Oxygen and the injured brain: how much is enough?

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  – Nestle Health Science Research
  – Integra Neurosciences
  – Bard Medical
PATHOPHYSIOLOGY
Thresholds for hypoxic cerebral vasodilation in volunteers

- ↓ Systemic oxygenation $\rightarrow$ ↑ Cerebral Blood Flow $\rightarrow$ ↑ Intracranial Pressure

Cerebral metabolism and oxygenation after brain injury

- Impaired CBF, regional ischemia
- Brain tissue hypoxia
- Barriers to oxygen diffusion
- Mitochondrial dysfunction
- Cerebral metabolic depression
Hyperoxia
experimental findings

benefit

✓ Improves $O_2$ delivery
✓ Improves $O_2$ diffusion
✓ Arterial vasoconstriction
✓ Reduces peri-contusional edema
✓ Reduces contusion size
✓ Attenuates apoptosis

harm

• Arterial vasoconstriction
• Oxidative damage
• Exacerbates neuroinflammation
• Delayed increase in WM injury
• Hypomyelination
INTERVENTIONAL TRIALS
Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: Preliminary findings*

Jurgens Nortje, FRCA; Jonathan P. Coles, PhD; Ivan Timofeev, FRCS; Tim D. Fryer, PhD; Franklin I. Aigbirhio, PhD; Peter Smielewski, PhD; Joanne G. Outtrim, BSc; Doris A. Chatfield, BSc; John D. Pickard, FRCS (SN); Peter J. Hutchinson, PhD; Arun K. Gupta, PhD; David K. Menon, PhD

**IBV baseline: 126 ml**

**IBV hyperoxia: 36 ml**
Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: Preliminary findings*

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<table>
<thead>
<tr>
<th></th>
<th>( \text{Pao}_2 ), mm Hg [kPa]</th>
<th>( \text{Pbo}_2 ), mm Hg [kPa]</th>
<th>Lactate, mmol/L</th>
<th>Pyruvate, ( \mu \text{mol/L} )</th>
<th>L/P ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ( \text{FiO}_2 )</td>
<td>99 ± 23 [13.2 ± 3.0]</td>
<td>28 ± 21 [3.7 ± 2.8]</td>
<td>3.3 ± 2.1</td>
<td>95 ± 47</td>
<td>34.1 ± 9.5</td>
</tr>
<tr>
<td>Hyperoxia ( \text{FiO}_2 )</td>
<td>226 ± 68 [30.1 ± 9.0]</td>
<td>57 ± 47 [7.6 ± 6.2]</td>
<td>3.3 ± 2.4</td>
<td>98 ± 60</td>
<td>32.5 ± 9.0</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt;.001</td>
<td>.015</td>
<td>NS</td>
<td>NS</td>
<td>.018</td>
</tr>
</tbody>
</table>
Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury

Michael N. Diringer, M.D., F.C.C.M.,1 Venkatesh Aiyagari, M.B.B.S., D.M.,1 Allyson R. Zazulia, M.D.,1,2 Tom O. Videen, Ph.D.,1,2 and William J. Powers, M.D.1,3

<table>
<thead>
<tr>
<th>PET Variable</th>
<th>Baseline</th>
<th>Hyperoxia</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>39 ± 12</td>
<td>38 ± 10</td>
<td>0.374</td>
</tr>
<tr>
<td>CBV (ml/100 g)</td>
<td>3.2 ± 0.7</td>
<td>3.1 ± 0.8</td>
<td>0.173</td>
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<tr>
<td>CMRO₂ (ml/100 g/min)</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.8</td>
<td>0.839</td>
</tr>
<tr>
<td>OEF</td>
<td>0.39 ± 0.07</td>
<td>0.37 ± 0.04</td>
<td>0.658</td>
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</tbody>
</table>

Cerebral Hemodynamic Effects of Acute Hyperoxia and Hyperventilation after Severe Traumatic Brain Injury

Leonardo Rangel-Castilla,¹ Lucia Rivera Lara,² Shankar Gopinath,² Paul R. Swank,³ Alex Valadka,⁴ and Claudia Robertson²

Table 3. Physiological Variables During the Hyperoxia (HO) Test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (mean ± standard error)</th>
<th>HO (mean ± standard error)</th>
<th>p Value</th>
<th>HO test (baseline versus HO)</th>
<th>Exam time</th>
<th>Interaction (HO test×exam)</th>
<th>HO test for exams 1–5 versus 6–10⁸</th>
<th>HO test for exams 6–10 versus 11–15⁸</th>
<th>HO test for exams 1–5 versus 11–15⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial pressure (mm Hg)</td>
<td>19.6±0.5</td>
<td>18.0±0.4</td>
<td>&lt;0.0001</td>
<td>0.0472</td>
<td>3260</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92.7±0.8</td>
<td>93.4±0.6</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>2267</td>
<td></td>
<td>0.0004</td>
<td>0.2093</td>
<td>0.1491</td>
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<tr>
<td>Jugular venous O₂ saturation (%)</td>
<td>71.9±0.6</td>
<td>78.2±0.6</td>
<td>&lt;0.0001</td>
<td>0.1217</td>
<td>3423</td>
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<tr>
<td>Jugular venous Po₂ (mm Hg)</td>
<td>44±1</td>
<td>54±1</td>
<td>&lt;0.0001</td>
<td>0.5604</td>
<td>3940</td>
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<tr>
<td>Brain tissue Po₂ (mm Hg)</td>
<td>27.8±2.5</td>
<td>60.2±4.2</td>
<td>&lt;0.0001</td>
<td>0.2745</td>
<td>0.448</td>
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<tr>
<td>End-tidal CO₂ (mm Hg)</td>
<td>34.7±0.3</td>
<td>32.6±0.3</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>3748</td>
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<tr>
<td>Inspired O₂ fraction</td>
<td>41±12</td>
<td>99±10</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0323</td>
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<td>0.0001</td>
<td>0.8614</td>
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<tr>
<td>Arterial Po₂ (mm Hg)</td>
<td>151±3</td>
<td>401±7</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.2064</td>
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<tr>
<td>Arterial Pco₂ (mm Hg)</td>
<td>37.0±0.3</td>
<td>36.1±0.2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0845</td>
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<tr>
<td>Flow velocity (cm/sec): Left</td>
<td>74.5±1.5</td>
<td>71.8±1.4</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0845</td>
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<tr>
<td>Flow velocity (cm/sec): Right</td>
<td>72.3±1.3</td>
<td>69.6±1.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.4769</td>
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<tr>
<td>Autoregulatory index: Left</td>
<td>2.6±0.8</td>
<td>3.0±0.9</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>0.4745</td>
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<tr>
<td>Autoregulatory index: Right</td>
<td>2.6±0.8</td>
<td>3.1±1.0</td>
<td>&lt;0.0001</td>
<td>0.0015</td>
<td>2.615</td>
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<td></td>
<td>Baseline (n = 14)</td>
<td>Oxygen Challenge (n = 14)</td>
<td>Change</td>
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<td>End Value</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>89 (83–95)</td>
<td>94 (90–99)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (1–9)</td>
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<td>ICP (mm Hg)</td>
<td>12 (9–15)</td>
<td>10 (7–13)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−2 (−3–−1)</td>
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<tr>
<td>CPP (mm Hg)</td>
<td>77 (70–84)</td>
<td>84 (78–91)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (3–11)</td>
<td></td>
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<tr>
<td>P&lt;sub&gt;a&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>39 (37–40)</td>
<td>39 (37–41)</td>
<td>0 (−2–2)</td>
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<tr>
<td>P&lt;sub&gt;a&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>127 (103–150)</td>
<td>441 (363–518)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>314 (257–371)</td>
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<tr>
<td>P&lt;sub&gt;+&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; (mm Hg)</td>
<td>45 (40–49)</td>
<td>50 (42–58)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (1–10)</td>
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<tr>
<td>CBF (mL/100 gm/min)</td>
<td>23.9 (16.5–31.2)</td>
<td>18.5 (12.2–24.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−5.4 (−9.2–−1.5)</td>
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</table>
INCREASING FIO2 TO TREAT BRAIN HYPOXIA?
RETROSPECTIVE STUDIES
Increasing FiO₂ is frequent in the NICU

Fig. 2 Medical interventions for compromised PbtO₂ (use/response rate)
Normobaric Hyperoxia is Associated with Increased Cerebral Excitotoxicity After Severe Traumatic Brain Injury

Hervé Quintard · Camille Patet · Tamarah Suys · Pedro Marques-Vidal · Mauro Oddo

sTBI (36 pts)
sSAH (28 pts),
Early phase (0-48 hrs)

Lactate/Pyruvate ratio

Lactate, mmol/L

Glutamate, µmol/L

Normoxia

Hyperoxia

Carteron L, unpublished data
RETROSPECTIVE COHORT ANALYSES
Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis

Elisa Damiani¹, Erica Adrario¹, Massimo Girardis², Rocco Romano¹, Paolo Pelaia¹, Mervyn Singer³ and Abele Donati¹*

Association between hyperoxia and increased mortality after brain injury
Stroke

Figure 4 Forest plot showing individual and pooled odds ratios for mortality of studies on patients with stroke. Odds ratios >1 (right side of the plot) indicate an association between hyperoxia and higher mortality. Heterogeneity was $Q(1) = 0.04, P = 0.844, I^2 = 0$. The size of the boxes is inversely proportional to the size of the result study variance, so that more precise studies have larger boxes. ES, effect size; CI, confidence interval; W, weight; Sig., P value.
Cardiac arrest

Figure 3 Forest plot showing individual and pooled odds ratios for mortality of studies on patients resuscitated from cardiac arrest. Odds ratios >1 (right side of the plot) indicate an association between hyperoxia and higher mortality. Heterogeneity was $Q(4) = 12.4, P = 0.015$; $I^2 = 67.73$. The size of the boxes is inversely proportional to the size of the result study variance; more precise studies have larger boxes. ES, effect size; CI, confidence interval; W, weight; Sig., $P$ value.
Figure 5 Forest plot showing individual and pooled odds ratio for mortality of studies on patients with traumatic brain injury. Odds ratios >1 (right side of the plot) indicate an association between hyperoxia and higher mortality. Heterogeneity was $Q(4) = 11.28, P = 0.024$; $\hat{I}^2 = 64.54$. The size of the boxes is inversely proportional to the size of the result study variance; more precise studies have larger boxes. ES, effect size; CI, confidence interval; W, weight; Sig., P value.
A CRITICAL APPRAISAL OF CLINICAL DATA
**Significant heterogeneity between studies**
**Hyperoxia, definition**

- First $\text{PaO}_2$: 2
- Highest $\text{PaO}_2$: 1
- Mean $\text{PaO}_2$: 1
- Worst $\text{PaO}_2$: 1

**Hyperoxia, time of assessment**

- First 24 hours: 4
- Beyond the first 24 hours: 1

**$\text{PaO}_2$ cutoff**

- $<300 \text{ mmHg}$ (moderate hyperoxia): 3
- $\geq300 \text{ mmHg}$ (extreme hyperoxia): 2

**Comparator group**

- Not exposed to hyperoxia: 2
- Normoxia: 3
DOI 10.1007/s00134-014-3555-6

Jonathan Elmer
Michael Scutella
Raghevesh Pullalarevu
Bo Wang
Nishit Vaghasia
Stephen Trzeciak
Bedda L. Rosario-Rivera
Francis X. Guyette
Jon C. Rittenberger
Cameron Dezfulian

A

Fraction of inspired oxygen

0.0 0.5 1.0

0 5 10 15 20

Hours after return of spontaneous circulation

B

\( \text{PaO}_2 \) (mmHg)

0 100 200 300 400

0 5 10 15 20

Hours after return of spontaneous circulation

Severe hyperoxia

Moderate hyperoxia

Normoxia
<table>
<thead>
<tr>
<th>Oxygen exposure category</th>
<th>Overall</th>
<th></th>
<th>Survivors</th>
<th></th>
<th>Non-survivors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td></td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Severe hyperoxia</td>
<td>1.4 ± 2.2</td>
<td>0–12.5</td>
<td>0.93 ± 1.7</td>
<td></td>
<td>1.7 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Moderate or probable hyperoxia</td>
<td>9.5 ± 6.6</td>
<td>0–24</td>
<td>9.7 ± 6.9</td>
<td></td>
<td>9.4 ± 6.3</td>
<td></td>
</tr>
<tr>
<td>Normoxia</td>
<td>12.9 ± 6.9</td>
<td>0–24</td>
<td>13.3 ± 6.9</td>
<td></td>
<td>12.6 ± 6.9</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0.2 ± 0.7</td>
<td>0–5.0</td>
<td>0.1 ± 0.6</td>
<td></td>
<td>0.3 ± 0.9</td>
<td></td>
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</tbody>
</table>

Results are presented in hours

**Unadjusted model**

<table>
<thead>
<tr>
<th>Arterial oxygen (per h)</th>
<th>Overall</th>
<th>Survivors</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hyperoxia</td>
<td>0.84 (0.72–0.98)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Moderate or probable hyperoxia</td>
<td>1.01 (0.96–1.05)</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Normoxia</td>
<td>1.01 (0.97–1.06)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0.74 (0.47–1.16)</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

**Multivariable model**

| Severe hyperoxia (per hour) | 0.83 (0.69–0.99) | 0.04      |
HIGH FIO2 VS. PROTECTIVE VENTILATION?
Acute Lung Injury Is an Independent Risk Factor for Brain Hypoxia After Severe Traumatic Brain Injury

**FIGURE.** Histograms of mean (standard deviation) brain tissue oxygen tension (PbtO₂) values according to the PaO₂/FiO₂ ratio range. **P < .01** for comparisons with samples obtained at PaO₂/FiO₂ ratio >300.
Effect of PEEP on ICP
clinical studies

• TBI
  – Increasing PEEP from 5 to 15 cmH₂O did not change ICP significantly
    • Huynh T et al. *J Trauma* 2002
      – Pts with ICP <20 mm Hg
      – Pts with both ICP normal and >20 mm Hg

• SAH
  – Increasing PEEP from 5 to 20 cmH₂O did not increase ICP
  – May reduce MAP and CPP, especially if altered cerebral autoregulation
    • Muench E et al. *Crit Care Med* 2005

• Stroke
  – Increasing PEEP up to 12 cmH₂O did not change ICP significantly
  – May reduce MAP and CPP
    • Georgiadis D et al. *Stroke* 2001
HYPEROXIA VS. CONTROLLED OXYGENATION
Oximetry-Guided Reoxygenation Improves Neurological Outcome After Experimental Cardiac Arrest

Irina S. Balan, PhD; Gary Fiskum, PhD; Julie Hazelton, MS; Cynthia Cotto-Cumba, MD; Robert E. Rosenthal, MD

Uncertainties & Areas of future investigation

• Normobaric hyperoxia
  – Lack of high-quality (RCTs) studies
  – Duration
    • *Short*- (1-2 hrs) vs. *Long*-term (up to 12-24 hrs)
  – Intensity
    • FiO$_2$ dose
  – Specific conditions
    • Brain swelling, edema, elevated ICP ➔ beneficial ?
    • Brain ischemia ➔ harmful ?

• Hyperbaric oxygen therapy (HBO)
    • *Beneficial effects of HBO in TBI patients*
In summary

• In general, after acute brain injury
  – Avoid hyperoxia, high $\text{FiO}_2$ & $\text{PaO}_2$ levels
  – Prefer controlled oxygenation
    • correct hypoxia (-emia)
      ➢ Protective ventilation, PEEP

• In conditions of edema and elevated ICP
  – Short periods (1 hr) of hyperoxia may be beneficial (?)
    • Particularly if impaired compliance and autoregulation