Supplemental Oxygen Why and When?

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What impacts survival in COPD patients?

There are four interventions that likely prolong the survival of patients with serious COPD.

1. Pneumococcal and influenza vaccinations reduce mortality (1,2).
2. Intensive management of those hospitalized for acute exacerbations of COPD. In particular, noninvasive positive-pressure ventilation in those with respiratory failure (3).
3. Lung volume reduction surgery improves survival in selected patients with severe emphysema (4).
4. Long-term oxygen treatment (LTOT) significantly reduces mortality in patients with COPD and severe resting arterial hypoxemia.

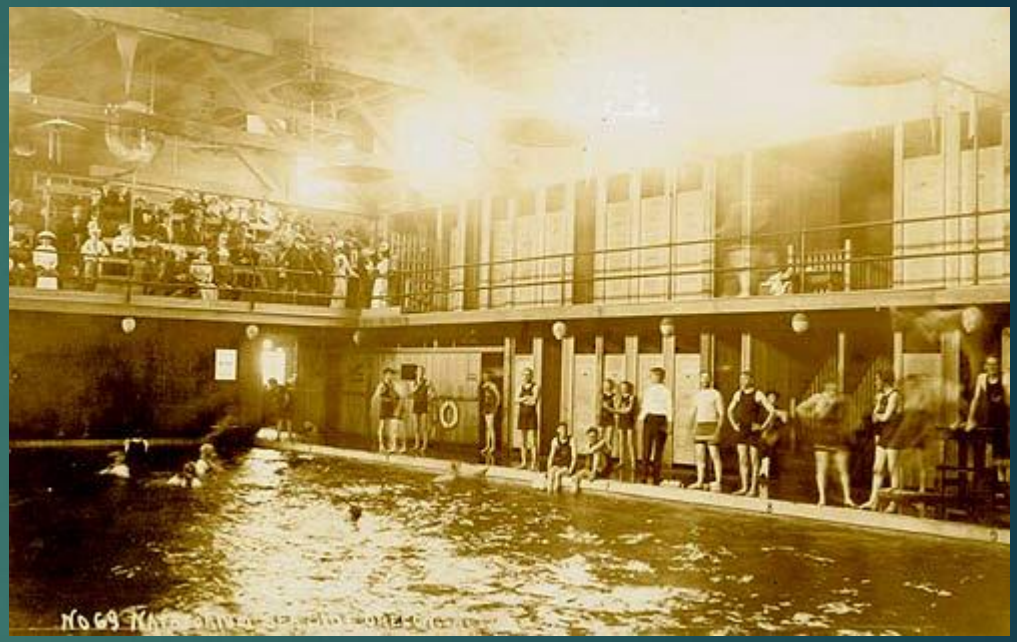
1.Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* 1999;130:397?403.
2.Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. *Arch Intern Med* 1999;159:2437?2442.
3.Ram FSF, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004;1:CD004104.
4.National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059?2073.

What is a Natatorium?

What is a Natatorium?

- It is a swimming pool that has a building of its own a.k.a indoor swimming pool in modern language.

- Natatoriums were a big deal on the Oregon coast. From about 1910 until the '30s, these were the meeting places and hotspots for fun along much of the coastline.



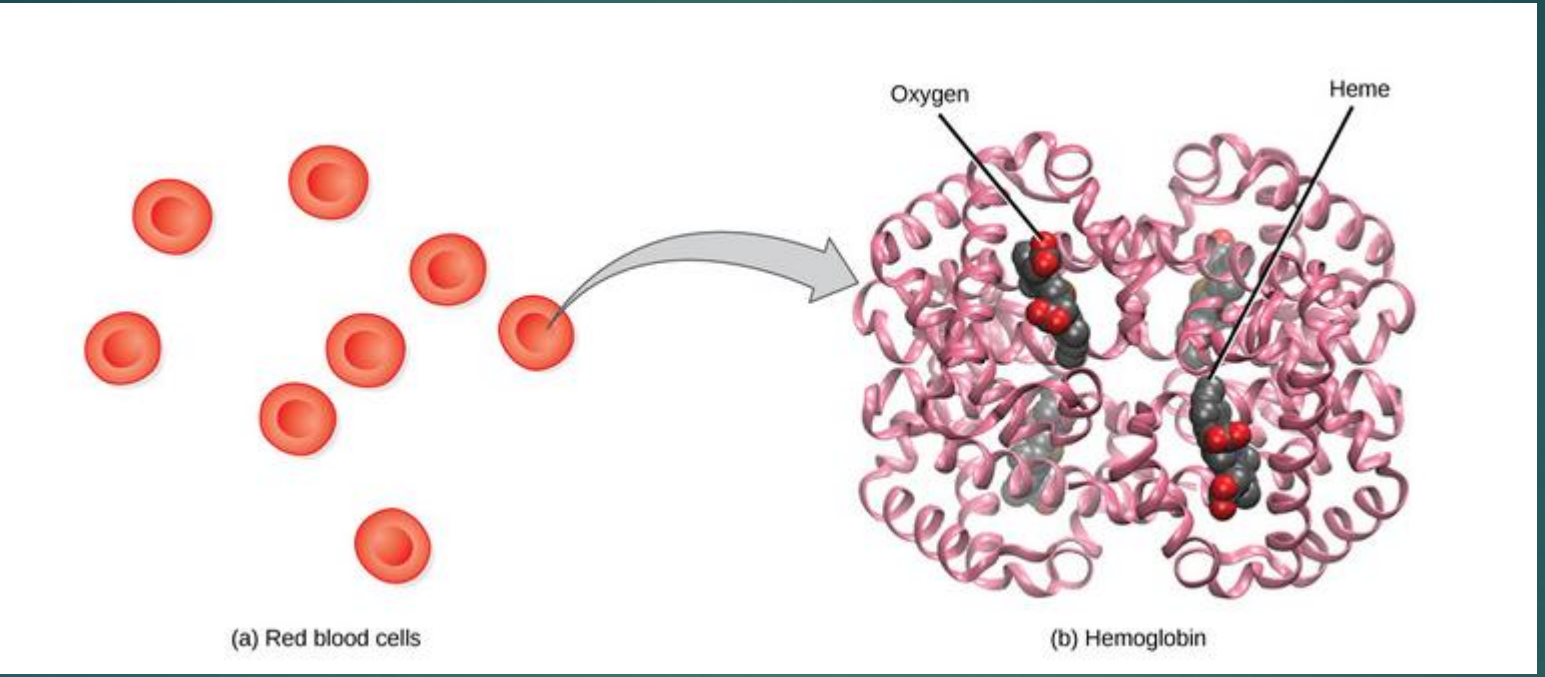
Background on Oxygen

- Oxygen was first discovered by **Joseph Priestley** on August 1, 1774, when he obtained a colorless gas by heating red mercuric oxide.
- First used clinically in dental anesthesia in 1868.
- After his expedition to Pike's Peak in 1913, **John S. Haldane** concluded in 1919 that "partial anoxia means not a mere slowing down of life, but progressive, and perhaps irreparable damage to human structure."
- **Alvan Barach** was the first to systematically employ oxygen for the treatment of bacterial pneumonia in 1955.
- **Cotes and Gilson** gave oxygen to ambulatory patients from small portable high pressure cylinders in the United Kingdom (UK).
- Cotes reported on increased walking time and improved arterial oxygen saturation with the use of supplemental oxygen during exercise

Barach AL: The therapeutic use of oxygen. JAMA 1922;79:693-699.

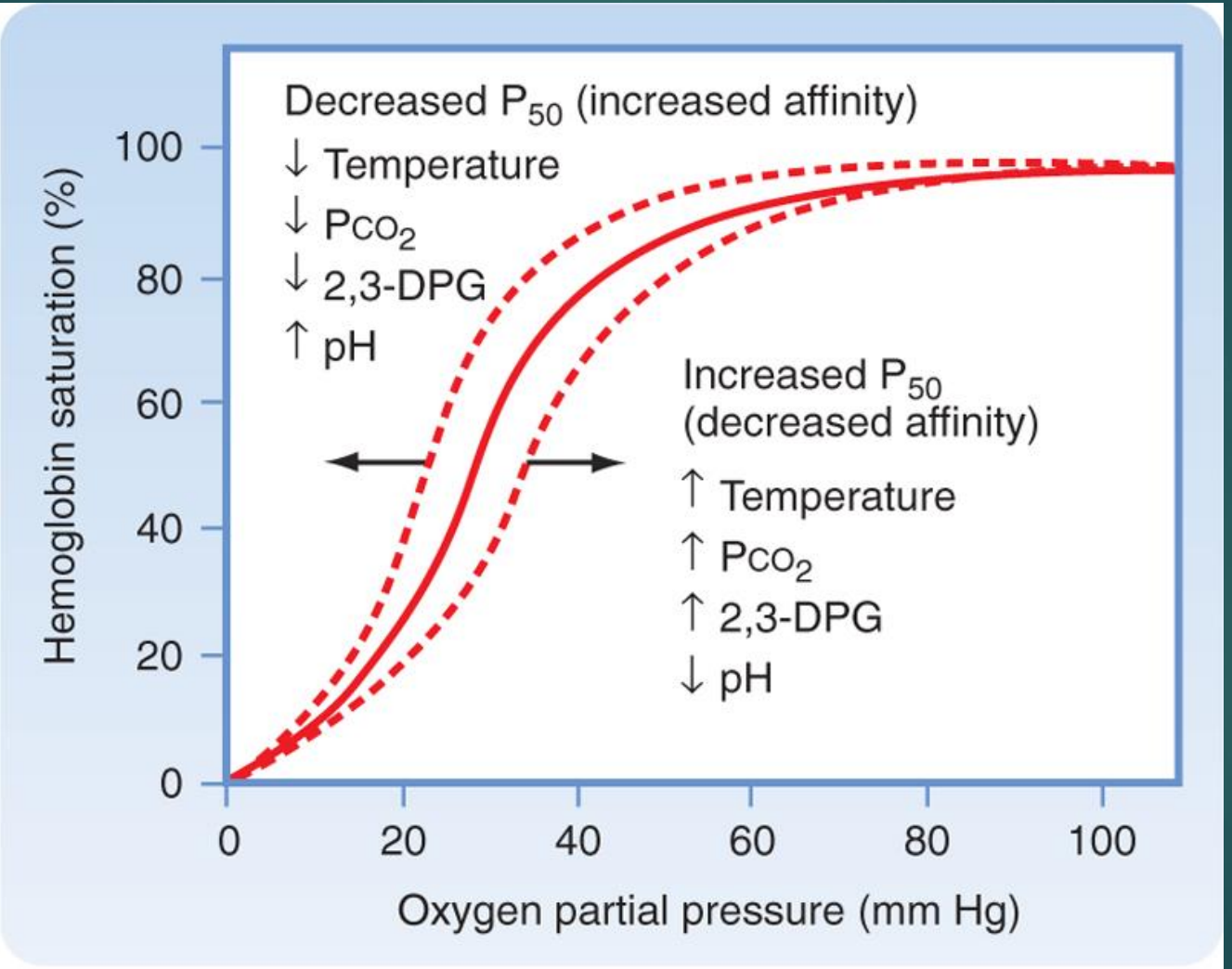
Cotes JE, Gilson JC: Effect of oxygen in exercise ability in chronic respiratory insufficiency: use of a portable apparatus. Lancet 1956;1:822-826

Oxygen transport



It is easier to bind a second and third oxygen molecule to Hb than the first molecule. This is because the hemoglobin molecule changes its shape, or conformation, as oxygen binds. The fourth oxygen is then more difficult to bind.

Hemoglobin dissociation



What are

Bohr Effect?

Haldane Effect?

Bohr effect:

Hemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide.

Haldane effect:

Deoxygenation of the blood increases its ability to carry carbon dioxide.

Conversely, oxygenated blood has a reduced capacity for carbon dioxide.

Guidelines

- ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe continuous oxygen therapy in patients with COPD who have severe resting hypoxemia (PaO2 55 mm Hg or SpO2 88%) (Grade: strong recommendation, moderate-quality evidence).

- Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93:391-8. [PMID: 6776858]
- Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1:681-6. [PMID: 6110912

Nocturnal Oxygen Therapy Trial Group

- Six centers, 203 patients with hypoxemic COPD
- Randomized to receive 12 hours vs 24 hours Oxygen therapy after 3 week stabilization period.
- Patients were exercised on a daily basis to improve physical conditioning during the stabilization period.
- The oxygen tension in 45 subjects improved while breathing room air to the extent that they no longer qualified for the study.
- Resting PaO2 ≤ 55 or 55-59 with cor pulmonale based on electrocardiograph criteria and/or a hematocrit value of 55 or higher.
- Exclusion criteria:
  - Presence of serious comorbidity,
  - Refusal by the patient to follow a complex protocol that required two cardiac catheterizations, and
  - Residence too far from the testing center for the necessary close observations required by this study

Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93:391-8. [PMID: 6776858]

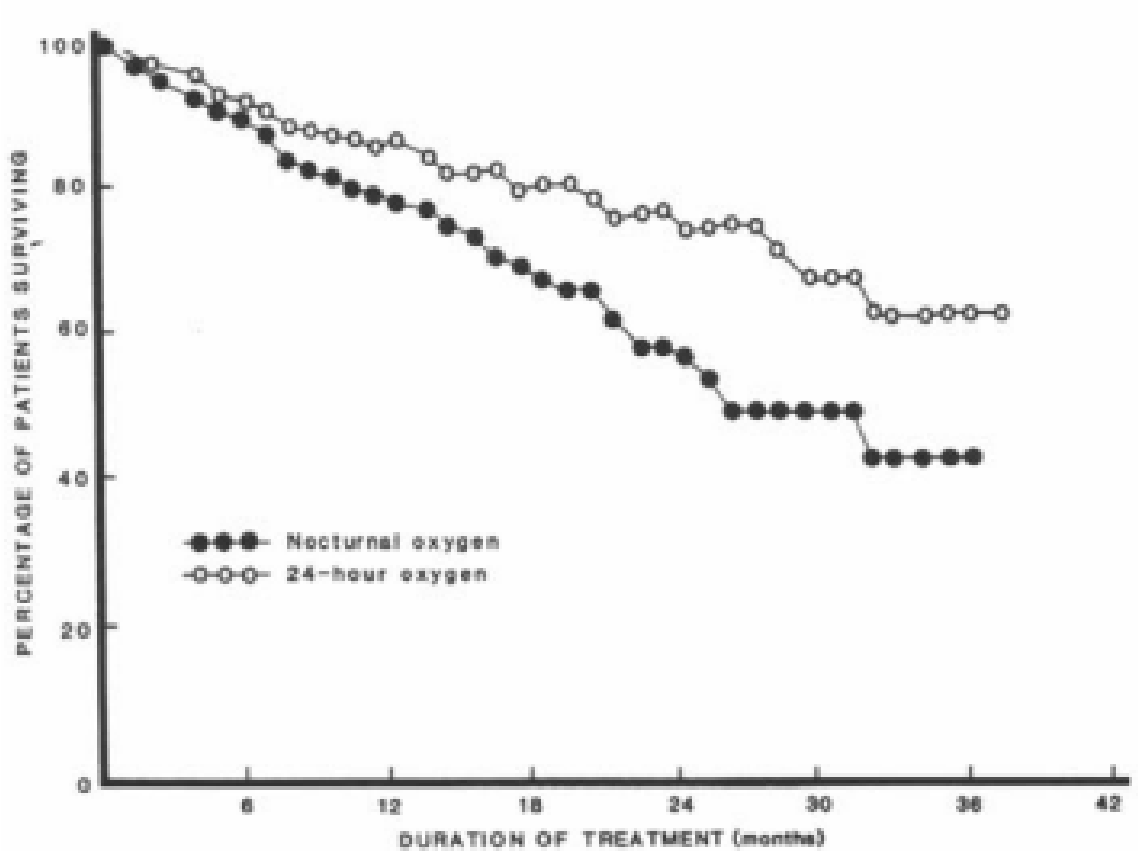


Figure 5. Survival in the Nocturnal Oxygen Therapy Trial where "24-hour oxygen" duration was actually 19.4 hours median and 17.7 hours mean. Nocturnal oxygen by diary was for 11.8 hours mean from a stationary system. (From Reference 18, with permission)

Overall mortality in the nocturnal O_2 therapy group was 1.94 times that in the continuous O_2 therapy group (P = 0.01).

More prominent difference:

- Carbon dioxide retention,
- Relatively poor lung function,
- Low mean nocturnal oxygen saturation,
- More severe brain dysfunction, and
- Prominent mood disturbances

THE BRITISH MEDICAL RESEARCH COUNCIL CLINICAL TRIAL

- Group led by Dr. David Flenley.
- The treatment of patients with COPD and chronic stable hypoxemia (arterial oxygen tension [PaO2] ≤ 55 mm Hg) and the effect of LTOT on survival.
- 87 patients, < 70 years: COPD, arterial hypoxemia, CO2 retention, and a history of CHF.
- The patients were randomized to receive either 15 hours of oxygen (including the hours of sleep) from a stationary system (2L/min) or no supplemental oxygen.

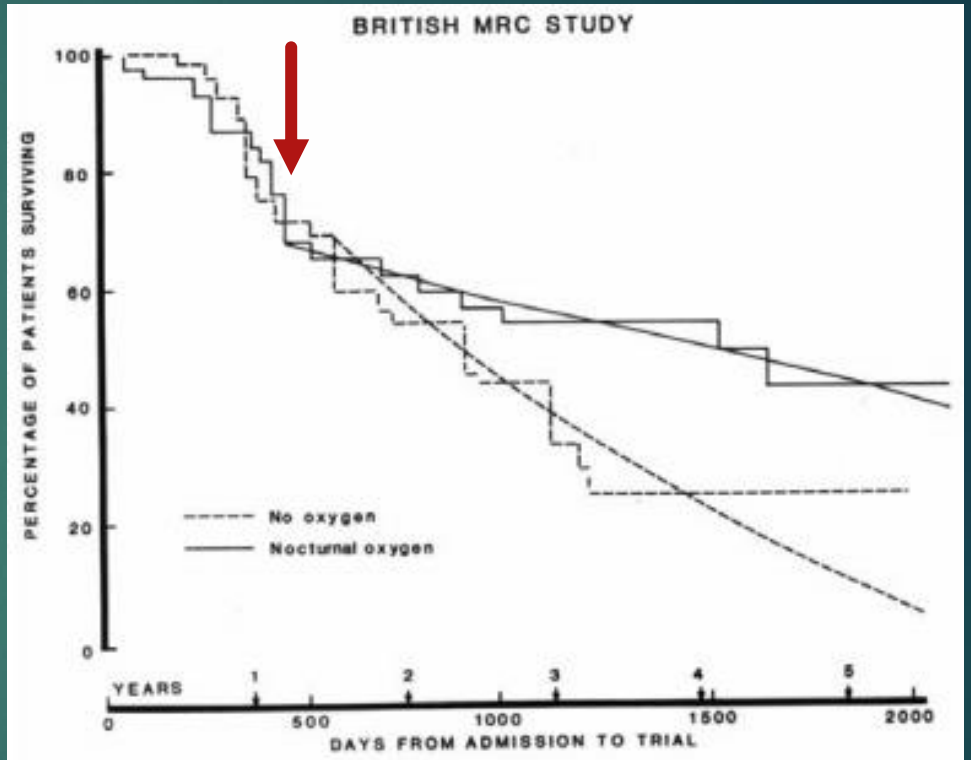


Figure 4. Survival in the British Medical Research Council study comparing oxygen for 15 hours a day from a stationary source, compared with no oxygen. (From reference 17, with permission)

Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1:681-6. [PMID: 6110912

- Survival for the 12 female controls was poor, 8 of them being dead at 3 years.
- Neither time spent in hospital because of exacerbations of respiratory failure nor work attendance were affected by oxygen therapy.
- But these patients were very ill at the start of the trial and many had already retired on grounds of age or ill-health.
- Oxygen did not slow the progress of respiratory failure in those who died early.
- In longer term survivors on oxygen, arterial oxygenation did seem to stop deterioration.

Oxygen dose

- Before NOTT, 2 studies with 17 patients each[1,2]
  - Patients admitted with COPD exacerbations
  - Used increasing dose of supplemental Oxygen and measured PaO2 and PCO2 to titrate
  - Defined 2L/min optimum level with near target (60-65 mm Hg or 90-94%) with minimal increase in PCO2.
- NOTT defined:
  - Majority of patients with advanced COPD and hypoxemia can be managed with oxygen delivered by nasal canula at 1 to 2 L/min (As measured at rest by ABG).
  - <10% with COPD required 3 L/min or more at rest to achieve adequate oxygenation.

[1]Cherniack RM, Hakimpour K: The rational use of oxygen in respiratory insufficiency. JAMA 1967;199:178-182.
[2]Bigelow DB, Petty TL, Levine BE, et al: The effect of oxygen breathing on arterial blood gases in patients with chronic airflow obstruction living at 5, 200 feet. Am Rev Respir Dis 1967;96:28-34.

What happens with Oxygen therapy?

- 6 patients
- Study to investigate the utility of supplemental oxygen on the basis of clinical evidence of severe pulmonary hypertension, erythrocytosis, hematocrit > 55%, and markedly reduced exercise tolerance.
- No Oxygen was used.
- During stabilization, bronchodilators, diuretics, cardiac glycosides and antibiotics were given. Patients were encouraged to eat a high-calorie diet and exercised systematically each day to improve physical conditioning and to increase exercise capability.
- Cardiac catheterization was done to measure pulmonary artery pressure, cardiac output, and pulmonary vascular resistance. Chromium-51-tagged red cell mass determinations were also made.
- During the 2nd month, the patients were maintained on the same diet and maintenance medications, and oxygen was administered by nasal canula to keep saturation above 90% during rest and exercise (1-3L/min)
- At the end of one month, cardiac catheterization and red cell mass studies were repeated.

Levine BE, Bigelow DB, Hamstra RD, et al: The role of long-term continuous oxygen administration in patients with chronic airway obstruction with hypoxemia. Ann Intern Med 1967;66(4):639-650

Results:

- Marked reductions in pulmonary artery pressure and pulmonary vascular resistance were observed in 4 of the 6 patients.
- The red cell mass improved in 4 of the six.

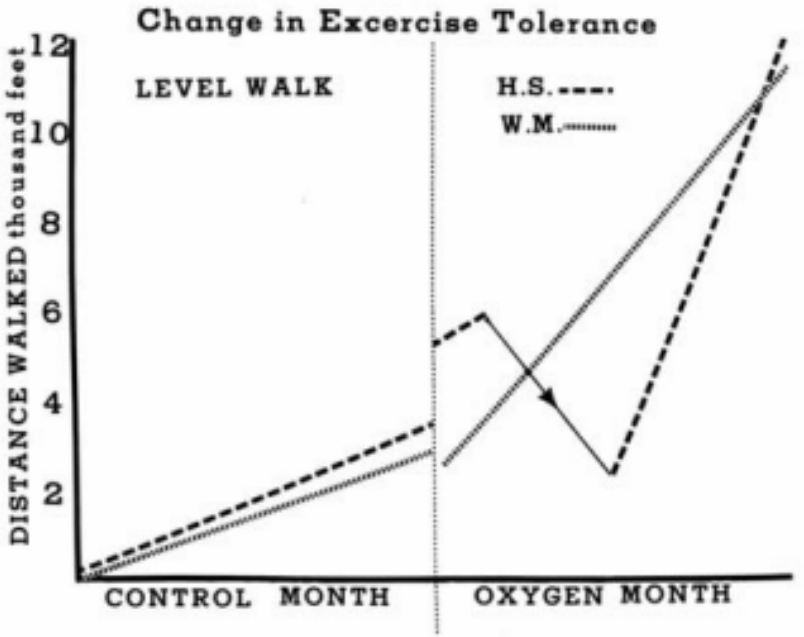


Figure 2. Improvement in exercise tolerance in two patients trained at level walk. Note the slow change during the control month, and the marked rapid rise in tolerance during the oxygen month. W.M. and H.S. are the patients' initials. Temporary decrease in H.S.'s exercise tolerance during the oxygen month was due to an episode of acute bronchitis.

Levine BE, Bigelow DB, Hamstra RD, et al: The role of long-term continuous oxygen administration in patients with chronic airway obstruction with hypoxemia. Ann Intern Med 1967;66(4):639-650

What happens with Oxygen therapy?

- 20 patients with advanced (COPD) received continuous ambulatory oxygen therapy from a liquid oxygen portable system for up to 18 months.

- Results:
  - Improvement in cor pulmonale, with evidence of improvement in electro-cardiograph tracings and in the cardiac silhouette, with resolution in right ventricular size as a result of 6 months of oxygen administration.
  - Progressive reduction in hematocrit
  - Increase in dry body weight over one year (nutritional or metabolic benefit)

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

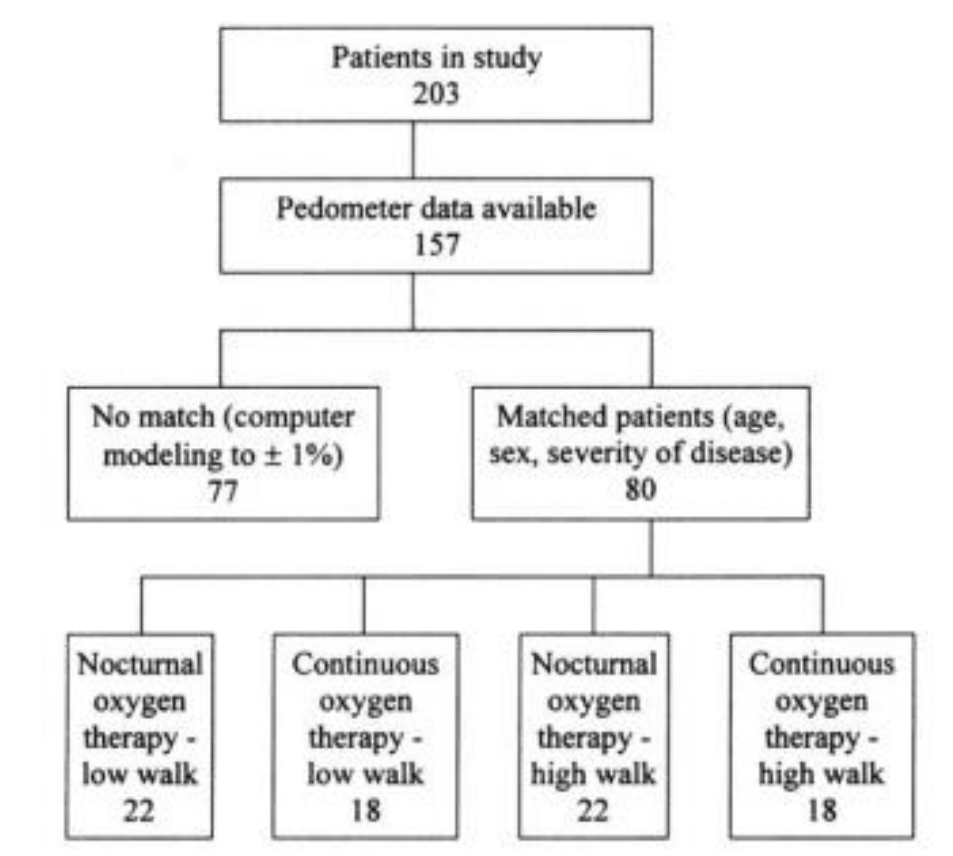
Petty TL, Finigan MM: Clinical evaluation of prolonged ambulatory oxygen therapy in chronic airway obstruction. Am J Med 1968;45:242-252

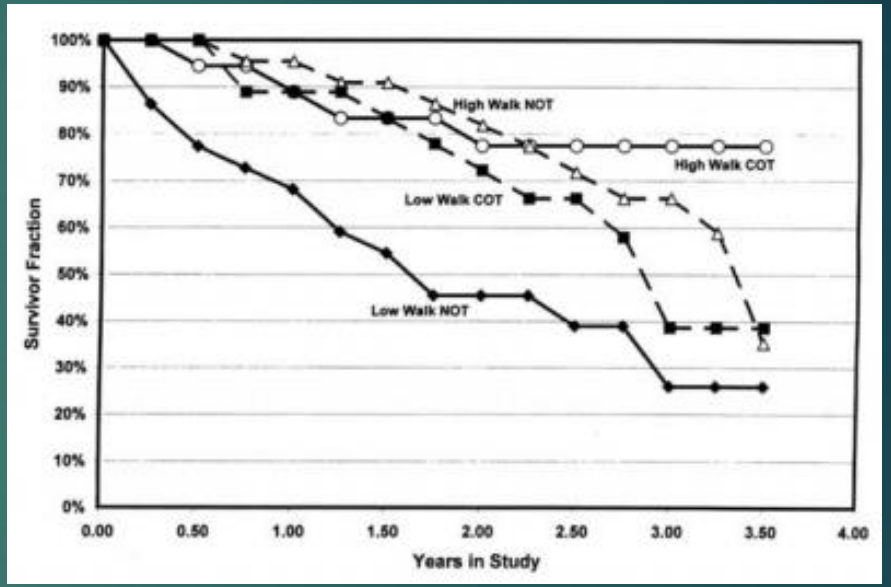
What happens to the brain?

- Improved brain function in patients with advanced COPD as the result of breathing supplemental oxygen compared with room air.[1]
- Significant impairment in brain function prior to receiving oxygen therapy in NOTT patients, compared with well matched controls.[2]
- Patients who received both NOT and COT had improved brain function at 6-months. But only COT patients had continued improvement in brain function at the end of one year, with a slight decline in the NOT patients.[3]

[1]Krop HD, Block AJ, Cohen E: Neuropsychologic effects of continuous oxygen therapy in chronic obstructive pulmonary disease. Chest 1973;64:317- 322.
[2]Grant I, Heaton RK, McSweeny AJ, et al: Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 1982;142:1470-1476.
[3]Heaton RK, Grant I, McSweeny AJ, et al: Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 1983;143:1941-1947.

Extrapolation from NOTT





Low walking level (39 mL/min),
High walking level (59mL/min)

Extrapolation from NOTT

- Increased metabolic demands of exercise
- Modest degree of hypoventilation during sleep with or without an additional degree of oxygen transport abnormality during sleep or both.

Table 1. General Prescribing Guidelines for Home Oxygen for Patients with Advanced COPD

Patient Selection Criteria

- *Stable course of disease on optimum indicated medical therapy, (e.g., bronchodilator, antibiotics, corticosteroids)*
- *At least two arterial blood gas determinations while breathing room air for at least 20 minutes*
- *Room air PO_2 that is consistently 55 mm Hg, or consistently 55-59 mm Hg plus cor pulmonale clinically diagnosed, or hematocrit 55%.*
- *Normoxic patients in whom less dyspnea and increased exercise capacity is demonstrated with the use of supplemental oxygen.*

Oxygen Dose

- *Continuous flow by a double or single nasal cannulae*
- *By demand system with demonstration of adequate oxygen saturation*
- *Lowest liter flow to raise PO_2 to 60-65 mm Hg or oxygen saturation to 88-94%*
- *Increase baseline liter flow by 1 L during exercise and sleep*

When was Seaside Aquarium Established?

Predicting survival?

- 28 patients
- Divided into 2 groups, responders (R) and nonresponders (NR), on the basis of the fall in their mean pulmonary artery pressure (ΔPAP) while breathing 28% O_2 for 24 h.
- R (N=17) had ΔPAP >5 mm Hg and NR (N=11) had ΔPAP<5 mm Hg.
- **Results:**
  - 88% of the R, but only 22% of the NR, were alive at the end of 2 years.
  - 85% of R, but only 11% of NR, achieved an end-exercise maximal oxygen consumption (VO2max) greater than 6.5 ml min^{-1} kg^{-1}.
  - Left ventricular ejection fraction improved while breathing O_2 for 48 h in the R only.
- **Conclusion:** ΔPAP >5 mm Hg or VO2max greater than 6.5 ml min^{-1} kg^{-1} is associated with better 2 year survival in LTOT patients.

Ashutosh K, Mead G, Dunsky M: Early effects of oxygen administration and prognosis in chronic obstructive pulmonary disease and cor pulmonale. Am Rev Respir Dis 1983;127:399-404

Other positive effects of LTOT

- Depression,
- Cognitive function,
- Quality of life,
- Exercise capability, and
- Frequency of hospitalizations

1.Stewart BN, Hood CI, Block AJ. Long-term results of continuous oxygen therapy at sea level. *Chest* 1975;68:486?492.
2.Heaton RK, Grant I, McSweeny AJ, Adams KM, Petty TL. Psychological effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med* 1983;143:1941?1947.
3.Weitzenblum E, Oswald M, Apprill M, Ratomaharo J, Kessler R. Evolution of physiological variables in patients with chronic obstructive pulmonary disease before and during long-term oxygen therapy. *Respiration (Herrlisheim)* 1991;58:126?131.
4.Borak J, Sliwinski P, Tobiasz M, Zielinski J. Psychological status of COPD patients before and after one year of long-term oxygen therapy. *Monaldi Arch Chest Dis* 1996;51:7?11.
5.Clini E, Vitacca M, Foglio K, Simoni P, Ambrosino N. Long-term home care programmes may reduce hospital admissions in COPD with chronic hypercapnia. *Eur Respir J* 1996;9:1605?1610.
6.Okubadejo AA, Paul EA, Jones PW, Wedzicha JA. Does long-term oxygen therapy affect quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia? *Eur Respir J* 1996;9:2335?2339.
7.Ringbaek TJ, Viskum K, Lange P. Does long-term oxygen therapy reduce hospitalisation in hypoxaemic chronic obstructive pulmonary disease? *Eur Respir J* 2002;20:38?42.
8.Eaton T, Lewis C, Young P, Kennedy Y, Garrett JE, Kolbe J. Long-term oxygen therapy improves health-related quality of life.*Respir Med* 2004;98:285?293.
9.Haidl P, Clement C, Wiese C, Dellweg D, Köhler D. Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia. *Respiration (Herrlisheim)* 2004;71:342?347.

Why Titrate?

- 83 patients of UIP and 22 of NSIP.
- 6 minute walk test: Measured exercise induced desaturation.

- Presence of desaturation was associated with a greater than fourfold hazard of death.
- All deaths in patients with NSIP occurred in patients who desaturated.
- A significant predictor of desaturation in patients with UIP was DLCO after adjusting for age, sex, smoking history, FVC, and the amount of fibrosis on HRCT.
- For each 1% decrease in saturation, mortality increased by 23%.

1.Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP III, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*2003;168:1084?1090.

- In the clinical-radiologic-physiologic scoring system devised to predict survival in IPF, resting gas exchange was not important.[1]
- Exercise PaO2 on CPET was significantly predictive of survival.[1]
- Exercise induced hypoxemia evaluated by $\Delta PaO_2 / \Delta \dot{V}O_2$ on CPET was strongly correlated with survival(41 patient study).[2]
- ATS consensus statement: a 4% decrease in saturation during exercise is an adverse prognostic sign in IPF.[3]
- Acute administration of supplemental oxygen improves ventilatory function and exercise endurance in subjects with advanced COPD.[4]

1. King TE Jr, Tooze JA, Schwarz MI, Brown K, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164:1171–1181.
2. Miki K, Maekura R, Hiraga T, Okuda Y, Okamoto T, Hirotani A, Ogura T. Impairments and prognostic factors for survival in patients with idiopathic pulmonary fibrosis. Respir Med 2003;97:482–490.
3. American Thoracic Society: idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement: American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646–664
4. O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:892-898.

Effect Of Pre-existing Psychiatric Illness On Home Oxygen Requirement In COPD Patients

- 77 patients, retrospective study
- Investigated presence of psychiatric illness at the time of initiation of LTOT (depression, anxiety, PTSD, schizophrenia, alcohol abuse).
- Adjusted for confounders: CHF, ILD, pulmonary hypertension.

- **Conclusions:** Presence of pre-existing psychiatric illness significantly delays the initiation of home O2 therapy.

- FEV1 is not the only factor deciding initiation of home O2, but lack of other objective measures makes it difficult to quantify the severity of disease.

Trivedi, K., Nellaiappan, V., Al-dliw, M., Nadeem, R.. Effect Of Pre-existing Psychiatric Illness On Home Oxygen Requirement In COPD Patients: A Pilot Study. *Chest.* 2013;144(4_MeetingAbstracts):738A. doi:10.1378/chest.1705360

Give Oxygen to ALL!!

Activity

Cost

- Total Medicare reimbursements for costs related to O2 exceed $2 billion/year (2004) and are increasing at an annual rate of 12 to 13%.
- Approximately 1 million patients receive LTOT through the Medicare program in a given year.

Toxicity

- Proliferative and fibrotic lung tissue changes in 6 of 12 autopsy cases suggesting oxygen toxicity in patients on LTOT who received oxygen for 7 to 61 months (average 26.7 months).
- Similar changes were not found in patients with like degrees of COPD who had not received continuous oxygen therapy.
- However, there was no evidence that these lesions caused harm by increasing morbidity or by hastening death.
- Duration dependent toxicity: 32-month mean survival in those with possible oxygen toxicity, compared with 23-month survival in those with no histologic evidence of oxygen toxicity.

Petty TL, Stanford RE, Neff TA: Continuous oxygen in chronic airway obstruction. Observations on possible oxygen toxicity and survival. Ann Intern Med 1971;75:361-307.
Petty TL, Neff TA, Creagh CE, et al: Outpatient oxygen therapy in chronic obstructive pulmonary disease: A review of 13 years' experience and an evaluation of modes of therapy. Arch Intern Med 1979;139:28-32.

Toxicity

- Oxidative stress may contribute to the progression of COPD through stimulation of many molecular pathways involved in COPD pathogenesis[1]
- Stepped increases in inhaled oxygen concentration produce acute increases in exhaled biomarkers of oxidative stress [2,3,4] and in markers of airway inflammation[4].

1.National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059-2073.
2.Loiseaux-Meunier MN, Bedu M, Gentou C, Pepin D, Coudert J, Caillaud D. Oxygen toxicity: simultaneous measurement of pentane and malondialdehyde in humans exposed to hyperoxia. *Biomed Pharmacother* 2001;55:163-169.
3.Hitka P, Vízek M, Wilhelm J. Hypoxia and reoxygenation increase H2O2 production in rats. *Exp Lung Res* 2003;29:585-592.
4.Carpagnano GE, Kharitonov SA, Foschino-Barbaro MP, Resta O, Gramiccioni E, Barnes PJ. Supplementary oxygen in healthy subjects and those with COPD increases oxidative stress and airway inflammation. *Thorax* 2004;59:1016-1019.

CMS guidelines

Measurement		Condition for Testing		
Arterial O2 (mm Hg)	O2 Saturation (%)	At Rest	During Exercise	During Sleep
<=55	*<=88*	*Available*	Available	Available
56-59	*89*	*Available for dependent edema, pulmonary hypertension, or hematocrit > 56*		
>=60	>=90	Coverage available only by special approval		
Devices Covered		Stationary ± Ambulatory	Ambulatory ± Stationary	Stationary Only

1) While breathing room air in a chronic stable state or no earlier than 2 days prior to hospital discharge. 2)Requires demonstration that supplemental O2 improves the exercise-associated hypoxemia. 3) Also available for subjects who show a greater than normal fall in Arterial O2 (> 10 mm Hg) or arterial O2 Saturation (> 5%) during sleep with associated symptoms or signs reasonably attributable to hypoxemia.

Future studies

- In 2004 , NHLBI and CMS have suggests 4 types of clinical trials evaluating:
  - Efficacy of ambulatory O2 supplementation in subjects who experience oxyhemoglobin desaturation during physical activity but are not severely hypoxemic at rest;
  - Efficacy of LTOT in subjects with severe COPD and only moderate hypoxemia;
  - Efficacy of nocturnal O2 supplementation in subjects who show episodic desaturation during sleep that is not attributable to obstructive sleep apnea; and
  - Effectiveness of an activity-dependent prescription for O2 flow rate that is based on clinical tests performed at rest, during exercise, and during sleep.

The Difference Between Medicine and Poison is…..

DOSE

Thank You