

History of Oxygen: From Discovery to Clinical Applications

CAPS 422

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Presentation Outline

- Discovery of oxygen and first uses
- Long Term Oxygen Therapy (LTOT)
- NOTT + MRC Trial
- Limitations of LTOT Knowledge

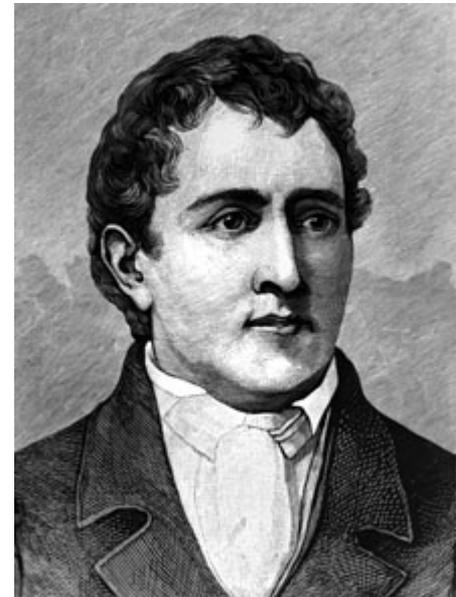
Discovery and Isolation of Oxygen

- Discovery of oxygen has been credited to three major scientists
 - Carl Wilhelm Scheele
 - Joseph Priestley
 - Antoine Lavoisier

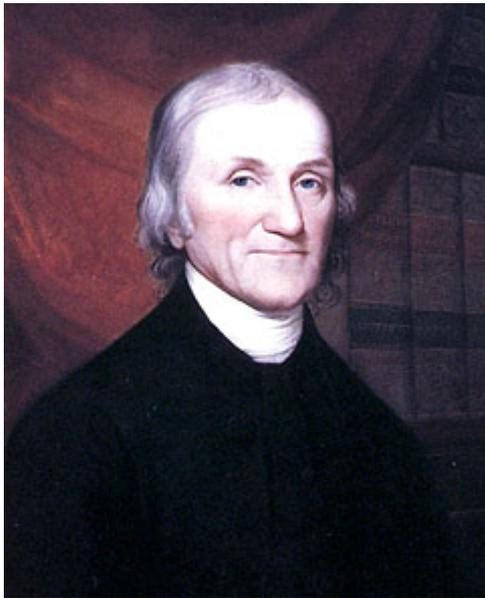
- Interestingly, these three all met with unfortunate circumstances near the end of life

Scheele was the first scientist to discover oxygen

- In 1771, Scheele generated oxygen by heating mercuric oxide, silver carbonate, and other nitrate salts
- Upon observing that the gas generated would burn, he termed the gas “fire air”
- Died prematurely from mercury poisoning

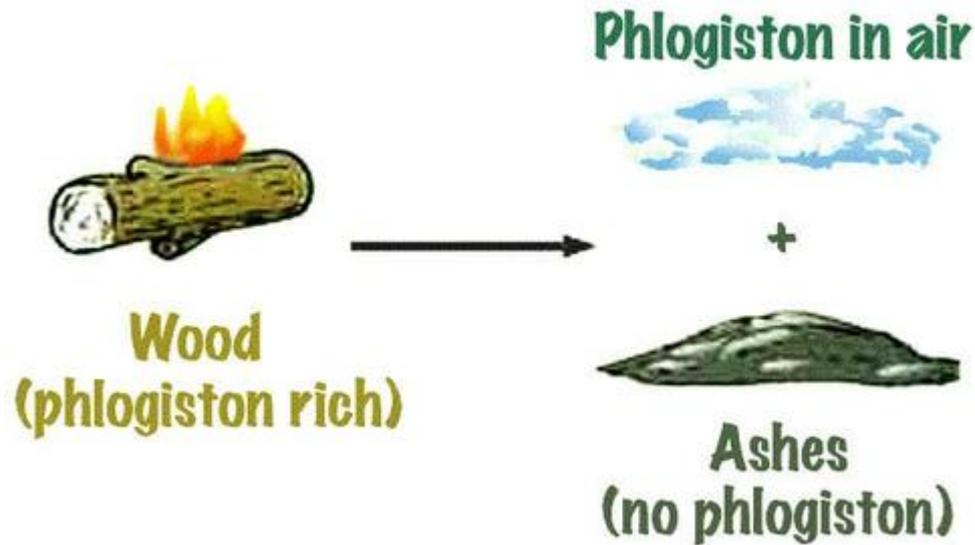


Priestley was first to publish his discovery of oxygen



- Priestley generated oxygen by heating mercuric oxide and published his results in 1774 (Scheele couldn't publish until 1777)
- Surprised to observe that a mouse placed in a chamber of this gas did not suffocate
- Argued against atomic theory, so his house and church were burned down by an angry mob

Phlogiston theory



Phlogiston rich materials were combustible because they could release phlogiston as it burned

Antoine Lavoisier advanced scientific knowledge of the properties of oxygen

- Named the gas oxygen (oxys- “sharp”, gen- “begetter”)
- By observing that an oxidized metal (eg. rusted iron) weighed more than the initial metal, he hypothesized oxygen’s role in the chemical reaction
- Demonstrated role of oxygen in respiration in the “slow combustion” of metabolic substrates in the body
- Sent to the guillotine during the French revolution because his lab was supported by royal funds



Discovery of the importance of oxygen in respiration led to development of oxygen therapies

- Clinicians quickly recognized the value of using oxygen to treat patients with respiratory conditions
- However, progress was slow due to clinician concerns of oxygen toxicity
 - Formation of reactive oxygen species (ROS)
 - Highlighted the importance of giving the correct dose of oxygen
- Concerns about hypercapnia due to decreased ventilatory response

Early evidence of O₂ benefits in chronic lung disease

- 1966 - Veterans Administration cooperative study
- Survival benefit of O₂ in COPD patients

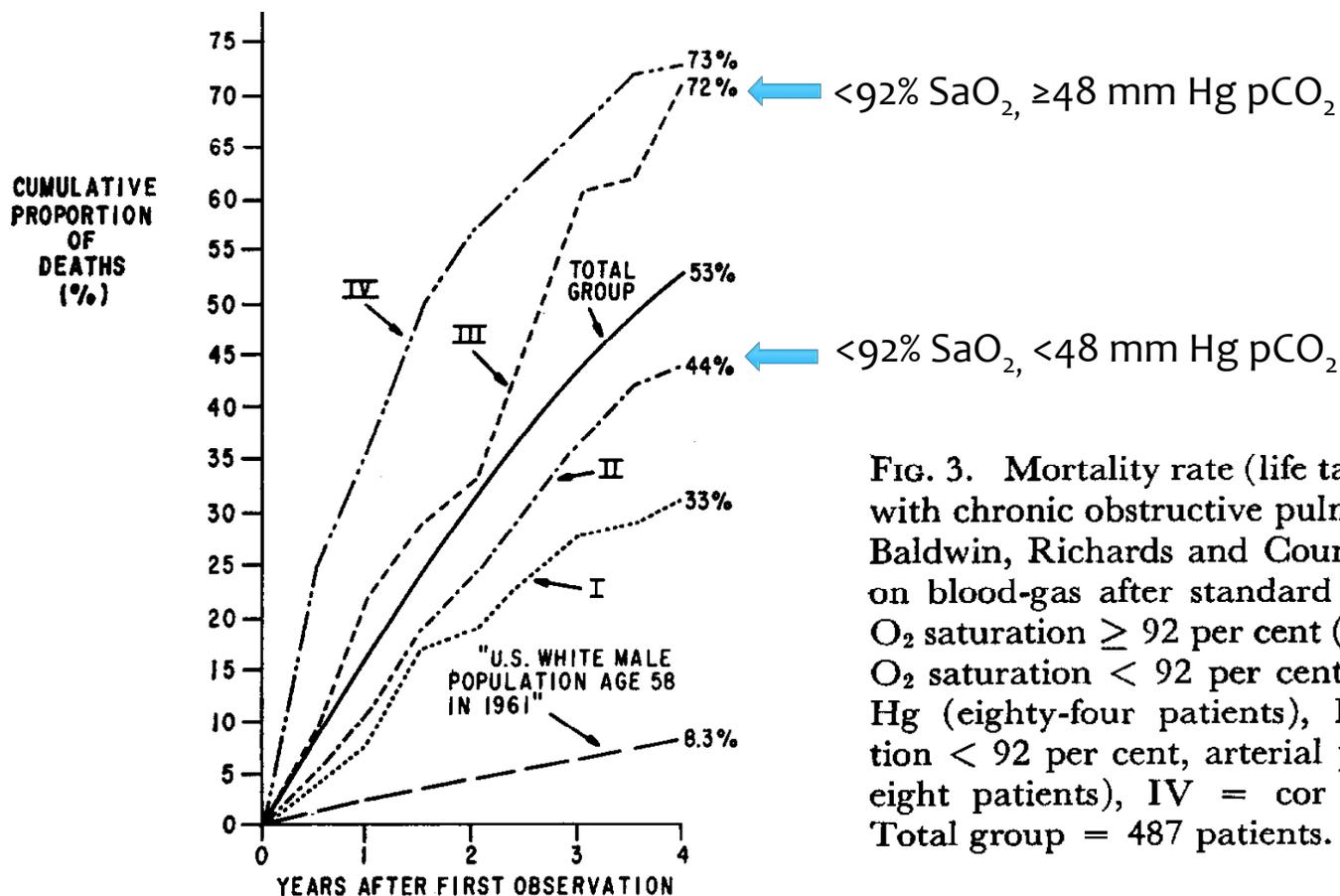


FIG. 3. Mortality rate (life table method) of 487 patients with chronic obstructive pulmonary disease according to Baldwin, Richards and Cournand [16] categories based on blood-gas after standard exercise test: I = arterial O₂ saturation ≥ 92 per cent (112 patients), II = arterial O₂ saturation < 92 per cent, arterial pCO₂ < 48 mm. Hg (eighty-four patients), III = arterial O₂ saturation < 92 per cent, arterial pCO₂ ≥ 48 mm. Hg (fifty-eight patients), IV = cor pulmonale (103 patients). Total group = 487 patients.

First Long Term O₂ Therapy (LTOT) clinical trials

➤ 1967 – 70 – Dr. Thomas Petty

Long term continuous O₂ administration to advanced COPD patients

➤ Portable Liquid Oxygen Transfilling system

➤ ↓ hypertension, polycythemia, ↑ survival in patients with cor pulmonale & heart disease

➤ Subjective improvements

➤ Exercise capacity

➤ Global sense of well being

➤ Ability to engage in daily activities

➤ Rare occurrence of hypercapnia
O₂ treated patients



Figure 3. Size of a patient's hospital record before and after oxygen, during an equal 18-month period.

Investigation of personal side benefits of O₂

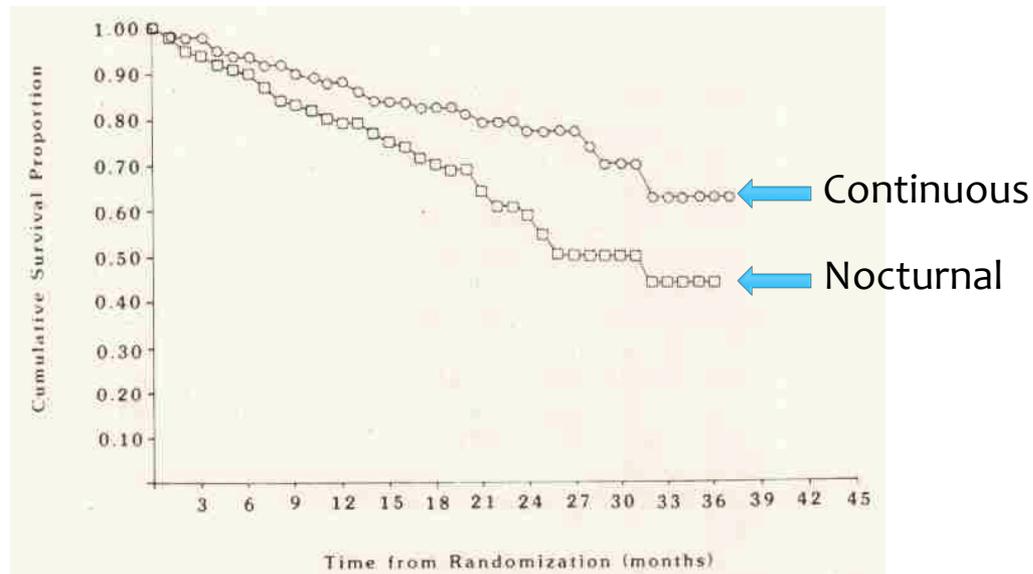
➤ Dr. Thomas Petty – Adventures of an Oxyphile

“How easy it was to walk at 12,000 feet, [...] having climbed these same mountains many times before with much more shortness of breath and effort than I experienced with the oxygen”



O₂ therapy duration to improve clinical outcomes

- **1980** Multicenter trials of LTOT with COPD patients
Nocturnal Oxygen Therapy Trial
- Nocturnal (12 h) vs. continuous O₂ (24 h)



- Continuous O₂ ↓ hypertension, polycythemia

O₂ therapy duration to improve clinical outcomes

➤ 1981 Multicenter trials of LTOT with COPD patients

UK MRC oxygen trial

- No supplemental O₂ vs. 15 h O₂
- Improved survival in 15 h O₂ group

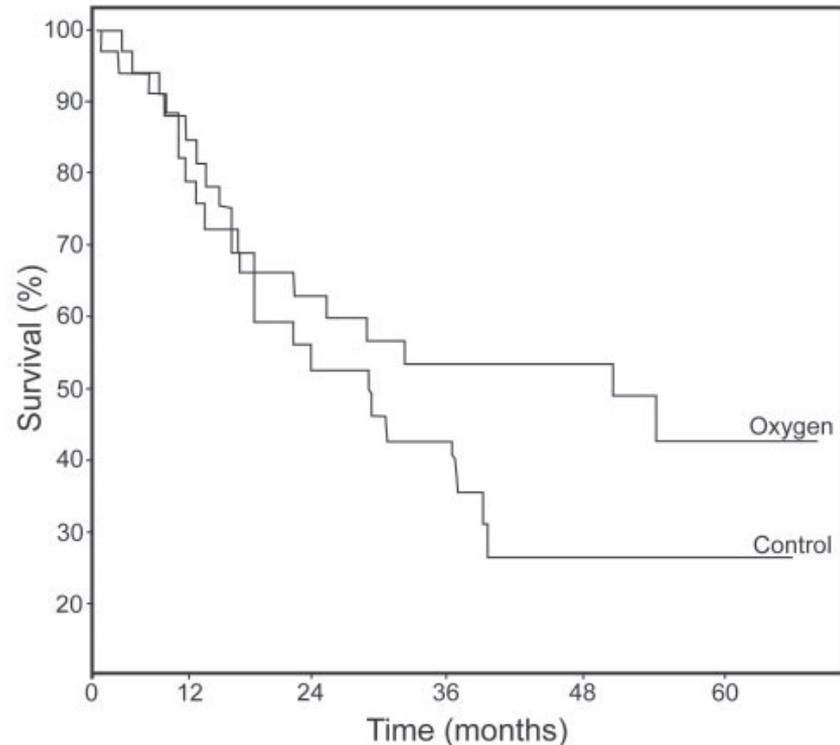
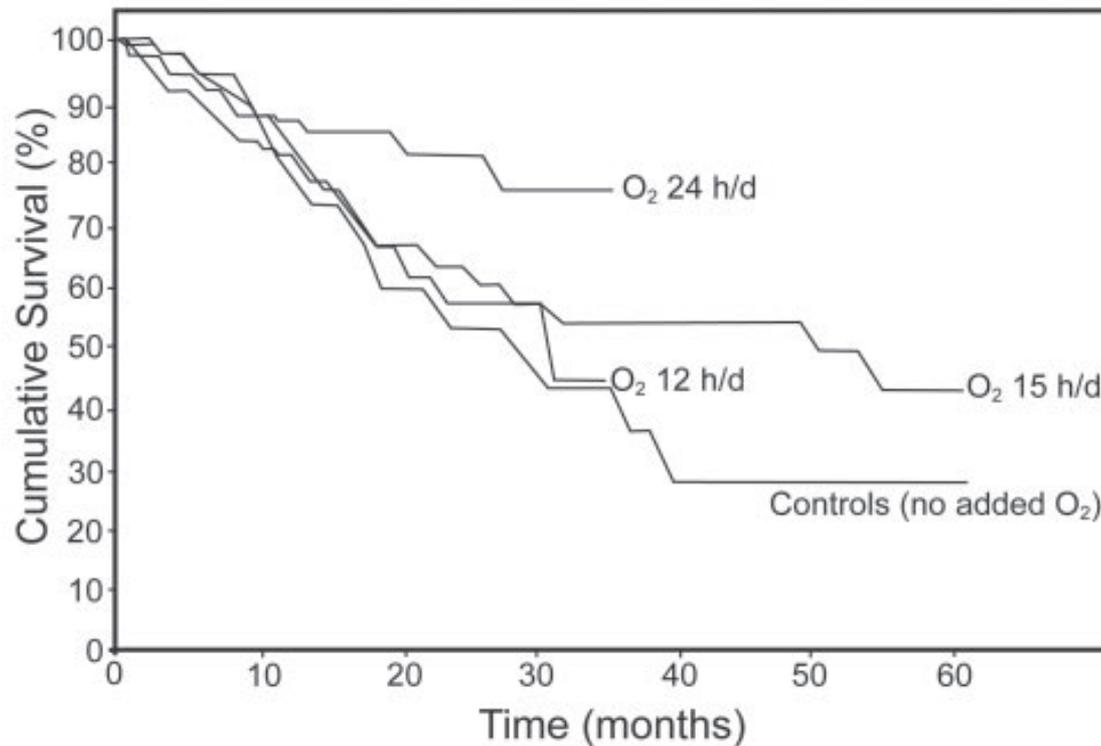


Fig. 3. Mortality in male patients enrolled in the Medical Research Council oxygen trial. (From Reference 25, with permission.)

NOTT & MRC set the scientific basis for current LTOT

➤ Collective NOTT and MRC dose response



➤ LTOT recognized as a therapeutic intervention to improve survival of COPD patients

Shortcomings of NOTT and MRC trials

- Not entirely comparable because MRC trial patients:
 - Were still allowed to smoke
 - Initially had higher resting hypercapnia and pulmonary hypertension
 - Did not show improvements in pulmonary vascular resistance and hematocrit (whereas NOTT patients did)
- Our understanding of LTOT comes from the NOTT and MRC trials and a few other randomized trials
 - Is LTOT really worth the time and money?

Limitations of LTOT Knowledge

- Pulmonary hypertension in severe COPD
- Moderate hypoxemia
- Nocturnal oxygen desaturation
- Health-related quality of life

The benefits of LTOT for pulmonary hypertension in severe COPD patients is controversial

- > 20% of patients with severe COPD have pulmonary hypertension
- Weitzenblum et al (1985).: With 15-18 hr/day LTOT, pulmonary arterial pressure decreased 4 mmHg on average between onset of LTOT and 31 +/- 19 months post-onset
 - Shortcomings of experimental methods
- Zieliński et al (1998).: With 14-15 hr/day LTOT, pulmonary arterial pressure decreased 2 mmHg on average between onset of LTOT and 2 years post-onset.
 - Pressure returned to baseline 6 years post-onset

LTOT does not appear to yield survival benefits for COPD patients with hypoxemia

- Górecka et al. (1997): No significant difference in survival rate of moderately hypoxemic COPD patients between LTOT (13.5 +/- 4.4 hr/day) and control groups

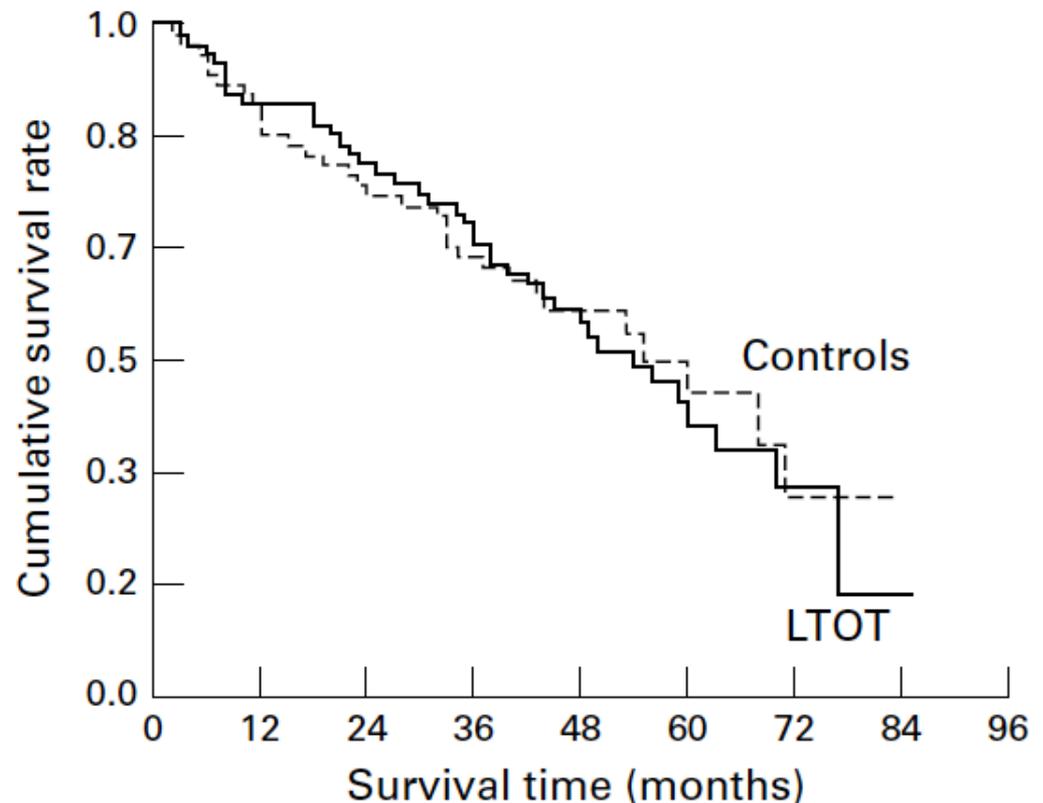


Figure 1 Cumulative survival rate in LTOT group and controls. Difference between groups is not statistically significant ($p = 0.892$).

Knowledge of whether LTOT alleviates nocturnal oxygen desaturation is limited

- COPD patients can experience nocturnal oxygen desaturation, even if oxygen saturation is normal when awake
- Limited and contradictory data on improving:
 - Sleep quality
 - Hemodynamic effects
 - Mortality
- No accepted definition of O_2 threshold and duration to categorize nocturnal desaturation

LTOT does not appear to improve health-related quality of life in COPD patients

- Few LTOT studies collect results on health-related quality of life (HRQOL)
- HRQOL trials have low internal validity
- Potential consequences:
 - Lack of mobility
 - Stress (due to finances, uncertainty of treatment benefit, ...)
 - Perceived social stigma
- Okubadejo et al. (1996): No improvements in HRQOL in COPD patients after 6 months of LTOT

Summary

- The discovery of the role of oxygen in respiration led to the development of oxygen therapies
- Early studies on COPD progression displayed evidence of oxygen benefits for survival
- NOTT and MRC were two major multicentre trials that set the scientific basis for modern LTOT
- The limitations of LTOT raise doubt about whether it is an effective therapeutic treatment, especially for COPD patients

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