Hypoxic Drive in Chronic Obstructive Lung Disease: is the Fear of Oxygen Therapy Based on Fact or Myth

presented by

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Oxygen Phobia and COPD

One of the most pervasive myths surrounding the treatment of patients with COPD is their dependence on hypoxic drive. Healthcare providers often hesitate to administer adequate oxygen therapy, fearing that patients will stop breathing. Despite evidence published more than 20 years ago that contradicts the hypoxic drive theory, this greatly overstated medical myth permeates the core of beliefs and practice of many healthcare providers.
One of the most pervasive myths surrounding the treatment of patients with COPD is their dependence on hypoxic drive. Healthcare providers often hesitate to administer adequate oxygen therapy, fearing that patients will stop breathing. Despite evidence published more than 20 years ago that contradicts the hypoxic drive theory, this greatly overstated medical myth permeates the core of beliefs and practice of many healthcare providers.

**FACT:**

Oxygen therapy is often withheld from COPD patients with severe hypoxemia because of the pervasive belief in the hypoxic drive theory.
Origins of the Hypoxic Drive Theory

Barach AL, Woodwell M,
Studies in oxygen therapy III in an extreme type of shallow breathing.
Archives of Internal Medicine 1921.

The hazards of administering high oxygen concentrations to patients with acute respiratory insufficiency was originally reported in cases of fatal respiratory acidosis with abrupt retention of CO2, marked decease in pH, and swift onset of coma, observed in two patients with shallow breathing.

“The body mechanism was manifestly incapable of marshalling its adaptive forces quickly enough and the fatal outcome was not reversed by intravenous injection of sodium bicarbonate”.
Origins of the Hypoxic Drive Myth
(John Murray 2006)

• Simple and rational explanation for a real and potentially fatal clinical phenomenon.

• Gained wide spread acceptance before the science and methodology to prove or disprove the theory was completed.

• Established before pulse oximetry, ABGs, and non-invasive ventilation were readily available in the clinical setting.
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**FACT:**
Oxygen administration can induce CO$_2$ retention, coma, and death in patients with COPD.
Causes of Oxygen Induced CO₂ Retention

• Elimination of Hypoxic Drive

• Worsening of Ventilation to Perfusion Matching Secondary to Reversal of Hypoxic Pulmonary Vasoconstriction

• Haldane Effect
In COPD patients with acute exacerbation, a fine line may exist between optimal and excessive oxygen therapy.
FACT:

In healthy human subjects hypoxia increases respiratory drive when PaO2 < 60 mm Hg.

“Hypoxic Threshold” tachycardia, myocardial ischemia, HPV, ↑PAP, PVR, RV dysfunction, mental status changes, tachypnea, dyspnea

VE (L/min)

PO2 (mmHg)

PCO2 = 40 mmHg

http://www.medicine.mcgill.ca/physio/resp-web/Figures/Fig122.jpg
FACT:

In healthy human subjects, hypoxia increases respiratory drive when PaO2 < 60 mm Hg. Hypercapnia accentuates ventilatory response to hypoxia, minute ventilation can increase to 40 – 60 L/min.

“Hypoxic Threshold”
tachycardia,
myocardial ischemia,
HPV,↑PAP,PVR,
RV dysfunction,
mental status changes,
tachypnea, dyspnea

http://www.medicine.mcgill.ca/physio/resp-web/Figures/Fig122.jpg
Normal Response to Hyperoxia

• In healthy subjects brief exposure to 100% oxygen causes an immediate and transient decrease in ventilation.
• After prolonged exposure lasting more than 5 minutes hyperventilation is often observed.
• Response is attributed to inhibited carotid body chemoreflex followed by stimulation of central chemoreceptors secondary to reduction of cerebral blood flow and by the Haldane effect.
Effect of Oxygen Breathing on Ventilation-Perfusion Matching and Dead Space Fraction

ROOM AIR

HYPOXIC PULMONARY VASOCONSTRICTION
Effect of Oxygen Breathing on Ventilation-Perfusion Matching and Dead Space Fraction

**ROOM AIR**

HYPOXIC PULMONARY VASOCONSTRICTION

**100% OXYGEN**

REDUCED PERFUSION AND WORSENED VENTILATION - PERfusion MATCHING

RELEASE OF HPV CAUSES A REDISTRIBUTION OF PULMONARY BLOOD FLOW

INCREASED DEAD SPACE FRACTION
Hypoxic Pulmonary Vasoconstriction
Determined by Local Oxygen Tension Stimulus ($P_{SO_2}$)

Normal $PaCO_2$ on Room Air
$P_{SO_2} \sim 80$ mm Hg

- $PAO_2 \ (156 - 40) \ 0.6 = 64$
- $PvO_2 \ (40) \ 0.4 = 16$

During Hypercapnia on Room Air
$P_{SO_2} \sim 50$ mm Hg

- $PAO_2 \ (156 - 83) \ 0.6 = 44$
- $PvO_2 \ (40) \ 0.4 = 16$

Marshall et al. JAP. 1983
HALDANE EFFECT

• Carbon Dioxide Transport:
  - bound to hemoglobin and other proteins
  - dissolved in blood
  - converted to bicarbonate

• Increasing PO$_2$ tension decreases the affinity of hemoglobin for CO$_2$.
  - in the lungs high PO$_2$ promotes CO$_2$ unloading.
  - in the periphery low PO$_2$ promotes CO$_2$ loading.

• During hyperoxia more O$_2$ binds to hemoglobin releasing CO$_2$ into blood.

• Desaturated hemoglobin carries more CO$_2$ and will cause a greater release of CO$_2$ during hyperoxia.
HALDANE EFFECT

- Potential rise in PCO2 when deoxygenated hemoglobin is rapidly oxygenated and CO2 is released.
HALDANE EFFECT

- Potential rise in PCO2 when deoxygenated hemoglobin is rapidly oxygenated and CO2 is released.

\[ \text{Volume \% CO}_2 \]

\[ PCO_2 \text{ mm Hg} \]

\[ 6.7 \text{ mm Hg} \]

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HALDANE EFFECT

- Potential rise in PCO2 when deoxygenated hemoglobin is rapidly oxygenated and CO2 is released.
HALDANE EFFECT

• Potential rise in PCO2 when deoxygenated hemoglobin is rapidly oxygenated and CO2 is released.

• Avoid administering 100% oxygen in a severely hypoxic and hypercarbic COPD patient.
\[ \text{PaCO}_2 \text{ determined by the relationship between CO}_2 \text{ production, minute ventilation, and dead space.} \]

\[
\text{PaCO}_2 = \frac{\dot{V}_{\text{CO}_2} \cdot K}{\dot{V}_E (1 - \frac{V_D}{V_T})}
\]
\[ \text{PaCO}_2 = \frac{\dot{V}_{\text{CO}_2} \cdot K}{\dot{V}_E (1 - \frac{V_D}{V_T})} \]
\[ \uparrow \text{PaCO}_2 = \uparrow \cdot \text{VCO}_2 \cdot K \cdot \dot{V}_E (1 - \frac{V_D}{V_T}) \]
\[ \uparrow \text{PaCO}_2 = \frac{V\text{CO}_2 \cdot K}{V_E (1 - \uparrow V_D/V_T)} \]
Carbon Dioxide Narcosis

Review of 25 cases of patients with CO₂ retention on variable levels of controlled oxygen therapy through the course of treatment.

Seeker, Hickam. Medicine 1952

- Variable susceptibility to CO₂ narcosis.
- PaCO₂ 80 – 90 mm Hg is generally associated with a decreased level of consciousness and respiratory depression.
- PaCO₂ > 130 mm Hg is associated with severe respiratory depression, coma, and death.
Evidence Against the Hypoxic Drive Explanation for Oxygen Induced CO$_2$ Retention
Aubier, Murciano, Fournier, Milic-Emili, Pariente, Derenne.
Central respiratory drive in acute respiratory failure of patients with COPD.
Am Rev Respir Dis. 1980

• Acutely ill COPD patients develop a rapid shallow breathing pattern

• Mouth occlusion pressure (P0.1), and index of neuromuscular respiratory drive was 5 times greater than in normal subjects.

• Administration of oxygen at 5 L/min caused a small decrease in minute ventilation that was associated with a decrease in P0.1 that was still 3 times greater than that of normal subjects.

• In the acute state the increase in PaCO2 observed after oxygen administration did not correlate with the decrease in minute ventilation.

Changes in PaCO2 were mainly due to increased inhomogeneity of alveolar ventilation and perfusion in the lungs and did not correlate with change in minute ventilation.

<table>
<thead>
<tr>
<th></th>
<th>PaO2 (mmHg)</th>
<th>PaCO2 (mmHg)</th>
<th>pH</th>
<th>VE (L/min)</th>
<th>f (cpm)</th>
<th>VT (ml)</th>
<th>VD/VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>38 ± 2</td>
<td>65 ± 3</td>
<td>7.34 ± 0.01</td>
<td>10.2 ± 0.5</td>
<td>32 ± 2</td>
<td>341 ± 26</td>
<td>77 ± 2</td>
</tr>
<tr>
<td>O2</td>
<td>225 ± 23</td>
<td>88 ± 5</td>
<td>7.25 ± 0.02</td>
<td>9.5 ± 0.7</td>
<td>31 ± 2</td>
<td>323 ± 21</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>Air versus O2 breathing</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.01</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Decrease in VE from carotid body reflex

\[ r = -0.21 \]
Eleven patients with moderate to severe COPD. Predicted hypoxic and hypercapnic ventilatory response for each patient did not differ from observed change in $V_E$. No correlation in $\Delta V_E$ to $\Delta PaCO_2$. $\Delta PaCO_2$ attributed to alterations in VQ matching and $V_d/V_T$. 

![Ventilatory Response and Change in PaCO2 After Breathing 100% Oxygen](image)

![Graphs showing VE, PaCO2, and SbO2 over time](image)

Measured PaCO2, VCO2, VE, and VD/VT in 17 patients with COPD. Results show that the changes in VD/VT accounted for 80% of the change in PaCO2. Concluded that hyperoxic-induced hypercapnia is primarily due to impairment in gas exchange rather than to depression of ventilation. A reduced FEV1 appears to be a significant risk factor.

\[ \text{PaCO}_2 = \frac{\text{VCO}_2 \cdot K}{\text{VE} \cdot (1 - \frac{\text{VD}}{\text{VT}})} \]
Robinson, Freiberg, Regnis, Young.  
The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease.  
Am J Respir Crit Care Med. 2000

- 22 patients studied during acute exacerbation of COPD  
- Classified as retainers and non-retainers of CO2 when breathing 100% oxygen (increase in PaCO2 by > 3 mm Hg)  
- Significant reduction in $V_E$ in retainers but $V_E$ remained unchanged in non-retainers (in support hypoxic drive theory)  
- Both groups had a significant increase in ventilation to perfusion inequality
Patients with the lowest baseline PaO$_2$ and the highest baseline PaCO$_2$ had the greatest change in PaCO$_2$ when breathing 100% oxygen.

Suggesting that severity of hypoxia and hypercarbia may be predictors of oxygen induced CO$_2$ retention.
Maintenance of Hypoxia Does Not Prevent Acute CO₂ Retention

Review of 25 cases of patients with CO₂ retention on variable levels of controlled oxygen therapy through their course of treatment.

Seeker, Hickam. Medicine 1952
Hypersensitivity to Oxygen and CO₂ Retention Fluctuates with the Severity of Illness
Response to 24 – 28 % oxygen during acute infective episode was very different from response when in remission.
Following a period of mechanical ventilation with an FIO$_2$ sufficient to maintain a normal PaO$_2$, a further increase in FIO$_2$ did not result in an increased PaCO$_2$ in this group of 12 chronic CO$_2$ retaining COPD patients on PSV.

Results suggest that any prior hypoxic pulmonary vasoconstriction had been reversed and a new ventilation perfusion relationship was established that eliminated the hypersensitivity to oxygen.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline FIO$_2$</th>
<th>FIO$_2$ of 0.7</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT (mL)</td>
<td>389 ± 102</td>
<td>383 ± 101</td>
<td>&gt; .4</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>24.0 ± 6.2</td>
<td>24.4 ± 7.2</td>
<td>&gt; .6</td>
</tr>
<tr>
<td>V̇E (L/min)</td>
<td>8.7 ± 1.5</td>
<td>9.0 ± 2.2</td>
<td>&gt; .5</td>
</tr>
<tr>
<td>Deadspace (%)</td>
<td>73 ± 7</td>
<td>72 ± 7</td>
<td>&gt; .7</td>
</tr>
<tr>
<td>P$_{0.1}$ (cm H$_2$O)</td>
<td>1.1 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.04</td>
<td>7.38 ± 0.05</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>Paco$_2$ (torr)</td>
<td>56.4 ± 6.2</td>
<td>56.7 ± 7.8</td>
<td>&gt; .7</td>
</tr>
<tr>
<td>PaO$_2$ (torr)</td>
<td>85.1 ± 17.6</td>
<td>226.8 ± 67.5</td>
<td>.0001</td>
</tr>
</tbody>
</table>
Hypersensitivity to Oxygen may occur in Asthmatics and Patients with Neuro Muscular Disease and Diaphragm Dysfunction

Adding Fuel to the Fire
Increase in PaCO2 in patients with and without pre-existing CO2 retention attributed to the physiologic manifestation of the Haldane effect and worsening gas exchange. Greatest effect seen in subjects with the most severe airway obstruction.
Severe hypercapnia after low-flow oxygen therapy in patients with neuromuscular disease and diaphragmatic dysfunction.

Low-flow oxygen therapy (0.5 – 2 L/min) was associated with a mean increase in PaCO2 28.2 ± 23.3. Although time between ABG measurements ranged from hours to several days the authors found no other explanation for the worsening CO2 retention.

(editorial comment by Tobin supporting hypoxic drive effect)
In patients with severe respiratory failure, 90% are at risk for worsened CO₂ retention and decrease in level of consciousness when uncontrolled oxygen is administered.

FIG. 2. Severity of respiratory failure represented on a carbon dioxide:oxygen diagram. The complete data of McNeill and Campbell (1). Each patient represented by one point.

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical state and P₉₂ either improve or do not change</td>
<td>10</td>
</tr>
<tr>
<td>2. Patient becomes or remains drowsy but can be roused and made to expectorate; the P₉₂ slowly rises in about 12 hours by up to 20 mm. and then stabilizes</td>
<td>60</td>
</tr>
<tr>
<td>3. Patient rapidly becomes unconscious, cough becomes ineffective, and the P₉₂ rises at a rate of 30 mm. or more per hour</td>
<td>30</td>
</tr>
</tbody>
</table>

* Experience of Campbell and McNicoll (unpublished data).

- 24 patients with severe airflow obstruction (FEV$_1$ 37% pred)
- Received 24 – 40 % oxygen by venturi mask
- 3 patients had clinically significant rise in PaCO2 (8 – 26 mm Hg)
- Patients who had the greatest rise in PaCO2 with oxygen therapy were generally more severely hypercapnic
- Conclusion: a small risk of aggravating hypercapnia with controlled oxygen supplementation (13 %).
In a small percentage of COPD patients with acute exacerbation, a relatively fine line exists between optimal and excessive oxygen therapy.
Patients with COPD in acute respiratory failure are often already breathing at or near their maximum sustainable minute ventilation.

Gilbert et al. Amer J Medicine 1965

- Due to lung hyperinflation the inspiratory muscles operate at a marked mechanical disadvantage.
- Airway obstruction alters the mechanical resistive load and further increases the work of breathing.
- A rapid shallow breathing pattern develops as a means to maintain a sustainable level of work that will prevent respiratory muscle fatigue.
- Due to this inefficient breathing pattern, patients are unable to increase minute ventilation without excessive dead space ventilation or without an excessive increase in CO₂ production.
- Thus, chronic hypercapnia in patients with COPD is not due to hypoventilation but to ineffective ventilation.
WON’T BREATHE MORE

VS

CAN’T BREATHE MORE

Breathing oxygen makes ventilation even more inefficient by altering the ventilation-perfusion relationship in the lungs.
Risk Factors Associated with Oxygen Induced Hypercapnia

• Severe Airway Obstruction
• Severe Hypoxemia Breathing Room Air
• Chronic Hypercapnia and Acute Acidosis
• Signs of Respiratory Muscle Fatigue (asynchronous abdominal displacement)
Dilemma of Oxygen Therapy in COPD patients

The patients with the greatest need for oxygen are those with the greatest risk for oxygen induced hypercapnia.
A PARADIGM SHIFT IS NECESSARY

A fundamental change in approach or assumptions; acceptance by a majority of a changed belief, attitude, or way of doing things.

THE PROBLEM IS

Oxygen Induced Hypercapnia

NOT

Hypoxic Drive

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Oxygen is a Drug.

Oxygen Induced Hypercapnia is a Drug Hypersensitivity and a Potential Adverse Effect.

- The dose of oxygen should be titrated to clinical effect.
- The dose response to oxygen is measured by SpO2, changes in level of consciousness, and blood gases.
- Titrate the dose of oxygen not withhold treatment.
Brief periods of hyperoxia in patients with COPD is safe.

- Bolus dose followed by dose titration to SpO2 > 92% (above hypoxic threshold).
- Close observation for changes in mental status
- Use of non-invasive CO₂ monitoring
- Early use and development of improved methods of non-invasive ventilation
RCPs must play a major role in reversing decades of teaching the fear of oxygen therapy.

HealthCare providers need a clear understanding of the risk factors associated with oxygen induced hypercapnia.

This knowledge needs to be applied in clinical practice to select patients identified to be at risk for oxygen induced hypercapnia instead of withholding treatment to all patients with the diagnosis of COPD.