Nocturnal Hypoxemia and Long-Term Domiciliary Oxygen Therapy in "Blue and Bloated" Bronchitics*

Physiopathologic Correlations

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The original reports of Neff and Petty1 that long-term domiciliary oxygen therapy could extend the life of patients with chronic bronchitis and emphysema were made in patients living at altitude in Denver. Although later studies have suggested that similar benefits can be obtained from patients living at sea level,2-5 this is yet to be confirmed by a formal controlled trial. The economic importance of chronic bronchitis and emphysema in Britain has led the Medical Research Council to establish a multicenter controlled trial of this treatment, in Birmingham, Sheffield and Edinburgh. The trial started in 1974, and has recruited 87 patients, suffering from cor pulmonale due to chronic bronchitis and emphysema, with pulmonary hypertension, secondary polycythemia and persistent hypoxemia (Po2 below 60 mm Hg when breathing air). These patients, who thus conformed to the "blue and bloated" pattern and are non-fighters, (type B)7,8 were allocated randomly after initial assessment to either the treatment or control groups. The trial is now entering its final stages and will be reported in 1980. In Edinburgh, 28 patients have entered the trial. Although those patients treated with domiciliary oxygen have shown an improved survival as compared to the randomly allocated matched control patients, the numbers from this one center are too few for the difference yet to be statistically significant.

In 21 such "blue and bloated" patients, ages 43-69 years, including those patients treated in the MRC trial, long-term domiciliary oxygen therapy has provided 1-3 liters oxygen/min by nasal prongs for 15 hours a day. Over 10-15 months this treatment reduced the mean pulmonary arterial pressure (PAP) in 16 out of the 21, and the red cell mass (RCM) in all. These patients were hypoxemic with arterial Po2 of 47 (SD 8) mm Hg, hypercapnic (Pco2 54, SD 8 mm Hg), with pulmonary hypertension (mean PAP 39, SD 10 mm Hg), and secondary polycythemia (RCM 44, SD 12 ml/kg) due to chronic bronchitis and emphysema, and had irreversible airways obstruction (FEV, 0.5-0.8 liters).

In 12 of these patients treated with long-term oxygen therapy and in three control patients, the extent of both centrilobular and panacinar emphysema at autopsy was very variable, some showing almost no lesions, whereas in others the frequency of this condition as assessed pathologically was very similar to that in a population of 606 male smokers taken from all parts of the United Kingdom (Fig 1). Furthermore, these studies showed that right ventricular hypertrophy, as assessed by the ratio of the weight of the left ventricle plus septum to the right ventricle was not correlated with the pulmonary vascular resistance as measured in life following long-term oxygen therapy, suggesting that despite the fall in pulmonary hypertension produced in most patients, long-term oxygen therapy did not restore the size of the right ventricle to normal. Again the carotid bodies in these patients also remained very much heavier than those in normal subjects.

This discrepancy between the severity of chronic bronchitis and emphysema, as shown by the hypoxemia, CO2 retention, pulmonary hypertension and secondary polycythemia, and the severity of either centrilobular or panacinar emphysema when seen at autopsy, has led us to suggest that there may be other mechanisms underlying the development of the "blue and bloated" syndrome in these patients.9 We have compared the physiologic measurements in these "blue bloaters" with those seen in others with similar degrees of irreversible airways obstruction, but who did not develop hypoxemia and CO2 retention, the so called "pink puffers" (fighters, type A). Many of these latter patients have similar but varia-

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Figure 1. Centrilobular emphysema by decade in male smokers, as found in 606 routine autopsies (Lamb, unpublished, 1978). Present cases (O) treated with long-term oxygen, (●) control cases. Despite similarity of clinical and physiologic features, there is a wide variation in the extent of centrilobular emphysema in these patients.
ble degrees of emphysema as assessed at autopsy. In on-going studies of these two types of patients with clinical chronic bronchitis and emphysema we have found that recurrent transient hypoxemia during sleep is very frequent in "blue bloaters." Thus, 15 such patients, all with irreversible airways obstruction, pulmonary hypertension and secondary polycythemia, who, when awake, were hypoxemic (arterial Po₂ 42, SD 7 mm Hg) and hypercapnic (PCO₂ 54, SD 10 mm Hg), all showed marked transient falls in ear oxygen saturation (Hewlett Packard ear oximeter) and transcutaneous Po₂ (Hugh electrode), as confirmed by direct measurements of arterial Po₂ during sleep, which fell to 26-47 mm Hg (mean 37 mm Hg) for periods of up to 20-60 min during sleep (Fig 2). This transient hypoxemia occurred particularly during REM sleep, but was rarely associated with sleep apnea if this was defined as cessation of respiratory airflow for more than 10 seconds. However, the breathing pattern was frequently abnormal during these transient hypoxic episodes. We have also found in two of these patients that the pulmonary arterial pressure, which was already elevated when these two patients were awake, showed a further transient rise in association with these transient hypoxic episodes. These observations have led us to postulate that pulmonary hypertension may develop in these "blue and bloated" patients as a result of recurrent pulmonary vasoconstriction produced by the transient hypoxemia, which may possibly occur many times per night for several years in these patients, and thus precede the development of the sustained pulmonary hypertension which characterizes the "blue bloaters."

In contrast to these abnormalities in oxygenation during sleep in the "blue bloaters," in eight "pink puffers" of similar age with persistent airways obstruction (FEV₁ 0.5-0.9 liters), but without either daytime hypoxemia (arterial Po₂ 72, SD 4.6 mm Hg) or CO₂ retention (PCO₂ 35, SD 6 mm Hg), such transient hypoxic episodes during sleep were much less frequent, and much less severe than in the "blue bloaters." In the "pink puffers" the ear-oxygen saturation (oximeter) only fell to 75-91 percent, indicating an arterial Po₂ at lowest of only around 61 mm Hg.

Preliminary studies are indicating that these transient hypoxic episodes in the "blue bloaters" are not abolished by 2 L O₂/min during sleep, but the severity of the transient hypoxic episodes is thus considerably diminished. Furthermore, we have not been able to abolish transient hypoxemia by continuous infusion of the respiratory stimulant doxapram throughout the night, at least in doses which allow the patient to undergo a reasonably normal sleep pattern as assessed by EEG.

Figure 2. Oxygen saturation (ear oximeter) and EEG sleep stage (1-4) throughout the night in a healthy subject (above) and in a "blue bloater" (below). Arrows indicate directly measured arterial Po₂ values (1 kPa = 7.5 mm Hg). Black areas on the EEG record of sleep stage are REM periods. (Reproduced with permission from Douglas et al, Lancet 1:1-4, 1979.)
We evaluated the effects of 15 hours per day oxygen (O₂) therapy on exercise tolerance and central hemodynamics in nine male subjects (ages 52 to 64 years), with chronic airway obstruction (CAO) (FVC, 1.84 to 3.85 L; FEV₁, 0.68 to 1.96 L) and arterial hypoxemia (PO₂, 46 to 58 mm Hg). In this double-blind crossover study, O₂ and “sham O₂” were each supplied for six weeks by an oxygen enricher at 2 L/min. Bicycle ergometry (nine subjects) and right heart catheterization (six subjects) were done in the control period and repeated after each six-week period. As a group, there was no improvement in exercise tolerance as measured by maximum work rate (WRmax), maximum ventilation (Ve(max)), maximum O₂ consumption (VO2(max)), and fitness (Δheart rate/ΔVO₂). Pulmonary function (FEV₁, FVC, TLC) and central hemodynamics (cardiac output [CO], pulmonary capillary wedge pressure [PCWP], mean pulmonary artery pressure [Ppa], pulmonary vascular resistance [PVR]) also did not change for the group when comparing control with O₂ data. However, three subjects who demonstrated arterial desaturation greater than 5 mm Hg during the initial exercise testing had improvement in exercise tolerance and pulmonary hemodynamics after six weeks of 15 hours per day O₂ therapy. Improvements included an increase in mean ΔWRmax of 23.7 watts (P < 0.05) and fitness (P < 0.05). Catheterization data, available in two, demonstrated decreases in Ppa (19.9 to 12.8 mm Hg and 33.3 to 28.7 mm Hg) and PVR (249 to 151 dyne*sec⁻¹*cm⁻⁵ and 604 to 282 dyne*sec⁻¹*cm⁻⁵) without significant changes in CO and PCWP. Although data on the entire group suggest no measurable effect from 15 hours per day O₂ on exercise tolerance or central hemodynamics in subjects with CAO with hypoxemia, we have identified a subgroup who do improve. These subjects were identified in our initial studies by: 1) arterial desaturation of greater than 5 mm Hg during exercise; 2) FEV₁ < 1.0 L; 3) Vemax < 30 L/min; 4) VO₂max < 10 ml/kg/min; and 5) DLco < 10 ml CO/mm Hg/min.

Q. (Knudson): Did the patients feel better on O₂?
A. (Levin): As a group, the patients could not tell air from O₂. Of the five patients who thought they knew which gas was O₂, only three were right.

C. (Burrows): Almost never have we given O₂ to a patient with FEV₁ less than 1.0; I don’t agree with your selection criteria.

Q. (Woolcock): Why did the majority of your patients have normal PaCO₂?
A. (Levin): We did not exclude high PaCO₂ patients, but just evaluated those referred for supplemental O₂. Of those, only two had high PaCO₂.

REFERENCES

Q. (Edelman): Are hypoxic states ended by arousal?
A. (Flenley): No.
Q. (Permutt): Does nocturnal oxygen change the pattern of dips?
A. (Flenley): We don’t know yet.
Q. (ZueUlich): Was awake ventilation stimulated by doxapram?
A. (Flenley): This dose stimulates ventilation in awake patients.
Q. (Thurlbeck): Are the patients blue bloaters because they dip?
A. (Flenley): We don’t know.
Q. (Loudon): Is coughing associated with these dips in oxygen saturation?
A. (Flenley): No.
Q. (Woolcock): Are you certain these patients don’t have typical obstructive sleep apnea?
A. (Flenley): Yes. None of these had apnea as defined by Guilleminault.

Effect of 15 Hours Per Day Oxygen Therapy on Patients with Chronic Airways Obstruction*

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