**Short Title**
Oxygen delivery during CPR (Neonatal)

**PICO Question**
In neonates receiving cardiac compressions (P), does the use of 100% oxygen as the ventilation gas (I), compared with lower concentrations of oxygen (C), change decrease time to ROSC; increase survival rates; improve neurological outcomes; decrease in oxidative injury (O)?

**Task Force**
NRP

**Evidence Reviewers**
Myra Wyckoff,#125

**Task Force Question Owner**
russell.griffin@heart.org

**Search Inclusion and Exclusion Criteria**

**Search Strategy**

**Search Note**

**Date Full Search Completed**

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*ILCOR Evidence Review*

*Question Status*
20-Apr-13 Pending Evidence Collection

*Task Force*
NRP

*Evidence Reviewers*
Myra Wyckoff,#125

*Task Force Question Owner*
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*Search Inclusion and Exclusion Criteria*

*Search Strategy*

*Search Note*

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<th>Population</th>
<th>Neonatal Piglets (true moderate asphyxia model)</th>
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<tr>
<td>Intervention</td>
<td>21% FiO2</td>
</tr>
<tr>
<td>Comparator</td>
<td>100% FiO2</td>
</tr>
<tr>
<td>Outcomes</td>
<td>oxidant injury</td>
</tr>
<tr>
<td>Notes</td>
<td>Primary outcome brain striatal Na+, K+-ATPase activity1 hour stepwise reduction in oxygen to 8% O2 and drops in ventilator rate (pH 6.9, PCO2 63, MABP 34). Reoxygenation for 2 hours.5 sham, 5 asphyxia, 5 21%, 5 100%. Decreased Na+, K+ ATPase activity implies increased oxidant injury</td>
</tr>
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</table>

**Study Design**

| Study Design | Cohort |

**Case-Control Study Measures**

<table>
<thead>
<tr>
<th>Case Definition Adequate</th>
<th>Cases Representative</th>
<th>Control Selection</th>
<th>Control Definition</th>
<th>Comparability of Cases and Controls</th>
<th>How was Exposure Ascertained</th>
<th>Ascertainment Consistent</th>
<th>Non Response Similar?</th>
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**Cohort Study Measures**

<table>
<thead>
<tr>
<th>Exposed Cohort Representative?</th>
<th>How was non-exposed selected?</th>
<th>How was exposure ascertained?</th>
<th>Outcome absent at start?</th>
<th>Cohorts Comparable</th>
<th>How was outcome assessed?</th>
<th>Adequate Time for Outcomes to occur?</th>
<th>Was follow up adequate?</th>
</tr>
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<tbody>
<tr>
<td>b) Somewhat representative of the community</td>
<td>a) Drawn from the same community as the exposed cohort</td>
<td>a) Secure record (eg surgical records)</td>
<td>a) Yes</td>
<td>b) Study controls for the most important factor and any additional factor</td>
<td>b) Record linkage</td>
<td>a) Yes</td>
<td>a) Complete follow up</td>
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</tbody>
</table>

**Comments**

Animal study so will have to be downgraded significantly because of this. No mention of blinding or randomly assigning treatment group
### Review of RCTs

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<th>Oxygen delivery during CPR (Neonatal)</th>
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### Dalen 2010

- **Population**: Neonatal Rats
- **Intervention**: Resuscitation with RA with and without subsequent hypothermia
- **Comparator**: Resuscitation with 100% O2 with and without subsequent hypothermia
- **Assessment of Outcomes**: neurologic injury
- **Notes**: Rice Vinucci model of HI (tie off left carotid) followed by 90 minutes in 8% oxygen. n=64 randomized to 4 groups 21%, 100%, 21% with hypothermia, 100% with hypothermia

### Included RCTs Quality Grid

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<table>
<thead>
<tr>
<th>Dalen 2010</th>
<th>Randomization described adequately?</th>
<th>Allocation concealment effective?</th>
<th>Were participants blinded?</th>
<th>Were assessors blinded?</th>
<th>Was outcome data complete?</th>
<th>Was selective outcome reporting avoided?</th>
<th>Was study otherwise free of important biases?</th>
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<tbody>
<tr>
<td>Dalen 2010</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
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</table>
Oxygen delivery during CPR (Neonatal)

Ahn, Edward S; Robertson, Courtney L; Vereczki, Viktoria; Hoffman, Gloria E; Fiskum, Gary;

Normoxic ventilatory resuscitation following controlled cortical impact reduces peroxynitrite-mediated protein nitration in the hippocampus.


Ventilatory resuscitation with 100% O2 after severe traumatic brain injury (TBI) raises concerns about the increased production of reactive oxygen species (ROS). The product of peroxynitrite-mediated tyrosine residue nitration, 3-nitrotyrosine (3-NT), is a marker for oxidative damage to proteins. The authors hypothesized that posttraumatic resuscitation with hyperoxia (100% fraction of inspired oxygen [FiO2] concentration) results in increased ROS-induced damage to proteins compared with resuscitation using normoxia (21% FiO2 concentration). Male Sprague-Dawley rats underwent controlled cortical impact (CCI) injury and resuscitation with either normoxic or hyperoxic ventilation for 1 hour (5 rats per group). Twenty-four hours after injury, rat hippocampi were evaluated using 3-NT immunostaining. In a second experiment, animals similarly underwent CCI injury and normoxic or hyperoxic ventilation for 1 hour (4 rats per group). One week after injury, neuronal counts were performed after neuronal nuclei immunostaining. The 3-NT staining was significantly increased in the hippocampi of the hyperoxic group. The normoxic group showed a 51.0% reduction of staining in the CA1 region compared with the hyperoxic group and a 50.8% reduction in the CA3 region (p < 0.05, both regions). There was no significant difference in staining between the injured normoxic group and sham-operated control groups. In the delayed analysis of neuronal survival (neuronal counts), there was no significant difference between the hyperoxic and normoxic groups. In this clinically relevant model of TBI, normoxic resuscitation significantly reduced oxidative damage to proteins compared with hyperoxic resuscitation. Neuronal counts showed no benefit from hyperoxic resuscitation. These findings indicate that hyperoxic ventilation in the early stages after severe TBI may exacerbate oxidative damage to proteins.

**PubMed ID** 18173321

Andresen, Jannicke H; Solberg, Rønnaug; Løberg, Else Marit; Munkeby, Berit H; Stray-Pedersen, Babill; Saugstad, Ola Didrik;

Resuscitation with 21 or 100% oxygen in hypoxic nicotine-pretreated newborn piglets: possible neuroprotective effects of nicotine.

**Neonatology** 2008; 93(1): 36-44

Perinatal asphyxia is a major concern in perinatal medicine. Resuscitation and ways to prevent and minimize adverse outcomes after perinatal asphyxia are subject to extensive research. In this study we hypothesized that, prior to hypoxia, intravenously administered nicotine might have an effect on how newborn piglets tolerate hypoxia, with regard to the time and degree of damage inflicted, due to its suggested neuroprotective abilities, and further that resuscitation with 21 compared with 100% oxygen in nicotine-pretreated animals would cause less cerebral damage. Thirty anesthetized newborn piglets were randomized to either hypoxia or control groups, and pretreatment with either saline or nicotine. In addition, the nicotine/hypoxia...
group was randomized to resuscitation with either 21 or 100% oxygen for 15 min following hypoxia. We found significantly more necrosis in the striatum and cortex combined (p = 0.036), and in the striatum alone (p = 0.026), in the animals pretreated with nicotine and resuscitated with 100% when compared to 21% oxygen. There was no significant difference in the cerebellum. We also found significantly increased tolerance to hypoxia as measured by the time interval that the animals endured hypoxia: 103.8 +/- 28.2 min in the nicotine-pretreated animals vs. 66.5 +/- 19.5 min in the saline-pretreated animals (p = 0.035). Nicotine enhances newborn piglets’ ability to endure hypoxia, and resuscitation with 21% oxygen inflicts less necrosis than 100% oxygen. The potential neuroprotective effects of nicotine in the newborn brain should be further investigated. (c) 2007 S. Karger AG, Basel.

Angelos, Mark G; Yeh, Steve T; Aune, Sverre E;
Post-cardiac arrest hyperoxia and mitochondrial function.

Resuscitation 2011; 82 Suppl 2: S48-51

Rapid post-ischemic re-oxygenation is necessary to minimize ischemic injury, but itself can induce further reperfusion injury through the induction of reactive oxygen species. Utilization of oxygen within the cell primarily occurs in the mitochondria. The objective of this study was to determine heart mitochondrial function after 1 h of controlled arterial oxygenation following cardiac arrest and restoration of spontaneous circulation (ROSC). We hypothesized that arterial hyper-oxygenation following ROSC would result in greater impairment of heart mitochondrial function. KCl cardiac arrest was induced in anesthetized rats. Following 6.5 min of cardiac arrest, animals were resuscitated with standard thumper CPR, ventilation and epinephrine. Following ROSC, all animals were ventilated for 60 min with either 100% O(2) or 40% O(2) titrated to achieve normoxia utilizing pulse oximetry. At the end of 1 h, heart mitochondria were isolated and mitochondrial respiratory function was measured. Post-ROSC arterial PaO2 was 280 ± 40 in the 100% O2 group and 105 ± 10 in the 40% O2 group. One hour after ROSC, heart mitochondrial state 3 respirations and respiration control ratio (state 3/4 respiration) were significantly reduced from baseline in animals ventilated with 100% O(2), but not with 40% O(2). Post-ROSC arterial hyperoxia after a short cardiac arrest exacerbates impaired mitochondrial function. The overall clinical significance of these findings is unclear and requires additional work to better understand the role of post-arrest hyperoxia on cardiac and mitochondrial function. Copyright © 2011 Elsevier B.V. All rights reserved.

Anju, T R; Korah, P K; Jayanarayanan, S; Paulose, C S;
Enhanced brain stem 5HT₂A receptor function under neonatal hypoxic insult: role of glucose, oxygen, and epinephrine resuscitation.
Molecular processes regulating brain stem serotonergic receptors play an important role in the control of respiration. We evaluated 5-HT(2A) receptor alterations in the brain stem of neonatal rats exposed to hypoxic insult and the effect of glucose, oxygen, and epinephrine resuscitation in ameliorating these alterations. Hypoxic stress increased the total 5-HT and 5-HT(2A) receptor number along with an up regulation of 5-HT Transporter and 5-HT(2A) receptor gene in the brain stem of neonates. These serotonergic alterations were reversed by glucose supplementation alone and along with oxygen to hypoxic neonates. The enhanced brain stem 5-HT(2A) receptors act as a modulator of ventilatory response to hypoxia, which can in turn result in pulmonary vasoconstriction and cognitive dysfunction. The adverse effects of 100% oxygenation and epinephrine administration to hypoxic neonates were also reported. This has immense clinical significance in neonatal care.

Bajaj, Naveen; Udani, Rekha H; Nanavati, Ruchi N;

Room air vs. 100 per cent oxygen for neonatal resuscitation: a controlled clinical trial.


The aim of the study was to determine whether neonates resuscitated with room air compared with 100 per cent oxygen in the delivery room were less likely to have hypoxic ischemic encephalopathy and/or death before discharge. A controlled clinical trial was carried out at a tertiary care institute. All newborns weighing 1000 g or more with apnea or gasping respiration and/or heart rate less than 100 beats/min requiring positive pressure ventilation after initial steps of resuscitation were included. All eligible neonates were randomized to receive room air or 100 per cent oxygen for the first 90 s after birth if they required positive pressure ventilation. The composite primary outcome variable was hypoxic ischemic encephalopathy (HIE) and/or death before discharge. A total of 204 neonates fulfilling the inclusion criteria were enrolled. Of these, 107 neonates received room air and 97 neonates received 100 per cent oxygen for resuscitation. The composite primary outcome occurred in 41.1 per cent of the neonates assigned to receive room air and 43.3 per cent of those in the 100 per cent oxygen group (odds ratio in the group assigned to room air, 0.92; 95 per cent confidence interval, 0.52-1.60). Resuscitation of a newborn baby with room air instead of the current practice of 100 per cent oxygen does not confer a benefit in terms of reduced HIE and/or mortality. Significantly, there is no increase in adverse outcome with the use of room air, which can be recommended for resuscitation if oxygen is not available.

Bookatz, G Bradley; Mayer, Catherine A; Wilson, Christopher G; Vento, Maximo; Gelfand, Steven L; Haxhiu, Musa A; Martin, Richard J;

Effect of supplemental oxygen on reinitiation of breathing after neonatal resuscitation in rat pups.

To test our hypothesis that resuscitation with 21% and 40% oxygen (O2) would shorten time to onset of respiratory activity when compared with resuscitation with 100% O2, diaphragmatic electromyogram (EMG) electrodes were inserted in Sprague-Dawley rat pups, age 8-10 d before intubation and mechanical ventilation with 5% O2 to induce cessation of respiratory activity. Each animal was then resuscitated with 100% and 21% O2 (n = 10) or 100% and 40% O2 (n = 11) for 30 s before the ventilator was disconnected. Recovery of diaphragm activity was compared between resuscitation groups. Blood gas status and heart rate data were characterized in additional rat pups. Time to first respiratory effort was 36 +/- 21 s (mean +/- SD) for room air resuscitation and 72 +/- 22 s for 100% O2, (p = 0.002). In contrast, there was no difference in time to onset of diaphragm activity when resuscitation with 40% O2 was compared with 100% O2: 84 +/- 27 s versus 76 +/- 23 s, respectively (p > 0.05). Resuscitation with 100% and 40% O2 both resulted in hyperoxia and hypocapnia when compared with room air, without effect on heart rate. Our findings indicate that even modest hyperoxic resuscitation will result in a delayed onset of respiration compared with normoxic gas, via a mechanism that may involve both hyperoxicemic and hypocapnic inhibition of chemoreceptors.

Cheung, Po-Yin; Johnson, Scott T; Obaid, Laila; Chan, Grace S; Bigam, David L;

The systemic, pulmonary and regional hemodynamic recovery of asphyxiated newborn piglets resuscitated with 18%, 21% and 100% oxygen.

Resuscitation 2008; 76(3): 457-64

The increase in oxidative stress following neonatal hypoxia-reoxygenation can be related to subsequent cardiovascular deficits. We compared the acute systemic, pulmonary and regional hemodynamic recovery in hypoxic newborn pigs reoxygenated by low (18%) or high (100%) concentration of oxygen with that by 21% oxygen. Pigs (1-3 days, 1.5-2.5 kg) were acutely instrumented to continuously measure pulmonary artery flow (surrogate for cardiac index), mean and pulmonary artery pressures, common carotid, superior mesenteric and renal artery flow indices. After 1h of normocapnic alveolar hypoxia (8-10% oxygen), animals were randomized to receive 18%, 21% or 100% oxygen for 1h then 21% oxygen for 3 h (n=7 per group). Sham-operated pigs (n=6) had no hypoxia-reoxygenation. Severe hypoxia caused significant compromises in systemic and regional hemodynamics and oxygen delivery (vs. shams). Despite reoxygenation, mean arterial pressure remained significantly lower than that of shams with no difference among hypoxic-reoxygenated groups. There was an oxygen-dependent recovery of pulmonary artery pressure. Cardiac index improved with reoxygenation but deteriorated over time in the 100% group. Both 18% and 100% groups had lower systemic oxygen delivery. Regional flows and oxygen delivery in all hypoxic-reoxygenated piglets were similarly reduced in all groups. In this swine model of neonatal hypoxia-reoxygenation, resuscitation with 18% and 100% oxygen results in differential compromises in systemic and pulmonary circulations when compared with 21% oxygen.

Dalen, Marit L; Liu, Xun; Elstad, Maja; Løberg, Else Marit; Saugstad, Ola D; Rootwelt, Terje; Thoresen, Marianne;
Resuscitation with 100% oxygen increases injury and counteracts the neuroprotective effect of therapeutic hypothermia in the neonatal rat.


Mild therapeutic hypothermia (HT) reduces brain injury in survivors after perinatal asphyxia. Recent guidelines suggest that resuscitation of term infants should be started with air, but supplemental oxygen is still in use. It is not known whether supplemental oxygen during resuscitation affects the protection offered by subsequent HT. Wilcoxon median (95% confidence interval) hippocampal injury scores (range 0.0-4.0; 0 to ≥90% injury) were 21% O(2) normothermia (NT): 2.00 (1.25-2.50), 21% O(2) HT: 1.00 (0.50-1.50), 100% O(2) NT: 2.50 (1.50-3.25), and 100% O(2) HT: 2.00 (1.25-2.50). Although HT significantly reduced hippocampal injury ($B = -0.721$, SEM = 0.297, $P = 0.018$), reoxygenation with 100% O(2) increased injury ($B = +0.647$, SEM = 0.297, $P = 0.033$). Regression constant $B = 1.896$, SEM = 0.257 and normally distributed residuals. We confirm an ~50% neuroprotective effect of therapeutic HT in the neonatal rat. Reoxygenation with 100% O(2) increased injury and worsened reflex performance. HT was neuroprotective whether applied after reoxygenation with air or 100% O(2). However, HT after 100% O(2) gave no net neuroprotection. In an established neonatal rat model, hypoxia-ischemia (HI) was followed by 30-min reoxygenation in either 21% O(2) or 100% O(2) before 5 h of NT (37 °C) or HT (32 °C). The effects of HT and 100% O(2) on histopathologic injury in the hippocampus, basal ganglia, and cortex, and on postural reflex performance 7 d after the insult, were estimated by linear regression.
Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children.

**Resuscitation** 2012; 83(12): 1456-61

Arterial hyperoxia after resuscitation has been associated with increased mortality in adults. The aim of this study was to test the hypothesis that post-resuscitation hyperoxia and hypocapnia are associated with increased mortality after resuscitation in pediatric patients. We performed a prospective observational multicenter hospital-based study including 223 children aged between 1 month and 18 years who achieved return of spontaneous circulation after in-hospital cardiac arrest and for whom arterial blood gas analysis data were available. After return of spontaneous circulation, 8.5% of patients had hyperoxia (defined as PaO(2)>300 mm Hg) and 26.5% hypoxia (defined as PaO(2)<60 mm Hg). No statistical differences in mortality were observed when patients with hyperoxia (52.6%), hypoxia (42.4%), or normoxia (40.7%) (p=0.61). Hypocapnia (defined as PaCO(2)<30 mm Hg) was observed in 13.5% of patients and hypercapnia (defined as PaCO(2)>50 mm Hg) in 27.6%. Patients with hypercapnia or hypocapnia had significantly higher mortality (59.0% and 50.0%, respectively) than patients with normocapnia (33.1%) (p=0.002). At 24h after return of spontaneous circulation, neither PaO(2) nor PaCO(2) values were associated with mortality. Multiple logistic regression analysis showed that hypercapnia (OR, 3.27; 95% CI, 1.62-6.61; p=0.001) and hypocapnia (OR, 2.71; 95% CI, 1.04-7.05; p=0.04) after return of spontaneous circulation were significant mortality factors. In children resuscitated from cardiac arrest, hyperoxemia after return of spontaneous circulation or 24h later was not associated with mortality. On the other hand, hypercapnia and hypocapnia were associated with higher mortality than normocapnia. Copyright © 2012 Elsevier Ireland Ltd. All rights reserved.

PubMed ID 22841610

Observational Study

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Faa, Armando; Iacovidou, Nicoletta; Xanthos, Theodoros; Lcci, Annalisa; Pampaloni, Pietro; Aroni, Filippia; Papalois, Apostolos; Faa, Gavino; Fanos, Vassilios;

Hypoxia/reoxygenation-induced myocardial lesions in newborn piglets are related to interindividual variability and not to oxygen concentration.

**Clinics (Sao Paulo)** 2012; 67(5): 503-8

Evaluation of myocardial histological changes in an experimental animal model of neonatal hypoxia-reoxygenation. Normocapnic hypoxia was induced in 40 male Landrace/Large White piglets. Reoxygenation was initiated when the animals developed bradycardia (HR <60 beats/min) or severe hypotension (MAP <15 mmHg). The animals were divided into four groups based on the oxygen (O(2)) concentration used for reoxygenation; groups 1, 2, 3, and 4 received 18%, 21%, 40%, and 100% O(2), respectively. The animals were further classified into five groups based on the time required for reoxygenation: A: fast recovery (<15 min); B: medium recovery (15-45 min); C: slow recovery (45-90 min); D: very slow recovery (>90 min), and E: nine deceased piglets. Histology revealed changes in all heart specimens. Interstitial edema, a wavy arrangement, hypereosinophilia and coagulative necrosis of cardiomyocytes were observed frequently. No differences in the incidence of changes were observed among groups 1-4, whereas marked differences regarding the frequency and the degree of changes were found among groups A-E. Coagulative necrosis was correlated with increased recovery time: this condition was detected post-asphyxia in 14%, 57%, and 100% of piglets with fast, medium, and slow or very slow recovery rates, respectively. The
significant myocardial histological changes observed suggest that this experimental model might be a reliable model for investigating human neonatal cardiac hypoxia-related injury. No correlation was observed between the severity of histological changes and the fiO(2) used during reoxygenation. Severe myocardial changes correlated strictly with recovery time, suggesting an unreported individual susceptibility of myocardiocytes to hypoxia, possibly leading to death after the typical time-sequence of events.

Feet, B A; Brun, N C; Hellström-Westas, L; Svenningsen, N W; Greisen, G; Saugstad, O D;
Early cerebral metabolic and electrophysiological recovery during controlled hypoxemic resuscitation in piglets.  
J. Appl. Physiol. 1998; 84(4): 1208-16
We tested the hypothesis that controlled hypoxemic resuscitation improves early cerebral metabolic and electrophysiological recovery in hypoxic newborn piglets. Severely hypoxic anesthetized piglets were randomly divided into three resuscitation groups: hypoxic, 21% O2, and 100% O2 groups (8 in each group). The hypoxemic group was mechanically ventilated with 12-18% O2 adjusted to achieve a cerebral venous O2 saturation of 17-23% (baseline; 45 +/- 1%). Base excess (BE) reached -22 +/- 1 mM at the end of hypoxia. During a 2-h resuscitation period, no significant differences in time to recovery of electroencephalography (EEG), quality of EEG at recovery, or extracellular hypoxanthine concentrations in the cerebral cortex and striatum were found among the groups. BE and plasma hypoxanthine, however, normalized significantly more slowly during controlled hypoxemic resuscitation than during resuscitation with 21 or 100% O2. We conclude that early brain recovery during controlled hypoxemic resuscitation was as efficient as, but not superior to, recovery during resuscitation with 21 or 100% O2. The systemic metabolic recovery from hypoxia, however, was delayed during controlled hypoxemic resuscitation.

Ferguson, Lee; Durward, Andrew; Tibby, Shane;
Relationship between arterial partial oxygen pressure after resuscitation from cardiac arrest and mortality in children.  
Circulation 2012; 126(3): 335-42
Observational studies in adults have shown a worse outcome associated with hyperoxia after resuscitation from cardiac arrest. Extrapolating from adult data, current pediatric resuscitation guidelines recommend avoiding hyperoxia. We investigated the relationship between arterial partial oxygen pressure and survival in patients admitted to the pediatric intensive care unit (PICU) after cardiac arrest. We conducted a retrospective cohort study using the Pediatric Intensive Care Audit Network (PICANet) database between 2003 and 2010 (n=122,521). Patients aged <16 years with documented cardiac arrest preceding PICU admission and arterial blood gas analysis taken within 1 hour of PICU admission were included. The primary outcome measure was death within the PICU. The relationship between postarrest oxygen status and outcome was modeled with logistic regression, with nonlinearities explored via multivariable fractional polynomials. Covariates included age, sex, ethnicity, congenital heart disease, out-of-hospital arrest, year, Pediatric Index of Mortality-2 (PIM2) mortality risk, and organ supportive
therapies. Of 1875 patients, 735 (39%) died in PICU. Based on the first arterial gas, 207 patients (11%) had hyperoxia (Pa(O)(2) ≥300 mm Hg) and 448 (24%) had hypoxia (Pa(O)(2) <60 mm Hg). We found a significant nonlinear relationship between Pa(O)(2) and PICU mortality. After covariate adjustment, risk of death increased sharply with increasing hypoxia (odds ratio, 1.92; 95% confidence interval, 1.80-2.21 at Pa(O)(2) of 23 mm Hg). There was also an association with increasing hyperoxia, although not as dramatic as that for hypoxia (odds ratio, 1.25; 95% confidence interval, 1.17-1.37 at 600 mm Hg). We observed an increasing mortality risk with advancing age, which was more pronounced in the presence of congenital heart disease. Both severe hypoxia and, to a lesser extent, hyperoxia are associated with an increased risk of death after PICU admission after cardiac arrest.

PubMed ID 22723307
Observational Study

Ferrari, Diana Carolina; Nesic, Olivera B; Perez-Polo, J Regino;
Oxygen resuscitation does not ameliorate neonatal hypoxia/ischemia-induced cerebral edema.

Neonatal hypoxia/ischemia (HI) is a common cause of cognitive and behavioral deficits in children with hyperoxia treatment (HHI) being the current therapy for newborn resuscitation. HI induces cerebral edema that is associated with poor neurological outcomes. Our objective was to characterize cerebral edema after HI and determine the consequences of HHI (40% or 100% O(2)). Dry weight analyses showed cerebral edema 1 to 21 days after HI in the ipsilateral cortex; and 3 to 21 days after HI in the contralateral cortex. Furthermore, HI increased blood-brain barrier (BBB) permeability 1 to 7 days after HI, leading to bilateral cortical vasogenic edema. HHI failed to prevent HI-induced increase in BBB permeability and edema development. At the molecular level, HI increased ipsilateral, but not contralateral, AQP4 cortical levels at 3 and up to 21 days after HI. HHI treatment did not further affect HI-induced changes in AQP4. In addition, we observed developmental increases of AQP4 accompanied by significant reduction in water content and increase permeability of the BBB. Our results suggest that the ipsilateral HI-induced increase in AQP4 may be beneficial and that its absence in the contralateral cortex may account for edema formation after HI. Finally, we showed that HI induced impaired motor coordination 21 days after the insult and HHI did not ameliorate this behavioral outcome. We conclude that HHI treatment is effective as a resuscitating therapy, but does not ameliorate HI-induced cerebral edema and impaired motor coordination.

PubMed ID 20143414
Observational Study

Fugelseth, D; Børke, W B; Lenes, K; Matthews, I; Saugstad, O D; Thaulow, E;
Restoration of cardiopulmonary function with 21% versus 100% oxygen after hypoxaemia in newborn pigs.
To assess the consequences of hypoxaemia and resuscitation with room air versus 100% O(2) on cardiac troponin I (cTnI), cardiac output (CO), and pulmonary artery pressure (PAP) in newborn pigs. Twenty anaesthetised pigs (12-36 hours; 1.7-2.7 kg) were subjected to hypoxaemia by ventilation with 8% O(2). When mean arterial blood pressure fell to 15 mm Hg, or arterial base excess was < or = -20 mmol/l, resuscitation was performed with 21% (n = 10) or 100% (n = 10) O(2) for 30 minutes, then ventilation with 21% O(2) for 120 minutes. Blood was analysed for cTnI. Ultrasound examinations of CO and PAP (estimated from tricuspid regurgitation velocity (TR-Vmax)) were performed at baseline, during hypoxia, and at the start of and during reoxygenation. cTnI increased from baseline to the end point (p<0.001), confirming a serious myocardial injury, with no differences between the 21% and 100% O(2) group (p = 0.12). TR-Vmax increased during the insult and returned towards baseline values during reoxygenation, with no differences between the groups (p = 0.11) or between cTnI concentrations (p = 0.31). An inverse relation was found between increasing age and TR-Vmax during hypoxaemia (p = 0.034). CO per kg body weight increased during the early phase of hypoxaemia (p<0.001), then decreased. Changes in CO per kg were mainly due to changes in heart rate, with no differences between the groups during reoxygenation (p = 0.298). Hypoxaemia affects the myocardium and PAP. During this limited period of observation, reoxygenation with 100% O(2) showed no benefits compared with 21% O(2) in normalising myocardial function and PAP. The important issue may be resuscitation and reoxygenation without hyperoxygenation.

Goplerud, J M; Kim, S; Delivoria-Papadopoulos, M;
The effect of post-asphyxial reoxygenation with 21% vs. 100% oxygen on Na+,K(+)-ATPase activity in striatum of newborn piglets.

To compare the effect of 21% vs. 100% oxygen during post-asphyxial reoxygenation on brain cell membrane function in the striatum, 20 anesthetized, ventilated newborn piglets were studied: group 1 (normoxia, n = 5), group 2 (asphyxia, no reoxygenation, n = 5), group 3 (asphyxia followed by reoxygenation with 21% O2, n = 5), and group 4 (asphyxia followed by reoxygenation with 100% O2, n = 5). Asphyxia was induced by a stepwise reduction in FiO2 at 20 min intervals from 21% to 14%, 11%, and 8%. Following a total 60 min of asphyxia, piglets in groups 3 and 4 were recovered for 2 h with either 21% or 100% O2. Na+,K(+)-ATPase activity (mumol Pi/mg protein/h) in striatal cell membranes was 31 +/- 1, 22 +/- 2, 32 +/- 2 and 26 +/- 1 in groups 1, 2, 3 and 4, respectively. Na+,K(+)-ATPase activities in groups 2 and 4 were significantly lower than in groups 1 and 3 (p < 0.01). Piglets recovered post-asphyxia for 2 h with 21% O2 had restoration of Na+,K(+)-ATPase activity to baseline levels, while those treated with 100% O2 during recovery had persistent Na+,K(+)-ATPase inhibition of 16%. This could result from increased free radical production during reoxygenation with 100% O2 which could contribute to post-asphyxial cellular injury in the striatum.

Guerra-Wallace, Melissa; Casey, Francis; Bell, Michael; Fink, Ericka; Hickey, Robert;
Hyperoxia and hypoxia in children resuscitated from cardiac arrest.

*Pediatr Crit Care Med* 2013; 14(3): e143-8

> Ischemia depletes antioxidant reserves and impairs mitochondrial electron transport. Oxygen within blood reperfusing ischemic tissue can form free radicals, worsen oxidative stress, and exacerbate tissue injury (reperfusion injury). One strategy for limiting reperfusion injury is to limit delivery of "luxuriant" oxygen during or after reperfusion. Resuscitation guidelines for children with cardiac arrest recommend early weaning of supplemental oxygen as tolerated. There are currently no studies demonstrating the frequency and outcomes of hyperoxia and hypoxia after pediatric cardiac arrest. To determine the frequency and outcomes of hyperoxia and hypoxia in patients following resuscitation from pediatric cardiac arrest admitted to a tertiary care center. This is a retrospective observational cohort study. Charts of children resuscitated from cardiac arrest and admitted to our hospital from 2004 to 2008 were reviewed. Partial pressures of oxygen (PaO2) obtained within the first 24 hours following return of spontaneous circulation and mortality at 6 months was recorded. Children who did not survive the initial 48 hours, patients having undergone extracorporeal oxygenation or had congenital heart disease, and those in whom arterial blood gases were not obtained were excluded.

Seventy-four patients met inclusion criteria. Of these, 38 (51%) had at least one arterial blood gases with a PaO2 > 300 mm Hg and 10 (14%) had a PaO2 < 60 mm Hg in the first 24 hours. Neither hyperoxia nor hypoxia on initial arterial blood gases (p = 0.912 and p = 0.384) nor any arterial blood gases within the first 24 hours after cardiac arrest (p = 0.325 and p = 0.553) was associated with 6-month mortality.

Hyperoxia occurs commonly within the first 24 hours of management in children resuscitated from cardiac arrest.

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**Resuscitation with 100% oxygen causes intestinal glutathione oxidation and reoxygenation injury in asphyxiated newborn piglets.**


To compare mesenteric blood flow, oxidative stress, and mucosal injury in piglet small intestine during hypoxemia and reoxygenation with 21%, 50%, or 100% oxygen. Necrotizing enterocolitis is a disease whose pathogenesis likely involves hypoxia-reoxygenation and the generation of oxygen-free radicals, which are known to cause intestinal injury. Resuscitation of asphyxiated newborns with 100% oxygen has been shown to increase oxidative stress, as measured by the glutathione redox ratio, and thus may predispose to free radical-mediated tissue injury. Newborn piglets subjected to severe hypoxemia for 2 hours were resuscitated with 21%, 50%, or 100% oxygen while superior mesenteric artery (SMA) flow and hemodynamic parameters were continuously measured. Small intestinal tissue samples were analyzed for histologic injury and levels of oxidized and reduced glutathione. SMA blood flow decreased to 34% and mesenteric oxygen delivery decreased to 9% in hypoxemic piglets compared with sham-operated controls. With reoxygenation, SMA blood flow increased to 177%, 157%, and 145% of baseline values in piglets resuscitated with 21%, 50%, and 100% oxygen, respectively. Mesenteric oxygen delivery increased to more than 150% of baseline values in piglets resuscitated with 50% or 100% oxygen, and this correlated significantly with the degree of oxidative stress, as measured by the oxidized-to-reduced glutathione ratio. Two of eight piglets resuscitated with 100% oxygen developed gross and microscopic evidence of pneumatosis intestinalis and severe mucosal injury, while all other piglets were grossly normal. Resuscitation of hypoxic newborn piglets with 100% oxygen is associated with an increase in oxygen delivery and oxidative stress, and may be associated with the development of small intestinal hypoxia-reoxygenation injury. Resuscitation of asphyxiated newborns with lower oxygen concentrations may help to decrease...
Hyperoxic reperfusion after global cerebral ischemia promotes inflammation and long-term hippocampal neuronal death.

**Journal Name** 2010; 27(4): 753-62

In this study we tested the hypothesis that long-term neuropathological outcome is worsened by hyperoxic compared to normoxic reperfusion in a rat global cerebral ischemia model. Adult male rats were anesthetized and subjected to bilateral carotid arterial occlusion plus bleeding hypotension for 10 min. The rats were randomized to one of four protocols: ischemia/normoxia (21% oxygen for 1 h), ischemia/hyperoxia (100% oxygen for 1 h), sham/normoxia, and sham/hyperoxia. Hippocampal CA1 neuronal survival and activation of microglia and astrocytes were measured in the hippocampi of the animals at 7 and 30 days post-ischemia. Morris water maze testing of memory was performed on days 23-30. Compared to normoxic reperfusion, hyperoxic ventilation resulted in a significant decrease in normal-appearing neurons at 7 and 30 days, and increased activation of microglia and astrocytes at 7, but not at 30, days of reperfusion. Behavioral deficits were also observed following hyperoxic, but not normoxic, reperfusion. We conclude that early post-ischemic hyperoxic reperfusion is followed by greater hippocampal neuronal death and cellular inflammatory reactions compared to normoxic reperfusion. The results of these long-term outcome studies, taken together with previously published results from short-term experiments performed with large animals, support the hypothesis that neurological outcome can be improved by avoiding hyperoxic resuscitation after global cerebral ischemia such as that which accompanies cardiac arrest.
more rapid Apgar score increase than did infants born in hospitals using a 100% oxygen strategy; however, no difference remained at 10 minutes. The mean Apgar score increased from 2.01 at 1 minute to 6.74 at 5 minutes in the 2 hospitals initiating resuscitation with 40% oxygen, compared with 2.01 to 6.38 in the 2 hospitals using 100% oxygen, with a mean difference in Apgar score increases of 0.36. At 5 minutes, 44.3% of infants born in the hospitals using 100% oxygen had an Apgar score of <7, compared with 34.0% of infants at the hospitals using 40% oxygen. At 10 minutes, the mean Apgar scores were 8.16 at the hospitals using 40% oxygen and 8.07 at the hospitals using 100% oxygen. There were no significant differences in rates of neonatal death, hypoxic ischemic encephalopathy, or seizures in relation to the 2 oxygen strategies. Severely depressed term infants born in hospitals initiating resuscitation with 40% oxygen had earlier Apgar score recovery than did infants born in hospitals using a 100% oxygen strategy.

Hoehn, T; Felderhoff, U; Altstaedt, J; Obladen, M; Bührer, C;

Hyperoxia- and hypoxia-mediated activation of polymorphonuclear leukocytes: a comparison of cord and adult venous blood.

Resuscitation 2001; 51(1): 63-8

Among the most prominent changes occurring in newborn infants is the exposure of tissues and blood cells to increased oxygen tension. This increase is even more pronounced in neonatal resuscitation using 100% oxygen, currently recommended in the published guidelines. To analyse the response of neonatal and adult polymorphonuclear neutrophils (PMN) to high or low oxygen tension in vitro. Neonatal cord blood and adult venous blood without previous contact to ambient air was exposed to 0, 21, or 100% oxygen for 30 min followed by incubation for up to 24 h. Flow cytometry was used to assess PMN activation as indicated by downregulation of L-selectin expression. Cell viability was quantified by the amount of propidium iodide uptake. In adult PMN, L-selectin downregulation was greatly accelerated by hypoxia (PO2=27.2+/-3.4 mmHg) compared with both normoxia (PO2=71.0+/-11.0 mmHg) or hyperoxia (PO2=653.2+/-9.4) (P<0.05). In contrast, hyperoxia was the most potent stimulus for cord blood PMN, compared with both normoxia and hypoxia (P<0.05). Evidence of necrosis as indicated by positive staining for propidium iodide was similar in cord blood (10 h: 5.83% in oxygen) and in adult blood (10 h: 6.45% in oxygen). No differences were found between exposure to hypoxia, normoxia, or hyperoxia. Oxygen exposure of neonatal PMN leads to a more pronounced activation as compared with adult cells. Exposure towards high concentrations of oxygen may contribute to inflammatory processes during early neonatal life.

Hoffman, David Joseph; Lombardini, Eric; Mishra, Om Prakash; Delivoria-Papadopoulos, Maria;

Effect of resuscitation with 21% oxygen and 100% oxygen on NMDA receptor binding characteristics following asphyxia in newborn piglets.

Neurochem. Res. 2007; 32(8): 1322-8
The present study investigated the effect of reventilation with 21% and 100% oxygen following asphyxia in newborn piglets on NMDA receptor binding characteristics, Na(+), K(+) -ATPase activity, and lipid peroxidation. After achieving a heart rate less than 60 beats per minute, asphyxiated piglets were reventilated with 21% oxygen or 100% oxygen. (3)[H]MK-801 binding showed the Bmax in the 21% and 100% groups to be 1.53 +/- 0.43 and 1.42 +/- 0.35 pmol/mg protein (p = ns). Values for Kd were 4.56 +/- 1.29 and 4.17 +/- 1.05 nM (p = ns). Na(+), K(+) -ATPase activity in the 21% and 100% groups were 23.5 +/- 0.9 and 24.4 +/- 3.9 micromol Pi/mg protein/h (p = ns). Conjugated dienes (0.05 +/- 0.02 vs. 0.07 +/- 0.03 micromol/g brain) and fluorescent compounds (0.54 +/- 0.05 vs. 0.78 +/- 0.19 microg quinine sulfate/g brain), were similar in both groups (p = ns). Though lipid peroxidation products trended higher in the 100% group, these data show that NMDA receptor binding and Na(+), K(+) -ATPase activity were similar following reventilation with 21% or 100% oxygen after a single episode of mild asphyxia.
Persistent neurochemical changes in neonatal piglets after hypoxia-ischemia and resuscitation with 100%, 21% or 18% oxygen.

**Resuscitation** 2008; 77(1): 111-20

Neonatal hypoxia-ischemia (HI) is a common complication of pregnancy and delivery. Conventional clinical practice is to resuscitate neonates with 100% O2, and evidence is building to suggest resuscitation with lower O2 concentrations is safer. Significant neurochemical changes are associated with HI injury and persistent changes in amino acids are related to cell death, therefore we used a swine survival model of neonatal HI-reoxygenation (HI/R) to investigate the effects of resuscitation with 100%, 21% or 18% O2 on amino acid neurotransmitters. In a blinded randomized fashion, following permanent ligation of the left common carotid artery, newborn pigs (1-4 d, 1.7-2.5 kg) received alveolar normocapnic hypoxia (FiO2=0.15, 2h) and were reoxygenated with 18%, 21% or 100% O2. After a 4-day survival period, brain regions were processed for amino acid levels using high-performance liquid chromatography (HPLC). Results showed that resuscitation with different O2 concentrations caused hemispheric and regional changes in all amino acids investigated including glutamate, alanine, gamma-aminobutyric acid, glycine and aspartate, 4 days post-HI. Resuscitation with 100% O2 significantly increased glutamate and glycine in the dorsal cortex contralateral to the ligated common carotid artery, compared to piglets resuscitated with 21% O2. Additionally, piglets resuscitated with 21% O2 had significantly lower alanine levels than those resuscitated with 18% O2. Significant resuscitation-dependent changes in amino acid neurotransmitters are still evident 4 days post-HI in the newborn piglet. These data suggest that persistent changes in neurochemistry occur 4 days after HI/R and further studies are warranted to elucidate the consequences of this on neonatal brain development.

Joy, Reeba;

**Question 1:** is room air better than 100% oxygen for the resuscitation of the depressed full-term newborn?

**Arch. Dis. Child.** 2010; 95(1): 68-70

Kilgannon, J; Jones, Alan; Parrillo, Joseph; Dellinger, R; Milcarek, Barry; Hunter, Krystal; Shapiro, Nathan; Trzeciak, Stephen; ,

**Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest.**

**Circulation** 2011; 123(23): 2717-22
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. 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 (PaO(2)) over the first 24 hours in the ICU. The primary outcome measure was in-hospital mortality. We tested the association between PaO(2) (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 PaO(2) 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 PaO(2) 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. In this large sample of postresuscitation patients, we found a dose-dependent association between supranormal oxygen tension and risk of in-hospital death.

Kuisma, M; Boyd, J; Voipio, V; Alaspää, A; Roine, R; Rosenberg, P;

Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study.

Resuscitation 2006; 69(2): 199-206

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. 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 FiO(2) to avoid hypoxaemia. Blood oxygen saturation <95% was the threshold for this intervention. Thirty-two patients were randomised and 28 (14 in group A and 14 in group B) remained eligible for the final analysis. The mean PaO(2) 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. PaO(2) values did not fall to the hypoxaemic level in group A. In another group FiO(2) 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 microg/l in group A and 13.0 and 18.6 microg/l in group B (ns). S-100 at corresponding time points was 0.21 and 0.23 microg/l in group A and 0.73 and 0.49 microg/l in group B (ns). In the subgroup not treated with therapeutic hypothermia in hospital NSE at 24h was higher in group B (mean 7.6 versus 13.5 microg/l, p=0.0487). 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 SpO(2) monitoring and oxygen backup to avoid SpO(2)<95% did worse that the group receiving 100% oxygen. The use of 100% oxygen was associated with increased level of NSE at 24h in patients not treated with therapeutic hypothermia. The clinical significance of this finding is unknown and an outcome-powered study is feasible.
Kutzsche, S; Ilves, P; Kirkeby, O J; Saugstad, O D;

Hydrogen peroxide production in leukocytes during cerebral hypoxia and reoxygenation with 100% or 21% oxygen in newborn piglets.


The aim of this study was to investigate whether reoxygenation with 21% O2 rather than 100% O2 results in reduced hydrogen peroxide (H2O2) concentrations in neutrophils (PMN). Piglets (2-4 d old) exposed to severe hypoxia (inspired fraction of oxygen, 0.08) were randomized to resuscitation with 21 (n = 13) or 100% O2 (n = 12). Five animals served as controls. H2O2 concentrations in PMN in terms of rhodamine 123 (Rho 123) fluorescence intensity from arterial and superior sagittal sinus blood were quantified by flow cytometry. Laser Doppler flowmetry (LDF) was used to assess cortical blood perfusion. During hypoxia, Rho 123 increased in arterial PMN in both study groups by 15 and 32%, respectively (p < 0.05). In cerebral venous PMN, the increase was less dominant (p = 0.06). Reoxygenation with 100 or 21% O2 had no different effect on Rho 123 in arterial PMN. In cerebral venous PMN, Rho 123 was approximately 40% higher after 60 min and 30% higher after 120 min compared with corresponding data in the 21% O2 group (p < 0.05), which were close to baseline levels. Further, O2 treatment in both groups induced PMN accumulation in arterial blood (p < 0.05). Laser Doppler flowmetry signals increased during transient hypoxia (p < 0.0001 compared with baseline) and were normalized after reoxygenation in both study groups. In conclusion, arterial and cerebral venous H2O2 concentration in PMN tended to increase during hypoxia. During reoxygenation, H2O2 concentration in PMN in the cerebral circulation was low with 21% O2 but remained high with 100% O2 ventilation. We speculate that oxygen should be reintroduced with more caution during neonatal resuscitation.

PubMed ID 11385146

Lakshminrusimha, Satyan; Steinhorn, Robin H; Wedgwood, Stephen; Savorgnan, Fabio; Nair, Jayasree; Mathew, Bobby; Gugino, Sylvia F; Russell, James A; Swartz, Daniel D;

Pulmonary hemodynamics and vascular reactivity in asphyxiated term lambs resuscitated with 21 and 100% oxygen.

J. Appl. Physiol. 2011; 111(5): 1441-7

An increase in oxygen tension is an important factor in decreasing pulmonary vascular resistance (PVR) at birth. Birth asphyxia results in acidosis and increased PVR. We determined the effect of resuscitation with 21 vs. 100% O(2) on pulmonary hemodynamics, pulmonary arterial (PA) reactivity, and oxidant stress in a lamb model of in utero asphyxia. Term fetal lambs were acutely asphyxiated by intrauterine umbilical cord occlusion for 10 min resulting in acidosis (pH 6.96 ± 0.05 and Pco(2) 103 ± 5 Torr), bradycardia, systemic hypotension, and increased PVR. Lambs were treated with 30 min of resuscitation with 21% or 100% O(2) (n = 6 each). PaO(2)) was significantly elevated with 100% O(2) resuscitation compared with 21% O(2) (430 ± 38 vs. 64 ± 8 Torr), but changes in pH and Pa(CO(2)) were similar. The 100% O(2) induced greater increase in pulmonary blood flow and decrease in PVR at 1 min of life, but subsequent values were similar to 21% O(2) group between 2 and 30 min of life. Oxygen uptake from the lung and systemic oxygen extraction was similar between the two groups. Pulmonary arteries showed increased staining for superoxide anions and increased contractility to norepinephrine following...
resuscitation with 100% O(2). The increased PA contractility induced by 100% O(2) was reversed by scavenging superoxide anions with superoxide dismutase and catalase. We conclude that resuscitation of asphyxiated lambs with 100% O(2) increases Pa(O2)) but does not improve lung oxygen uptake, decrease PVR at 30 min, or increase systemic oxygen extraction ratios. Furthermore, 100% O(2) also induces oxidative stress and increases PA contractility. These findings support the new neonatal resuscitation guidelines recommending 21% O(2) for initial resuscitation of asphyxiated neonates.

Lakshminrusimha, Satyan; Swartz, Daniel D; Gugino, Sylvia F; Ma, Chang-Xing; Wynn, Karen A; Ryan, Rita M; Russell, James A; Steinhorn, Robin H;

Oxygen concentration and pulmonary hemodynamics in newborn lambs with pulmonary hypertension.


The effect of oxygen concentration on lowering pulmonary vascular resistance (PVR) during resuscitation in a model of persistent pulmonary hypertension of the newborn (PPHN) is not known. PPHN was induced in fetal lambs by ductal ligation 9 d before delivery. After delivery by cesarean section, resuscitation of PPHN lambs with 21%, 50%, or 100% O2 (n = 6 each) for 30 min produced similar decreases in PVR. Lambs were then ventilated with 50% O2 for 60 min and exposed to inhaled nitric oxide (iNO, 20 ppm). Initial resuscitation with 100% O2 significantly impaired the subsequent response to iNO compared with 21% O2 (42 +/- 9% vs 22 +/- 4% decrease from baseline PVR). Finally, each lamb was randomly and sequentially ventilated with 10%, 21%, 50%, or 100% O2. PVR decreased with increased concentrations of inhaled O2 up to 50%, there being no additional decrease in PVR with 100% O2. When PVR was correlated with Pao2, the maximal change in PVR was achieved at Pao2 values <60 mm Hg. We conclude that resuscitation with 100% O2 does not enhance pulmonary vasodilation compared with 21% and 50% O2, but impairs the subsequent response to iNO in PPHN lambs. Hypoxia increases PVR but hyperoxia does not confer significant additional pulmonary vasodilation in lambs with PPHN.

Linner, Rickard; Werner, Olof; Perez-de-Sa, Valeria; Cunha-Goncalves, Doris;

Circulatory recovery is as fast with air ventilation as with 100% oxygen after asphyxia-induced cardiac arrest in piglets.


We investigated return of spontaneous circulation and of cerebral oxygenation after asphyxia-induced cardiac arrest, using ventilation with air, through, or with 100% oxygen for a shorter or longer period. Arterial pressure, heart rate, regional cerebral oxygen saturation (CrSO2), and brain tissue oxygen tension (PbtO2) were measured in 1-d-old piglets that were hypoventilated with air and left in apnea until cardiac arrest. They were randomly assigned to be resuscitated with air (n = 13), or with oxygen for 3 (n = 12) or 30 min (n = 13) and then with air. Nine, 10, and 10 animals, respectively, needed closed chest cardiac massage. One, none, and one, respectively, died. Median (quartile range) times from start of ventilation until heart rate...
reached 150 bpm were 67 (60-76), 88 (76-126), and 68 (56-81) s. They were not significantly different, nor were the arterial pressure responses, times until CrSO2 reached 30%, or times until PbtO2 had increased by 0.1 kPa from its nadir. Peak PbtO2 values during resuscitation were 4.2 (3.3-5.4), 12 (6.4-15), and 25 (15-36) kPa. Thus, pure oxygen did not accelerate the recovery of circulation or of cerebral oxygenation, while even a brief exposure caused cerebral hyperoxia.

Lipinski, C; Hicks, S; Callaway, C;
Normoxic ventilation during resuscitation and outcome from asphyxial cardiac arrest in rats.

Resuscitation 1999; 42(3): 221-9
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 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.

Liu, Y; Rosenthal, R E; Haywood, Y; Miljkovic-Lolic, M; Vanderhoek, J Y; Fiskum, G;
Normoxic ventilation after cardiac arrest reduces oxidation of brain lipids and improves neurological outcome.

Stroke 1998; 29(8): 1679-86
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 postischemic ventilation with 21% inspired O2, rather than 100% O2, results in reduced levels of oxidized brain lipids and decreased neurological impairment. 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. 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 = 7.1 +/- 0.7 SE, 17.3 +/- 2.7, 14.2 +/- 3.2, 16.1 +/- 1.0, and 14.0 +/- 0.8, respectively; n=4, 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 (1.7 +/- 0.1 versus 3.12 +/- 0.78 microg 13-HODE/g wet wt cortex., n=4 to 6, P<0.05) and lower neurological deficit scores (45.1 +/- 3.6 versus 58.3 +/- 3.8, n=9, P<0.05). 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.

Martin, Richard J; Bookatz, G Bradley; Gelfand, Steven L; Sastre, Juan; Arduini, Alessandro; Aguar, Marta; Escrig, Raquel; Vento, Máximo; Consequences of neonatal resuscitation with supplemental oxygen.


There has been considerable controversy surrounding the optimal inspired oxygen concentration for resuscitation of term and preterm infants. We have developed a rat pup model to quantify both physiologic and biochemical parameters associated with normoxic vs. hyperoxic resuscitation. We have confirmed existing human data that hyperoxic resuscitation of rat pups is associated with a significant delay in onset of spontaneous respiratory efforts. Both 40% and 100% inspired oxygen delayed onset of respiratory activity when compared to 21% oxygen. We have also documented, in the rat pup model, that hyperoxic resuscitation is associated with reduced levels of glutathione at 24 hours post resuscitation. The implications of these and other findings for human infants are that term asphyxiated babies can be safely resuscitated in 21% oxygen and that supplementary oxygen can be reserved for non-responders. In contrast, resuscitation of extremely low gestational age infants does appear to require an initial low inspired oxygen concentration (eg, 30%) with subsequent pulse oximetry titration to optimize oxygenation status.

Matsiukevich, Dzmitry; Randis, Tara M; Utkina-Sosunova, Irina; Polin, Richard A; Ten, Vadim S; The state of systemic circulation, collapsed or preserved defines the need for hyperoxic or normoxic resuscitation in neonatal mice with hypoxia-ischemia.

Resuscitation 2010; 81(2): 224-9
The return of spontaneous circulation (ROSC) is a primary goal of resuscitation. For neonatal resuscitation the International Liaison Committee on Resuscitation (ILCOR) recommends oxygen concentrations ranging from 21% to 100%. This study (a) compared the efficacy of resuscitation with room air (RA) or 100% O(2) in achieving ROSC in 46 neonatal mice with circulatory collapse induced by lethal hypoxia-ischemia (HI) and (b) determined whether re-oxygenation with RA or 100% O(2) alters the extent of HI cerebral injury in mice with preserved systemic circulation (n=31). We also compared changes in generation of reactive oxygen species (ROS) in cerebral mitochondria in response to re-oxygenation with RA or 100% O(2). In HI-mice with collapsed circulation re-oxygenation with 100% O(2) versus RA resulted in significantly greater rate of ROSC. In HI-mice with preserved systemic circulation and regional (unilateral) cerebral ischemia the restoration of cerebral blood flow was significantly faster upon re-oxygenation with 100% O(2), than RA. However, no difference in the extent of brain injury was detected. Regardless of the mode of re-oxygenation, reperfusion in these mice was associated with markedly accelerated ROS production in brain mitochondria. In murine HI associated with circulatory collapse the resuscitation limited to re-oxygenation with 100% O(2) is superior to the use of RA in achievement of the ROSC. However, in HI-mice with preserved systemic circulation hyperoxic re-oxygenation has no benefit over the normoxic brain recovery. Copyright 2009 Elsevier Ireland Ltd. All rights reserved.
Supplementary oxygen and risk of childhood lymphatic leukaemia.

Acta Paediatr. 2002; 91(12): 1328-33

Childhood leukaemia has been linked to several factors, such as asphyxia and birthweight, which in turn are related to newborn resuscitation. Based on the findings from a previous study a population-based case-control study was performed to investigate the association between childhood leukaemia and exposure to supplementary oxygen and other birth-related factors. Children born in Sweden and diagnosed with lymphatic leukaemia between 1973 and 1989 (578 cases) were individually matched by gender and date of birth to a randomly selected control. Children with Down's syndrome were excluded. Exposure data were blindly gathered from antenatal, obstetric and other standardized medical records. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by conditional logistic regression. Resuscitation with 100% oxygen with a facemask and bag immediately postpartum was significantly associated with an increased risk of childhood lymphatic leukaemia (OR = 2.57, 95% CI 1.21-6.82). The oxygen-related risk further increased if the manual ventilation lasted for 3 min or more (OR = 3.54, 95% CI 1.16-10.80). Low Apgar scores at 1 and 5 min were associated with a non-significantly increased risk of lymphatic leukaemia.

There were no associations between lymphatic leukaemia and supplementary oxygen later in the neonatal period or other birth-related factors. Resuscitation with 100% oxygen immediately postpartum is associated with childhood lymphatic leukaemia, but further studies are warranted to confirm the findings.

Nong, Shao-Han; Xie, Yan-Ming; Huang, Xiao-Sui; Zhang, Yu-Xin;

Cerebral intracellular calcium concentrations in asphyxiated rat fetuses resuscitated with oxygen.


To investigate the effects of resuscitation with three different oxygen concentrations on cerebral intra- and extra-cellular calcium, sodium and potassium changes in asphyxiated rat fetuses. Fifty-six fetal rats of gestational age of 20 days were randomly assigned into five study groups: sham operation group (control, n = 11), room-air resuscitation group (n = 10), and 3 oxygen-resuscitated groups (n = 14, 11, and 10 respectively). Different inhaled oxygen concentrations and different timings of oxygen delivery were assigned. Except for control all fetal rats were rendered ischemic and hypoxic in utero by interrupting the placental circulation. After re-circulation, intra- and extra-cellular concentrations of calcium, sodium, and potassium in the brains were measured for each individual group. The mean intracellular free calcium concentration of fetal rat brains was similar for the room-air resuscitation group (552.1 +/- 93.5 nmol/L) and the group resuscitated with 92.8% oxygen (520.6 +/- 79.1 nmol/L) and both were significantly higher than in the control (315.3 +/- 86.9 nmol/L) (P < 0.001). After resuscitation with 65% oxygen, be it instituted before or immediately after hypoxia, their mean intracellular free calcium concentrations in the brain cells (441.5 +/- 47.9 and 452.9 +/- 36.4 nmol/L respectively) were significantly lower than those in the room-air resuscitation (P < 0.01) and 92.8% oxygen group (P < 0.05), though still higher than in the control (P > 0.05). There was no difference in the total concentrations of calcium, sodium, or potassium among all groups. Resuscitation with 92.8% oxygen or room air exerted a similar effect on the parameters measured, indicating that resuscitation of asphyxiated neonates using 100% oxygen might not be superior to using room air. Resuscitation with 65% oxygen resulted in lower cerebral intracellular calcium concentrations and might produce a better outcome than using 100% oxygen or room air.
Impaired diastolic function and disruption of the force-frequency relationship in the right ventricle of newborn pigs resuscitated with 100% oxygen.

**Neonatology** 2012; 101(2): 147-53

Resuscitation with 100% oxygen increases oxidative stress and is detrimental for organ function. To study the effects of resuscitation with 100% oxygen compared to room-air on myocardial function. Twenty-eight newborn pigs underwent global hypoxia (8% oxygen/N2) until base excess reached -20 mmol/l. The animals were randomized into two groups and resuscitated with either 100% or room air for 30 min. Myocardial tissue Doppler velocities and acceleration of the mitral and tricuspid valve annuli during systole and diastole were assessed before global hypoxia and after resuscitation together with troponin I. Peak early diastolic velocity (E') and acceleration (pEac) in the septum and pEac in the lateral tricuspid valve annulus were lower after resuscitation with 100% oxygen, suggesting impaired diastolic relaxation in the right ventricle. Lower systolic velocities and acceleration in the right ventricle relative to heart rate indicate disruption of the right ventricular force-frequency relationship after resuscitation with 100% oxygen. Troponins were higher in the 100% oxygen group, suggesting increased myocardial damage in this group. Resuscitation with 100% oxygen compared to room air induces diastolic dysfunction, disrupts the systolic force-frequency relationship and increases myocardial damage in the newborn pig. Copyright © 2011 S. Karger AG, Basel.

High brain tissue oxygen tension during ventilation with 100% oxygen after fetal asphyxia in newborn sheep.


The optimal inhaled oxygen fraction for newborn resuscitation is still not settled. We hypothesized that short-lasting oxygen ventilation after intrauterine asphyxia would not cause arterial or cerebral hyperoxia, and therefore be innocuous. The umbilical cord of fetal sheep was clamped and 10 min later, after delivery, ventilation with air (n = 7) or with 100% oxygen for 3 (n = 6) or 30 min (n = 5), followed by air, was started. Among the 11 lambs given 100% oxygen, oxygen tension (PO2) was 10.7 (1.8-56) kPa [median (range)] in arterial samples taken after 2.5 min of ventilation. In those ventilated with 100% oxygen for 30 min, brain tissue PO2 (PbtO2) increased from less than 0.1 kPa in each lamb to individual maxima of 56 (30-61) kPa, whereas in those given oxygen for just 3 min, PbtO2 peaked at 4.2 (2.9-46) kPa. The maximal PbtO2 in air-ventilated lambs was 2.9 (0.8-5.4) kPa. Heart rate and blood pressure increased equally fast in the three groups. Thus, prolonged ventilation with 100% oxygen caused an increase in PbtO2 of a magnitude previously only reported under hyperbaric conditions. Reducing the time of 100% oxygen ventilation to 3 min did not consistently avert systemic hyperoxia.
Pilcher, Janine; Weatherall, Mark; Shirtcliffe, Philippa; Bellomo, Rinaldo; Young, Paul; Beasley, Richard;
The effect of hyperoxia following cardiac arrest - A systematic review and meta-analysis of animal trials.

Resuscitation 2012; 83(4): 417-22

There are conflicting findings from observational studies regarding the nature of the association between hyperoxia and risk of mortality in patients admitted to intensive care following cardiac arrest. This systematic review and meta-analysis evaluates animal data investigating the effect of administration of high concentrations of oxygen following cardiac arrest on neurological outcome and the clinical applicability of this data. A systematic search of Medline and Embase identified controlled animal studies modelling cardiac arrest with subsequent cardiopulmonary resuscitation that compared ventilation with 100% oxygen to lower concentrations following return of spontaneous circulation. Eligible studies were included in a meta-analysis in which the inverse variance weighted differences were calculated for the standardised mean difference of the primary outcome measure, the neurological deficit score. Ten studies met the criteria for inclusion in the systematic review. In a meta-analysis of six studies, with 95 animals, treatment with 100% oxygen resulted in a significantly worse neurological deficit score than oxygen administered at lower concentrations, with a standardised mean difference of -0.64 (95% CI -1.06 to -0.22). In four of five studies, histological evidence of increased neuronal damage was present in animals that received 100% oxygen therapy. The administration of 100% oxygen therapy is associated with worse neurological outcome than lower oxygen concentrations in animal models of cardiac arrest. However, due to limitations in study design and poor generalisability of the animal models to the situation of post cardiac arrest resuscitation in humans, the clinical applicability of this data is uncertain. Copyright © 2012 Elsevier Ireland Ltd. All rights reserved.

Poulsen, J P; Oyasaeter, S; Saugstad, O D;
Hypoxanthine, xanthine, and uric acid in newborn pigs during hypoxemia followed by resuscitation with room air or 100% oxygen.

Crit. Care Med. 1993; 21(7): 1058-65

To determine if resuscitation with room air is as effective as resuscitation with an FIO2 of 1.0. Prospective, randomized laboratory study. Experimental laboratory (neonatal or delivery ward). Twenty piglets, 1 to 2 wks of age. Piglets were randomized into two groups. Both groups underwent hypoxemia for 2 hrs and then underwent reoxygenation for 1 hr (group 1 with an FIO2 of 1.0 and group 2 with an FIO2 of 0.21). Hypoxanthine, xanthine, uric acid, PaO2, oxygen saturation, pH, base excess or deficit, and arterial pressure. During hypoxemia (PaO2 26 to 49 torr [3.5 to 6.5 kPa]), the mean hypoxanthine concentrations increased (p < .02) from 26.1 to 115.4 mumol/L in plasma, from 20.9 to 81.7 mumol/L in cerebrospinal fluid, and from 12.9 to 21.5 mumol/L in vitreous humor. Xanthine concentrations changed in a similar way, whereas uric acid concentrations increased only in plasma. During reoxygenation, hypoxanthine concentrations increased both in cerebrospinal fluid and in the vitreous humor. Final concentrations in these two fluid areas were 81.8 and 39.4 mumol/L, respectively (p < .02). Xanthine concentrations increased similarly. In plasma, hypoxanthine and xanthine concentrations decreased during
reoxygenation. The final mean concentration of hypoxanthine was 76.8 mumol/L (p < .02). No change in plasma or cerebrospinal fluid uric acid concentrations were found during reoxygenation. The other measurements varied throughout the experiment, but no differences were found between the groups. There were no significant differences between the two treatment groups at any stage in the experiments. In this porcine model of hypoxemia, resuscitation with room air was as effective as was resuscitation with an FIO2 of 1.0, when circulating concentrations of oxypurines were used as an end-point.

PubMed ID 8319464 Read Abstract Read Full Text Article Source PubMed

**Randomized Control Trial**

Rabi, Yacov; Singhal, Nalini; Nettel-Aguirre, Alberto;

**Room-air versus oxygen administration for resuscitation of preterm infants: the ROAR study.**

*Pediatrics* 2011; 128(2): e374-81

We conducted a blinded, prospective, randomized control trial to determine which oxygen-titration strategy was most effective at achieving and maintaining oxygen saturations of 85% to 92% during delivery-room resuscitation. Infants born at 32 weeks' gestation or less were resuscitated either with a static concentration of 100% oxygen (high-oxygen group) or using an oxygen-titration strategy starting from a concentration of 100% (moderate-oxygen group), or 21% oxygen (low-oxygen group). In the moderate- and low-oxygen groups, the oxygen concentration was adjusted by 20% every 15 seconds to reach a target oxygen saturation range of 85% to 92%. Treatment failure was defined as a heart rate slower than 100 beats per minute for longer than 30 seconds. The moderate-oxygen group spent a greater proportion of time in the target oxygen saturation range (mean: 0.21 [95% confidence interval: 0.16-0.26]) than the high-oxygen group (mean: 0.11 [95% confidence interval: 0.09-0.14]). Infants in the low-oxygen group were 8 times more likely to meet the criteria for treatment failure than those in the high-oxygen group (24% vs 3%; P = .022). The 3 groups did not differ significantly in the time to reach the target oxygen saturation range. Titrating from an initial oxygen concentration of 100% was more effective than giving a static concentration of 100% oxygen in maintaining preterm infants in a target oxygen saturation range. Initiating resuscitation with 21% oxygen resulted in a high treatment-failure rate.

PubMed ID 21746729 Read Abstract Read Full Text Article Source PubMed

**Randomized Control Trial**

Rabi, Yacov; Rabi, Doreen; Yee, Wendy;

**Room air resuscitation of the depressed newborn: a systematic review and meta-analysis.**

*Resuscitation* 2007; 72(3): 353-63

Understanding of the potential dangers of hyperoxia in the newborn is growing. Several studies have examined the use of room air for the resuscitation of newborns. To assess the effects of room air resuscitation versus 100% oxygen resuscitation on mortality at 1 week and 1 month in asphyxiated newborn infants. Systematic review and meta-analysis of seven randomized and quasi-randomised controlled trials comparing room air and 100% oxygen resuscitation of newborn infants. Compared to the 100% oxygen resuscitation group, neonates in the room air resuscitation group had a lower mortality both in the first week of life (odds ratio 0.70, 95% CI 0.50, 0.98) and at 1 month and beyond (odds ratio 0.63, 95% CI 0.42, 0.94). The incidence of
severe hypoxic ischemic encephalopathy (Stage II and Stage III) was similar between the two groups. This meta-analysis supports the hypothesis that room air is superior to 100% oxygen as the initial choice for resuscitating clinically depressed newborns as it may result in a lower mortality rate. However, adequately powered studies of long-term neurodevelopmental outcomes are not yet available.

Ramji, S; Rasaily, R; Mishra, P K; Narang, A; Jayam, S; Kapoor, A N; Kambo, I; Mathur, A; Saxena, B N;
Resuscitation of asphyxiated newborns with room air or 100% oxygen at birth: a multicentric clinical trial.
Indian Pediatr 2003; 40(6): 510-7

To compare the short-term efficacy of room air versus 100% oxygen for resuscitation of asphyxic newborns at birth. Multicentric quasi randomized controlled trial. Teaching hospitals. Asphyxiated babies weighing greater than 1000 grams, with heart rate less than 100 per min and/or apnea, unresponsive to nasopharyngeal suction and tactile stimuli and having no lethal abnormalities. Asphyxiated neonates born on odd dates were given oxygen and those on even dates room air for resuscitation. Primary: Apgar score at 5 minutes; Secondary: Mortality and Hypoxic ischaemic encephalopathy (HIE) during first 7 days of life. A total of 431 asphyxiated babies, 210 in the room air and 221 in 100% oxygen group were enrolled for the study. Both the groups were comparable for maternal, intrapartum and neonatal characteristics. The heart rates in room air and 100% oxygen groups were comparable at 1 minute (94 bpm and 88 bpm), 5 minutes (131 bpm and 131 bpm) and 10 minutes (135 bpm and 136 bpm). Median apgar scores at 5 min [7 versus 7] and 10 minutes [8 versus 8 ], in the room air and oxygen groups respectively, were found to be comparable. Median time to first breath (1.5 versus 1.5 minutes) was similar in the room air and oxygen group. Median time to first cry (2.0 versus 3.0 minutes) and median duration of resuscitation (2.0 versus 3 minutes) were significantly shorter in the room air group. The number of babies with HIE during first seven days of life in the two treatment groups (35.7% babies in room air and 37.1% in the 100% oxygen group) were similar. There was also no statistically significant difference in the overall and asphyxia related mortality in the two treatment groups (12.4% and 10.0% in room air versus 18.1% and 13.6% in oxygen group). Room air appears as good as 100% oxygen for resuscitation of asphyxic newborn babies at birth.

Ramji, S; Ahuja, S; Thirupuram, S; Rootwelt, T; Rooth, G; Saugstad, O D;
Resuscitation of asphyxic newborn infants with room air or 100% oxygen.

To test the hypothesis that room air is superior to 100% oxygen when asphyxiated newborns are resuscitated, 84 neonates (birth weight > 999 g) with heart rate < 80 and/or apnea at birth were allocated to be resuscitated with either room air (n = 42) or 100% oxygen (n = 42). Serial, unblinded observations of heart rates at 1, 3, 5, and 10 min and Apgar scores at 1 min revealed no significant differences between the two groups. At 5 min, median (25th and 75th percentile) Apgar scores were
Richards, Erica M; Fiskum, Gary; Rosenthal, Robert E; Hopkins, Irene; McKenna, Mary C;

Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism.

*Stroke* 2007; 38(5): 1578-84

Previous reports indicate that compared with normoxia, 100% ventilatory O(2) 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% O(2) 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. After 10 minutes of cardiac arrest, animals were resuscitated and ventilated for 1 hour with 100% O(2) (hyperoxic) or 21% to 30% O(2) (normoxic). At 30 minutes reperfusion, [1-(13)C]glucose was infused, and at 2 hours, brains were rapidly removed and frozen. Extracted metabolites were analyzed by (13)C nuclear magnetic resonance spectroscopy. Compared with nonischemic controls, the hippocampi from hyperoxic animals had elevated levels of unmetabolized (13)C-glucose and decreased incorporation of (13)C 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. 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 ventilatory O(2).
It is controversial to choose an appropriate oxygen concentration to resuscitate asphyxiated newborns regarding the clinical and biochemical oxidative effects. We examined the vasomotor response to reoxygenation with graded reoxygenation and the effects on matrix metalloproteinases and amino acids of the immature brain. Thirty-two piglets (1-3 days, 1.5-2.1 kg) were instrumented for continuous monitoring of left common carotid and pulmonary arterial flows (Transonic). Piglets were randomized to a sham-operated control group (without hypoxia/reoxygenation) or 2 h hypoxia induced by decreasing the inspired oxygen concentration to 10-15%, followed by reoxygenation with 21, 50 or 100% oxygen for 1 h and then 21% oxygen for 3 h (n=8 each). The brains were then flash frozen and analyzed for matrix metalloproteinases and amino acid levels by zymography and HPLC, respectively. After 2 h oxygen deprivation, the absolute carotid flow remained similar but accounted for 38% of cardiac output (increased from 17% at baseline, p=0.001). During early reoxygenation, the flow rose in the piglets resuscitated with air (p<0.05), but not in those with supplemental oxygen. Carotid vascular resistance correlated significantly with the arterial partial pressure of oxygen (r=0.7). There was an oxygen-dependent increase in global cerebral activity of matrix metalloproteinase-2 with specific increases in the basal ganglia of all hypoxic-reoxygenated brains. There were no significant differences in glutamate and other amino acids in any brain regions. Although using high oxygen concentration to resuscitate asphyxiated newborn piglets increased carotid vascular resistance and cerebral matrix metalloproteinase-2 activity, there is no detrimental effect observed in this acute model of hypoxia-reoxygenation.

Rubertsson, S; Karlsson, T; Wiklund, L;

Systemic oxygen uptake during experimental closed-chest cardiopulmonary resuscitation using air or pure oxygen ventilation.


Although clinical cardiopulmonary resuscitation always includes ventilation with pure oxygen, this kind of ventilation has been reported to be associated with worse neurological outcome than ventilation with air in experimental cardiopulmonary resuscitation (CPR). The aim of the present investigation was to compare the systemic oxygen uptake during experimental closed-chest CPR including ventilation with pure oxygen or ambient air and, furthermore, to elucidate possible mechanisms of action in the regulation of pulmonary gas exchange. In 24 anesthetized piglets, 2 min of induced ventricular fibrillation and no ventilation was followed by 10 min of closed-chest CPR including i.v. administration of 0.5 mg adrenaline (at 8 min), and in one of the experimental groups alkaline buffer (at 5 min). The piglets were randomly divided into 3 groups: air ventilation during the entire CPR period with saline administration (n=8), air ventilation during the entire CPR period plus tris buffer mixture (n=8), and air ventilation for 3 min followed by 100% oxygen with saline administration (n= 8). In the group ventilated with air and treated with tris buffer mixture, cardiac output was significantly greater than in the group ventilated with pure oxygen. The arterial-mixed venous oxygen content difference was approximately 25% greater with pure oxygen than with air ventilation; however, there was no difference in systemic oxygen uptake. Systemic oxygen uptake increased after administration of tris buffer mixture in the group ventilated with air. Pulmonary hypoxic vasoconstriction appeared to be abolished during CPR including pure oxygen ventilation. Blood flow, not ventilation or pulmonary gas exchange, is the limiting factor during experimental closed-chest CPR.
Resuscitation of newborn infants with 21% or 100% oxygen: follow-up at 18 to 24 months.

**Pediatrics** 2003; 112(2): 296-300

To follow-up children who had been resuscitated at birth with either 21% or 100% oxygen (O2). A multicenter study with 10 participating centers recruited 609 infants to the Resair 2 study where resuscitation was performed with either 21% or 100% O2. A follow-up between ages 18 and 24 months was performed. However, during follow-up registration, it was found that 18 infants had been enrolled twice in the original Resair 2 study with different registration numbers, leaving 591 enrolled in the Resair 2 study and 410 enrolled in the 7 centers participating in the follow-up. Of these 410 infants, 79 died (76 in the neonatal and 3 in the postneonatal period). Furthermore, for 8 infants informed consent was not obtained, leaving 323 eligible for follow-up. Of these, 213 infants (66%) were followed-up: 91 (62%) had been resuscitated with 21% O2, and 122 (69%) with 100% O2. At a median age of 22 and 20 months (not significant) in the 21% and 100% groups, respectively, a simple questionnaire was filled out and neurologic assessment was performed in addition to measuring anthropometric data. There were no significant differences in weight, height, or head circumference between the 2 groups. Cerebral palsy developed in 10% and 7% (not significant) in the 21% and 100% groups respectively. In total, 11 cases (12%) in the 21% versus 11 cases (9%) in the 100% O(2) group (odds ratio: 1.39, 95% confidence interval: 0.57-3.36) developed cerebral palsy and/or mental or other delay. Furthermore, it was concluded that 14 (15%) in the 21% group and 12 (10%) in the 100% group were not normal (odds ratio: 1.67, 95% confidence interval: 0.73-3.80). There were no significant differences in somatic growth or neurologic handicap at an age of 18 to 24 months in infants resuscitated with either 21% or 100% O2 at birth. Based on these data, resuscitation with ambient air seems to be safe, at least in most cases. More studies are needed to settle this issue.
consent was not obtained until after the initial resuscitation, an arrangement in agreement with the new proposal of the US
Food and Drug Administration's rules governing investigational drugs and medical devices to permit clinical research on
emergency care without the consent of subjects. The protocol was approved by the ethical committees at each participating
center. Entry criterion was apnea or gasping with heart rate <80 beats per minute at birth necessitating resuscitation. Exclusion
criteria were birth weight <1000 g, lethal anomalies, hydrops, cyanotic congenital heart defects, and stillbirths. Primary outcome
measures were death within 1 week and/or presence of hypoxic-ischemic encephalopathy, grade II or III, according to a
modification of Sarnat and Sarnat. Secondary outcome measures were Apgar score at 5 minutes, heart rate at 90 seconds,
time to first breath, time to first cry, duration of resuscitation, arterial blood gases and acid base status at 10 and 30 minutes of
age, and abnormal neurologic examination at 4 weeks. The existing routines for resuscitation in each participating unit were
followed, and the ventilation techniques described by the American Heart Association were used as guidelines aiming at a
frequency of manual ventilation of 40 to 60 breaths per minute. Forms for 703 enrolled infants from 11 centers were received
by the steering committee. All 94 patients from one of the centers were excluded because of violation of the inclusion criteria in
86 of these. Therefore, the final number of infants enrolled in the study was 609 (from 10 centers), with 288 in the room air
group and 321 in the oxygen group. Median (5 to 95 percentile) gestational ages were 38 (32.0 to 42.0) and 38 (31.1 to 41.5)
weeks (NS), and birth weights were 2600 (1320 to 4078) g and 2560 (1303 to 3900) g (NS) in the room air and oxygen groups,
respectively. There were 46% girls in the room air and 41% in the oxygen group (NS). Mortality in the first 7 days of life was
12.2% and 15.0% in the room air and oxygen groups, respectively; adjusted odds ratio (OR) = 0.82 with 95% confidence
intervals (CI) = 0.50-1.35. Neonatal mortality was 13.9% and 19.0%; adjusted OR = 0. 72 with 95% CI = 0.45-1.15. Death within
7 days of life and/or moderate or severe hypoxic-ischemic encephalopathy (primary outcome measure) was seen in 21.2% in
the room air group and in 23.7% in the oxygen group; OR = 0.94 with 95% CI = 0.63-1.40. (ABSTRACT TRUNCATED)

Sejersted, Yngve; Aasland, Anne L; Bjørås, Magnar; Eide, Lars; Saugstad, Ola D;

Accumulation of 8-oxoguanine in liver DNA during hyperoxic resuscitation of newborn mice.


Supplementary oxygen during resuscitation of the asphyxiated newborn is associated with long-term detrimental effects
including increased risk of childhood cancer. It is suspected that the resuscitation procedure results in accumulated DNA
damage and mutagenesis. Base excision repair (BER) is the major pathway for repair of premutagenic oxidative DNA lesions.
This study addresses DNA base damage and BER in brain, lung, and liver in neonatal mice (P7) after hyperoxic resuscitation.
Mice were randomized to 8% oxygen or room air for 60 min in a closed chamber and subsequent reoxygenation with 100%
oxygen for 0 to 90 min. During this treatment, 8-oxoguanine accumulated in liver but not in lung or cerebellum. We observed a
linear relation between 8-oxoguanine and reoxygenation time in liver DNA from hypoxic animals (n = 28: B = 0.011 [0.001,
0.020]; p = 0.037). BER activity was not significantly changed during resuscitation. Our data suggest that after hypoxia, the
capacity for immediate repair in liver tissue is inadequate to meet increasing amounts of DNA damage. The duration of
supplementary oxygen use during resuscitation should be kept as short as justifiable to minimize the risk of genetic instability.
Resuscitation of newborn piglets: short-term influence of FiO2 on matrix metalloproteinases, caspase-3 and BDNF.

PLoS ONE 2010; 5(12): e14261

Perinatal hypoxia-ischemia is a major cause of mortality and cerebral morbidity, and using oxygen during newborn resuscitation may further harm the brain. The aim was to examine how supplementary oxygen used for newborn resuscitation would influence early brain tissue injury, cell death and repair processes and the regulation of genes related to apoptosis, neurodegeneration and neuroprotection. Anesthetized newborn piglets were subjected to global hypoxia and then randomly assigned to resuscitation with 21%, 40% or 100% O(2) for 30 min and followed for 9 h. An additional group received 100% O(2) for 30 min without preceding hypoxia. The left hemisphere was used for histopathology and immunohistochemistry and the right hemisphere was used for in situ zymography in the corpus striatum; gene expression and the activity of various relevant biofactors were measured in the frontal cortex. There was an increase in the net matrix metalloproteinase gelatinolytic activity in the corpus striatum from piglets resuscitated with 100% oxygen vs. 21%. Hematoxylin-eosin (HE) staining revealed no significant changes. Nine hours after oxygen-assisted resuscitation, caspase-3 expression and activity was increased by 30-40% in the 100% O(2) group (n=9/10) vs. the 21% O(2) group (n=10; p<0.04), whereas brain-derived neurotrophic factor (BDNF) activity was decreased by 65% p<0.03. The use of 100% oxygen for resuscitation resulted in increased potentially harmful proteolytic activities and attenuated BDNF activity when compared with 21%. Although there were no significant changes in short term cell loss, hyperoxia seems to cause an early imbalance between neuroprotective and neurotoxic mechanisms that might compromise the final pathological outcome.

PubMed ID 21151608 Read Abstract Read Full Text Article Source PubMed

Randomized Control Trial

Resuscitation of hypoxic newborn piglets with supplementary oxygen induces dose-dependent increase in matrix metalloproteinase-activity and down-regulates vital genes.


The optimal oxygen concentration for newborn resuscitation is still discussed. Oxygen administration during reoxygenation may induce short- and long-term pathologic changes via oxidative stress and has been associated to later childhood cancer. The aim was to study changes in oxidative stress-associated markers in liver and lung tissue of newborn pigs after acute hypoxia followed by reoxygenation for 30 min with 21, 40, or 100% oxygen compared with room air or to ventilation with 100% oxygen without preceding hypoxia. Nine hours after resuscitation, we found a dose-dependent increase in the matrix metalloproteinase gelatinase activity in liver tissue related to percentage oxygen supply by resuscitation (100% versus 21%; p = 0.002) pointing at more extensive tissue damage. Receiving 100% oxygen for 30 min without preceding hypoxia decreased the expression of VEGFR2 and TGFBR3 mRNA in liver tissue, but not in lung tissue. MMP-, VEGF-, and TGFbeta-superfamily are vital for the development, growth, and functional integrity of most tissues and our data raise concern about both short- and long-term consequences of even a brief hyperoxic exposure.

PubMed ID 20010314 Read Abstract Read Full Text Article Source PubMed
Solberg, Rønnaug; Andresen, Jannicke H; Escrig, Raquel; Vento, Maximo; Saugstad, Ola Didrik; Resuscitation of hypoxic newborn piglets with oxygen induces a dose-dependent increase in markers of oxidation. 


Newborn resuscitation with pure oxygen may be associated with long-term detrimental effects. Due to the change in attitude toward use of less oxygen upon resuscitation, there is a need to study effects of intermediate hyperoxia. The aim was to study dose-response correlation between inspiratory fraction of oxygen used for resuscitation and urinary markers of oxidative damage to DNA and amino acids. Hypoxemia was induced in newborn piglets following a standardized model; they were resuscitated for 15 min with either 21%, 40%, 60% or 100% oxygen and observed for 1 h. Urine samples were collected. Urinary elimination of 8-hydroxy-2'-deoxyguanosine (8-oxo-dG), 2'deoxyguanosine (2dG), ortho-tyrosine (o-Tyr) and phenylalanine (Phe) were determined by HPLC and tandem mass spectrometry (HPLC-MS/MS). Quotient of 8-oxo-dG/2dG and o-Tyr/Phe ratios were significantly and dose-dependent higher in piglets resuscitated with supplementary oxygen. 8-oxodG/dG: Mean (SD) 5.76 (1.81) versus 22.44 (12.55) p < 0.01 and o-Tyr/Phe: 19.07 (10.7) versus 148.7 (59.8) for 21% versus 100%, p < 0.001. Hypoxia and subsequent resuscitation for 15 min with graded inspiratory fraction of oxygen causes increased oxidative stress and a dose-dependent oxidation of DNA and Phenylalanine. The increase in the hydroxyl attack may lead to a pro-oxidative status and risk for genetic instability.

PubMed ID 18049371

Solevåg, Anne L; Dannevig, Ingrid; Nakstad, Britt; Saugstad, Ola D; Resuscitation of severely asphyctic newborn pigs with cardiac arrest by using 21% or 100% oxygen. 

Neonatology 2010; 98(1): 64-72

In spite of evidence suggesting that resuscitation with 100% O(2) is detrimental, international guidelines still recommend its use. Clinical studies comparing 21% and 100% O(2) included many infants with only mild and moderate asphyxia. We aimed to investigate the effect of these oxygen fractions on haemodynamic parameters, arterial blood gases, oxygen saturation indices and markers of inflammation and hypoxic damage when resuscitating asystolic newborn pigs following asphyxia. Newborn swine (n = 32, age 12-36 h, weight 2.0-2.7 kg) were progressively asphyxiated until asystole occurred. Cardiopulmonary resuscitation was initiated with ventilation with either 21% (n = 16) or 100% O(2) (n = 16). Return of spontaneous circulation (ROSC) was defined as a heart rate >or= 100 min(-1). Mean time of hypoxia, pH, base excess and pCO(2) at asystole were comparable between the groups. All animals except 2 in the 100% group achieved ROSC. One animal in the 21% group suffered bradycardia at baseline and was excluded. For the remaining 15 animals resuscitated with 21% O(2), median time to ROSC (interquartile range) was 150 s (115-180), whereas animals in the 100% group achieved ROSC after 135 s (113-168); p = 0.80. There were no differences in the temporal changes in mean arterial blood pressure, heart rate, pH, pCO(2), interleukin-1beta or lactate/pyruvate ratios. However, systemic and regional cerebral oxygen saturations were higher in the animals resuscitated with 100% oxygen. In this animal model of severe perinatal asphyxia, resuscitation with room air seemed to be as safe and effective as the use of 100% oxygen.
Spector, Logan G; Klebanoff, Mark A; Feusner, James H; Georgieff, Michael K; Ross, Julie A;

Childhood cancer following neonatal oxygen supplementation.

**J. Pediatr.** 2005; 147(1): 27-31

To evaluate the relationship between neonatal oxygen supplementation (O2) and childhood cancer in the Collaborative Perinatal Project (CPP). The CPP consisted of 54,795 children born between 1959 and 1966 and followed to age 8 years. We used Cox proportional hazards modeling to examine the association between history of neonatal O2 and cancer (n = 48). The hazard ratio (HR) for any O2 was 1.77 (95% confidence interval [CI] = 0.94 to 3.35). The HR for continuous duration of O2 was near 1 and not significant. However, the HRs were 0.69 (95% CI = 0.17 to 2.88) and 2.87 (95% CI = 1.46 to 5.66) when comparing 0 to 2 and 3 or more minutes of O2, respectively, to no O2. The latter association was weaker (HR = 2.00; 95% CI = 0.88 to 4.54) and not significant (P = .10) when analysis was restricted to cancers diagnosed after age 1 year (n = 41). These findings are consistent with an association between O2 for 3 minutes or longer and cancer in childhood, and should serve as a basis for further study.

Stevens, Jonathan P; Haase, Erika; Churchill, Thomas; Bigam, David L; Cheung, Po-Yin;

Resuscitation with 21% or 100% oxygen is equally effective in restoring perfusion and oxygen metabolism in the liver of hypoxic newborn piglets.

**Shock** 2007; 27(6): 657-62

The differential effects of the use of high or low oxygen levels during resuscitation on the neonatal liver are unknown. We compared the hepatic hemodynamics and oxygen metabolism in hypoxic newborn piglets resuscitated with 21% or 100% oxygen. Twenty-seven piglets (age, 1-3 days; weight, 1.5-2.0 kg) were acutely instrumented to measure cardiac output, hepatic artery, and portal venous blood flows (hepatic artery flow index [HAFI] and portal venous flow index [PVFI], respectively). The animals underwent 2 h of hypoxia (fraction of inspired oxygen, 0.10-0.15), then reoxygenation with 21% (n = 9) or 100% (n = 9) oxygen for 1 h, then 1 h with 21% oxygen. The controls (n = 9) were sham-operated without hypoxia-reoxygenation. Oxygen transport and plasma lactate concentrations were studied. Hypoxic animals had hypotension and decreased cardiac index with metabolic acidosis (mean pH, 7.00-7.02; P < 0.05 vs. controls). The PVFI and the total hepatic blood flow (THFI = PVFI + HAFI), despite the absence of significant change in HAFI, decreased to 16 +/- 2 mL/min/kg and 19 +/- 3 mL/min/kg, respectively (versus 24 +/- 2 mL/min/kg and 28 +/- 2 mL/min/kg of controls; P < 0.05). Fifteen minutes after reoxygenation, the cardiac index improved, PVFI recovered, HAFI was maintained, and THFI was not different between the groups. The hepatic oxygen consumption decreased (59%; P < 0.05) and the extraction increased (89%; P < 0.001) during hypoxia. Similarly, on reoxygenation, the hepatic oxygen consumption improved; however, extraction decreased versus controls on 100% but not on 21% oxygen (P < 0.05). The plasma lactate concentrations increased in both groups with hypoxia and were not different during
Impaired early neurologic outcome in newborn piglets reoxygenated with 100% oxygen compared with room air after pneumothorax-induced asphyxia.


Birth asphyxia is a serious problem worldwide, resulting in 1 million deaths and an equal number of neurologic sequelae annually. It is therefore important to develop new and better ways to treat asphyxia. In the present study we tested the effects of reoxygenation with room air or with 100% oxygen (O2) after experimental pneumothorax-induced asphyxia on the blood oxidative stress indicators, early neurologic outcome, and cerebral histopathology of newborn piglets. Twenty-six animals were studied in three experimental groups: 1) sham-operated animals (SHAM, n = 6), 2) animals reoxygenated with room air after pneumothorax (R21, n = 10), and 3) animals reoxygenated with 100% O2 after pneumothorax (R100, n = 10). In groups R21 and R100, asphyxia was induced under anesthesia with bilateral intrapleural room air insufflation. Gasping, bradyarrhythmia, arterial hypotension, hypoxemia, hypercarbia, and combined acidosis occurred 62 +/- 6 min (R21) or 65 +/- 7 min (R100; mean +/- SD) after the start of the experiments; then pneumothorax was relieved, and a 10-min reoxygenation period was started with mechanical ventilation with room air (R21) or with 100% O2 (R100). The newborn piglets then breathed room air spontaneously during the next 3 h. Blood oxidative stress indicators (oxidized and reduced glutathione, plasma Hb, and malondialdehyde concentrations) were measured at different stages of the experiments. Early neurologic outcome examinations (neurologic score of 20 indicates normal, 5 indicates brain-dead) were performed at the end of the study. The brains were next fixed, and various regions were stained for cerebral histopathology. In the SHAM group, the blood gas and acid-base status differed significantly from those measured in groups R21 and R100. In group R100, arterial PO2 was significantly higher after 5 (13.8 +/- 5.6 kPa) and 10 min (13.2 +/- 6.3 kPa) of reoxygenation than in group R21 (8.7 +/- 2.8 kPa and 9.2 +/- 3.1 kPa). The levels of all oxidative stress indicators remained unchanged in the study groups (SHAM, R21, and R100). The neurologic examination score in the SHAM group was 18 +/- 0, in group R21 it was 13.5 +/- 3.1, and in group R100 it was 9.5 +/- 4.1 (significant differences between SHAM and R21 or R100, and between R21 and R100). Cerebral histopathology revealed marked damage of similar severity in both asphyxiated groups. We conclude that the blood oxidative stress indicators and cerebral histopathology did not differ significantly after a 10-min period of reoxygenation with room air or with 100% O2 after pneumothorax-induced asphyxia, but reoxygenation with 100% O2 might impair the early neurologic outcome of newborn piglets.
Impact of room air resuscitation on early growth response gene-1 in a neonatal piglet model of cerebral hypoxic ischemia.


Early growth response gene-1 (Egr-1) is up-regulated by hypoxia-ischemia (HI) and reactive oxygen species (ROS) in adult animals, functioning as a master switch in inflammation and thrombogenesis. We hypothesized that resuscitation from HI with 100% O2 would result in greater Egr-1 expression, ROS, and cell death (CD) in the brains of newborn piglets than 21% O2. Two control groups breathed 21% O2 for 1 h followed by 21% or 100% O2 for 1 h. Two HI groups underwent carotid artery occlusion and breathed 8-12% O2 for 1 h followed by occlusion release and 21% or 100% O2 for 1 h. Brain Egr-1 mRNA and protein were analyzed via quantitative PCR and Western blot. CD and ROS were measured by fluorescence microscopy. Egr-1 mRNA expression increased throughout the brain in response to HI with regional heterogeneity, but protein levels did not. Resuscitation with 100% oxygen did not cause any additional Egr-1 mRNA, Egr-1 protein, CD, or ROS production as compared with 21% oxygen. There was no difference in physiologic recovery after HI with room air compared with 100% O2 resuscitation. However, 100% O2 administration was associated with increased CD in the brainstem independent of HI. Therefore, 100% O2 may have been toxic to some brainstem cells and potentially have significance in long-term neurologic sequelae seen after neonatal HI/resuscitation. Egr-1 protein levels may be tightly regulated in an attempt to diminish neurotoxicity or to enhance plasticity at this stage of development.

PubMed ID 16492983

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Randomized Control Trial

Vento, Maximo; Moro, Manuel; Escrig, Raquel; Arruza, Luis; Villar, Gema; Izquierdo, Isabel; Roberts, L Jackson; Arduini, Alessandro; Escobar, Justo Javier; Sastre, Juan; Asensi, Miguel A;

Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease.

*Pediatrics* 2009; 124(3): e439-49

The goal was to reduce adverse pulmonary adverse outcomes, oxidative stress, and inflammation in neonates of 24 to 28 weeks of gestation initially resuscitated with fractions of inspired oxygen of 30% or 90%. Randomized assignment to receive 30% (N = 37) or 90% (N = 41) oxygen was performed. Targeted oxygen saturation values were 75% at 5 minutes and 85% at 10 minutes. Blood oxidized glutathione (GSSG)/reduced glutathione ratio and urinary o-tyrosine, 8-oxo-dihydroxyguanosine, and isoprostane levels, isofuran elimination, and plasma interleukin 8 and tumor necrosis factor alpha levels were determined. The low-oxygen group needed fewer days of oxygen supplementation (6 vs 22 days; P < .01) and fewer days of mechanical ventilation (13 vs 27 days; P < .01) and had a lower incidence of bronchopulmonary dysplasia at discharge (15.4% vs 31.7%; P < .05). GSSG/reduced glutathione x 100 ratios at day 1 and 3 were significantly higher in the high-oxygen group (day 1: high-oxygen group: 13.36 +/- 5.25; low-oxygen group: 8.46 +/- 3.87; P < .01; day 3: high-oxygen group: 8.87 +/- 4.40; low-oxygen group: 6.97 +/- 3.11; P < .05). Urinary markers of oxidative stress were increased significantly in the high-oxygen group, compared with the low-oxygen group, in the first week after birth. GSSG levels on day 3 and urinary isofuran, o-tyrosine, and 8-hydroxy-2'-deoxyguanosine levels on day 7 were correlated significantly with development of chronic lung disease.

Resuscitation of preterm neonates with 30% oxygen causes less oxidative stress, inflammation, need for oxygen, and risk of bronchopulmonary dysplasia.

PubMed ID 19661049  Read Abstract  Read Full Text  Article Source PubMed
Randomized Control Trial

Vento, Máximo; Sastre, Juan; Asensi, Miguel A; Viña, José;
Room-air resuscitation causes less damage to heart and kidney than 100% oxygen.


Pure oxygen causes more oxidative stress than room air in resuscitation of asphyctic neonates, and consequently could be associated with increased tissue damage. To compare damage caused to heart and kidneys on reoxygenation in severely asphyctic term neonates resuscitated with room air (RAR) or 100% oxygen (OxR). Nonasphyctic term newborn infants served as a control group. This is a prospective randomized clinical trial masked for the gas mixture. Reduced glutathione (GSH), oxidized glutathione (GSSG), and superoxide dismutase (SOD) activity were measured to assess oxidative stress. Plasma cardiac troponin T (cTnT) and urinary N-acetyl-glucosaminidase (NAG) assessed cardiac and renal damage, respectively. Daily determinations of NAG for a 2-wk period were performed to monitor postasphyctic renal damage. Both asphyctic groups showed oxidative stress when compared with the control group as evidenced by diminished GSH/GSSG ratios, adaptive increases in SOD activity, and higher values of NAG and cTnT (markers of tissue damage). However, the OxR group showed significantly higher values of NAG and cTnT, lower GSH/GSSG ratios, and higher SOD activity than the RAR group. Moreover, NAG values persisted in being higher than normal in the OxR group for 2 wk after birth, whereas NAG in the RAR group dropped to normal within the first week. A linear correlation between cTnT or NAG and GSSG was found. The use of room air on resuscitation causes less oxidative stress and damage to heart and kidney than pure oxygen.

**Semin. Perinatol.** 2002; 26(6): 406-10

In a prospective, randomized, blinded trial we have studied the effects of resuscitation upon oxygenation in a group of asphyxiated newly born infants receiving room air or 100% oxygen as the gas source. During the acute phase of asphyxia and until the resuscitation procedure concluded, we determined serial blood gases as well as reduced and oxidized glutathione, enzymes involved in the glutathione redox cycle, and antioxidant enzyme activities. The use of 100% oxygen caused a remarkable increase of partial pressures of oxygen in arterial blood, with values that were frequently above physiological levels (> 100 mm Hg). In addition, we have found a significant correlation between hyperoxemia and the intra-erythrocyte GSSG (oxidized glutathione) concentration. We hypothesize that hyperoxemia may be 1 of the triggering factors responsible for an increased oxidation of GSH (reduced glutathione). Moreover, an increased antioxidant enzyme activity, which reflects an oxidative stress, indicates that the antioxidant capacity of the newly born infant may have been surpassed.
Observational Study

Vento, M; Asensi, M; Sastre, J; Garcia-Sala, F; Pallardó, F V; Viña, J;

Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates.

*Pediatrics* 2001; 107(4): 642-7

Traditionally, asphyxiated newborn infants have been ventilated using 100% oxygen. However, a recent multinational trial has shown that the use of room air was just as efficient as pure oxygen in securing the survival of severely asphyxiated newborn infants. Oxidative stress markers in moderately asphyxiated term newborn infants resuscitated with either 100% oxygen or room air have been studied for the first time in this work. Eligible term neonates with perinatal asphyxia were randomly resuscitated with either room air or 100% oxygen. The clinical parameters recorded were those of the Apgar score at 1, 5, and 10 minutes, the time of onset of the first cry, and the time of onset of the sustained pattern of respiration. In addition, reduced and oxidized glutathione concentrations and antioxidant enzyme activities (superoxide dismutase, catalase, and glutathione peroxidase) were determined in blood from the umbilical artery during delivery and in peripheral blood at 72 hours and at 4 weeks' postnatal age. Our results show that the room-air resuscitated (RAR) group needed significantly less time to first cry than the group resuscitated with 100% oxygen (1.2 +/- 0.6 minutes vs 1.7 +/- 0.5). Moreover, the RAR group needed less time undergoing ventilation to achieve a sustained respiratory pattern than the group resuscitated with pure oxygen (4.6 +/- 0.7 vs 7.5 +/- 1.8 minutes). The reduced-to-oxidized-glutathione ratio, which is an accurate index of oxidative stress, of the RAR group (53 +/- 9) at 28 days of postnatal life showed no differences with the control nonasphyxiated group (50 +/- 12). However, the reduced-to-oxidized-glutathione ratio of the 100% oxygen-resuscitated group (OxR) (15 +/- 5) was significantly lower and revealed protracted oxidative stress. Furthermore, the activities of superoxide dismutase and catalase in erythrocytes were 69% and 78% higher, respectively, in the OxR group than in the control group at 28 days of postnatal life. Thus, this shows that these antioxidant enzymes, although higher than in controls, could not cope with the ongoing generation of free radicals in the OxR group. However, there were no differences in antioxidant enzyme activities between the RAR group and the control group at this stage. There are no apparent clinical disadvantages in using room air for ventilation of asphyxiated neonates rather than 100% oxygen. Furthermore, RAR infants recover more quickly as assessed by Apgar scores, time to the first cry, and the sustained pattern of respiration. In addition, neonates resuscitated with 100% oxygen exhibit biochemical findings reflecting prolonged oxidative stress present even after 4 weeks of postnatal life, which do not appear in the RAR group. Thus, the current accepted recommendations for using 100% oxygen in the resuscitation of asphyxiated newborn infants should be further discussed and investigated.

PubMed ID 11335737

Randomized Control Trial

Vereczki, Viktoria; Martin, Erica; Rosenthal, Robert E; Hof, Patrick R; Hoffman, Gloria E; Fiskum, Gary;

Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death.

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 E1alpha 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 nons ischemic 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.

Walson, Karen H; Tang, Minke; Glumac, Ashley; Alexander, Henry; Manole, Mioara D; Ma, Li; Hsia, Carelton J; Clark, Robert S; Kochanek, Patrick M; Kagan, Valerian E; Bayr, Hülya;

Normoxic versus hyperoxic resuscitation in pediatric asphyxial cardiac arrest: effects on oxidative stress.

Crit. Care Med. 2011; 39(2): 335-43

To determine the effects of normoxic vs. hyperoxic resuscitation on oxidative stress in a model of pediatric asphyxial cardiac arrest. Prospective, interventional study. University research laboratory. Postnatal day 16-18 rats (n = 5 per group). Rats underwent asphyxial cardiac arrest for 9 min. Rats were randomized to receive 100% oxygen, room air, or 100% oxygen with polynitroxyl albumin (10 mL·kg⁻¹ intravenously, 0 and 30 min after resuscitation) for 1 hr from the start of cardiopulmonary resuscitation. Shams recovered in 100% oxygen or room air after surgery. Physiological variables were recorded at baseline to 1 hr after resuscitation. At 6 hrs after asphyxial cardiac arrest, levels of reduced glutathione and protein-thiols (fluorescent assay), activities of total superoxide dismutase and mitochondrial manganese superoxide dismutase (cytochrome c reduction method), manganese superoxide dismutase expression (Western blot), and lipid peroxidation (4-hydroxynonenal Michael adducts) were evaluated in brain tissue homogenates. Hippocampal 3-nitrotyrosine levels were determined by immunohistochemistry 72 hrs after asphyxial cardiac arrest. Survival did not differ among groups. At 1 hr after resuscitation, Pao2, pH, and mean arterial pressure were decreased in room air vs. 100% oxygen rats (59 ± 3 vs. 465 ± 46 mm Hg, 7.36 ± 0.05 vs. 7.42 ± 0.03, 35 ± 4 vs. 45 ± 5 mm Hg; p < .05). Rats resuscitated with 100% oxygen had decreased hippocampal reduced glutathione levels vs. sham (15.3 ± 0.4 vs. 20.9 ± 4.1 nmol·mg protein⁻¹; p < .01). Hippocampal manganese superoxide dismutase activity was significantly increased in 100% oxygen rats vs. sham (14 ± 2.4 vs. 9.5 ± 1.6 units·mg protein⁻¹, p < .01), with no difference in protein expression of manganese superoxide dismutase. Room air and 100% oxygen plus polynitroxyl albumin groups had hippocampal reduced glutathione and manganese superoxide dismutase activity levels comparable with sham. Protein thiol levels were unchanged across groups. Compared with all other groups, rats receiving 100% oxygen had increased immunopositivity for 3-nitrotyrosine in the hippocampus and increased lipid peroxidation in the
Resuscitation with 100% oxygen leads to increased oxidative stress in a model that mimics pediatric cardiac arrest. This may be prevented by using room air or giving an antioxidant with 100% oxygen resuscitation.

Wang, Casey L; Anderson, Christina; Leone, Tina A; Rich, Wade; Govindaswami, Balaji; Finer, Neil N; Resuscitation of preterm neonates by using room air or 100% oxygen.

*Pediatrics* 2008; 121(6): 1083-9

In this study of preterm neonates of <32 weeks, we prospectively compared the use of room air versus 100% oxygen as the initial resuscitation gas. A 2-center, prospective, randomized, controlled trial of neonates with gestational ages of 23 to 32 weeks who required resuscitation was performed. The oxygen group was initially resuscitated with 100% oxygen, with decreases in the fraction of inspired oxygen after 5 minutes of life if pulse oxygen saturation was >95%. The room air group was initially resuscitated with 21% oxygen, which was increased to 100% oxygen if compressions were performed or if the heart rate was <100 beats per minute at 2 minutes of life. Oxygen was increased in 25% increments if pulse oxygen saturation was <70% at 3 minutes of life or <80% at 5 minutes of life. Twenty-three infants in the oxygen group (mean gestational age: 27.6 weeks; range: 24-31 weeks; mean birth weight: 1013 g; range: 495-2309 g) and 18 in the room air group (mean gestational age: 28 weeks; range: 25-31 weeks; mean birth weight: 1091 g; range: 555-1840 g) were evaluated. Every resuscitated patient in the room air group met rescue criteria and received an increase in the fraction of inspired oxygen by 3 minutes of life, 6 patients directly to 100% and 12 with incremental increases. Pulse oxygen saturation was significantly lower in the room air group from 2 to 10 minutes (pulse oxygen saturation at 3 minutes: 55% in the room air group vs 87% in the oxygen group). Heart rates did not differ between groups in the first 10 minutes of life, and there were no differences in secondary outcomes. Resuscitation with room air failed to achieve our target oxygen saturation by 3 minutes of life, and we recommend that it not be used for preterm neonates.

Whitehurst, M E; Blount, A D; Austin, P E; Carroll, R G; Ventilatory strategies affect gas exchange in a pig model of closed-chest cardiac compression.


To identify the arterial and mixed venous blood gas changes caused by different ventilatory strategies during resuscitation from ventricular fibrillation in a pig model of closed-chest cardiac compression. A prospective randomized animal study was performed using 27 domestic pigs (body weight, 30 to 35 kg). Pentobarbital-anesthetized pigs were assigned to receive one of three treatments: (1) chest compression without assisted ventilation (n = 8), (2) assisted ventilation with room air (n = 8), and (3) assisted ventilation with 100% oxygen (n = 8). A fourth group, with the airway completely blocked, was added at the end of the experiment (n = 3). After instrumentation, the ventricles were fibrillated, and chest compression was begun 30 seconds after fibrillation with the use of the Thumper Mechanical CPR system (Michigan Instruments). Arterial and mixed venous blood
gas samples were collected at 1, 3, 10, and 20 minutes of resuscitation. Defibrillation was attempted after the 20-minute sample was taken. Fibrillation followed by chest compression alone caused a significant drop in arterial and mixed venous partial pressure of oxygen (PO2) and a significant increase in arterial and mixed venous partial pressure of carbon dioxide (PCO2). Compared with the chest compression only, ventilation with room air significantly increased arterial and mixed venous PO2 and decreased arterial and mixed venous PCO2. Ventilation with 100% oxygen further increased arterial and mixed venous PO2 but did not affect PCO2, when compared with room air ventilation. The only successful defibrillations (3 animals) occurred in the group receiving 100% oxygen. This study indicates that passive air movement during chest compression does not allow physiologically significant pulmonary gas exchange and that room air ventilation alone is not sufficient to maintain mixed venous PO2.

Yeh, Steve T; Cawley, Rebekah J; Aune, Sverre E; Angelos, Mark G;
Oxygen requirement during cardiopulmonary resuscitation (CPR) to effect return of spontaneous circulation.

Resuscitation 2009; 80(8): 951-5

Recent scientific evidence has demonstrated the importance of good quality chest compressions without interruption to improve cardiac arrest resuscitation rates, and suggested that a de-emphasis on minute ventilation is needed. However, independent of ventilation, the role of oxygen and the optimal oxygen concentration during CPR is not known. Previous studies have shown that ventilation with high oxygen concentration after CPR is associated with worse neurologic outcome. We tested the hypothesis that initial ventilation during CPR without oxygen improves resuscitation success. Sprague-Dawley rats were anesthetized with ketamine/xylazine (IP), intubated and ventilated with room air. A KCl bolus (0.04 mg/g) was given (IV) to induce asystolic cardiac arrest and ventilation was stopped. At 6 min, CPR was started with an automated chest compressor at a rate of 200-240/min and epinephrine (0.01 mg/kg) was given 1 min later. During CPR, the ventilation rate was 50% of baseline with one of three oxygen concentrations: (1) 0% O2 (100% N2), (2) 21% O2, or (3) 100% O2. The prescribed oxygen concentration was continued for 2 min after return of spontaneous circulation (ROSC) and then all animals were switched to 100% oxygen for 1h prior to extubation. Blood gases were measured at baseline, 2 min and 1h after ROSC. Group comparisons were done using Fisher's exact test and ANOVA. ROSC was achieved in 1/10 (0% O2), 9/11 (21% O2) and 10/12 (100% O2, p<0.001). ROSC times after starting CPR were 80s in the 0% O2, 115+/-87 s in the 21% O2 group and 95+/-33 s in the 100% O2 group (mean+/-SD, p=0.5). Aortic end-diastolic pressure before ROSC was not different among groups. 100% oxygen ventilation in the first 2 min resulted in higher PaO2 at ROSC 2 min (109+/-44 mm Hg vs. 33+/-8 mm Hg, p<0.001). Survival to 72 h was 0/1 (0% O2), 7/9 (21% O2) and 8/10 (100% O2) with a low neurologic deficit score in both O2 groups (NDS range 5-25). In a mild cardiac arrest model with generally good neurologic recovery, initial CPR ventilation with no O2 did not allow for ROSC. In contrast, CPR coupled with room air or higher oxygen levels result in a high rate of ROSC with good neurologic recovery. During CPR, the level of oxygenation must be considered, which if too low may preclude initial ROSC.
Hypoxic cardiopulmonary-cerebral resuscitation fails to improve neurological outcome following cardiac arrest in dogs.

Resuscitation 1995; 29(3): 225-36

Hyperoxic cardiopulmonary resuscitation (CPR) is associated with an increase in neurologic dysfunction upon successful resuscitation with much of the damage attributable to an increase in reperfusion oxidant injury. We hypothesized that by contrast, hypoxic ventilation during resuscitation would improve neurologic outcome by reducing available substrate necessary for oxidant injury. Specifically, this study investigated the effects of 2 levels of hypoxic ventilation during resuscitation: F1O2 = 0.085, PaO2 = 26.6 +/- 3.4 mmHg, (HY8), and F1O2 = 0.12, PaO2 = 33.0 +/- 4.2 mmHg, (HY12), and normoxic resuscitation: F1O2 = 0.21, PaO2 = 60.6 +/- 17.0 mmHg, (N) on survival and neurological outcome following 9 min of normothermic cardiac arrest. Concentrations of malonaldehyde (MDA) and 4-hydroxynonenal (4-OH) in plasma and concentrations of glutathione (GSH) in erythrocyte lysates were measured to quantify possible radical damage. Physiological variables including arterial blood gases were followed for 24 h after resuscitation. Neurologic outcome was assessed using a standardized scoring system. Hypoxically (HY8) resuscitated dogs tended to have a greater neurologic deficit than normoxically resuscitated dogs and had reduced overall survival (16.9 +/- 8.9 h) compared to N dogs (24.0 +/- 0.0 h). Overall survival time correlated negatively (-0.693) and significantly (P = 0.0018) with plasma glucose concentration. Arterial plasma glucose concentrations were higher in the HY8 group compared to the N group immediately (HY8, 312 +/- 86 mg/dL; N, 196 +/- 82 mg/dL; P = 0.17) and 30 min (HY8, 331 +/- 74 mg/dL; N, 187 +/- 74 mg/dL; P = 0.077) following resuscitation. No statistically discernible differences in markers of oxidant injury were apparent among the 3 groups, but pooled data increased significantly with time for MDA and 4-OH. Pooled data for GSH showed a significant drop at 1 h following resuscitation and returned to normal by 6 h. Data from these markers suggested attendant oxidant injury in all groups. Thus, hypoxic ventilation at 2 depths of hypoxia during resuscitation failed to improve neurologic outcome beyond that achieved by ventilation with air, suggesting that normoxia rather than hyperoxia or hypoxia is the ideal target for arterial oxygenation during resuscitation.

Zwemer, C F; Whitesall, S E; D'Alecy, L G;

Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs.

Resuscitation 1994; 27(2): 159-70

This study investigated the effects of normoxic (FIO2 = 0.21), hyperoxic (FIO2 = 1.0), and hyperoxic (FIO2 = 1.0) plus antioxidant pretreatment (tirilazad mesylate) [corrected] resuscitation on neurologic outcome following 9 min of normothermic (39 +/- 1.0 degrees 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 +/- 3 and 49 +/- 8, respectively) than did antioxidant pretreated hyperoxically resuscitated dogs (mean scores: 22 +/- 1, P = 0.0007 and 22 +/- 1, P = 0.004, respectively) and normoxically resuscitated dogs (mean scores: 28 +/- 4, P = 0.025 and 33 +/- 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 FIO2's may contribute to and further exacerbate neurologic dysfunction.
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Question  Oxygen delivery during CPR (Neonatal)

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