Oxygen – a new look at an old therapy

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SWIM BETWEEN FLAGS
Conflict of Interest Statement

• Richard Beasley has received research funding from Fisher & Paykel Healthcare and is a member of the 2014 BTS Oxygen Guidelines Group.
Current dogma with oxygen therapy

- Routine administration of oxygen in breathless patients is useful, harmless and clinically indicated.
- Exposure to FIO$_2$ $\leq$60% is without adverse effects (except in COPD).
- It is important to keep patients well above the slippery slope of the OHDC.
- A patient at risk of developing hypoxaemia can be protected by administering high concentration oxygen.
Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality

J. Hope Kilgannon; Alan E. Jones; Nathan I. Shapiro; et al.

**Figure.** In-Hospital Death Between Hyperoxia and Normoxia

![Graph showing survival proportions over days with comparison between Hyperoxia and Normoxia.](image)

- **Survival Proportion**
  - **Hyperoxia**
  - **Normoxia**

- **Days**
  - Range from 0 to 28

- **Log-rank P<.001**

- **No. at risk**
  - **Normoxia**: 1171, 514, 236, 129, 83
  - **Hyperoxia**: 1156, 406, 211, 115, 70
Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest

J. Hope Kilgannon, MD; Alan E. Jones, MD; Joseph E. Parrillo, MD; R. Phillip Dellinger, MD; Barry Milcarek, PhD; Krystal Hunter, MBA; Nathan I. Shapiro, MD; Stephen Trzeciak, MD, MPH; on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators

[Circulation 2011]
Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis

Peter G Davis, Anton Tan, Calm P F O'Donnell, Andreas Schulze

Lancet 2004; 364: 1329–33
Figure: Pooled analyses
Relative risks assessed with fixed-effects model. *No events in either group.
Effect of oxygen on coronary blood flow

RCT oxygen therapy in myocardial infarction

High flow oxygen: ↑ AST, indicating greater myocardial damage

[Rawles & Kenmure, BMJ, 1976]
# RCT oxygen therapy in myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>High flow O$_2$</th>
<th>Room air</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality rate:</strong></td>
<td>11.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td><strong>Risk of mortality:</strong></td>
<td>2.9 (95% CI 0.81 to 10.3)</td>
<td>P=0.08</td>
</tr>
</tbody>
</table>

[Rawles & Kenmure, BMJ 1976]
Meta-analysis of three studies of O₂ therapy in MI

Odds ratio for mortality of high concentration oxygen compared with room air or titrated oxygen: 2.2 (95% CI 0.8 to 6.0)

[Ranchord et al AHJ 2012]
Oxygen in COPD

- High flow oxygen therapy commonly administered to patients with AECOPD, often despite previously documented hypercapnia.

- High flow oxygen therapy contributes to an increased length of admission, more frequent admission to HDU and use of NIPPV.
Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial

Michael A Austin, honorary associate,\(^1\) emergency medicine registrar,\(^2\) wilderness helicopter, intensive care paramedic,\(^3\) Karen E Wills, biostatistician,\(^1\) Leigh Blizzard, senior biostatistician,\(^1\) Eugene H Walters, professorial fellow,\(^1\) Richard Wood-Baker, honorary fellow,\(^1\) director\(^2\)
### Oxygen therapy and mortality

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Titrated</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>21/226</td>
<td>7/179</td>
<td>0.42 (0.20 to 0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(9%)</td>
<td>(4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed COPD</td>
<td>11/117</td>
<td>2/97</td>
<td>0.22 (0.05 to 0.91)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>(9%)</td>
<td>(2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Austin et al, BMJ 2010]
### Oxygen therapy and arterial blood gases

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Titrated</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.29</td>
<td>7.41</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>PaCO$_2$ (mmHg)</td>
<td>76.5</td>
<td>42.9</td>
<td>-33.6</td>
<td>0.02</td>
</tr>
<tr>
<td>PaO$_2$ (mmHg)</td>
<td>98.4</td>
<td>81.5</td>
<td>-16.9</td>
<td>0.46</td>
</tr>
</tbody>
</table>

[Austin et al BMJ 2010]
Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma

Kyle Perrin,¹,² Meme Wijesinghe,¹,² Bridget Healy,¹,² Kirsten Wadsworth,¹
Richard Bowditch,¹,² Susan Bibby,¹,² Tanya Baker,¹ Mark Weatherall,²,³
Richard Beasley¹,²,³

[Thorax 2011]
The proportion of patients with a predetermined rise in PtCO$_2$ from baseline at 60 minutes

<table>
<thead>
<tr>
<th></th>
<th>High concentration n (%)</th>
<th>Titrated n (%)</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in PtCO$_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 4$ mmHg</td>
<td>22 (44%)</td>
<td>10 (19%)</td>
<td>2.3 (1.2 to 4.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Change in PtCO$_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 8$ mmHg</td>
<td>11 (22%)</td>
<td>3 (6%)</td>
<td>3.9 (1.2 to 13.1)</td>
<td>0.016</td>
</tr>
</tbody>
</table>
All 10 patients with a final PtCO$_2 \geq$45 mmHg received high concentration oxygen; in 5 patients the increase in PtCO$_2 \geq$10 mmHg

[Perrin et al Thorax 2011]
Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia

Meme Wijesinghe¹,² • Kyle Perrin¹,² • Bridget Healy¹,² • Mark Weatherall²,³ • Richard Beasley¹,²

[JRSM 2012]
The proportion of patients with a predetermined rise in \( \text{PtCO}_2 \) from baseline at 60 minutes

<table>
<thead>
<tr>
<th>Change in ( \text{PtCO}_2 )</th>
<th>High concentration n (%)</th>
<th>Titrated n (%)</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 4 \text{ mmHg} )</td>
<td>36 (50%)</td>
<td>11 (14.7%)</td>
<td>3.4 (1.9 to 6.2)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>( \geq 8 \text{ mmHg} )</td>
<td>11 (15.3%)</td>
<td>2 (2.7%)</td>
<td>5.7 (1.3 to 25.0)</td>
<td>P= 0.007</td>
</tr>
</tbody>
</table>
The Effect of Supplemental Oxygen on Hypercapnia in Subjects With Obesity-Associated Hypoventilation

A Randomized, Crossover, Clinical Study

Meme Wijesinghe, MBBS; Mathew Williams, DipExSci; Kyle Perrin, PhD; Mark Weatherall, MBChB; and Richard Beasley, DSc
The test was terminated in 3/24 subjects when breathing 100% oxygen, due to a rise in PtCO$_2$ of ≥10mmHg which occurred after 10:35, 13:20 and 15:51 minutes.
Mixed linear model estimates of the differences 100% oxygen minus air adjusted for baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtCO₂ (mmHg)</td>
<td>5.0 (3.1 to 6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR (bpm)</td>
<td>-0.9 (-2.4 to 0.67)</td>
<td>0.25</td>
</tr>
<tr>
<td>MV (L/min)</td>
<td>-1.4 (-2.6 to -0.11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Vd/Vt</td>
<td>0.067 (0.035 to 0.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
High concentration oxygen has the potential to increase \( \text{PaCO}_2 \) in a wide range of conditions with V/Q mismatch and/or chronic respiratory failure.
Oxygen therapy and COPD

- About half of patients in titrated group had high concentration oxygen at some point in pre-hospital treatment.

- Entrenched culture

- Need to win ‘hearts and minds’

[ Austin et al BMJ 2010 ]
Why is it?

- Most clinicians will tolerate (or not notice) a 30% reduction in cardiac output
- Most clinicians will tolerate a 30% reduction in haemoglobin concentration
- Few clinicians would tolerate a 10% reduction in oxyhaemoglobin concentration (except in OSA)
The problem with an oxygen saturation of 85-90% is not that there is a life-threatening reduction in oxygen delivery, but that the condition may well be life-threatening:

::: The reduced oxygen saturation is a marker of severe disease
Physiologists’ OHDC

[Beasley et al Lancet 2006]
Clinicians’ OHDC

[Beasley et al Lancet 2006]
Intrapulmonary Shunt (%)

(a) $\text{FiO}_2 = 0.3$
(b) $\text{FiO}_2 = 0.6$

PaO$_2$ (mmHg)

Time (mins)
High concentration oxygen therapy delays recognition of clinical deterioration

:: Low concentration oxygen therapy allows deterioration to be detected earlier, and gives more time to intervene before life-threatening situation develops
Current dogma with oxygen therapy

- Routine administration of oxygen in breathless patients is useful, harmless and clinically indicated.
- Exposure to FIO$_2$ $\leq$ 60% is without adverse effects (except in COPD).
- It is important to keep patients well above the slippery slope of the OHDC.
- A patient at risk of developing hypoxaemia can be protected by administering high concentration oxygen.
TSANZ Oxygen Guidelines

To provide simple practical evidence-based recommendations for the acute use of oxygen in adults in clinical practice.
1. Oxygen should be considered as a drug, prescribed and administered for specific indications, with target SpO$_2$ range, and regular monitoring of response.

2. Oxygen is prescribed for the relief of hypoxaemia, not breathlessness.

3. Hypoxaemia is both a marker of risk of a poor outcome due to severity of underlying disease(s), and independent risk factor of poor outcome.
Basic concepts

4. There are risks associated with both hypoxaemia and hyperoxaemia, which underlie the importance of prescribing oxygen, only if required, to within a target SpO$_2$ range.

5. The ‘swimming between the flags’ concept of titrating oxygen therapy, to within a specific target SpO$_2$ range applies to a wide range of clinical situations, in addition to AECOPD.
Basic concepts

6. The variable accuracy of pulse oximetry in the estimation of $\text{SaO}_2$ represents the major limitation in its use to guide the titration of oxygen therapy.

7. The use of high concentration oxygen in a breathless patient to protect against hypoxaemia in the event of a subsequent deterioration has the potential to cause delay in recognising clinical deterioration and reduce the time available to initiate additional treatment.

8. If a patient who requires a high $\text{FiO}_2$ to maintain adequate $\text{SpO}_2$ deteriorates, there is limited opportunity to increase $\text{FiO}_2$ to avoid life threatening hypoxaemia.
Assessment (1)

Pulse oximetry should be available in all situations in which emergency oxygen is used. [Grade D]
Assessment: practice points

• There is variable accuracy of pulse oximetry to predict SaO$_2$ in acutely ill patients, with SpO$_2$ measurements both over and under estimating SaO$_2$, with wide limits of agreement.

• Clinicians need to be aware of the variable accuracy of SpO$_2$ in the utilization of pulse oximetry in clinical practice.

• An SpO$_2$ ≥92% effectively rules out hypoxaemia [PaO$_2$ <60mmHg or SaO$_2$ <90%]
Assessment (2)

Blood gas measurements should be undertaken in:

- Critically ill patients with cardiorespiratory or metabolic dysfunction
- In patients with an $\text{SpO}_2 < 92\%$
- Deteriorating $\text{SpO}_2$ requiring increased $\text{FiO}_2$
- Patients at risk of hypercapnia
- Breathless patients in whom reliable oximetry cannot be obtained

[Grade C]
Assessment practice points

1. Arterialised capillary blood gas measurement represents an alternative if unable to obtain ABG
   - Accurate information about PaCO$_2$ and pH
   - Underestimates PaO$_2$

2. Peripheral venous blood gas assessment of PCO$_2$ cannot be used as a substitute for ABG to estimate PaCO$_2$
A specific oxygen prescription should be documented in the patient records and the drug chart. [Grade D]
Prescription: practice points

Options:

• Prescribe delivery system, interface devices and the target $\text{SpO}_2$ range

• Prescribe target $\text{SpO}_2$ range
Administration

• In the presence of hypoxaemia in acute medical conditions, oxygen should be administered to achieve a target SpO₂ range of 92% to 96% [Grade D]

• Lower target of 88% to 92% in AECOPD [Grade A] and other conditions associated with chronic respiratory failure. [Grade D]
A general target SpO₂ range of 92-96% has been recommended, incorporating a lower range than that recommended in the BTS guidelines (94-98%). This lower target recognises that:

- No known risk of hypoxic tissue injury at SaO₂ 90%.
- Older healthy subjects have SaO₂ to this lower level of 90%.
- Healthy subjects have mean nadir SpO₂ of 90% in sleep.
- Subjects with sleep disordered breathing commonly tolerate SpO₂ between 80 and 90% for prolonged periods.
- Adults with comorbidities tolerate SpO₂ between 80 and 90% during long distance travel.
Evidence-base for titration of oxygen therapy to a target \(\text{SpO}_2\) range of 93 to 95\% in acute severe asthma, and community-acquired pneumonia.

There is an evidence-base for the safety of oxygen therapy to a target \(\text{SpO}_2\) range of 88 to 92\% in acute exacerbation of COPD.

In adults with coronary artery disease, anaerobic metabolism indicative of myocardial ischaemia in some patients \(\text{SaO}_2\) 70-85\% suggesting ‘safe’ lower limit of 85\%.

Guidelines for myocardial infarction and heart failure recommend administration of oxygen if \(\text{SpO}_2\) <93\% and <90\%, respectively.
SpO₂ target 92-96%

- This recommendation is likely to reduce excessive use of high concentration oxygen therapy.
- An upper level of 96% allows for patient improvement to be recognised earlier during monitoring, so that oxygen can be down-titrated.
A target SpO$_2$ range of 88-92% is recommended in the treatment of COPD and other conditions associated with chronic respiratory failure:

- >2-fold reduction in mortality with pre-hospital oxygen therapy titrated to this target, compared with high concentration oxygen therapy in patients with an AECOPD.

- An increase in PaCO$_2$ with 100% oxygen therapy in patients with chronic respiratory failure due to obesity hypoventilation syndrome.
In the absence of COPD or known chronic respiratory failure:

- $\text{SpO}_2 \geq 92\%$, oxygen therapy not routinely required.

- $\text{SpO}_2$ 85% to 91%, initially oxygen 2-4 L/min via nasal cannulae.

- $\text{SpO}_2 < 85\%$, oxygen 4 L/min via nasal prongs, 5-10 L/min via simple mask, 10-15 L/min reservoir mask or high flow nasal cannulae ($\text{FiO}_2 > 0.35$).
Administration: practice points

In COPD or conditions associated with respiratory failure:

- SpO$_2$ >88%, no oxygen therapy.
- SpO$_2$ <88%, 1-2 L/min nasal prongs or 2-4 L/min 24% or 28% Venturi mask.
Administration: practice points

• FiO$_2 \geq 40\%$ to maintain an adequate SpO$_2$, should receive senior clinician review and may require transfer to HDU.

• FiO$_2 \geq 50\%$ to maintain an adequate SpO$_2$, should receive ICU review and most will require ICU transfer.
Monitoring

SpO₂ recordings and accompanying delivery system and flow rate should be recorded on the patient’s monitoring chart. [Grade D]
Monitoring: practice point

Oxygen saturation should be considered the “fifth vital sign” incorporated within recognised physiological and “track and trigger systems”.
Monitoring

A reduction in $\text{SpO}_2 \geq 4\%$ within or outside the oxygen target range should lead to a further assessment of the patient.
Bronchodilator administration

In COPD the preferred method is air-driven nebuliser or MDI +/- spacer, with supplementary oxygen continued as required to maintain SpO$_2$ target. [Grade A]
Devices

For most patients nasal cannulae are the preferred method of oxygen delivery, with the flow rate varied to achieve the target $\text{SpO}_2$. [Grade C]
Potential advantages of nasal cannulae

- Wide range $\text{FiO}_2$
- Varying flows to achieve target $\text{SpO}_2$
- Oxygen can be prescribed to target $\text{SpO}_2$
- Less likely to be taken off
- No risk of $\text{CO}_2$ rebreathing
- Ability to co-administer bronchodilator
- Comfort, ease of use, low cost
Ventilatory support

- In patients with hypercapnic respiratory failure, pH <7.35 or PaCO$_2$ >45mmHg, non-invasive ventilation with BIPAP or invasive ventilation should be considered. [Grade A]

- COPD patients with a pH <7.26 managed with BiPAP require intensive monitoring with a low threshold for intubation. [Grade A]
Ventilatory support

• In patients who require high FiO$_2$ to maintain a target SpO$_2$ range, CPAP using a non-invasive mask-interface should be considered. Evidence is strongest in severe pulmonary oedema. [Grade A]

• Patients receiving ventilatory support should be located in a ward area with appropriate numbers of staff able to provide monitoring and titration of therapy, such as an HDU or ICU. [Grade D]
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