Clinical question.

"In adult patients with ROSC (return of spontaneous circulation) after cardiac arrest (prehospital or in-hospital) (P), does the use of a controlled oxygenation strategy (including specific oxygenation goal) (I) as opposed to standard care (C), improve outcome (O) (eg. > survival)?"

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

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

Search strategy (including electronic databases searched).

The Cochrane Library December 23rd 2009
Search Strategy
1. Heart Arrest and Oxygen
Cochrane Reviews (2)
Clinical Trials (83)

Ovid MEDLINE(R) <1950 to November Week 3 2009>
Search Strategy:
1. cardiac arrest.mp. or exp Heart Arrest/ (28114)
2. exp Cardiopulmonary Resuscitation/ or spontaneous circulation.mp. (9934)
3. oxygen inhalation therapy.mp. or exp Oxygen Inhalation Therapy/ (19112)
4. oxygenation.mp. (34562)
5. reoxygenation.mp. (4249)
6. oximetry.mp. or exp Oximetry/ (12131)
7. 4 or 3 or 5, or 6 (58201)
8. 1 and 7 and 2 (170)
14. "Extracorporeal Membrane Oxygenation"/ (3586)
15. 13 not 14 (117)
16. exp Hyperbaric Oxygenation/ (9140)
17. 15 not 16 (113)

Pubmed, December 23rd 2009
Search Strategies
1. ischemia [Text Word] and reperfusion [Text Word] and oxygen [Text Word] (6377)
2. Heart arrest [Text Word] or cardiac arrest [Text Word]
1 and 2 (303)

• State inclusion and exclusion criteria
Inclusion Criteria
1. Original Research Manuscripts
2. Human or whole animal studies of cardiac arrest, whole body or global organ ischemia and reperfusion
3. Comparison of at least two levels of normobaric oxygenation during the post-arrest or reperfusion period

Exclusion criteria
1. Review articles
2. Abstract only publications
3. Non-peer reviewed publications
4. Cell culture and isolated organ studies
5. Studies exclusively involving hyperbaric oxygen therapy
6. Studies that do not address the stated question.

• Number of articles/sources meeting criteria for further review:
12 articles met criteria for further review (see citation list)
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<tr>
<td>Balan 2006 (E)*</td>
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<td>Marsala 1992 (E)*</td>
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<td>Zwemer 1994 (B,E)*</td>
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<td>Liu 1998 (E)*</td>
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<td>Vereczki 2006(E)*</td>
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<td>Richards 2006 (E)</td>
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<td>Richards 2007 (E)</td>
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<td>Abdel-Rahman (E)</td>
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### Level of evidence

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
* compared normoxia to hyperoxia  

Italics = Animal studies
## Evidence Neutral to Clinical question

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**Zwemer 1995 (B,E)**

**Lipinski 1999 (E)**

**Kuisma 2006 (C, D, E)**

**Smith 2006 (E)**

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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*

** compared normoxia to hypoxia  
*** compared ventilation with 30% and 100% oxygen

## Evidence Opposing Clinical Question

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A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
The preponderance of animal data (LOE5) suggests that ventilation with 100% oxygen (generating \( \text{PaO}_2 > 350 \) mmHg) in the immediate post-arrest period (first 15 to 60 minutes after ROSC) causes increased oxidative stress, increased metabolic dysfunction, increased neurodegeneration, and worse short-term functional neurologic outcome when compared to ventilation with room air or inspired oxygen titrated to an arterial pulse oximetry reading between 94% and 96% (Balan, 2006, 3008; Marsala, 1992, 121; Zwemer, 1994, 159; Liu, 1998, 1679; Vereczki, 2006, 821; Richards, 2006, 1960; Richards, 2007, 15780). However, these animal studies were not adequately powered to detect an impact on survival. Furthermore, the only study that examined outcome beyond 24 hours was neutral (Lipinski 1999, LOE5). No studies were identified that reported a detrimental effect of using room air or titrated oxygenation compared to ventilation with 100% oxygen. Finally none of these studies used a model that included acute myocardial infarction.

One supporting swine study compared myocardial function following 90-minute cardioplegic cardiac arrest and cardiopulmonary bypass reperfusion using \( \text{PaO}_2 \) of 250-350 mm Hg versus \( \text{PaO}_2 \) 40-90 mm Hg for the first 10 minutes of reperfusion (Abdel-Rahman, 2009, 978). Myocardial function 60 minutes after reperfusion was better in the low oxygen group. Another neutral swine study using a similar model compared reperfusion with \( \text{PaO}_2 \) 90-110mmHg vs. a gradual increase form \( \text{PaO}_2 \) of 40 mm Hg to 110 mmHg over the first 15 minutes of reperfusion (Smith, 2006, 153). In this study there were no statistically significant differences in organ function and histopathologic damage.

One prospective clinical pilot trial randomized 32 patients after witnessed OOH VF cardiac arrest to ventilation with 30% oxygen or 100% oxygen for the first 60 minutes after ROSC. Reported outcomes included serum biomarkers at 24 and 48 hours after ROSC, survival to hospital discharge and CPC at hospital discharge. 28 patients (14 per group) were included in the final analysis. Although 24 and 48 hour NSE and S100 levels were numerically higher in patients ventilated with 100% oxygen, differences were not statistically significant. Post-hoc subgroup analysis of patients not treated with therapeutic hypothermia revealed that statistically greater NSE level at 24 hours in patients ventilated with 100% oxygen. 10/14 patients survived to hospital discharge in each group. The number of patients discharged with good neurologic outcome (CPC 1 or 2) was 8/14 in the 30% oxygen group and 6/14 in the 100% oxygen group (not statistically different). This study is considered Level 1 neutral evidence of poor quality relative to the worksheet question because it was underpowered to detect differences in survival or neurologic outcome. Five patients ventilated with 30% oxygen required increased FIO2 due to persistent pulse ox < 95%. More patients in the 100% oxygen ventilation group were diagnosed with and treated for STEMI.

The existing evidence suggest the need for a prospective randomized clinical trial to determine if the concentration of inspired oxygen during the first 60 minutes after ROSC has a measurable impact on outcome. In the absence of such evidence, it should be considered acceptable to immediately after ROSC 1) titrate inspired oxygen to an arterial pulse oximetry goal less that 100% but above 94% or 2) ventilate with room air as long as there is no evidence of hypoxemia (i.e. pulse ox > 94%).

Specific research required:

Prospective randomized controlled clinical trial comparing ventilation with 100% oxygen versus ventilation with inspired oxygen titrated to a pulse oximetry goal (possibly 94% to 96%) for the first hour after ROSC.

Large animal cardiac arrest studies with adequate power to determine the impact of post-cardiac arrest arterial hyperoxia on long term (>24 hours) survival, neurologic outcome, and neurodegeneration.

Combined myocardial infarction cardiac arrest animal studies to evaluate the impact of post-cardiac arrest arterial hyperoxia on cardiovascular outcomes.

Animal cardiac studies to determine the impact of arterial hyperoxia beyond one hour after ROSC on cardiovascular function, survival, neurologic outcome, and neurodegeneration.

Acknowledgements:
**Citation List**

   Title: Hypoxic reoxygenation during initial reperfusion attenuates cardiac dysfunction and limits ischemia-reperfusion injury after cardioplegic arrest in a porcine model.
   Citation: J Thorac Cardiovasc Surg. 2009 Apr;137(4):978-82.
   Institution: Department of Thoracic and Cardiovascular Surgery, Johann Wolfgang Goethe-University, Frankfurt/Main, Germany.

   Comment:
   This swine study compared myocardial function following 90-minute cardioplegic cardiac arrest and cardiopulmonary bypass reperfusion using PaO$_2$ of 250-350 mm Hg versus 40-90 mm Hg for the first 10 minutes of reperfusion. Myocardial function 60 minutes after reperfusion was better in the low oxygen reperfusion group. This paper is considered Level 5 supportive evidence of fair quality.

2. Authors: Balan, I.S.; Fiskum, G.; Hazelton, J.; Cotto-Cumba, C.; Rosenthal, R.E.
   Title: Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest.
   Periodical, Abbrev: Stroke
   Pub Year: 2006
   Volume: 37
   Issue: 12
   Start Page: 3008
   Other Pages: 3013
   Author Address/Affiliation: Departments of Anesthesiology, Program in Trauma, University of Maryland School of Medicine, Baltimore, MD, USA.
   Accession Number: 17068310
   Language: English

   Funding: This work was supported by National Institutes of Health grants NS34152 and NS49425.
   COI: No COI statement in manuscript

   Comment:
   This study compared neurologic deficit score and CA1 pyramidal neuron degeneration at 24 hours after 10 minute cardiac arrest in dogs ventilated with either 100% oxygen or FiO$_2$ titrated to an arterial pulse ox of 94% for the first hour after ROSC. Pulse-ox guided oxygenation resulted in better neurologic deficits scores and less CA1 pyramidal neuron degeneration. This paper is considered Level 5 supportive evidence of high quality.

3. Authors: Kuisma, M.; Boyd, J.; Voipio, V.; Alaspaa, A.; Roine, R.O.; Rosenberg, P.
   Title: Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study.
   Periodical, Abbrev: Resuscitation
   Pub Year: 2006
   Volume: 69
   Issue: 2
   Start Page: 199
   Other Pages: 206
   Author Address/Affiliation: Helsinki EMS, Helsinki University Central Hospital, P.O. Box 112, FIN-00099 Helsingin Kaupunki, Finland. markku.kuisma@hel.fi
   Accession Number: 16500018
   Language: English

   Funding: Helsinki University, Finland and AGA Foundation, Sweden.
   COI: Paper includes statement declaring no COI.
Comments:
This prospective clinical pilot trial randomized 32 patients after witnessed OOH VF cardiac arrest to ventilation with 30% oxygen or 100% oxygen for the first 60 minutes after ROSC. Outcomes included serum biomarkers at 24 and 48 hours after ROSC. 24 patients (14 per group) were included in the final analysis. Although 24 and 48 hour NSE and S100 levels were numerically higher in patients ventilated with 100% oxygen, differences were not statistically significant. Post-hoc subgroup analysis of patients not treated with therapeutic hypothermia revealed that statistically greater NSE level at 24 hours in patients ventilated with 100% oxygen. 10/14 patients survived to hospital discharge in each group. The number of patients discharged with good neurologic outcome (CPC 1 or 2) was 8/14 in the 30% oxygen group and 6/14 in the 100% oxygen group (not statistically different). This study is considered Level 1 neutral evidence of poor quality relative to the worksheet question because it was underpowered to detect differences in survival or neurologic outcome.

4.
Authors: Lipinski CA, Hicks SD, Callaway CW.
Title: "Normoxic ventilation during resuscitation and outcome from asphyxial cardiac arrest in rats."
Periodical: Resuscitation
Pub Year: 1999
Volume: 43
Issue: 3
Start Page: 221
Other Pages: 229
Author Address/Affiliation: The Department of Emergency Medicine, Wayne State University, Detroit Receiving Hospital, MI 48201, USA.
Accession Number: 10625163
Language: English
Funding: Emergency Medicine Foundation and Bristol-Myers Squibb.
COI: No COI statement

Comment:
This study compared hemodynamic parameters, survival, neurologic deficit score, hippocampal neuron survival at 72 hours after 8 minute asphyxial cardiac arrest when rats were ventilated with room air (n=10) or 100% oxygen (n=12) during CPR and for the first hour after ROSC. During the first hour post-ROSC, pO2 averaged 347-395 mm Hg in the 100% oxygen group and 71-114 mm Hg in the room air group. No statistical difference was detected in any of the above outcome measures. This paper is considered Level 5 neutral evidence of high quality.

5.
Authors: Liu,Y.; Rosenthal,R.E.; Haywood,Y.; Miljkovic-Lolic,M.; Vanderhoek,J.Y.; Fiskum,G.
Title: Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome.
Periodical, Abbrev: Stroke
Pub Year: 1998
Volume: 29
Issue: 8
Start Page: 1679
Other Pages: 1686
Accession Number: 1998265886
Language: English
Funding: This study was supported by a grant from the NIH (NS34152).
COI: No COI statement in manuscript

This canine study compared neurologic deficit score in dogs ventilated with 21% oxygen compared to 100% oxygen for the first hour after 10 minute VF cardiac arrest. Animals ventilated with 100% oxygen had worse neurologic deficit score at 24 hours post-arrest. This paper is considered Level 5 supportive evidence of fair quality.
6. Authors: Marsala, J.; Marsala, M.; Vanicky, I.; Galik, J.; Orendacova, J.
Title: Post cardiac arrest hyperoxic resuscitation enhances neuronal vulnerability of the respiratory rhythm generator and some brainstem and spinal cord neuronal pools in the dog.
Pub Year: 1992
Volume: 146
Issue: 2
Start Page: 121
Other Pages: 124
Author Address/Affiliation: Department of Physiology and Surgery, University of Michigan Medical School, Ann Arbor 48109-0622.
Accession Number: 8086011
Language: English
Author Address/Affiliation: Institute of Neurobiology, Slovak Academy of Sciences, Kosice.
Accession Number: 1491777
Language: English

Funding: No funding statement in manuscript
COI: No COI statement in manuscript

Comments
This study compares ventilation with room air vs. 100% oxygen (n=5/group) for the first hour of ROSC following 15-min cardiac arrest in anesthetized dogs. Primary outcome was regional quantification of degenerating neurons. Authors report the 100% oxygen ventilation (PaO2 440 ± 37 mm Hg) statistically significant increase in dying neurons by histologic analysis in 4 brain regions compared to room air ventilation (PaO2 87 ±13 mm Hg) at a single time point after ROSC that is not stated. It does not appear the treatment was randomized and it is unclear if blinding was used for quantification of dying neurons. This paper is considered Level 5 supporting evidence of fair quality.

7. Authors: Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC
Title: Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism.
Periodical: Stroke
Publication year: 2007
Volume: 38
Start Page: 1578
End Page: 1584
Author Address/Affiliation: Program in Neuroscience, the Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, MD, USA.
Accession Number:
Language: English

Funding: NIH NS055450, NS34152, NS049425, HD16596, and US Army DAMD 17-99-1-9483.
COI: No COI statement in manuscript

Comment:
This canine study compared brain glucose metabolism (1 hour after ROSC) in dogs ventilated with 21% oxygen or 100% oxygen for the first hour after 10 minute VF cardiac arrest. Animals ventilated with 100% oxygen impaired glucose metabolism in the hippocampus but not cortex when compared to animals ventilated with 100% oxygen. No other outcome measures were reported. This paper is considered Level 5 supportive evidence of fair quality based on use of intermediate metabolic outcome parameters.

8. Authors: Richards EM, Rosenthal RE, Kristian T, Fiskum G
Title: Postischemic hyperoxia reduces hippocampal pyruvate dehydrogenase activity.
Periodical: Free Radic Biol Med
Year: 2006
Volume: 40
Start Page 1960
9.
Authors: Smith, M.J.; Roberts, W.H.; Miller, J.D.; Hasselfeld, K.A.; Pat Hendy, M.
Title: Controlled cardiac reoxygenation does not improve myocardial function following global myocardial ischemia
Pub Year: 2006
Volume: 4
Issue: 3
Start Page: 153
Other Pages: 159
Author Address/Affiliation: Department of Surgery, Good Samaritan Hospital, Cincinnati, OH 45220, USA.
Accession Number: PMID: 17462339; S1743-9191(06)00119-1 [pii]
Language: eng
Funding: This work was funded by a grant from the Medical Education and Research Fund of Good Samaritan Hospital.
COI: No COI statement in manuscript
Comments:
This is prospective animal study in swine model of isolated global myocardial ischemia (aortic cross clamp). The investigators compared reperfusion with normoxia (90-110 mm Hg) vs. gradually increasing pO2 form 40 to 110 mmHg over 15 minutes. No statistically significant differences in functional outcome or histology injury were detected. This study did not compare normoxic reperfusion with hyperoxic reperfusion which is the primary focus of the worksheet question. This paper is considered neutral LOE 5 and poor quality as it is not randomized and not a true cardiac arrest study.

10.
Authors: Vereczki, V.; Martin, E.; Rosenthal, R.E.; Hof, P.R.; Hoffman, G.E.; Fiskum, G.
Title: Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death.
Pub Year: 2006
Volume: 26
Issue: 6
Start Page: 821
Other Pages: 835
Author Address/Affiliation: Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.
Accession Number: 16251887
Language: English
Funding: This work was supported by NIH grants NS34152 and NS49425 to G Fiskum and AHA grant 0215331U to E Martin.
COI: No COI statement in manuscript
Comments
This study compared CA1 pyramidal neuron degeneration at 24 hours after 10-minute cardiac arrest in dogs ventilated with either 100% oxygen or 21% oxygen for the first hour after ROSC. 21% oxygen ventilation resulted in less CA1 pyramidal neuron degeneration. This paper is considered Level 5 supportive evidence of fair quality.

11.
Authors: Zwemer, C.F.; Whitesall, S.E.; D'Alecy, L.G.
Title: Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs
Periodical, Abbrev: Resuscitation
Pub Year: 1994
Volume: 27
Issue: 2
Start Page: 159
Other Pages: 170
Descriptors: IM; Animals; Central Nervous System Diseases/et [Etiology]; Dogs; Free Radical Scavengers; Heart Arrest/th [Therapy]; Lipid Peroxides/ai [Antagonists & Inhibitors]; Male; Oxygen Inhalation Therapy/ae [Adverse Effects]; Pregnatrienes/tu [Therapeutic Use]; Reactive Oxygen Species; Reperfusion Injury/et [Etiology]; Resuscitation/mt [Methods]; Time Factors
Funding: Michigan AHA (G10934), The Upjohn Company of Kalamazoo, MI, NIH (F32 HL08792-01), Physio-Control Corporation, Redmond, WA.
COI: No COI statement

Comments:
This canine study compares neurologic deficit scores of dogs resuscitated from 9-minute cardiac arrest with FIO2 of 0.21 or 1.0 during CPR and for 60 minutes post ROSC followed by room air. Neurologic deficit scores were higher in dogs ventilated with FIO2 1.0. The difference was statistically significant at both 12 and 24 hours after ROSC. This paper is considered Level 5 supporting evidence of fair quality.

12.
Authors: Zwemer, C.F.; Whitesall, S.E.; D'Alecy, L.G.
Title: Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs
Periodical, Abbrev: Resuscitation
Pub Year: 1995
Volume: 29
Issue: 3
Start Page: 225
Other Pages: 236
Author Address/Affiliation: Department of Physiology, University of Michigan Medical School, Ann Arbor 48109-0622, USA.
Accession Number: 7667554
Language: English
Funding: Supported by American Heart Association, Upjohn Company, Bio-Tek Instruments Company, and Physio-Control Corp.
Conflict of Interest: No formal COI statement

This canine study compares survival and neurologic deficit scores (NDS) of dogs resuscitated from 9-minute cardiac arrest with FIO2 of 0.085, 0.12, or 0.21 during CPR and for 15 minutes post ROSC. After 15 minutes all animals were ventilated with room air. No statistical difference is 24-hour survival or 24-hour NDS was detected. This paper is considered Level 5 neutral evidence of poor quality related to outcomes after hypoxic ventilation vs. normoxic ventilation during CPR and for the first 15 minutes after ROSC. The study had inadequate power to detect important differences in survival and NDS.