**Clinical question.**
In pediatric patients in cardiac arrest associated with asphyxia (prehospital [OHCA] or in-hospital [IHCA]) (P) does ventilation with a specific oxygen concentration (room air or a titrated concentration between 0.21 and 1.0) (I), compared with standard treatment (100% oxygen) (C), improve outcome (ROSC, survival to hospital discharge, survival with favorable neurologic outcome) (O)?

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<th>Is this question addressing an intervention/therapy, prognosis or diagnosis?</th>
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<td>State if this is a proposed new topic or revision of existing worksheet:</td>
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<td>Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?</td>
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**Search strategy (including electronic databases searched).**

- **State inclusion and exclusion criteria**
  - Included pubs after 2004 if not cited in 2005 worksheet
  - Excluded pubs cited in 2005 worksheet
  - Excluded neonatal literature (neonatal has a worksheet on this topic)

**MEDLINE:**
- “Heart Arrest” [MeSH] OR Heart Arrest, induced [MeSH]) AND Oxygen toxicity → 35 hits → no new relevant hits compared to C2005
- (“Heart Arrest” [MeSH] OR Heart Arrest, induced [MeSH]) AND Oxygen inhalation therapy → 167 hits → 3 new relevant hits (Richards 2007; Kuisma 2006; Vereczki 2006)

Web of Science Search for articles that cited Zwemer et al 1994 → 2 new relevant hits (Balan 2006; Koch 2008)

There are 9 topics identified by a search of the Cochrane Library using the terms Oxygen Toxicity → none relevant to cardiac arrest

Refs from hand searches: Idris 2005; Richards 2006; Munkeby 2004

There are a total of 8 new relevant articles in addition to the C2005 data.

**NOTE:** search strategy was run again on Dec 24, 2009. One new relevant study was found: a study showing a benefit to hyperbaric oxygen use during resuscitation of very prolonged porcine cardiac arrest (Van Meter et al. 2008; 200-214). This study has been placed into the evidence evaluation grid but it does not change the COS or Treatment Recommendation.

| Number of articles/sources meeting criteria for further review: | see above |
## Summary of evidence

### Evidence Supporting Clinical Question

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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
- *Italics = Animal studies*

**Evidence Supporting Clinical Question**

- [Marsala, 1992, 121-4]
- [Zwemer, 1994, 159-70]
- [Katz, 1998, 1587-93]
- [Liu, 1998, 1679-86]
- [Balan, 2006, 3008-13]
- [Vereczki, 2006, 821-35]
- [Richards, 2006, 1960-70]
- [Richards, 2007, 1578-84]

- [Douzinas, 2001, 269-75]
- [Douzinas, 2001, 905-10]
- [Feet, 1997, 1384-91]
- [Feng, 1998, 33-41]
- [Mickel, 1987, 426-30]
- [Temesvari, 2001, 812-9]
- [Koch, 2008, 1294-306]
- [Langhelle, 2003, 247-63]
### Evidence Neutral to Clinical question

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[Lipinski, 1999, 221-9]

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E = Other endpoint  

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### Evidence Opposing Clinical Question

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[Rosenthal, 2003, 1311-6]  
[Van Meter, 2008, 200-14]  
[Krakovskiy, 1998, 412-6]  
[Takahashi, 1992, 1588-94]  

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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*

Notes on assignment of quality: Most animal studies are good quality studies relative to the hypothesis posed and outcome measures chosen. However, for the purpose of this evidence evaluation there were no studies with sufficiently rigorous and long-term neurologic outcomes and thus I did not categorize any of them as “good” quality. I categorized all of the animal studies using a cardiac arrest model as “fair” and all other models as “poor”. Almost all studies have other (E) outcomes that include histology, immunoblots, enzymatic assays, etc. I have removed the studies examining neonatal hypoxic ischemia that were included in the C2005 WS (however, they remain in the annotated bibliography)—for an update of this literature, see the neonatal worksheet.
Since 2005, there have been a number of publications in the neonatal literature: see the neonatal worksheet for a review of this topic relative to neonates.

David Zideman and I completed worksheets on this topic for C2005 (WS 14A, WS 14B). Of note, this topic arose out of the Pediatric Taskforce because of the literature and interest amongst the neonatal community (the young end of pediatrics). However, salient issues and research for the remainder of the pediatric population is likely closer to those in the adult population because of the different physiology in the newborn (transitional circulation) is not present in the pediatric population and the cause of neonatal “depression” rarely includes true cardiac arrest.

Immediately below is the discussion section from the C2005 worksheet followed by a section on “new information.”

**C2005 Discussion:**

**Background:**

Oxygen is necessary for aerobic energy production. However, oxidative metabolism and other oxidative pathways also yield byproducts (reactive oxygen species (ROS) and free radicals) that can be toxic. Accordingly, cells have numerous antioxidant strategies/molecules to quench reactive oxygen species and much of oxidation is compartmentalized within mitochondria. Normoxia and even brief hyperoxia is efficiently managed by these defenses under physiologic conditions. However, during reperfusion from hypoxia-ischemia the cellular (especially mitochondrial) management of oxygen is disrupted and the increased production of ROS can overwhelm the cell’s defense mechanisms and cause damage to cell membranes, proteins, and DNA (reperfusion injury). ROS-mediated reperfusion injury is a well-documented and accepted cause of injury and numerous anti-oxidant strategies have been tested (with mixed success). One theoretic and controversial approach is to limit the amount of oxygen available during reperfusion to sufficient, but not excessive, oxygen. Determining the threshold for excessive oxygenation is obviously problematic. Nonetheless, there are now animal data suggesting that resuscitating with room air is equivalent, and perhaps superior, to resuscitating with 100% oxygen. These data will be reviewed below. Clinical studies have been limited to resuscitation of newborns. Data from the trials in newborns will also be reviewed below but a more comprehensive review is presented in the worksheet from the ILCOR neonatal taskforce.

**Evidence Evaluation:**

There are no excellent quality studies in the evidence evaluation grid. The neonatal trials have limited relevance to other patient populations and thus I did not consider them to be excellent studies for the purposes of this review. Many of the animal studies were well-designed to answer a narrow question. However, I would judge an animal study to be excellent quality for purposes of this review if the model incorporated cardiac arrest and the outcome measures included markers of oxidative stress, long-term survival with assessment of histology and neurologic outcome.

The potential for harm from “excessive” oxygenation is reviewed in two provocative editorials published in Pediatrics [Lefkowitz, 2002, 517-9] and the BMJ [Thomson, 2002, 1406-7].

The most relevant studies for the post-cardiac arrest condition are the studies by Zwemer et al [Zwemer, 1994, 159-70], Katz et al [Katz, 1998, 1587-93], and Liu et al [Liu, 1998, 1679-86] that examine animal models incorporating cardiac arrest. Zwemer et al showed improved outcomes in dogs resuscitated with room air vs 100% oxygen following 9 min of VF cardiac arrest (see annotated bibliography for additional comments and limitations of individual studies). Katz et al showed oxidative stress with depletion of anti-oxidants as early as 10 minutes following resuscitation from asphyxial arrest in rats; however, the same group showed no difference in neurologic outcome in rats resuscitated with room air vs 100% oxygen [Lipinski, 1999, 221-9]. Liu showed lower levels of oxidized brain lipids and improved neurologic outcome in dogs resuscitated with room air vs 100% oxygen following 10 min of cardiac arrest. One important limitation of most cardiac-arrest animal models is the use of healthy animals without underlying lung or cardiac dysfunction—in this instance, room air during resuscitation and recovery might provide adequate oxygenation in otherwise healthy animals that would be inadequate in animals with underlying lung disease.

There are several studies examining non-cardiac arrest models of global brain ischemia that show worse outcomes when animals are recovered using 100% oxygen vs. room [Feet, 1997, 1384-91, Feng, 1998, 33-41, Mickel, 1987, 426-30]. Indeed, some experiments show hyperoxia to be worse than hypoxia [Douzinas, 2001, 269-75, Douzinas, 2001, 905-10].

Paradoxically, there are studies showing hyperbaric oxygen treatment can be beneficial following global brain ischemia [Krakovsky, 1998, 412-6, Rosenthal, 2003, 1311-6, Takahashi, 1992, 1588-94]. It is difficult to reconcile the studies showing hyperbaric oxygen is beneficial with the studies showing 100% supplemental oxygen is harmful. Unfortunately, there is no study comparing room air vs. 100% supplemental oxygen vs. hyperbaric oxygen in the same animal model. It is possible that the seemingly conflicting results are due to differences in the injury models and/or outcome measures. Alternatively, it is possible that hyperbaric oxygen has a unique biologic effect that 100% supplemental oxygen does not have.

Let’s accept for a moment the premise that oxygen delivery is a Goldilocks phenomenon: delivery can be “too little, too much, or just right”. Complicating this premise is the fact that reperfusion is not a uniform and homogenous event. For example, cerebral blood flow following resuscitation is initially increased but this is followed by a period of prolonged, multifocal, heterogeneous low flow. During this period of heterogeneous low CBF, some cells are exposed to inadequate oxygen while others are exposed to luxuriant oxygen. Supplemental oxygen might benefit the first population of cells while harming the second. Ideally, oxygen delivery should be titrated to maximize benefit and minimize harm. Unfortunately, there are no readily available, rapid, non-invasive measures of organ-specific tissue oxygenation. In addition, measures of systemic oxygen delivery/utilization...
might not reflect cerebral conditions [Oku, 1994, 141-52]. Until improved technology becomes available, clinicians must individualize care and attempt to titrate oxygen using imperfect titration parameters.

There are no clinical trials comparing room air to 100% oxygen in patients with cardiac arrest. However, there are clinical trials comparing room air to 100% oxygen for resuscitation of depressed newborns [Ramji, 1993, 809-12, Ramji, 2003, 510-7, Saugstad, 1998, e1, Vento, 2001, 642-7, Vento, 2003, 240-6]. The initial underlying motivation to test room air resuscitation for newborns was the difficulty/expanse of equipping developing countries with the equipment and supplies to deliver oxygen therapy. Thus, the initial goal of testing room air for newborn resuscitations was to demonstrate equivalence to 100% oxygen. The results from the initial clinical trials and the emerging experimental literature on potential harm of supplemental oxygen have now switched the focus to the hypothesis that room air is superior to supplemental oxygen. In general, the clinical trials show that rates for hypoxic encephalopathy and mortality are equivalent but room air resuscitation is superior with respect to total resuscitation time, time till first cry and time till first breath. In addition, newborns resuscitated with 100% oxygen have prolonged evidence of oxidative stress [Vento, 2001, 642-7, Vento, 2003, 240-6].

The newborn trials are provocative. However, the clinical significance of delayed resuscitation as measured by Apgar scores is unknown. Apgar scores, unless very low for prolonged periods, are poor predictors of eventual neurologic outcome. Also, delayed initiation of respirations in patients treated with supplemental oxygen may merely reflect decreased stimulation of chemoreceptors that sense hypoxia. Finally, many of the trials incorporated rescue arms (100% oxygen) for patients with continued depression following 90 sec of room air ventilation—if room air is inferior, it could be argued that the patients most likely to demonstrate harm from room air were “rescued” with 100% oxygen and the harmful effects of room air resuscitation were masked. Although this is a limitation of the studies, it would have been very difficult (or impossible) to design studies without oxygen rescue arms.

There are several important limitations with respect to generalizing the results of the neonatal trials to older patients. First, newborns are accustomed to the relatively acidic and hypoxic environment of the uterus and are equipped with different oxygen handling physiology (hemoglobin F, for example). Second, a key event during the birthing process is the initiation of respirations. The delayed initiation of respirations seen in depressed newborns frequently responds to vigorous stimulation and mechanical stretching of the lungs, independent of oxygen concentration—the first phase of the newborn period—this differs markedly from the physiology of cardiac arrest. Third, immediately after birth, newborns have a “transitional physiology” marked by pulmonary hypertension and shunting of blood through the ductus arteriosus (bypassing the lungs). This transitional physiology creates a pulmonary shunt that limits ability of supplemental oxygen to increase systemic oxygen saturation.

In summary, there are several animal studies suggesting that room air is preferable to 100% oxygen during reperfusion from global brain ischemia. However, there are no studies in humans comparing room air to 100% oxygen for resuscitation from cardiac arrest. The trials comparing room air to 100% oxygen for resuscitation of depressed newborns have problems with both internal validity and external validity that significantly limit their relevance to resuscitations beyond the newborn period. Ideally, oxygen therapy should be titrated to the needs of individual patients but we lack the appropriate technology to do so. At present there is insufficient information to recommend for or against the use of room air, as opposed to 100% oxygen, during resuscitation from cardiac arrest. This topic should be a priority for future clinical research.

What is new since the C2005 statement:

Fiskum’s group has published two additional studies examining oxygen delivery following resuscitation from 10 min of VF cardiac arrest in dogs. In the first study they randomized animals to 1 h of room air or 100% oxygen following defibrillation [Vereczki, 2006, 821-35]. The study showed increased brain oxidative stress (increased 3-nitrotyrosine staining accompanied by loss of pyruvate dehydrogenase immunohistochemistry) and increased neuronal (hippocampal) loss in dogs treated with 100% oxygen compared with room air. A limitation of this study is the short survival time for assessing oxidative stress (2h) and a short survival time for assessing neuronal (hippocampal) loss in dogs treated with 100% oxygen compared with room air. A limitation of this study is the short survival time for assessing oxidative stress (2h) and a short survival time for assessing neuronal death (24 h). Another limitation is that a transition to room air immediately following resuscitation would be a “tough sell” to providers who believe that 100% O$_2$, at least initially, is desireable to maximize resuscitation. Paradoxically, the authors point out that their work with hyperbaric oxygen in the same animal model showed a benefit to hyperoxia (hyperbaric O$_2$) when administered from 1-2 h following resuscitation. The authors speculate that “abnormally high brain O$_2$ levels are toxic primarily during the first 30 mins after global ischemia when abnormal Ca$^{2+}$, pH, and redox state all promote the production of reactive O$_2$ and N$_2$ species and impair their detoxification. At later times when these factors normalize, high tissue O$_2$ can promote recovery, particularly if tissue oxygenation is the limiting factor for aerobic cerebral energy metabolism.”

In the second study [Balan, 2006, 3008-13], the authors use the same animal model to compare 1 h of 100% oxygen therapy with “rapid lowering of arterial O$_2$ saturation to <96% but >94% with pulse oximeter guidance.” They show improved neurologic deficit scores in the animals with titration (titrated dogs seemed aware of their surroundings at 24 h but most hypoxic animals were stuporous) and less injury to the hippocampus in titrated dogs. Limitations of this study include the healthy state of the animals prior to cardiac arrest and the short survival time for neurologic assessment (24 h). However, this design incorporates the notion that immediate, transient administration of 100% O$_2$ is desireable to maximize initial resuscitation.

A pediatric-like study by Koch et al merits mention [Koch, 2008, 1294-306]. This study compared brief (30 min) exposure to 100% oxygen vs room air during recovery from the Rice-Vannucci model of brain ischemia in mice (unilateral ligation of the coratid accompanied by a period of hypoxia). The study is unusual in that it uses the classic Rice-Vannucci model of “neonatal” hypoxic ischemia but the animals were older than usual for “neonatal-like” studies (typically PND 7). The mice were 14 days old at the time of injury. This developmental stage can be considered equivalent to a “toddler” human. The focus of the study was on
immature oligodendrocytes that peak during late gestation in humans (but are also found in adult brain and may be relevant to “post-natal pediatric brain injury because greater than 2/3 of human brain growth occurs postnatally and is almost exclusively glial in nature). I corresponded with the author to determine the how long immature oligodendrocytes are found in human brain—he replied “oligo progenitors are almost certainly increased in children at least through the age of 4 or so when myelination is most active though this increase probably persists long after this. Unfortunately there's little direct data for this probably because it's a fairly new field and nobody's looked. ” Immature oligodendrocytes are of particular interest to the neonatologists because it is hypothesized that these immature cells are especially vulnerable to oxidative stress and their loss may be an important contributor to cerebral palsy following intranatal birth injury. The study showed worsened histologic and functional recovery of mice exposed to this brief period of 100% O$_2$ compared with the room air group. Myelination (the main function of oligodendrocytes) was disrupted more in mice treated with 100% O$_2$ compared to room air. The deficit was reversed with administration of the antioxidant ebselen.

Additional publications of interest include:
- [Richards, 2006, 1960-70] Fiskum’s group demonstrate in their model that 1 h of hyperoxia diminishes the enzymatic activity of pyruvate dehydrogenase (the previous study examined only immunohistochemistry).
- [Richards, 2007, 1578-84] Fiskum’s group demonstrate in their model that 1 h of hyperoxia diminishes incorporation of 13C-glucose into the tricarboxylic acid cycle (impaired glucose metabolism).
- [Idris, 2005, 2043-8] Idris et al show that oxidant injury (as measured by brain and serum F2-isoprostane levels) increases 2 to 3-fold and peaks between 15-30 min of reperfusion, returning to baseline at 90 min following cardiac arrest in swine.
- [Katz, 1998, 1587-93] Katz et al used electron spin resonance to measure brain antioxidant activity during and following asphyxial cardiac arrest in rats. Similar to the study by Idris in swine, they showed that oxidative stress occurs mostly during reperfusion, rather than during arrest.
- [Rubertsson, 1998, 32-8]. This study in piglets examined oxygen delivery during CPR in pigs with VF. Either room air or 100% oxygen provided sufficient oxygenation of arterial blood. The amount of blood flow generated by CPR was the most important factor for oxygen delivery (rather than the FiO2 used during CPR).
- [Kuisma, 2006, 199-206] Kuisma et al performed a small clinical trial randomizing humans to 30% or 100% oxygen in “the early post-resuscitation period, i.e. 60 min after ROSC” from VF arrest (14 in each group). Of note, 5 patients (36%) in the 30% O$_2$ group had to have their oxygen increased because of a pulseoximetry reading <95. There was increased neuron specific enolase (but not S100), presumptive measures of neuronal injury, at 24 h (but not 48 h) in the subgroup (n = 7) of patients treated with 100% oxygen and not cooled (vs room air and not cooled; n = 8). There was no difference in survival or neurologic outcome in this small pilot study. Of interest, they state that “currently the lowest inspiratory oxygen alternative in many transport ventilators is 60%”.
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Summary:
Animal data suggests that hyperoxia immediately following ROSC can exacerbate brain injury. Biologic plausibility is provided by studies showing oxidative stress is an important mediator of ischemic brain injury and oxidative stress is increased by provision of 100% oxygen immediately following ROSC. The animal data published since C2005 have extended and supported the early animal research. However, outside of the neonatal period, there are still no adequately powered clinical trials examining supplemental oxygen for resuscitation. In balance, I believe that the newly published animal research as well as the clinical data in neonates reinforces the need for a clinical trial in children (and adults) but it does not reach the threshold for substantially changing the wording in the C2005 Statement.

Note: this worksheet was presented in New Orleans at the 2008 Fall ILCOR meeting. Substantial discussion revolved around the C2005 Treatment Recommendation endorsing the use of 100% oxygen during CPR. It was noted that many of the animal studies discussed above obtained ROSC using room air during CPR. However, extrapolating from the animal models to the clinical scenario is problematic because: 1) the ability to obtain ROSC using room air in healthy animals exposed to brief periods of VF may be compromised with longer durations of arrest (in animals or humans), and 2) asphyxia, but not short durations of VF, rapidly depletes blood oxygen and causes arterial acidosis, thus it is possible that supplemental oxygen would be beneficial during CPR in patients with cardiac arrest of respiratory etiology. The result of the discussion was that the sentence endorsing initial supplemental oxygen during CPR was removed from the treatment recommendation and a sentence was added referring to the experimental data that shows increased injury from supplemental oxygen.

Acknowledgements:
**Citation List**


LOE=5 Quality=fair. Outcomes: neurologic recovery and histology. In this study of canine cardiac arrest the authors compare 1 h of 100% oxygen therapy with “rapid lowering of arterial O$_2$ saturation to <96% but >94% with pulse oximeter guidance.” They show improved neurologic deficit scores in the animals with titration (titrated dogs seemed aware of their surroundings at 24 h but most hyperoxic animals were stuporous) and less injury to the hippocampus in titrated dogs. Limitations of this study include the healthy state of the animals prior to cardiac arrest and the short survival time for neurologic assessment (24 h). However, this design incorporates the notion that immediate, transient administration of 100% O$_2$ is desirable to maximize initial resuscitation.


LOE: 5 Quality=Poor. Outcomes: E (Neurological recovery; lipid peroxidation). The main limitations of this study are the unusual methods for global brain ischemia (carotid artery occlusion, systemic hypotension and asphyxia), the short term (24 h) survival, and the lack of histology. Also, the study compared hypoxic (FiO$_2=0.12$) to hyperoxic (FiO$_2=1.0$) resuscitation and there was no normoxic group. Nonetheless, the data suggests that hyperoxia may be a more dangerous condition than hypoxia in this particular model.


LOE: 5 Quality=Poor. Outcomes: E (Histology). This is an extension of the authors’ previous work in this model. In this publication they use histopathology as the primary outcome. The relevance of the model remains a limitation. Also there was no normoxia treatment group. Nonetheless, hyperoxia was worse than hypoxia in this study design.


LOE: 5 Quality=Poor. Outcomes: E (cerebral extracellular hypoxanthine serum markers of oxidative stress; histopathology; neurological outcome). Although it is called a “newborn piglet” model, the piglets are most likely out of the period of transitional physiology and thus mimic neonatal rather than newborn physiology. The model is a model of “near arrest”. Specifically, 2-5 day old pigs were exposed to hypoxia (FiO$_2=0.08$) until MAP was less than 20mm Hg. Pigs were than randomized to room air or 100% oxygen for 10 minutes. Pigs treated with room air had lower concentrations of the ATP metabolite hypoxanthine, suggesting less severe energy impairment. The clinical relevance of this finding in unknown. There is an accompanying editorial: Carcillo, J. A. "100% oxygen in the delivery room is just fine, for now." Crit Care Med 1997; 25(8): 1269.


LOE: 5 Quality=Poor. Outcomes: E (mitochondrial redox status; evoked potentials). A limitation of this model is the use of bilateral carotid artery occlusion (20-30 min) plus vertebral artery ligation, rather than cardiac arrest, to induce global brain ischemia. This study suggests that the mitochondria are a target for oxidative injury by supplemental oxygen delivered during resuscitation from global brain ischemia. Limitations of this paper include the relevance of the model, the short survival time (4 h), and the lack of neurologic/histologic outcome.


This study is not included in the evidence evaluation grid because it does not compare room air to supplemental oxygen. It is a “proof of concept study” demonstrating that oxidant injury (as measured by brain and serum F2-isoprostane levels) increases 2 to 3-fold and peaks between 15-30 min of reperfusion, returning to baseline at 90 min following cardiac arrest in swine.

LOE: 5 Quality=Fair. Outcomes: E (brain tissue antioxidants). The model is highly relevant (asphyxial cardiac arrest). This study shows a decrease in antioxidant activity following resuscitation from cardiac arrest (suggesting reperfusion-mediated oxidative stress).


LOE=5 Quality=Poor. Outcome: histology and functional outcome. This study compared brief (30 min) exposure to 100% oxygen vs room air in PND 14 mice injured via the Rice-Vannuci prep. The deficit was reversed with administration of the antioxidant ebselen.


LOE: 5 Quality=Poor. Outcomes: E (mortality). A limitation of this study is the use of temporary (60 min) bilateral carotid artery occlusion plus permanent vertebral artery occlusion, rather than cardiac arrest, to cause global brain ischemia. Other limitations include the lack of histology, neurological outcome and etiology of mortality. The study also asks a different question: is hyperbaric oxygen helpful? However, the paper is of value because it shows that “supplemental” oxygen, under some circumstances/models, can be beneficial. It is difficult to reconcile the hyperbaric papers with the 100% oxygen at atmospheric pressure papers. It appears that the issue is more complex than “too much or too little is bad”.


LOE=5 Quality=Poor. Outcome: serum markers NSE and S100B. This is a small clinical trial randomizing humans to 30% or 100% oxygen in “the early post-resuscitation period, i.e. 60 min after ROSC” from VF arrest (14 in each group). Of note, 5 patients (36%) in the 30% O2 group had to have their oxygen increased because of a pulseoximetry reading <95. There was increased neuron specific enolase (but not S100), presumptive measures of neuronal injury, at 24 h (but not 48 h) in the subgroup (n = 7) of patients treated with 100% oxygen and not cooled (vs room air and not cooled; n = 8). There was no difference in survival or neurologic outcome in this small pilot study. NOTE: I would characterize the LOE as 1 but Peter Morley preferred that it be characterized as a 5 for the pediatric question.


LOE=5 Quality=Poor. This retrospective review of 4 regions in Norway attempted to find in-hospital factors associated with survival following admission to the hospital after resuscitation from cardiac arrest. The regions with the best survival had lower oxygen sats within the first hour of patient care. However, this factor did not hold up in multivariate analysis. There were many (many!) differences in care between the regions. NOTE: I would characterize the LOE as 3 but Peter Morley preferred that it be characterized as a 5 for the pediatric question.


This editorial in Pediatrics discusses the lack of evidence that supplemental oxygen is beneficial in resuscitation and lists reasons why it may exacerbate reperfusion injury. There is an excellent discussion of the strengths and weaknesses of the human newborn resuscitation trials. The author concludes, “The real question is this: in our age of evidence-based medicine, should we continue to use this historical, yet unsupported, therapy until it is proven harmful? Or, should we step back and recognized that supplemental oxygen is a medicine with potentially significant side effects that should be used only when there is an indication? Until we accept that the only reason we so strongly cling to supplemental oxygen as a therapy in resuscitation is because we were taught simplistically the “oxygen is good,” with the implication that “more must be better,” we are doomed to perpetuate the myth.”


LOE: 5 Quality=Fair. Outcomes: E (histology, neurologic recovery). The model is very relevant (asphyxial cardiac arrest). The study failed to show any differences in rats resuscitated with room air vs. 100% oxygen (1 h treatment).


LOE: 5 Quality=Fair. Outcomes: E (neurologic outcome, oxidized brain lipids, brain tissue lactate). This is a more relevant model of cardiac arrest with hyperoxia provided only during resuscitation and in a 1 hour post-resuscitation period. Oxygen was titrated to maintain PaO_2 70-100 in the normoxic group (avg FiO_2=0.3) and the hyperoxia group was given 100% O_2. The hyperoxia group had a higher concentration of oxidized lipids, worse neuro outcome, and, interestingly, higher lactate. A limitation of the study is the short-term survival period (24 h) and the lack of histology. Also, the experiment was performed on healthy animals without underlying lung or cardiac dysfunction. Nonetheless, the authors conclude, “…results of this study taken together with the study by Mickel et al and the neurological results of Zwemer et al cast serious doubt on the appropriateness of the present Advanced Cardiac Life Support guidelines
that recommend the use of 100% ventilatory O₂ for undefined periods during and after resuscitation from cardiac arrest...Clearly, clinical trials will be necessary to resolve this issue.”


LOE: 5 Quality=Fair. Outcomes: E (histology). KCl-mediated cardiac arrest. Worse histo in dogs with 100% oxygen for 1 h following resuscitation compared with room air group.


LOE: 5 Quality=Poor. Outcomes: E (oxidized brain lipids, mortality). A limitation of this study is the use of bilateral carotid artery occlusion, rather than cardiac arrest, to cause global brain ischemia. Other limitations include the lack of histology, neurological outcome and etiology of mortality. However, the threefold increase in 14 day mortality associated with 3-6 hrs of post-ischemic 100% oxygen is provocative. They note that in a subsequent experiment, a 30 min exposure to 100% oxygen did not increase mortality.


This study is not placed into the evidence grid because it does not compare different concentrations of post-resuscitation oxygen. However, it is included here because it demonstrates that there is continued, prolonged perturbation in oxygen delivery to the brain following resuscitation from cardiac arrest. Other studies by this group have documented a delayed, prolonged, multifocal, heterogeneous decrease in CBF following resuscitation from cardiac arrest. Thus, assessment of peripheral circulation is an inadequate predictor of conditions in the CNS.


This study was included in the previous worksheet and is included here only because it is part of the C2000 discussion. However, the recent literature on neonatal resuscitation is not updated in this worksheet and I have removed the neonatal studies from the evidence evaluation grid for C2010. See the neonatal worksheet for a more recent and complete update.


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LOE 5 Quality=Fair. Outcomes E (pyruvate dehydrogenase activity, nitrotyrosine immunoreactivity). In this model of canine cardiac arrest, hyperoxia inhibited PDHC activity and was associated with increased nitrotyrosine immunoreactivity (a marker of free radical damage).


LOE 5 Quality=Fair. Outcomes E (glucose metabolism, glutamate synthesis). In this model of canine cardiac arrest, hyperoxia impaired neuronal metabolism in the selectively vulnerable hippocampus.


LOE: 5 Quality=Fair. Outcomes: E (neurologic recovery; histology; CBF; cerebral metabolism). This study is similar to the study in rodents by Krakovsky et al 1998. However, the model is a more relevant model of VF arrest. A limitation of this model is the short (24 h) survival time. Interestingly, although hyperbaric therapy was neuroprotective, oxygen delivery and utilization was not changed—thus, the effect was not secondary to augmenting oxidative metabolism. The same comments about hyperbaric therapy made for Krakovsky’s paper apply to this paper.

This study is not in the evidence evaluation grid because it is not directly related to the question. However, it does show sufficient oxygenation of the arterial blood during CPR occurs with either room air or 100% oxygen. The amount of oxygen in the lungs is far less important than the amount of blood flow generated by CPR.


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LOE: 5 Quality=Poor. Outcomes: E (CBF; extracellular glutamate, glycerol, and lactate/pyruvate). The model was an unusual model. Specifically, pigs 1-3 days old were exposed to 25 min global brain hypoxic ischemia hypercapnea (FiO2 0.8, bilateral carotid occlusion, supplemental CO2) followed by resuscitation with room air vs 100% O2 for 5 min vs 100% O2 for 1 h. Limitations of the study include the very short survival time (2 h) and the lack of neuro outcome or histology. Nonetheless, the room air resuscitation group had worse MAP and worse CBF.


LOE: 6 Quality=Poor. Outcomes: E (neurologic recovery; mortality). This study is similar to the study in rodents by Krakovsky et al 1998. However, the model is a more relevant model of global brain ischemia (with accompanying total body ischemia). Limitations include the lack of histology, and etiology of mortality. The same comments about hyperbaric therapy made for Krakovsky’s paper apply to this paper.


LOE: 5 Quality=Poor. Outcomes: E (serum markers of oxidative stress; histopathology; neurological outcome). The model was an unusual model. Specifically, 3-6 hour old pigs were given a pneumothorax for 1 h that resulted in hypotension, bradycardia, gasping, and hypoxia. The pneumothorax was then relieved and pigs were treated with either room air or 100% oxygen for 10 minutes. Limitations of the study include the short exposure to 100% oxygen and the very short survival time (4 h). Indeed, neurologic outcome and histology at 4 hours is a poor predictor of ultimate (long term) outcome.


This editorial in the BMJ points out the potential adverse effects of hyperoxia including reduced cardiac output and increased BP and SVR in pts with MI or CHF (possibly via reflex vasoconstriction). They reference randomized clinical trials showing adverse effects (including increased mortality) in pts with MI or stroke treated with supplemental oxygen in the absence of underlying hypoxia.


LOE=5 Quality=Fair. Extrapolation is limited by the very long no flow time (25 min) and the very short (2 h) survival time. Another limitation is the use of open chest massage with a ventricular assist device.


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LOE 5 Quality=Fair. Outcomes: histology to measure neuronal death and immunohisotchemistry to measure ROS damage. In this model of canine cardiac arrest, hyperoxia was associated with increased neuronal death and immunohistochemical evidence of ROS damage (loss of PDHC staining and increased nitrotyrosine staining).

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

LOE: 5 Quality=Fair. Outcomes: E (Neurologic deficit score). The main limitations of this study are the use of supplemental oxygen preceding the cardiac arrest, the short term outcome (only 24 h) and the lack of histology. The use of hyperoxia prior to arrest mimics in-hospital arrests in patients already receiving an FiO2 of 1.0 but does not model out of hospital arrest. Dogs in the hyperoxia group were weaned to room air 1 hr after ROSC.