may worsen anoxic brain injury; however, clinical data are lacking. OBJECTIVE: To test the hypothesis that postresuscitation hyperoxia is associated with increased mortality. DESIGN, SETTING, AND PATIENTS: Multicenter cohort study using the Project IMPACT critical care database of intensive care units \(ICUs\) at 120 US hospitals between 2001 and 2005. Patient inclusion criteria were age older than 17 years, nontraumatic cardiac arrest, cardiopulmonary resuscitation within 24 hours prior to ICU arrival, and arterial blood gas analysis performed within 24 hours following ICU arrival. Patients were divided into 3 groups defined a priori based on PaO\(2\) on the first arterial blood gas values obtained in the ICU. Hyperoxia was defined as PaO\(2\) of 300 mm Hg or greater; hypoxia, PaO\(2\) of less than 60 mm Hg \(or ratio of PaO\(2\) to fraction of inspired oxygen <300\); and normoxia, not classified as hyperoxia or hypoxia. MAIN OUTCOME MEASURE: In-hospital mortality. RESULTS: Of 6326 patients, 1156 had hyperoxia \(18%\), 3999 had hypoxia \(63%\), and 1171 had](#)

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normoxia (19%). The hyperoxia group had significantly higher in-hospital mortality (732/1156 [63%; 95% confidence interval {CI}, 60%-66%]) compared with the normoxia group (532/1171 [45%; 95% CI, 43%-48%]; proportion difference, 18% [95% CI, 14%-22%]) and the hypoxia group (2297/3999 [57%; 95% CI, 56%-59%]; proportion difference, 6% [95% CI, 3%-9%]). In a model controlling for potential confounders (eg, age, preadmission functional status, comorbid conditions, vital signs, and other physiological indices), hyperoxia exposure had an odds ratio for death of 1.8 (95% CI, 1.5-2.2). CONCLUSION: Among patients admitted to the ICU following resuscitation from cardiac arrest, arterial hyperoxia was independently associated with increased in-hospital mortality compared with either hypoxia or normoxia.

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LA - eng

GR - GM076659/GM/NIGMS NIH HHS/United States

GR - GM76652/GM/NIGMS NIH HHS/United States

GR - GM83211/GM/NIGMS NIH HHS/United States

GR - HL091757/HL/NHLBI NIH HHS/United States

PT - Journal Article

PT - Multicenter Study

PT - Research Support, N.I.H., Extramural

PT - Research Support, Non-U.S. Gov't

PL - United States

TA - JAMA

JT - JAMA : the journal of the American Medical Association

JID - 7501160

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[CIN - JAMA. 2010 Oct 6;304\(13\):1440; author reply 1441. PMID: 20924005](#)
[CIN - JAMA. 2010 Jun 2;303\(21\):2190-1. PMID: 20516423](#)
[MH - Aged](#)
[MH - Aged, 80 and over](#)
[MH - *Cardiopulmonary Resuscitation](#)
[MH - Cohort Studies](#)
[MH - Databases, Factual](#)
[MH - Female](#)
[MH - Heart Arrest/*mortality/therapy](#)
[MH - *Hospital Mortality](#)
[MH - Humans](#)
[MH - Hyperoxia/*mortality](#)
[MH - Intensive Care Units/statistics & numerical data](#)
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[AID - 303/21/2165 \[pii\]](#)
[AID - 10.1001/jama.2010.707 \[doi\]](#)
[PST - ppublish](#)
[SO - JAMA. 2010 Jun 2;303\(21\):2165-71](#)

1. U. Abdel-Rahman, MD,a P. Risteski, MD,a K. Tizi,a S. Kerscher, MD, PhD,b S. Bejati,a K. Zwicker, MD,b M. Scholz, MD, PhD,c U. Brandt, MD, PhD,b and A. Moritz, MD, PhD. 2009. "Hypoxic reoxygenation during initial reperfusion attenuates cardiac dysfunction and limits ischemia-reperfusion injury after cardioplegic arrest in a porcine model." *J Thorac Cardiovasc Surg.* 137:978-82.

Comments:

LOE6

Quality: non target species, underpowered, randomized, non- blinded

Results: Opposing

ABSTRACT:

Objective: In clinical practice, reperfusion of ischemic myocardium usually occurs under high arterial oxygen levels. However, this might aggravate cardiac ischemia-reperfusion injury caused by excessive oxidative stress. In an experimental in vivo study, the cardioprotective role of hypoxic reoxygenation during initial reperfusion was assessed.

Methods: Twenty-one adult pigs were started on cardiopulmonary bypass with aortic crossclamping (90 minutes) and cardioplegic arrest. During initial reperfusion, 10 pigs underwent standard hypoxic reoxygenation (PaO₂, 250–350 mm Hg), whereas gradual reoxygenation (PaO₂, 40–90 mm Hg) was performed in 11 pigs. Cardiac function was analyzed by means of the thermodilution method and conductance catheter technique.

Results: In both groups cardiac index was decreased 10 minutes after cardiopulmonary bypass compared with preoperative values. Sixty minutes after cardiopulmonary bypass, cardiac index improved significantly after gradual reoxygenation compared with that after hypoxic reoxygenation (3.2 ± 0.6 vs 2.5 ± 0.5 L · min⁻¹ · m⁻², P = .04). Correspondingly, end-systolic pressure-volume relationship and peak left ventricular pressure increase were significantly less decreased in the gradual reoxygenation group. During and after reperfusion, malondialdehyde and troponin T values within the coronary sinus were significantly lower after gradual reoxygenation (60 minutes after declamping: malondialdehyde, 7.6 ± 0.8 vs 4.6 ± 0.5 mmol/L [P = .007]; troponin, 0.12 ± 0.02 vs 0.41 ± 0.12 ng/mL [P = .02]).

Conclusion: Hypoxic reoxygenation at the onset of reperfusion attenuates myocardial ischemia–reperfusion injury and helps to preserve cardiac performance after myocardial ischemia in a pig model.

2. Irina S. Balan, Gary Fiskum, Julie Hazelton, Cynthia Cotto-Cumba and Robert E. Rosenthal. 2006. "Oximetry-Guided Reoxygenation Improves Neurological Outcome After Experimental Cardiac Arrest." *Stroke* 37: 3008-3013.

Comments:

LOE 3

Quality: underpower, target species, randomized, blinded,
Results: Opposing

ABSTRACT:

Background and Purpose—Current guidelines suggest that cardiac arrest (CA) survivors should be ventilated with 100% O₂ after resuscitation. Breathing 100% O₂ may worsen neurological outcome after experimental CA. This study tested the hypothesis that graded reoxygenation, with oximetry guidance, can safely reduce FiO₂ after resuscitation, avoiding hypoxia while promoting neurological recovery.

Methods—Mature dogs underwent 10 minutes of CA and restoration of spontaneous circulation with 100% O₂. Animals were randomized to 1-hour additional ventilation on 100% FiO₂ or to rapid lowering of arterial O₂ saturation to 96% but 94% with pulse oximeter guidance. Animals were awakened at hour 23, and the neurological deficit score (0 normal; 100 brain-dead) was measured. Reanesthetized animals were perfusion-fixed and the brains removed for histopathology.

Results—The neurological deficit score was significantly better in oximetry (O) dogs. O dogs appeared aware of their surroundings, whereas most hyperoxic (H) animals were stuporous (neurological deficit score 43.0_5.9 [O] versus 61.0_4.2 [H]; n_8, P_0.05). Stereological analysis revealed fewer injured CA1 neurons in O animals (cresyl violet: 35.5_4.3% [O] versus 60.5_3.3% [H]; P_0.05). There were also fewer fluoro-Jade B-stained degenerating CA1 neurons in O animals (3320_267 [O] versus 6633_356 [H] per 0.1 mm³; P_0.001).

Conclusions—A clinically applicable protocol designed to reduce postresuscitatory hyperoxia after CA results in significant neuroprotection. Clinical trials of controlled normoxia after CA/restoration of spontaneous circulation should strongly be considered.

3. M. Kuusmaa, J. Boyda, V. Voipio b, A. Alaspää ac, R.O. Roined, P. Rosenberg. 2006. "Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomized controlled pilot study." *Resuscitation* 69:199-206.

Comments:

LOE 6

Quality: randomized, controlled, non target species, blinded

Results: Neutral

ABSTRACT:

Objectives: High oxygen concentration in blood may be harmful in the reperfusion phase after cardiopulmonary resuscitation. We compared the effect of 30 and 100% inspired oxygen concentrations on blood oxygenation and the level of serum markers (NSE, S-100) of neuronal injury during the early post-resuscitation period in humans.

Methods: Patients resuscitated from witnessed out-of-hospital ventricular fibrillation were randomised after the return of spontaneous circulation (ROSC) to be ventilated either with 30% (group A) or 100% (group B) oxygen for 60 min. Main outcome measures were NSE and S-100 levels at 24 and 48 h after ROSC, the adequacy of oxygenation at 10 and 60 min after ROSC and, in group A, the need to raise FiO₂ to avoid hypoxaemia. Blood oxygen saturation <95% was the threshold for this intervention.

Results: Thirty-two patients were randomised and 28 (14 in group A and 14 in group B) remained eligible for the final analysis. The mean PaO₂ at 10 min was 21.1 kPa in group A and 49.7 kPa in group B. The corresponding values at 60 min were 14.6 and 46.5 kPa. PaO₂ values did not fall to the hypoxaemic level in group A. In another group FiO₂ had to be raised in five cases (36%) but in two cases it was returned to 0.30 rapidly. The mean NSE at 24 and 48 h was 10.9 and 14.2 μ g/l in group A and 13.0 and 18.6 μ g/l in group B (ns). S-100 at corresponding time points was 0.21 and 0.23 μ g/l in group A and 0.73 and 0.49 μ g/l in group B (ns). In the subgroup not treated with therapeutic hypothermia in hospital NSE at 24 h was higher in group B (mean 7.6 versus 13.5 μ g/l, p = 0.0487).

Conclusions: Most patients had acceptable arterial oxygenation when ventilated with 30% oxygen during the immediate post-resuscitation period. There was no indication that 30% oxygen with SpO₂ monitoring and oxygen backup to avoid SpO₂ < 95% did worse than the group receiving 100% oxygen. The use of 100% oxygen was associated with increased level of NSE at 24 h in patients not treated with therapeutic hypothermia. The clinical significance of this finding is unknown and an outcome-powered study is feasible.

4. Christopher A. Lipinski a, Shawn D. Hicks b, Clifton W. Callaway b. 1999. "Normoxic ventilation during resuscitation and outcome from asphyxial cardiac arrest in rats". *Resuscitation* 42:221-229.

Comments:

LOE 6

Quality: non target species, lack of power, randomized, non blinded.

Results: Neutral

ABSTRACT:

The formation of reactive oxygen species during reperfusion is one trigger for neuronal injury after global cerebral ischemia. Because formation of reactive oxygen species requires delivery of molecular oxygen to ischemic tissue, restricting inspired oxygen during reperfusion may decrease neurological damage. This study examined whether ventilation with room air rather than pure oxygen during resuscitation would improve neurological recovery after cardiac arrest in rats. Adult, male rats were subjected to 8 min of asphyxia resulting in cardiac arrest. During resuscitation, rats were ventilated either with hyperoxia (FiO₂_1.0) or

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Comment [2]: LOE 3, as this is an experimental laboratory study in target species. LOE 1 would be clinical RCT in target species.

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normoxia (FiO₂ 0.21, room air). Neurobehavioral deficits were scored daily for 72 h after resuscitation, after which brains were collected for histology. Normoxia decreased arterial oxygen content. Other physiological parameters and mortality did not differ between groups. All surviving rats exhibited behavioral and histological signs of brain damage. Neurological deficit scores did not differ between normoxia and hyperoxia conditions at any time point. The number of ischemic neurons in the hippocampus also did not differ between groups. These data indicate neither benefit nor detriment of reducing inspired oxygen concentration during resuscitation from asphyxial cardiac arrest in rats.

5. Yuanbin Liu, Robert E. Rosenthal, Yolanda Haywood, Milena Miljkovic-Lolic, Jack, Y. Vanderhoek, Gary Fiskum and Richard J. Traystman. 1998. "Normoxic Ventilation After Cardiac Arrest Reduces Oxidation of Brain Lipids and Improves Neurological Outcome." *Stroke* 29:1679-1686.

Comments:

LOE 3

Quality: target species, randomized, blinded

Results: opposing

ABSTRACT:

Background and Purpose—Increasing evidence that oxidative stress contributes to delayed neuronal death after global cerebral ischemia has led to reconsideration of the prolonged use of 100% ventilatory O₂ following resuscitation from cardiac arrest. This study determined the temporal course of oxidation of brain fatty acyl groups in a clinically relevant canine model of cardiac arrest and resuscitation and tested the hypothesis that posts ischemic ventilation with 21% inspired O₂, rather than 100% O₂, results in reduced levels of oxidized brain lipids and decreased neurological impairment.

Methods—Neurological deficit scoring and high performance liquid chromatography measurement of fatty acyl lipid oxidation were used in an established canine model using 10 minutes of cardiac arrest followed by resuscitation with different ventilatory oxygenation protocols and restoration of spontaneous circulation for 30 minutes to 24 hours.

Results—Significant increases in frontal cortex lipid oxidation occurred after 10 minutes of cardiac arrest alone with no reperfusion and after reperfusion for 30 minutes, 2 hours, and 24 hours (relative total 235-nm absorbing peak areas 57.160.7 SE, 17.362.7, 14.263.2, 16.161.0, and 14.060.8, respectively; n54, P,0.05). The predominant oxidized lipids were identified by gas chromatography/mass spectrometry as 13- and 9-hydroxyoctadecadienoic acids (13- and 9-HODE). Animals ventilated on 21% to 30% O₂ versus 100% O₂ for the first hour after resuscitation exhibited significantly lower levels of total and specific oxidized lipids in the frontal cortex (1.760.1 versus 3.1260.78 mg 13-HODE/g wet wt cortex., n54 to 6, P,0.05) and lower neurological deficit scores (45.163.6 versus 58.363.8, n59, P,0.05).

Conclusions—With a clinically relevant canine model of 10 minutes of cardiac arrest, resuscitation with 21% versus 100% inspired O₂ resulted in lower levels of oxidized brain lipids and improved neurological outcome measured after 24 hours of reperfusion. This study casts further doubt on the appropriateness of present guidelines that recommend the indiscriminate use of 100% ventilatory O₂ for undefined periods during and after resuscitation from cardiac arrest.

6. J. Marsala, M. Marsala, I. Vanicky, J. Galik and J. Orendacova. 1992. "Post cardiac arrest hyperoxic resuscitation enhances neuronal vulnerability of the respiratory rhythm generator and some brainstem and spinal cord neuronal pools in the dog". *Neuroscience* 146:121-124.

Comments:

LOE 3

Quality: target species, lack of power, controlled, blinded, non randomized.

Results: opposing

ABSTRACT:

Selective neuronal vulnerability of the motor cortex, basal ganglia, brainstem, medulla, cerebellum, C₆ and L₆ segments of the spinal cord were studied after 15 min of cardiac arrest followed by 1 h of normoxic or hyperoxic resuscitation using the suppressive Nauta method in dogs. Hyperoxic resuscitation causes characteristic somatodendritic argyrophilia of the interneuronal pool in the spinal cord and lower medulla. Cuneate, lateral reticular, supraspinal, and caudal trigeminal nuclei as well as the dorsal and ventral respiratory neuronal groups were heavily involved. Similarly, the Purkinje cells, neurons in the middle and deep portions of the mesencephalic tectum, peribrubal, pretectal, posterior commissure, middle-sized striatal and giant pyramidal (Betz's) neurons in the motor cortex became argyrophilic. Hyperoxic resuscitation versus normoxic resuscitation causes statistically significant somatodendritic argyrophilia of the dorsal respiratory group, cuneate, dorsal lateral geniculate and thalamic reticular nuclei.

7. HS Mickel, YN Vaishnav, O Kempfski, D von Lubitz, JF Weiss and G Feuerstein. 1986. "Breathing 100% oxygen after global brain ischemia in Mongolian Gerbils results in increased lipid peroxidation and increased mortality." *Stroke*. 18: 426-430.

Comments:

LOE 6

Quality: non target species, lack of power, non randomized, non-blinded

Results: opposing

ABSTRACT:

Exposure of Mongolian gerbils to a 100% oxygen atmosphere after 15 minutes of global brain ischemia resulted in a marked increase in the production of pentane, an in vivo product of lipid peroxidation. Much less pentane production occurred in animals subjected to global brain ischemia then exposed to an air atmosphere and in animals exposed to a 100% oxygen atmosphere

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without ischemia. Gerbils placed in 100% oxygen for 3-6 hours after 15 minutes of ischemia also had a threefold increase in 14-day mortality compared with gerbils subjected to ischemia and then placed in an air atmosphere. These findings raise a serious question about the use of oxygen-enriched atmospheres during reperfusion following ischemia.

8. Erica M. Richards, Gary Fiskum, Robert E. Rosenthal, Irene Hopkins and Mary C. McKenna. 2007. "Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism." *Stroke* 38:1578-1584.

Comments:

LOE 3

Quality: target species, randomized, not blinded

Results: opposing

ABSTRACT:

Background and Purpose—Previous reports indicate that compared with normoxia, 100% ventilatory O₂ during early reperfusion after global cerebral ischemia decreases hippocampal pyruvate dehydrogenase activity and increases neuronal death. However, current standards of care after cardiac arrest encourage the use of 100% O₂ during resuscitation and for an undefined period thereafter. Using a clinically relevant canine cardiac arrest model, in this study we tested the hypothesis that hyperoxic reperfusion decreases hippocampal glucose metabolism and glutamate synthesis.

Methods—After 10 minutes of cardiac arrest, animals were resuscitated and ventilated for 1 hour with 100% O₂ (hyperoxic) or 21% to 30% O₂ (normoxic). At 30 minutes reperfusion, [1-¹³C]glucose was infused, and at 2 hours, brains were rapidly removed and frozen. Extracted metabolites were analyzed by ¹³C nuclear magnetic resonance spectroscopy.

Results—Compared with nonischemic controls, the hippocampi from hyperoxic animals had elevated levels of unmetabolized ¹³C-glucose and decreased incorporation of ¹³C into all isotope isomers of glutamate. These findings indicate impaired neuronal metabolism via the pyruvate dehydrogenase pathway for carbon entry into the tricarboxylic acid cycle and impaired glucose metabolism via the astrocytic pyruvate carboxylase pathway. No differences were observed in the cortex, indicating that the hippocampus is more vulnerable to metabolic changes induced by hyperoxic reperfusion.

Conclusions—These results represent the first direct evidence that hyperoxia after cardiac arrest impairs hippocampal oxidative energy metabolism in the brain and challenge the rationale for using excessively high resuscitative ventilator O₂.

9. Erica M. Richards a,b, Robert E. Rosenthal c, Tibor Kristian a, Gary Fiskum. 2006. "Posts ischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity." *Free Radical Biology & Medicine* 40:1960-1970.

Comments:

LOE 3

Quality: target species, randomized, non-blinded.

Results: opposing

ABSTRACT:

The pyruvate dehydrogenase complex (PDHC) is a mitochondrial matrix enzyme that catalyzes the oxidative decarboxylation of pyruvate and represents the sole bridge between anaerobic and aerobic cerebral energy metabolism. Previous studies demonstrating loss of PDHC enzyme activity and immunoreactivity during reperfusion after cerebral ischemia suggest that oxidative modifications are involved. This study tested the hypothesis that hyperoxic reperfusion exacerbates loss of PDHC enzyme activity, possibly due to tyrosine nitration or S-nitrosation. We used a clinically relevant canine ventricular fibrillation cardiac arrest model in which, after resuscitation and ventilation on either 100% O₂ (hyperoxic) or 21-30% O₂ (normoxic), animals were sacrificed at 2 h reperfusion and the brains removed for enzyme activity and immunoreactivity measurements. Animals resuscitated under hyperoxic conditions exhibited decreased PDHC activity and elevated 3-nitrotyrosine immunoreactivity in the hippocampus but not the cortex, compared to nonischemic controls. These measures were unchanged in normoxic animals. In vitro exposure of purified PDHC to peroxynitrite resulted in a dose-dependent loss of activity and increased nitrotyrosine immunoreactivity. These results support the hypothesis that oxidative stress contributes to loss of hippocampal PDHC activity during cerebral ischemia and reperfusion and suggest that PDHC is a target of peroxynitrite.

10. J. Michael Smith a,*, William H. Roberts b, Jeffrey D. Miller c, Kimberly A. Hasselfeld c, Mary Pat Hendy. 2006. "Controlled cardiac reoxygenation does not improve myocardial function following global myocardial ischemia" *Int J Surg.* 4:153-159.

Comments:

LOE6

Quality: non target species, blinded, non randomized, lack of power.

Results: neutral

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ABSTRACT:

Abstract Background: It has been shown that abrupt re-exposure of ischemic myocardium to oxygen can lead to increased peroxidative damage to myocytes (oxygen paradox). Controlled cardiac reoxygenation, as an adjunct to substrate-enhanced cardioplegia, has been shown to improve myocardial function and limit reperfusion injury when utilizing standardized hyperoxic cardiopulmonary bypass (CPB). The objective of our study was to evaluate the effect of controlled reoxygenation on myocardial function following global ischemia employing normoxic CPB. Study design: Nineteen female swine (30e40 kg) were placed on vented, normoxic CPB. They were subjected to 45e50 min of unprotected global ischemia (aortic cross clamping) followed by 30 min of controlled cardiac reperfusion utilizing substrate-enhanced cardioplegia. Group 1 maintained normoxic pO₂ (O₂ tension of 90e110 mmHg). In Group 2, reoxygenation was titrated gradually and increased from venous to arterial levels (O₂ tensions from 40 to 110 mmHg over 15 min). We measured coronary sinus blood samples for CK, CK-MB, nitric oxide, and conjugated dienes at baseline, 5 min into the cardioplegic resuscitation, 5 min after the cross clamp removal, and just prior to the termination of the study. Hearts were pathologically studied and scored for evidence of tissue peroxidation. Results: Although not significantly different, Group 1 (normoxic reperfusion) animals were more likely to wean from CPB (p Z 0.141) and had a higher mean arterial pressure (pZ 0.556). In Group 1, conjugated dienes were significantly higher 5 min into the resuscitative protocol (p Z 0.018) and at the termination of bypass (pZ 0.035). Five of six animals in Group 1 eventually attained normal sinus rhythm as opposed to three out of 13 in Group 2 (pZ 0.041).

11. Viktoria Vereczki, Erica Martin, Robert E Rosenthal, Patrick R Hof, Gloria E Hoffman and Gary Fiskum. 2006. "Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death". J cerebral blood flow & Metabolism 26:821-835.

Comments:

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Quality: randomized, not blinded, target species
Results: opposing

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ABSTRACT:

Resuscitation and prolonged ventilation using 100% oxygen after cardiac arrest is standard clinical practice despite evidence from animal models indicating that neurologic outcome is improved using normoxic compared with hyperoxic resuscitation. This study tested the hypothesis that normoxic ventilation during the first hour after cardiac arrest in dogs protects against prelethal oxidative stress to proteins, loss of the critical metabolic enzyme pyruvate dehydrogenase complex (PDHC), and minimizes subsequent neuronal death in the hippocampus. Anesthetized beagles underwent 10 mins ventricular fibrillation cardiac arrest, followed by defibrillation and ventilation with either 21% or 100% O₂. At 1 h after resuscitation, the ventilator was adjusted to maintain normal blood gas levels in both groups. Brains were perfusion-fixed at 2 h reperfusion and used for immunohistochemical measurements of hippocampal nitrotyrosine, a product of protein oxidation, and the E1a subunit of PDHC. In hyperoxic dogs, PDHC immunostaining diminished by approximately 90% compared with sham-operated dogs, while staining in normoxic animals was not significantly different from nonischemic dogs. Protein nitration in the hippocampal neurons of hyperoxic animals was 2-3 times greater than either sham-operated or normoxic resuscitated animals at 2 h reperfusion. Stereologic quantification of neuronal death at 24 h reperfusion showed a 40% reduction using normoxic compared with hyperoxic resuscitation. These results indicate that postischemic hyperoxic ventilation promotes oxidative stress that exacerbates prelethal loss of pyruvate dehydrogenase and delayed hippocampal neuronal cell death. Moreover, these findings indicate the need for clinical trials comparing the effects of different ventilatory oxygen levels on neurologic outcome after cardiac arrest.

12. Charles F. Zwemer, Steven E. Whitesall, Louis G. D'Alecy. 1994. "Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs." Resuscitation 27:159-170.

Comments:

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Quality: controlled, non randomized, non blinded, target species.
Results: opposing

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ABSTRACT:

This study investigated the effects of normoxic (F_o, = 0.21), hyperoxic (F_o, = 1 .O), and hyperoxic (F_o, = 1 .O) plus antioxidant pretreatment (tirilizad mesylate) resuscitation on neurologic outcome following 9 min of normothermic (39 * 1.O°C) cardiac arrest. Physiologic variables including arterial blood gases and neurologic outcome, which was assessed using a standardized scoring system, were followed over a 24-h period following resuscitation from cardiac arrest. Hyperoxically resuscitated dogs sustained significantly worse neurological deficit at 12 and 24 h (mean scores: 39 f 3 and 49 f 8, respectively) than did antioxidant pretreated hyperoxically resuscitated dogs (mean scores: 22 f 1, P = 0.0007 and 22 f 1, P = 0.004, respectively) and normoxically resuscitated dogs (mean scores: 28 f 4, P = 0.025 and 33 i 8, P = 0.041 respectively). These data suggest that oxidant injury has a major role in central nervous system dysfunction following successful resuscitation from 9 min of cardiac arrest. Also, resuscitation from cardiac arrest with hyperoxic F_o's may contribute to and further exacerbate neurologic dysfunction.

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