

WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**Worksheet author(s)**

Colin A Graham

Date Submitted for review: 9 February 2010 (Revision 3 – Taskforce Approved and Accepted by Dr Peter Morley)**Clinical question**

In adult cardiac arrest (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of an FIO₂ titrated to oxygenation during cardiac arrest (I) compared with the use of 100% oxygen (C), improve outcome (eg. ROSC, neurologically intact survival) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy (oxygen)

State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question

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

Search strategy (including electronic databases searched)

MEDLINE (via OVID SP): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1950 to Present> Search Strategy:

- 1 exp Heart Arrest/ (25212)
- 2 exp Cardiopulmonary Resuscitation/ (7477)
- 3 oxygen (ab) (201647)
- 4 (1 or 2) and 3 (639)
- 5 limit 4 to (humans and ("all adult (19 plus years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")) (228)

0 relevant papers found from 228 possible papers

EMBASE (via OVID SP): Database: EMBASE <1980 to 2009 May 8> Search Strategy:

- 1 exp Heart Arrest/ (16258)
- 2 exp Cardiopulmonary Resuscitation/ (24817)
- 3 oxygen (ab) (170623)
- 4 (1 or 2) and 3 (1960)
- 5 limit 4 to (human and (school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>)) (387)

0 relevant papers from 387 possible papers

Database: All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED Search Strategy:

- 1 exp Heart Arrest/ (738)
- 2 exp Cardiopulmonary Resuscitation/ (326)
- 3 oxygen (ab) (11800)
- 4 (1 or 2) and 3 (24)

0 relevant trials identified from 24 possible papers

AHA Endnote Master Database – ['Heart arrest' OR 'cardiopulmonary resuscitation'] AND 'oxygen' as word in any field – 3 relevant papers from 289 possible papers (Zwemer 1995, Liu 1998 & Lipinski 1999)

Review of references from the papers/studies retrieved – 1 relevant paper identified (Zwemer 1994)

Citation search using Web of Science for Zwemer 1994 & Liu 1998 – 3 further relevant papers identified (Richards 2006; Vereczki 2006; Richards 2007)

• State inclusion and exclusion criteria

Include all studies where there was a comparison of high flow oxygen ('100%') with room air or any other limited form of oxygen delivery during cardiac resuscitation AND an identifiable result showing that the FiO₂ was titrated to the objective level of oxygenation (blood gas estimation or pulse oximetry) during cardiopulmonary resuscitation AND reported clinical outcome from cardiac arrest.

Exclude all neonatal and infant studies and those involving children (<8 years of age), and all studies where modification or titration of FiO₂ was performed after ROSC rather than during cardiac arrest. Exclude studies where no clinical outcomes (only laboratory outcomes) are reported.

• Number of articles/sources meeting criteria for further review:

Three animal studies (LOE5).

Summary of evidence

Evidence Supporting Clinical Question

Good					<i>Liu 1998 E</i>
Fair					<i>Zwemer 1994 E</i>
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

Evidence Neutral to Clinical Question

Good					
Fair					<i>Lipinski 1999 E</i>
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

Evidence Opposing Clinical Question

Good					
Fair					
Poor					
	1	2	3	4	5
Level of evidence					

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Animal studies

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

Two of the three animal studies (Liu 1998 and Zwemer 1994) suggested significant associations between hyperoxic resuscitation and increased neurological injury (clinically and in Liu's study, on histopathology). Lipinski's study (1999) did not show any benefit from normoxic resuscitation in their rat study (n=22) which used an asphyxial model of arrest, whereas the other two studies induced cardiac arrest electrically.

Extrapolation of these data to adult humans is difficult, but there is little animal evidence (LOE5) to support the continuation of hyperoxic (FiO₂ 1.0) resuscitation during cardiac arrest.

Large scale, prospective, randomized clinical trials are warranted to explore normoxic resuscitation approaches in humans, titrated to blood gas analysis or pulse oximetry.

Acknowledgements: Nil

Citation List

Lipinski CA, Hicks SD, Callaway CW. Resuscitation 1999;42(3):221-229. Normoxic ventilation during resuscitation and outcome from asphyxial cardiac arrest in rats.

Level 5. Fair quality, neutral (animal study, small numbers, n=22). Asphyxial rat model used to induce arrest, not randomized. Room air ventilation for 2 minutes prior to asphyxia. FiO₂ of 0.21 (normoxic) or 1.0 (hyperoxic) for duration of CPR and at least 10 minutes following ROSC. FiO₂ only increased in room air group to maintain PaO₂ of 95-110mmHg if necessary (n=2). After 1 hour, weaned from oxygen and ventilation. No differences in neurological injury at any time point. Blinded neuropathological assessment of rat brains at 72 hours post arrest. First author supported by work was supported by a research grant from the Emergency Medicine Foundation and Bristol-Myers Squibb.

Liu Y, Rosenthal RE, Haywood Y, Miljkovic-Lolic M, Vanderhoek JY, Fiskum G. Stroke 1998;29(8):1679-1686. Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome.

Level 5. Good quality, supporting question (animal study, small numbers, n=20). Validated canine model used, ventilated with room air (FIO₂ 0.21) pre-arrest. 10-minute duration cardiac arrest induced by electric current to right ventricle via thoracotomy. Randomized animals equally to each group. Normoxic group: 21% O₂ during CPR and adjustments made starting approximately 5 minutes later to maintain PO₂ between 80 and 100 mm Hg and PCO₂ between 25 and 35 mm Hg. Hyperoxic group: 100% O₂ during CPR and for 1 hour thereafter followed by standard adjustments. Neurological testing by blinded trained assessors at 23 hours post arrest. Neurological injury worse in the hyperoxic group compared to the normoxic group which correlated with lower oxidized brain lipids in the normoxic group. Supported by NIH research grant.

Richards EM, Rosenthal RE, Kristian T, Fiskum G. Free Radic Biol Med. 2006 Jun 1;40(11):1960-70. Postischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity.

This study was rejected as no clinical outcomes were reported.

Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Stroke. 2007 May;38(5):1578-84. Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism.

This study was rejected as no clinical outcomes were reported.

Vereczki V, Martin E, Rosenthal RE, Hof PR, Hoffman GE, Fiskum G. J Cereb Blood Flow Metab. 2006 Jun;26(6):821-35. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death.

This study was rejected as no clinical outcomes were reported.

Zwemer CF, Whitesall SE, D'Alecy LG. Resuscitation 1994;27(2):159-70 (Erratum in: Resuscitation 1994;27(3):267). Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs.

Zwemer CF, Whitesall SE, D'Alecy LG. Resuscitation 1995;29(3):225-236. Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs.

This study was rejected as it did not compare 100% oxygen with titrated normoxia during cardiac arrest; it compared hypoxia with normoxia.