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Natural History of Obstructive Airways Disease and Hypoxia: Implications for Therapy

P. Howard

University of Sheffield, Royal Hallamshire Hospital, Sheffield, United Kingdom

Abstract. Chronic irreversible obstructive airways disease (COAD) is the end result of a number of disorders: airway damage from tobacco smoke, atmospheric pollution and occupational dust and fume, bronchiectasis, cystic fibrosis, bronchial asthma and a number of congenital disorders of defective airway defence. The clinical features include sputum, wheeze, breathlessness and infective and noninfective airway inflammation. The pathological consequences are airways obstruction, emphysema and respiratory failure.

Except in bronchiectasis, the volume of daily sputum and bronchial infection is less than 20–30 years ago. At autopsy, bronchial gland hypertrophy is now an inconstant feature. Bronchial infection probably contributes little to airways obstruction, but the load of activated neutrophils in bronchiectasis is an important feature.

Wheeze comes late to many patients with COAD. It is associated with less reversibility to bronchodilator drugs and more fixed airways obstruction compared to the conventional asthmatic and is probably of different aetiology. Breathlessness is of variable severity when the forced expiratory volume (FEV_1) falls below 1.0 liters resulting in disability ranging from manageable to severe.

The FEV_1 declines an average by 70–80 ml/year (normal approx. 25 ml/year) until the value falls below 1.0 liters, then the rate of decline slows to a plateau which can persist for several years. During this period, hyperinflation, breathlessness and respiratory failure continue to worsen.

Significant respiratory failure may be a terminal event or be present for many years. Arterial oxygen tension (PaO_2) slowly declines in most patients—"pink puffers" generally have a minimal rate of fall until weeks or months before death, "blue bloaters," by contrast, several times as great.

Offprint requests to: Dr. P. Howard, University of Sheffield, Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

Oxygen therapy, corticosteroids and other bronchodilator drugs do not influence the rate of deterioration. Pulmonary vascular remodelling is an important part of the pathology of hypoxic COAD. Oxygen therapy relieves hypoxia but does not arrest deterioration of airways obstruction. New therapeutic approaches are needed to tackle the steady decline of airway function.

Key words: Chronic obstructive airways disease—Hypoxia—Forced expiratory volume in one second—Natural history.

Chronic bronchitis and emphysema are the most common cause of irreversible airways obstruction. Clinical features include sputum expectoration, wheeze, breathlessness and clinical manifestations of inflammation, infective or noninfective. The most important symptom is breathlessness, its appearance heralding disability. At this point, results of tests of airway function, notably the forced expiratory volume in one second (FEV), and the forced vital capacity (FVC), have fallen to less than half of predicted normal values. The decline of the FEV_1, probably the most reliable test of the natural history of airways obstruction, is exponential, with an accelerated fall in earlier but asymptomatic years. In the later stages, the FEV_1 plateaus for a number of years at very low levels, below values of 1 liter. It is often surprising how long patients can survive with forced expiratory volumes of around half a liter. The decline of FEV_1 in earlier years has been admirably described by Fletcher and Peto [1] in their study of London postmen (Fig. 1).

Decline is related to the susceptibility of smoking effects and the amount smoked. The decline returns to more normal levels if smoking ceases before extreme disability is realized. The average normal rate of decline with age is said to be between 20 and 30 ml/year of FEV_1. In the urban smoking individual the rate of decline is between 70 and 100 ml/year of FEV_1, but it is likely to be somewhat higher than this in earlier phases of the disease. Most patients die in respiratory failure. Disability from breathlessness is variably expressed in relation to the FEV_1 when it falls below 2 liters. For example, a patient with an FEV_1 of 1.0 liters may sometimes have serious limitation to effort and walking and yet others have only disability on heavy exercise, hills or stairs (Fig. 2). Equally, the appearance of respiratory failure of either Type 1 or Type 2 formulation may be an early feature of the fall of FEV_1 below 2 liters or a very late feature appearing only a few weeks before death. Therefore it seems likely that the decline of airway function, disability and respiratory failure are discontinuous features. This is substantiated by Biernacki et al. [2] who recently found little association between pulmonary haemodynamics, gas exchange and the severity of emphysema as assessed by quantitative CT scan.

Death rate attributable to bronchitis and emphysema has declined in recent years probably due to reduction of smoking and atmospheric and occupational pollution (Fig. 3) [3]. In contrast, for patients attending hospital clinics, the rate of decline of FEV_1 below 2 liters has changed little despite these improve-

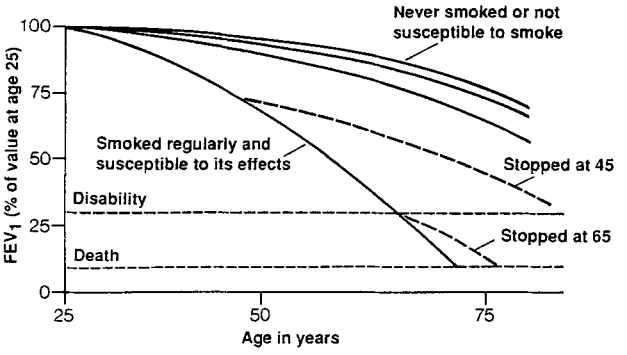

Fig. 1. Graph of the decline in FEV_1 in smokers and nonsmokers. Cessation of an established smoking habit is associated with a reduced rate of subsequent deterioration. (Reproduced by permission, [1].)

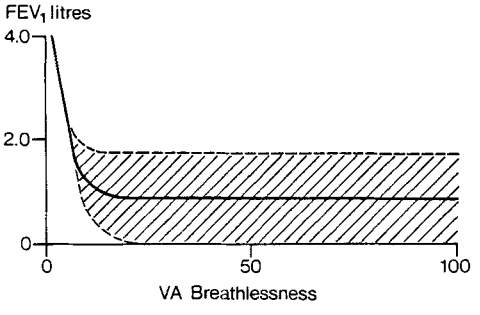

Fig. 2. Breathlessness measured by visual analogue scale in relation to FEV_1. Breathlessness varies widely in severity once FEV_1 falls below 2.0 liters.

ments. Thus, although there are less patients with bronchitis and emphysema compared with 20 years ago, those who acquire the most aggressive forms of the disorder continue to deteriorate at the same rate.

The Problem of Hypoxia

Once the FEV_1 falls below 2 liters most patients will have a degree of hypoxaemia—some being severely hypoxaemic and hypercapnic almost simultaneously and others having arterial oxygen levels only a few mmHg below accepted normal values. The rate of decline of arterial oxygen tension is equally variable. In those with the clinical manifestations of emphysema—hyperinflation, wasting, inappropriate dyspnoea—the decline of arterial oxygen tension tends to be slower giving rise to the synonym "pink puffer." The rather more obese, somnolent patient has a more rapidly deteriorating hypoxaemia and, in many instances, also hypercapnia. He develops oedema early giving rise to the synonym "blue bloater." There is a spectrum of effect with patients whose features are midway between the extremes, but the rate of deterioration of arterial hypoxaemia at the "cor pulmonale end" can be very severe between 10 and 20 mmHg or 1–3 kPa per annum.

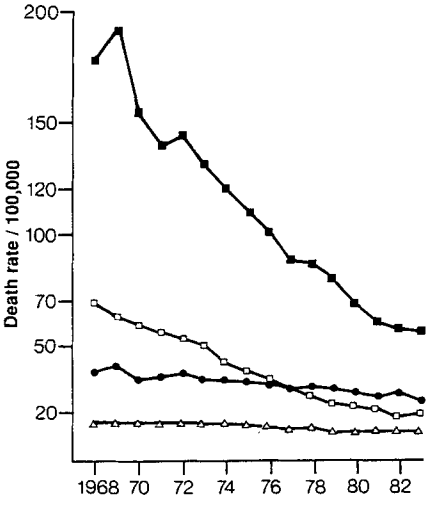

Fig. 3. Decline in death rate from bronchitis in British and American patients: England/Wales, males (■) and females (●); USA, males (□) and females (△). (Reproduced by permission, [3].)

Table 1. Features of hypoxic cor pulmonale associated with COAD

Clinical	Physiologic
Overweight	$PaO_2 < 7.3$ kPa (55 mmHg)
Somnolent	$PaCO_2 > 6.0$ kPa (45 mmHg)
Less dyspnoea	Hct > 45%
Central cyanosis	PAP > 22 mmHg (range 18–50 mmHg)
Recurrent edema	$FEV_1 < 1.5$ l
	FVC < 2.0 l

PaO_2 and $PaCO_2$—arterial oxygen and carbon dioxide tensions, Hct haematocrit, PAP mean pulmonary artery pressure supine, FEV_1 and FVC—forced expiratory volume and vital capacity, respectively

Table 1 shows the critical physiological findings when patients commence with exacerbations of oedema. Such patients were studied using oxygen therapy in the now famous NOTT [4] and MRC trials [5] which quite clearly demonstrated benefit to survival. It is now possible to follow-up such patients after 10 years of long term domiciliary oxygen therapy [6]. Table 2 shows the characteristics of 72 such patients. They had all of the physiological characteristics described in Table 1. The mean values are given in Table 2, and the mean survival compared with the control group of the MRC males, is shown in Table 3. The survival of the Sheffield patients at 10 years approximates that of the MRC no-oxygen control male group (the only control population available) at five years. There is clearly a sharp difference in survival of both groups compared with the derived normal population. The conclusion must be that LTOT

Table 2. Features of 72 patients with hypoxic cor pulmonale and COAD treated with oxygen for up to 10 years

M/F	53/19
Age (years)	60.5 ± 7.5
FEV_1 (liters)	0.78 ± 0.31
FVC (liters)	1.90 ± 0.64
TLCO (kPa $.l^{-1}.s^{-1}$)	3.48 ± 1.87
PaO_2 (kPa)	6.1 ± 1.0
PaO_2 (on O_2) (kPa)	9.1 ± 1.4
$PaCO_2$ (kPa)	6.9 ± 1.2
$PaCO_2$ (on O_2) (kPa)	7.3 ± 1.4

TLCO, transfer factor for carbon monoxide; mean ± SD (courtesy of *Thorax*, 1987–see [5])

Table 3. Cumulative survival proportions at 5 and 10 years from onset of LTOT in 72 Sheffield patients compared with Medical Research Council Control subjects and a derived normal population

Group	Survival at 5 years (%)	Survival at 10 years (%)
MRC control males	20	—
Sheffield patients	65	20
Normal population of same age and sex	90	78

Cumulative survival proportions are rounded up for comparison

is worth about five years of extended survival, which is useful but somewhat shorter than originally anticipated. The cause of death was investigated and correlations made with survival characteristics. In the treated group, survival was not related to arterial blood gases, haematocrit or the level of mean pulmonary artery pressure but to the FEV_1. Oxygen therapy thus relieves the troublesome effects of hypoxaemia but fails to influence the continuing decline of airway function which eventually determines the clinical outcome.

This point is reinforced in a further study of 37 deaths [7] in patients with hypoxaemic cor pulmonale associated with COAD (Table 4). There were 27 males and 10 females. Table 4 compares physiological parameters at the start of treatment with those immediately prior to death. The mean period of treatment was five years. The FEV_1 continued to deteriorate throughout the period of therapy. This is also true of the arterial blood gases breathing air, confirming that oxygen therapy does not arrest the underlying natural history of the disease.

Table 4. Study of 37 deaths in patients with hypoxic cor pulmonale and COAD, physiological measurements

	Onset of LTOT	Prior to death
Age yrs	60.1 ± 8.0	65 ± 7.9
FEV_1	0.78 ± 0.33	0.57 ± 0.20
PaO_2, air, kPa	6.6 ± 1.0	5.1 ± 1.1
$PaCO_2$, air, kPa	6.7 ± 0.9	7.2 ± 1.3

27 males and 10 females, mean ± SD

Table 5. Summary of indications for long-term oxygen therapy—British Guidelines

Category	Clinical features	Physiologic features			
		PaO_2* (kPa)	$PaCO_2$** (kPa)	FEV_1 (liters)	FVC (liters)
1	"Blue bloater" syndrome of bronchitis and emphysema	<7.3	>6.0	<1.5	<2.0
2	Breathlessness; emphysema and respiratory failure	<7.3		<1.5	<2.0
3	Respiratory failure associated with any terminal disease; palliative short-term therapy	<7.3			

* 55 mmHg; ** 45 mmHg

Outcome of Current Domiciliary Oxygen Treatment

All of these studies have selected patients with particularly severe hypoxaemia, hypercapnia and oedema, which poses problems for the selection of patients for oxygen therapy in everyday clinical practice. This was recognized in the writing of the British Guidelines to General Practitioners for the selection of patients (Table 5).

Category 1 describes the classic "blue bloater" patient. There seems little doubt that oxygen therapy in this group is beneficial. Category 2 patients are more of a problem. These are likely to be patients with clinical features of emphysema—breathless, hyperinflated and wasted—but who actually have hypoxaemia. Hypercapnia and oedema will usually appear only in preterminal phases. In effect they compose the "pink puffer" patients who will finally enter the stage of respiratory failure. What are their prospects for benefit from long-term domiciliary oxygen therapy (LTOT). The FEV_1 is extremely low, usually less than 1.0 liters, and, as the more important determinant of survival than treated hypoxaemia, will truncate survival prospects. In the United Kingdom,

General Practitioners are selecting patients on the grounds of central cyanosis and dyspnoea. The average duration of an oxygen concentrator installation is less than one year. Although more precise studies are needed, it seems that Category 2 patients will have limited benefit from LTOT.

Hypoxaemia without Oedema

It is possible to look at the survival characteristics of hypoxaemia alone from two studies, the IPPB American trial [8] and the Multicenter VIMS European Almitrine study [9]. Both groups of patients had advanced obstructive airways disease. The former study selected patients with no hypoxaemia to determine whether intermittent assisted breathing would help survival and disability. The second study investigated the effects of Almitrine bismesylate, a chemoreceptor agonist, on hypoxic patients with COAD, very few having reached the oedematous phase. Five hundred patients treated with IPPB of mean age 60.5 yrs had an initial arterial oxygen tension of 9.4 kPa (70 mmHg) and were normocapnic. For the 701 patients in the VIMS study, the mean age at entry was 62 yrs., the mean arterial oxygen tension was 7.6 kPa (57 mmHg) and they were, on average, normocapnic, 6.0 kPa (45 mmHg). The major difference clinically was that the VIMS patients were notably more hypoxaemic. Cumulative survival proportions of approximately 85% in both studies showed no major differences at two years. Moderate hypoxaemia in association with advancing obstructive airways disease would therefore seem not to be a risk factor for survival.

Which features of severe hypoxaemia cause rapid death of the "blue bloater" patient when in earlier phases it creates little problem? It is now appreciated that, as hypoxaemia progresses, tissue responses to the chronic deficiency may change. Acclimatization can break down. Alterations of function occur in vitally affected organs such as the carotid body, the kidney, the autonomic nervous system, the peripheral nervous system and perhaps the lung. These features should now be studied to elucidate the effects of lack of oxygen to enable more precise targeting of long-term domiciliary oxygen therapy (LTOT) to those patients showing metabolic disturbances.

Treatment of Early Hypoxaemia without Oedema

Oxygen therapy has failed to alter the natural history of COAD. It merely relieves tissue hypoxaemia temporarily. In early phases it is unlikely to influence survival. The emphasis must surely be on prevention of progressive hypoxaemia which is more likely to yield to pharmacologic therapy. Almitrine bismesylate should be reexamined in this light, and other compounds should be studied which might prevent the loss of tissue acclimatization to advancing hypoxic disease.

References

1. Fletcher C, Peto R (1977) The natural history of chronic airflow obstruction. Brit Med J i:1645–1648
2. Biernacki W, Gould GA, Whyte KF, Flenley DC (1989) Pulmonary haemodynamics, gas exchange and the severity of emphysema as assessed by quantitative CT scan in chronic bronchitis and emphysema. Amer Rev Respir Dis 139:1509–1515
3. Seaton A, Seaton D, Leitch Gordon A (1989) Croften and Douglas Respiratory Diseases, 4th edition. Blackwell Scientific: Oxford
4. Nocturnal Oxygen Therapy Trial Group (1980) Continuous or nocturnal oxygen therapy in hypoxaemic chronic obstructive airways disease—a clinical trial. Ann Intern Med 93:391–398
5. Medical Research Council Working Party (1981) Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet i:681–683
6. Cooper CB, Waterhouse JC, Howard P (1987) Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy. Thorax 42:105–110
7. Personal observations—unpublished
8. Intermittent Positive Pressure Breathing Trial Group (1983) Report of a trial. Ann Intern Med 99:612–620
9. Voisin C, Howard P, Ansquer JC (1987) Almitrine bismesylate—a placebo controlled trial in COAD—VIMS. Bull Europ Physiopathol Respir 23 (suppl 11):169–182