

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

A BACKGROUND PAPER FOR THE ADULT LUNG HEALTH INITIATIVE

This paper is designed to accompany the scholarly review prepared for the World Bank on COPD by J. Richard Bumgarner and Frank E. Speizer¹, which considers in detail the epidemiology and Public Health aspects of COPD, and the recent Guidelines for the management of COPD published by the British Thoracic Society².

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1. CASE DEFINITIONS

COPD is a non-specific term developed to describe chronic lung disease characterised by diffuse, largely irreversible obstruction to airflow within the lung. *COPD cannot be diagnosed without some, albeit simple, lung function tests.*

Earlier attempts to define COPD in an operationally useful way avoid the use of the word asthma. For example it was defined by the American Thoracic Society (3) as “a disease state characterised by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyper-reactivity, and may be partially reversible.”. A similar position at that time -1995- was taken by the European Respiratory Society (4). More recently the need to include some cases of chronic asthma within the envelope of COPD has been recognised (2) . The difficulty of distinguishing between COPD and asthma is discussed later in this paper.

The pathological processes or diseases which lead to COPD can now be conventionally taken as three.

- (1) **Chronic bronchitis** is defined symptomatically as “cough and sputum on most days for as much as three months of the year for at least two years”. Other diseases which might cause such symptoms, such as tuberculosis or bronchiectasis, must be excluded.
- (2) **Emphysema** is defined pathologically as “an increase beyond the normal in the size of air spaces distal to the terminal bronchiole accompanied by destruction of their walls and without obvious fibrosis”.
- (3) **Asthma** is characterised by “marked variation in the calibre of the intrapulmonary airways over short periods of time”.

2. PATHOPHYSIOLOGY

Since chronic bronchitis is described in terms of *symptoms*, emphysema in terms of *pathology* and asthma in terms of *lung function*, since none of the definitions are precise, and since all three conditions may exist in the same patient, it is not surprising that considerable confusion may be generated at the margins. Chronic bronchitis and emphysema frequently co-exist. Any or all of these three conditions, persisting and deteriorating for a period of some years, may result in the clinical picture of a patient with obvious chronic airflow obstruction which is not responsive to steroid therapy, and only marginally responsive to bronchodilator drugs. This is COPD. Although the final clinical picture is often a mixture, it is helpful first to consider the pathophysiology separately.

- (1) **Chronic bronchitis** Continued stimulation of the airways by irritants, especially tobacco smoke, causes, in some individuals, hypertrophy of bronchial submucosal glands and proliferation of goblet cells leading to excess production of mucous secretions. While it has long been thought that chronic bronchitis itself leads to diffuse airflow obstruction, the connection is somewhat tenuous. Gland hypertrophy occurs in the central airways, whereas the important site of obstruction in COPD is peripheral. Smokers may have chronic mucus hypersecretion without abnormal airways obstruction, or conversely may have severe obstruction without hypersecretion.
- (2) **Emphysema.** Some thirty years ago, a few patients were discovered who had both unusually early severe emphysema and absence of the α_1 -protein band on the protein

electrophoretic strip. This band consists mainly of α_1 -antitrypsin, a potent proteinase inhibitor. Subsequent research with animal models, where proteolytic enzymes were instilled into the lung, showed that pathological changes very similar to human emphysema could be produced provided that the instilled substance could degrade elastin.

The proteinase-antiproteinase theory of emphysema developed from this early work. It now seems likely that neutrophil elastase is the most important of the potentially destructive proteinases and α_1 -antiproteinase is its most potent inhibitor. Neutrophil elastase is produced during neutrophil differentiation and has several notable effects other than elastin degradation. For examples, it will digest collagen, impair mucociliary function, and cause mucous gland hypertrophy and hypersecretion. It also stimulates the bronchial epithelium to produce cytokines which attract more neutrophils which secrete more elastase -there is positive feedback.

The proteinase- antiproteinase theory is not simple. For example, not all subjects with homozygous antitrypsin deficiency (serum concentration about one-tenth of normal) develop emphysema of clinical importance, especially if they do not smoke. But there must in general within the healthy lung be a balance between proteinase and inhibitor such that inflammatory damage does not occur. Imbalance might be due to insufficient or ineffective inhibitor, or to excess neutrophil recruitment, or to both.

Deficiency of α_1 -antitrypsin is the only genetically straightforward cause of emphysema, and it is rare. It is possible that other genes, presently under investigation, may prove to be of importance in the aetiology of COPD - for example α_1 -antichymotrypsin, α_2 -macroglobulin, vitamin D-binding protein and blood group antigens (5).

What is very clear is that regardless of mechanism, damage to the elastin framework of the lung is irreparable.

The two major structural effects of emphysema are:

- (i) loss of alveolar capillary gas-exchanging membrane through coalescence of alveolar spaces, often with obvious bullous structures resulting. The ability of the lung to exchange gas across this membrane is measured by the diffusing capacity, or its synonym transfer factor, expressed in terms of **flow** of a specified gas (usually carbon monoxide in standard lung function testing) across this membrane divided by the driving **pressure** or partial pressure difference of that gas across the membrane. This process of gas transfer will be impaired if the membrane is too thick, due say to fibrosis or oedema, or more importantly in emphysema if the total available area of alveolar-capillary membrane is diminished. For a given driving pressure, the total gas transfer is directly proportional to the membrane area, and this is diminished in emphysema by alveolar wall destruction. The abnormally large air spaces created by alveolar coalescence also impair gas exchange because of the long diffusion distances resulting within abnormally large air spaces.
- (ii) loss of elastin throughout the lung parenchyma which leads to diminished elastic recoil and inadequate support for airways to remain patent during expiration. When expiration is forceful, a positive pressure is produced within the alveoli by the respiratory muscles which drives expiratory flow, with a flow gradient between the

alveoli and atmospheric pressure (reference zero) at the mouth. A highly simplified model of this flow-dependent process is shown in Fig. 1. A pressure gradient is created, not only down the airway, but also across the airway wall, which must tend to narrow. In the normal lung this process limits the expiratory flow which can be produced by maximum effort, but the airway is supported both by its intrinsic stiffness and by the elastic meshwork within the alveolar parenchyma, which is attached to the walls of all the airways. This supporting meshwork is progressively destroyed in emphysema.

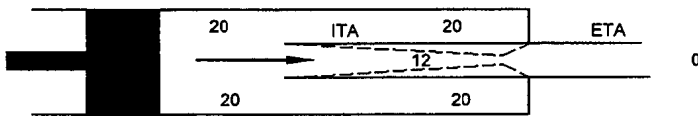


Figure 1. The simplest model of airways collapse during expiration. Flow is produced within a single chamber by a piston moving left-to-right. The chamber contains a collapsible “intrathoracic” airway ITA and an “extrathoracic” airway ETA. The piston produces a driving pressure of 20 arbitrary units within the chamber, and a gradient from 20 to atmospheric zero along the airway. A gradient must also be produced across the airway wall (shown at a single point as 20 outside minus 12 inside = 8), which then narrows the airway (dotted lines).

- (3) **Asthma.** Bronchial biopsies taken both from asthmatic subjects who have died from some other cause, and more recently by biopsies obtained at fibre-optic bronchoscopy, show first, evidence of inflammation - vasodilatation and oedema with infiltrates of eosinophils, neutrophils and T-lymphocytes; and second, more longstanding changes with epithelial denudation, basement membrane thickening, subepithelial fibrosis and smooth muscle hypertrophy - airway remodelling.

The airways are hyper-responsive in that they can be shown to bronchoconstrict abnormally in response to nonspecific stimulants such as cold air, and to nonspecific bronchoconstrictors such as methacholine.

This has led to the characterisation of asthma as a disease associated primarily with bronchial mucosal inflammation which results in the release, from mast cells and cells derived from the blood, of a wide variety of potentially bronchoconstricting mediators - leukotrienes, histamine, PAF and prostaglandins. Some of these mediators may also cause vasodilatation, mucosal oedema and increased bronchial secretions. These multiple actions of multiple mediators have different time courses, so that at any one moment airflow obstruction may be due to various degrees of bronchoconstriction, mucosal swelling and intraluminal secretory blockage.

It is probable that this complex inflammatory response, triggered by allergic mechanisms, nonspecific irritants or infection, is then responsible for the symptomatic variability of asthma and for such phenomena as nocturnal asthma, exercise-induced asthma and the increased diurnal variability of airways resistance shown by some

asthmatics even during complete remission of symptoms. In short, the most important feature of asthma is **reversibility**, either spontaneous, or in response to treatment.

- (4) **COPD.** We may expect to find in most cases a combination of the features described above under chronic bronchitis and emphysema, with perhaps some additional evidence of persistent airways inflammation. In small bronchi and bronchioles there is patchy thickening of the wall with some muscle hypertrophy, together with fibrosis and stenosis. This, worsened by the tendency to exaggerated expiratory collapse, is the main site of airflow obstruction in COPD.

The inflammation seen in COPD is not the same as in asthma. In the latter there is an increase in CD4 lymphocytes, an increase in eosinophils, thickening of the basement membrane and epithelial damage. In COPD there is a predominance of CD8 cells, an increase in neutrophils, no basement membrane thickening and an intact epithelium, but with squamous metaplasia (6). Studies on induced sputum show increased tumour necrosis factor- α and cytokine interleukin-8 in COPD (7) (as opposed to interleukin-5 in asthma (8)), but effects of oral or inhaled steroids on these and other inflammatory mediators were not significant in COPD (9) . However others have found that inhaled steroids decreased chemotaxis and therefore neutrophil recruitment to airways in COPD, and some improvement in the proteinase-antiproteinase balance ¹⁰.

The loss of elastic recoil together with peripheral airways obstruction leads to progressive air trapping and hyperinflation, which proceeds in tandem with airspace coalescence and loss of alveolar-capillary membrane. Residual volume and functional residual capacity increase. Vital capacity is at first relatively well preserved, so total lung capacity often increases. Eventually the well-known picture of hyperexpanded thorax with flat diaphragms¹ and poor respiratory movements - "barrel chest"-develops. The respiratory muscles must then work under a mechanical disadvantage with impaired efficiency.

3. COPD: AETIOLOGICAL FACTORS

By far the most important cause of COPD is smoking. Smoking interferes with mucociliary function, is associated with mucous gland hypertrophy and hypersecretion, and increases the leucocyte numbers in the lungs with a resulting greater load of proteolytic enzymes. Free oxygen radicals from tobacco smoke and from stimulated neutrophils can oxidise and inactivate α_1 -antiproteinase, upsetting the proteinase-antiproteinase balance.

Not every life-time smoker gets COPD. Lung function, as measured by forced expiratory volume in one second (FEV_1 - see below) reaches a maximum at about the age of 25, then slowly declines at about 35 ml per year (11) in normal non-smokers (Fig. 2). This slow decline, losing about one quarter of the original FEV_1 by age 75, rarely causes problems except in extreme old age. Some smokers follow this benign path, but others, the group susceptible to smoking, follow a steeper track, presenting in middle life with symptoms and signs of COPD, symptomatic perhaps in their fifties and disabled in their sixties. There is an important beneficial effect of giving up smoking, since the rapid decline in FEV_1 reverts to the

¹ In severe COPD, a chest X-ray will show changes of hyperinflation etc, but the vital use of the chest X-ray at district hospital level is to diagnose or exclude more important and treatable conditions such as TB or pneumonia.

normal gentler slope. The vertical distance between the normal line and the line followed by the ex-smoker (Fig. 2) reflects the irreversible damage done by previous smoking.

The reason why some smokers react to tobacco smoke by developing COPD and others do not is unknown. Two reasonable hypotheses exist (12). The 'Dutch' hypothesis is that the susceptible smoker has an asthmatic tendency with airways hyper-responsiveness which is too mild to present as overt asthma (in the non-smoker), but which is brought out by smoking in the form of COPD. The 'English' hypothesis is that in some smokers recurrent bronchopulmonary infections lead to progressive damage to small airways. The slow time course of this process and the impossibility of controlled (smokers vs non-smokers) prospective studies accounts for the fact that neither hypothesis has been proven.

There is a gender difference for the effects of smoking, with more severe effects on lung function, and more hospitalisation, in women (13) ²

Other important, but less dominant causes of COPD include environmental pollution both outdoor and indoor, occupational dust exposure, socioeconomic status and childhood respiratory infections. These are fully considered by Bumgarner and Speizer ¹ pp 597-600. Special cases of indoor air pollution are to be found in developing countries. Fluctuations in air pollution can be correlated with hospital admission rates, so air pollution has acute as well as long term effects ¹⁴.

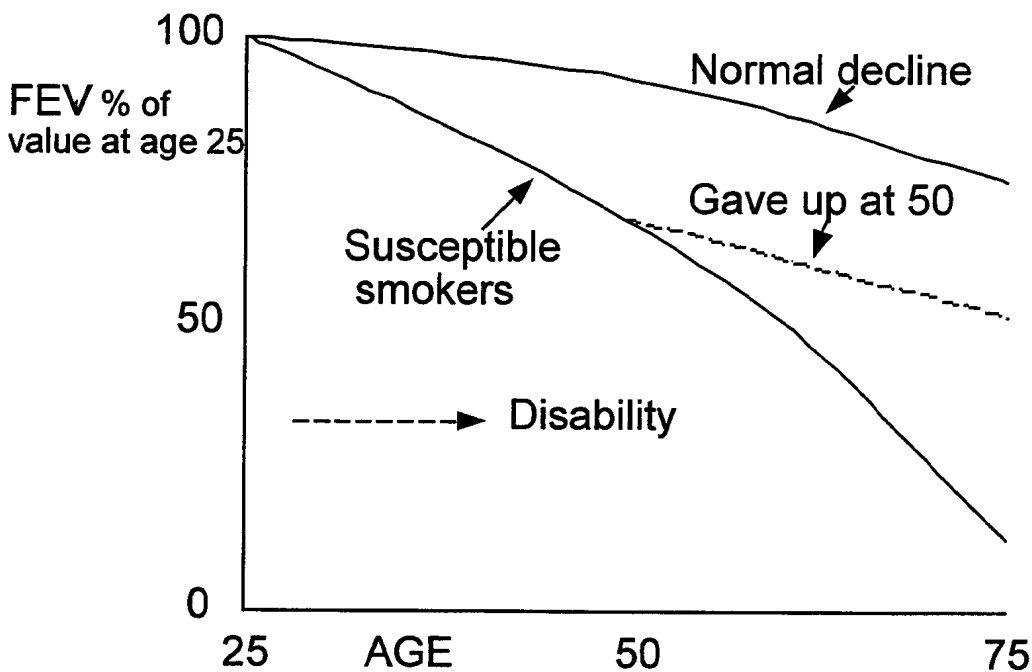


Figure 2. The normal decline of FEV₁ with age, compared with that of susceptible smokers. The potential effect of giving up smoking is shown by a dotted line. This is a schematic representation after Fletcher and Peto (11).

² This gender difference may be aggravated by the effects of indoor pollution in the home to which mainly women are exposed to (e.g. cooking on biofuels and inadequate ventilation).

4. CLINICAL FEATURES

COPD presents typically in middle or later life (Fig. 2) with the primary symptom of breathlessness, often with chronic productive cough. With excessive air pollution as well as smoking, or if there is α_1 -antitrypsinase deficiency, it may present at a younger age. By the time of presentation, airflow obstruction is at least moderate and essentially irreversible, in the sense that no form of treatment can return lung function to normal. As FEV₁ approaches and falls below 1 litre, breathlessness becomes progressively disabling, and respiratory failure (see below) ensues. Wheeze is a frequent but not invariable feature.

Frequent bronchial infections may occur without evidence of serious systematic illness, especially in patients with chronic bronchitis, where the excess secretions, poor mucociliary function and abnormal small airways are thought to predispose first to bacterial colonisation and then to infection, particularly with *H. Influenzae*, *Strep. Pneumoniae* and *Moraxella catarrhalis*. Bronchopneumonia, not surprisingly, may follow the airways infection, when the bacteriological possibilities extend to cover the range of community-acquired or nosocomial pneumonia, depending on the environment.

Although the progress of the disease is slow and (if smoking continues) inexorable, as opposed to the story in asthma, which is characteristically variable and episodic, patients with COPD do suffer intermittent episodes of deterioration with increased breathlessness which may make the differential diagnosis from asthma difficult. These are superimposed on the general slow downhill course, and are often called "acute exacerbations" of COPD. Sometimes they are patently due to superimposed infection, but frequently no precipitating cause for these exacerbations can be found.

Many patients with COPD and an FEV₁ less than 50% predicted normal will have Type I respiratory failure, with low arterial partial pressure of oxygen (PaO₂), but normal or slightly low PaCO₂. A minority of patients subsequently develop Type II respiratory failure. Here PaO₂ is typically very low, causing central cyanosis, while PaCO₂ rises. Prolonged severe hypoxia stimulates the release of erythropoietin with resulting compensatory polycythaemia and causes pulmonary arteriolar vasoconstriction with subsequent vessel wall remodelling and fixed pulmonary hypertension, itself exacerbated by the high viscosity of the polycythaemic blood. Right ventricular hypertrophy and right heart failure with peripheral oedema follows. This is the commonest cause of cor pulmonale.

5. LUNG FUNCTION TESTS

In COPD we expect to find evidence of

diminished elastic recoil;

relatively fixed airflow obstruction with hyperinflation; and

impaired gas exchange.

(1) Diminished elastic recoil

Lung compliance can be measured using oesophageal pressure as an approximation to pleural pressure, but the necessary oesophageal catheter is invasive and uncomfortable for the subject. Compliance measurements are used therefore in research with appropriate ethical permission, but rarely in clinical practice.

(2) While vital capacity (VC) is easily measured by spirometry, absolute lung volumes (total lung capacity -TLC, residual volume -RV, and residual functional capacity -FRC) are needed to assess *hyperinflation* and need more complicated and expensive apparatus. They can be measured by whole body plethysmography or, more usually in clinical practice, by a helium dilution technique.

Airways resistance can be measured directly by whole body plethysmography, but surrogate measurements derived from single forced expiratory manoeuvres are relatively simple, cheap and adequate for both epidemiological and clinical studies.

In the context of COPD, the relevant measurements can best be understood by considering the maximum expiratory flow-volume (MEFV) loop (Fig 3). The manoeuvre required by the subject is a single forced expiratory vital capacity (FVC), that is from TLC to RV. It cannot be over-emphasised that while this may seem a simple manoeuvre on paper, it is not always easy to obtain an accurate recording in the field. It is essential that the subject should

take an absolutely full breath in;

grip the mouth-piece so that no leak of gas occurs at the mouth;

have the nose occluded by nose-clip or finger and thumb;

breathe out with maximum force;

go on breathing out until all possible gas has been expelled.

Expelling the last fraction of gas close to RV can be exquisitely uncomfortable for patients with asthma or COPD - indeed it may induce coughing which inaccurately terminates the manoeuvre. To obtain technically correct and repeatable results from subjects in the field requires great skill from the supervisor, who therefore needs careful training.

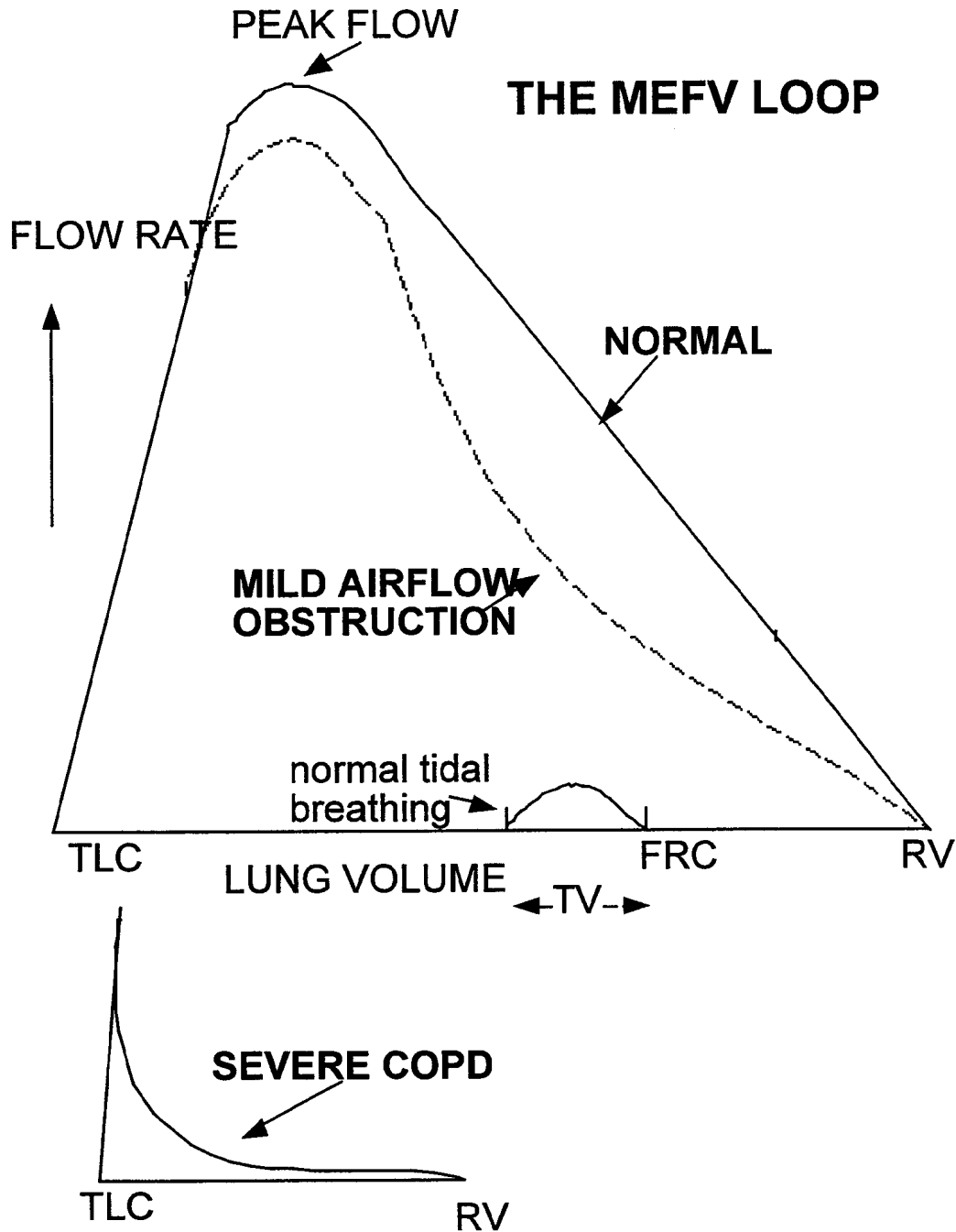


Figure 3 A maximum expiratory flow-volume (MEFV) loop shown schematically for a typical normal subject and a patient with mild airflow obstruction (dotted line), superimposed on the same volume scale. Below is a loop from a patient with severe COPD ; same volume scale. TLC - total lung capacity. TV - tidal volume. FRC - functional residual capacity. RV - residual volume

In the resulting flow-volume loop, volume is electronically plotted on the x-axis, moving during the manoeuvre from left to right, from TLC to RV. Flow is simultaneously recorded on the y-axis. The peak flow rate is reached early in the vital capacity manoeuvre and then in normal subjects there is usually a rather linear fall to RV. When the MEFV loop is compared with the small loop obtained, on the same volume scale, during tidal breathing at rest, there is a large vertical distance between the two loops which reflects the flow reserve which can be mobilised if ventilation needs to be increased - as during exercise.

In mild airflow obstruction, peak flow is relatively well preserved, but flow in the right hand half of the VC impinging on RV is disproportionately decreased, giving a general concave-up shape. Flow measurements taken in this part of the MEFV loop are more sensitive to detect minor degrees of obstruction. A further advantage of flow measurements in this area is that they are relatively effort independent. This is because flow is limited as RV is approached by airways narrowing on forced expiration (Fig 1), rather than by the maximum effort of the subject - provided that a certain critical (but less than maximum) effort is achieved, all greater efforts produce the same curve. Hence flow measurements in the lower half of VC are more repeatable than peak flow rates.

In severe COPD, RV is increased with hyperinflation and VC is diminished, and the area of the MEFV loop is grossly diminished (Fig 3) with a narrowly spiked peak flow rate and a rapid diminution to very low peak flows. The tidal volume flow loop (not shown in Fig. 3) coincides with the maximum expiratory flow rate, so there is no flow reserve which can be recruited to increase ventilation. During exercise, expiratory flow can only be increased by moving FRC to the left, which worsens the hyperinflation.

The peak flow rate ¹⁵ in normal subjects and patients with mild and moderate airflow obstruction (most asthmatics) changes directionally with other indices of airways obstruction, since it occurs before significant expiratory airways collapse occurs. In severe COPD the peak flow spike reflects the sudden expulsion of gas from rapidly collapsing central airways, bears no relation to spontaneous breathing in these patients, and is of no use for following changes in their respiratory state.

Apparatus which measures the MEFV loop will, given a timing mechanism, also record the volume which is recorded in the first second of the FVC manoeuvre, the forced expiratory volume in one second (FEV₁). A low FEV₁ by itself does not signify airways obstruction, since it must be diminished if VC diminishes for any cause, and will be diminished, for example, in severe restrictive lung disease such as pulmonary fibrosis. The ratio of FEV₁/FVC, if low, does diagnose airways obstruction. In recently published guidelines ², COPD is characterised by FEV₁ <80% predicted **and** FEV₁/FVC ratio <70%. Once the diagnosis is made, FEV₁ may be used, and is most commonly used, to follow changes in airways obstruction, spontaneous or induced by treatment. It is then a surrogate measurement for airways resistance. Although FEV₁/FVC is essential to diagnose airways obstruction, it is a potentially misleading index of change in clinical state. For example a bronchodilator given to an asthmatic with low FEV₁/FVC will generally cause improvement in both FEV₁ and in FVC, but sometimes the improvement in FVC may be proportionately greater than that in FEV₁, so that while airflow obstruction has undoubtedly improved, FEV₁/FVC has in fact decreased.

Forced expiratory time (FET) going from TLC to RV correlates well with FEV₁ and with FEV₁/FVC, a FET of >6 seconds indicating airways obstruction. The longer the FET, the worse the obstruction. A watch with a second hand and a stethoscope to listen over the trachea are the only tools required. However in a study designed to test the suitability of FET as a clinical and epidemiological tool ¹⁶, it was found to have satisfactory sensitivity (92%) but poor specificity (only 43%), with 56% of nonobstructed subjects being misclassified.

Historically, first spirometric measurements were of timed volume changes, so that FEV₁ and FVC were introduced early. Later flow was obtained by differentiation of the volume signal to enable a flow-volume loop to be recorded. Still later, because volume spirometers are bulky

and flow-meters small, the primary measurement changed to flow (e.g. from a turbine flow-meter) which was then integrated to give volume. Such instruments with electronic read-outs of required variables, are easily portable.

Measurements of peak flow rate, made with specially designed small cheap meters, are widely used in asthmatics where the characteristically rapid changes in airflow resistance demand frequent measurement, often several times daily, in the home by the patient¹⁵. In COPD, where changes in airways resistance are relatively slow, and peak flow rate may be unrepresentative of airway calibre (see above), measurements of more prolonged forced expiration, particularly FEV₁, are adequate to follow clinical progress or response to treatment at relatively infrequent intervals.

Impaired gas exchange in COPD is routinely assessed by measurement of diffusing capacity, or transfer factor for carbon monoxide (CO), using a single inspiration of a very low concentration of CO followed by a 10 sec breath-hold, followed by a measurement of CO in the following expirate. This is often done with the same apparatus used to measure absolute volumes by helium dilution. Blood gas measurements are required for detecting and monitoring respiratory failure in or between acute exacerbations and especially in cor pulmonale, and for assessment for suitability for long-term domiciliary oxygen therapy. Measurement of arterial O₂ saturation by non-invasive pulse oximetry is used in special circumstances - for example to measure hypoxia during sleep, or on exercise - and can be used to guide treatment with oxygen when PaCO₂ is known to be normal or low.

6. TREATMENT AND PREVENTION

The only present treatment which might in theory radically alter the prognosis in patients with COPD would be to replace α_1 -antitrypsin in those patients with abnormally low plasma levels. Intravenous therapy with a human product has been available in several countries since 1989. Unfortunately it has not proved possible at any site to do a controlled trial, and it seems unlikely that such a trial will take place¹⁷. The most recent results with a large uncontrolled series in 443 patients with severe α_1 -antitrypsin deficiency, recruited between 1989 and 1995, show that long-term treatment is feasible and safe¹⁸. The rate of decline in FEV₁ observed in these treated patients is *probably* less than in historical controls with COPD not so treated.

The remainder of this section contains highly summarised selections from the British Thoracic Society Guidelines for the Management of COPD¹⁹. It is helpful to follow their division of cases into mild (FEV₁ 60-80% predicted normal), moderate (40- 59%) and severe (<40%).

Nonpharmacological treatment. Smoking cessation is the most important modality of treatment. It is worth encouraging weight loss in the obese and regular natural exercise. Immunisation against influenza is recommended, as for any patient with chronic lung disease.

Pharmacological treatment is for mild cases: inhaled bronchodilators as required, either β_2 -agonists or anticholinergics, for moderate cases: bronchodilator treatment as above, but both types of drugs may be required, and at regular intervals rather than as required. for severe cases: regular continued bronchodilator therapy with both types.

A formal trial of oral steroid therapy should be performed at the moderate or severe stage.

In more advanced disease, the following expensive treatment modes are available in developed countries.

Outpatient pulmonary rehabilitation programmes. Trials of rehabilitation programmes generally show significant benefit, but many involve more than one modality of treatment, and not all of these have been separately tested, so it is difficult then to separate beneficial from non-beneficial effects. For example taught diaphragmatic breathing improves blood gases but may worsen breathlessness (20). It is likely that effective programmes which involve controlled exercise require long-term supervision (21). More effective programmes may imply more technical and therefore more expensive facilities. A device which assists, via a nasal mask, ventilation proportionately to the effort generated by the patient can increase exercise tolerance in patients with severe COPD, and has been suggested for trial in exercise rehabilitation (22).

Long-term oxygen therapy (LTOT)³. Two trials have shown that this prolongs life in severely hypoxic patients (23,24). It is best provided by an oxygen concentrator and nasal prongs. It should in general be provided for patients with $\text{PaO}_2 < 7.3$ kPa (55 mm Hg), with or without hypercapnia, and $\text{FEV1} < 1.5$ l, and in those who have had an episode of cor pulmonale. It requires measurement of blood gases and long-term clinical supervision. The combination of LTOT and assisted ventilation in outpatients is now being explored (25).

Surgery. Lung volume reduction surgery has produced good results in selected patients (26).

6.1 Treatment of acute exacerbations

Patients sufficiently ill to require hospital admission require

Low flow oxygen with concentration and flow rate controlled by measurement of blood gases⁴ **Antibiotics** if two of the following three features are present: increased breathlessness; increased sputum volume; purulent sputum.

Nebulised bronchodilators, in higher than standard doses.

Diuretics for overt right heart failure (cor pulmonale)

Oral corticosteroids only if the patient is already on them, or there is a previously documented response to corticosteroids, or airflow obstruction does not respond to increased bronchodilators, or this is the first presentation of airflow obstruction.

Chest physiotherapy is traditionally recommended for patients with increased or purulent sputum, but there are few data to support or refute its use²

Some patients will prove to need

Assisted ventilation, intermittent positive pressure ventilation, either following intubation or by some non-invasive application (for example per-nasal).

6.2 Anti-smoking programmes

It should be realised that a successful programme in primary prevention will not produce beneficial health or economic effects for about 30 years, for it is only after that length of time

³ In the absence of long-term oxygen therapy, which means at least 15 hours per day and oxygen concentrators palliation consists purely in the appropriate use of bronchodilators and treatment of chest infections.

⁴ In the absence of measurement of blood gases, the oxygen flow per nasal prongs should be restricted to 2 litres per minute in patients with COPD.

that the patient with COPD becomes symptomatic and then potentially expensive in any health care system. This contrasts with the position in myocardial infarction and stroke, where smoking cessation induces a decrease in risk of about 50% within one year (27) .

Moreover, no primary prevention programme has so far been effective in Western countries (28) .

In secondary prevention, again in European countries, although 14% of smokers intend to quit in the next six months, only 2-3% of smokers attempting to quit finally succeed, and only half of those who have ever smoked can quit during their lifetime. Thus the majority of motivated quitters fail. (Quoted from Jiménez-Ruiz and colleagues (29), who give relevant references). They have suggested that reduced smoking should be explored as a valid method of reducing tobacco-related harm in those unwilling or unable to quit smoking (29,30).

It is certain that cessation programmes must include nicotine replacement by some route (31). Many trials take cessation for one year as the end-point for success, and a success rate of about 30% is typical. However about half of the one-year successes relapse within the next two years (32).

6.3 Future possibilities in treatment

Barnes (33) has outlined the possibilities of drugs now in development which may prove useful in COPD. These include leukotriene B4 antagonists, 5-lipoxygenase inhibitors, new phosphodiesterase inhibitors, new antioxidants, and neutrophil elastase inhibitors.

7. PUBLIC HEALTH SIGNIFICANCE OF COPD

This is covered in detail by Bumgarner and Speizer (1) pp 598-602. To summarise important points;

- (1) COPD is a major public health problem. (In general practice in the UK consultation rates relating to COPD are 2-4 times the equivalent rates for angina).
- (2) Death rates from COPD are increasing, more rapidly for women than for men.
- (3) Morbidity for COPD is underestimated.
- (4) Epidemiological evidence for prevalence and incidence is impeded by inconsistent reporting which reflects difficulties with definition, and perhaps lack of interest compared with illnesses more prominently publicised such as cancer, heart disease and infections.
- (5) Data on COPD in the developing world are sparse, but COPD is probably a more important cause of death and illness there than in industrial nations.
- (6) The incidence of COPD in developing countries is set to increase, first because of the increasing fraction of the population which will reach middle and later life, when COPD becomes symptomatic, and second because of the progressive increase of smoking throughout the developing world.
- (7) Reasoned estimates of projected mortality due to COPD (Bumgarner and Speizer (1) p600, Table 24:1) suggest that this will more than double, worldwide, between 1985

and 2015, and that this rise will be largely influenced by increases approaching three-fold in developing countries.

8. MORE PROBLEMS WITH DEFINITIONS AND TREATMENT.

THE READER MAY WELL HAVE BECOME INCREASINGLY UNEASY ABOUT THESE IN THE CONTEXT OF DESIGNING EFFECTIVE PUBLIC HEALTH PROGRAMMES, AND WITH JUSTIFICATION.

The diagnosis of chronic bronchitis is still based on the symptoms of chronic cough with sputum, and this is likely to continue since the relevant pathology is inaccessible except on a research basis, and no practical surrogate tests exist, or are likely to. It is often difficult to exclude other diseases which could cause chronic productive cough and when this is done cases where chronic bronchitis might coexist (e.g. smoking patients with left ventricular failure) may be wrongly excluded. It is now accepted that cough, often productive, is a frequent symptom in undoubted asthma, and that indeed asthma may present with cough and without wheeze (34).

Emphysema, on the other hand, will continue to be defined pathologically, although the pathology is again inaccessible during life, even by biopsy. The grosser changes can now be better visualised and quantified by modern imaging techniques, especially CT scanning, but this is expensive and unsuited to work with large numbers of patients, or to routine investigation.

The definition of COPD is becoming even further complicated by the problem of distinguishing chronic asthma, and of steroid resistance in asthma. In the BTS Asthma Guidelines (19), for example, treatment protocol depends on the answer to the question “If the airways obstruction “ is generalised, is it asthma (predominantly reversible) or COPD (predominantly irreversible) or a combination of the two?”

Thus present BTS guidelines suggest that before making a diagnosis of COPD in a patient with chronic airflow obstruction, a trial of high-dose oral steroids is needed to separate responding patients who will then be classified as having chronic asthma. Such a trial requires close medical supervision. In a group of patients diagnosed as having COPD, given a trial of high-dose oral steroids, and investigated by examination of broncho-alveolar lavage fluid and bronchial biopsies, those patients who responded had significantly more features of asthma - more eosinophils, a higher level of eosinophil cationic protein, and a thicker basement membrane (35).

But we should be reminded of the “Dutch” hypothesis, that patients who are susceptible to smoking and develop COPD are in fact sub-clinical asthmatics; and that the airways of patients with COPD often show some inflammatory changes; and of the hypothesis that patients with COPD, although apparently not responsive to a short (two week) trial of high-dose oral steroids might yet respond to long-term inhaled steroids in safe dosages.

This is the thinking behind three controlled trials of inhaled steroids in COPD (36-38), and results from Paggiaro and colleagues (36), just published, and reviewed by Barnes (39), are that treated patients had no fewer exacerbations, but that the exacerbations they had were significantly less severe. Small but significant improvements were found in lung function, cough and sputum volume, and walking distance. (Many physicians have treated patients with

COPD with inhaled steroids in advance of evidence of efficacy, but on the basis that side effects from such treatment are minimal, and benefit possible).

The border between COPD and chronic asthma in smokers is becoming less rather than more defined.

8.1 Primary prevention

The prevention of COPD requires action

- (1) to institute (if not already started) and continue intensive smoking control programmes focussed particularly on children and young adults;
- (2) to set in place investments and programmes to reduce both indoor and outdoor pollution; and
- (3) to improve care and the general environment, including nutrition, of children suffering from frequent respiratory illnesses.

These aims require action at several levels within government and community, set out and rationally prioritised by Bumgarner and Speizer (1) p 602.

8.2 Case management and secondary prevention

It would clearly be advantageous to find patients with early COPD, in the 20-40 age group, where the FEV₁ is falling at the abnormally fast rate which characterises susceptible smokers, and then actively promote smoking cessation in this special situation which will produce proven benefit.

Unfortunately at present there are no clear methods of identifying such patients routinely. The FEV₁ will have decreased, but at the rate of 35 ml/year will have fallen only 350 ml at age 35, and 700 ml at age 45. The residual standard deviation about the regression line for the normal range of FEV₁ in a 40 year old white male is about 0.5 l (40) . Thus FEV₁ from many such patients will be within the normal range.

Questionnaire techniques were originally used to identify patients with chronic bronchitis, and have more recently been used to identify asthmatics (41), but patients with early COPD often neither cough nor wheeze, nor do they complain of breathlessness. Since they typically present eventually with already moderate derangement of lung function, it may be that they have spontaneously diminished their normal day-today exercise levels to match their progressively diminishing lung function. If this is so, it may be that questionnaires designed to assess, in smokers, habitual maximum exercise levels, together with mild breathlessness and cough, combined with lung function measurements, might identify a useful proportion of these patients with potentially remedial disease. Lung function tests derived from flow measurements in the lower part of the vital capacity range (Fig 3) might here prove more discriminative than FEV₁. At the present moment, we have no way of identifying these patients. It is all the more important that smoking cessation should be strongly recommended to *all* smokers.

Turning to patients with symptomatic COPD, they can be found by questionnaires which test for cough, sputum, breathlessness and wheeze, together with measurements of FEV₁, in the >35 years age group. (It should be noted that questionnaires have been developed and

validated which measure symptoms, quality of life, or changes in these variables, specifically designed for patients with COPD. They require translation and revalidation when applied to populations with different languages and ethnic composition (42,43).

The population found by identifying the above symptoms plus evidence of airflow obstruction will include patients with asthma, heart failure, bronchiectasis, tuberculosis and other rarer conditions. Further definition of diagnosis within this group demands individual clinical attention, and in the case of overlap between COPD and chronic asthma, a trial of high-dose oral steroids. A conventional course in Europe would be 30-40 mg prednisolone daily for 2 - 3 weeks (12), but higher doses, up to the order of 100 mg/day, may be used in the US (35). Both these dosage levels will produce diabetes, hypertension or fluid retention in an important fraction of predisposed patients in this age group. Thus such a trial demands close individual supervision from a physician. It must also be assessed by intermittent measurement of FEV₁, since the placebo effect of any oral therapy may be exaggerated by the euphoria commonly produced by oral steroids in these doses. If spirometry is too expensive, twice daily PEFr may be sufficient in patients with COPD of moderate severity.

Therefore, unless there is considerable determination, combined with expansive facilities both in field surveys and in later clinical supervision, it seems unlikely that a specific search for symptomatic, but undiagnosed COPD would be financially viable.

On the other hand we know that not only COPD but also asthma (44) is still underdiagnosed. It would seem then more profitable to look for undiagnosed but effectively treatable asthma, which could be done with existing questionnaires and simple lung function testing. A COPD project might then ride on the back of such asthma programmes, identifying smokers with relatively fixed airways obstruction who could reasonably be motivated and assisted to stop smoking and rationally treated, perhaps with routine simple bronchodilators, and, if presently running trials prove favourable, inhaled steroids.

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APPENDIX 1

Peak flow meters⁵

Clement Clarke (Mini Wright)	£7
Vitallograph	£5
Multispiro	£10
Ferrari	£300
Respironics: Healthscan	£9

Spirometers⁶

Micromedical	£195
Mir	£235
Clement Clarke	£295

⁵ Study of Hans Folgering et al in ERJ 1998, 11, 188-193.

⁶ Battery driven, measuring both FVC and FEV₁