Bronchial and extrabronchial factors in chronic airflow obstruction

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Leaver, D. G., Tattersfield, A. E., and Pride, N. B. (1974). Thorax, 29, 394–400. Bronchial and extrabronchial factors in chronic airflow obstruction. Chronic airflow obstruction may be due either to disease of the airway wall and lumen or to loss of airway-distending forces acting on the outer wall of the bronchus. In 17 patients with chronic airflow obstruction the relative importance of bronchial and extrabronchial factors was assessed by analysing the relation between airways conductance and static transpulmonary pressure over a range of lung volumes. Using previously established clinical, radiological, and functional criteria (which did not include measurements of the mechanical properties of the lungs), six of these patients had evidence of widespread emphysema and six patients had predominant 'bronchial' disease. In four of the six 'emphysematous' patients there was no functional evidence of disease of the bronchial wall or lumen during quiet breathing, and airway narrowing could be explained by loss of airway-distending forces. The six patients with characteristic 'bronchial' features showed functional evidence of disease of the bronchial wall or lumen.

In 1955 Dornhorst described two contrasting types of patient with chronic irreversible airways obstruction—the first characterized by disabling breathlessness without cyanosis or tendency to heart failure ('pink and puffing') and the second in whom the clinical picture was dominated by cyanosis and recurrent right heart failure ('blue and bloated'). Subsequently numerous clinical and physiological studies have confirmed this broad distinction (Ogilvie, 1959; Richards, 1960; Fletcher, Hugh-Jones, McNicol, and Pride, 1963; Mitchell, Vincent, Ryan, and Filley, 1964; Briscoe and Nash, 1965). On the basis of an extensive clinicopathological study, Burrows *et al.* (1966) proposed that these two contrasting presentations of chronic airways obstruction could be regarded as respectively the 'emphysematous' and the 'bronchial' types of airway obstruction. In their study the distinction between these two types in life was based on clinical and radiological features and three tests of pulmonary function (CO transfer factor by the single breath method, total lung capacity, and the arterial carbon dioxide pressure), none of which was a direct measurement of airflow obstruction. Recently we have analysed the contributions of disease of the bronchial wall and lumen and of loss of extrabronchial distending forces to the airway narrowing of 17 patients with chronic airflow obstruction (Leaver, Tattersfield,

and Pride, 1973). It might be anticipated that these two contrasting mechanisms of airway narrowing would be characteristic of 'bronchial' and 'emphysematous' disease respectively. In the present paper we have used the criteria of Burrows *et al.* (1966) to classify the patients in our previous study into subgroups with marked 'bronchial' and 'emphysematous' features and have examined whether there are differences in the mechanisms of airflow obstruction between these two subgroups.

MATERIAL AND METHODS

PATIENTS STUDIED AND CLINICAL AND PHYSIOLOGICAL TECHNIQUES Seventeen patients (16 men and 1 woman, average age 61.4 years) with chronic airflow obstruction were studied. The forced expiratory volume in one second (FEV₁) varied between 0.4 and 1.7 litres, with a mean of 1.02 litres. All the patients had chronic cough and expectoration, were present or ex-smokers, and had been under medical observation for at least two years during which time there had been little variation in their airflow obstruction either spontaneously or after treatment. Ten normal subjects (9 men and 1 woman, average age 34.5 years) were studied using the same methods. Only two of these subjects were cigarette smokers, none had any respiratory symptoms, and in all spirometry and the chest radiographs were normal.

Heart failure was diagnosed if oedema was accompanied by a raised jugular venous pressure. Sputum volumes

were assessed by collections made in the first hour after waking. The radiological diagnosis of emphysema was based on the presence of widespread attenuation of the smaller pulmonary vessels and was made by one radiologist. The FEV₁ was measured with a dry spirometer with automatic timer. The transfer factor for CO (TFco) was measured by the single breath technique (Ogilvie, Forster, Blakemore, and Morton, 1957) and results were also expressed as transfer factor per litre lung volume (TF/VA). In calculating this ratio lung volume was expressed in litres of dry gas at standard temperature and pressure. Mixed venous carbon dioxide pressure (PvCO₂) was measured by the rebreathing method (Campbell and Howell, 1962); the PvCO₂ predicted from the FEV₁ was derived from the formula of Burrows, Strauss, and Niden (1965): $PvCO_2 (\text{mmHg}) = 11.5/FEV_1 + 36.7$, where FEV₁ is expressed in litres. Total lung capacity (TLC) was measured in a constant-volume body plethysmograph (DuBois *et al.*, 1956a). Airways conductance was measured in the plethysmograph by the panting technique (DuBois, Botelho, and Comroe, 1956b) at a variety of lung volumes; at each lung volume conductance was measured at an inspiratory flow rate of 0.5 litre sec⁻¹. Static transpulmonary pressure (difference between mouth and oesophageal pressure) was measured by the oesophageal balloon technique. A balloon volume of 0.5 ml was used and static expiratory pressure-volume curves were obtained after a standard volume history of three full inflations (Milic-Emili, Mead, Turner, and Glauser, 1964). From these measurements at different lung volumes a conductance-static transpulmonary pressure plot was constructed for each patient. A line of best fit was drawn by eye to obtain the slope (Δ conductance/ Δ static transpulmonary pressure) of this plot. Static lung compliance was taken as the slope of the expiratory transpulmonary pressure-volume curve between the resting expiratory level (functional residual capacity, FRC) and 500 ml above FRC. Normal values of FEV₁, TFco, and TLC were obtained from the nomograms published by Cotes (1968).

SUBDIVISION OF PATIENTS INTO 'EMPHYSEMATOUS', 'BRONCHIAL' AND INDETERMINATE SUBGROUPS The 17 patients were divided into those with type A disease ('emphysematous'), type B (absent or mild emphysema and marked 'bronchial' features), and type X disease (indeterminate) by clinical, radiological, and functional criteria similar to those used by Burrows *et al.* (1966). Type A disease was diagnosed if the chest radiograph showed widespread attenuation of the peripheral vascular pattern. Type B disease was diagnosed when there was no radiological evidence of emphysema and there were in addition at least two (and usually three) of the following features: (1) persistent expectoration of 5 ml or more of sputum in the first hour; (2) PvCO₂ 6 mmHg or more above the level predicted from the FEV₁; (3) TF/VA over 3.50; (4) chronic or recurrent heart failure due to persistent cor pulmonale. Patients who could not be classed as either type A or type B by these criteria were classed as type X. Two criteria used for this subdivision by Burrows *et al.* were not used in the current study—radiographic evidence of chronic inflammatory disease in the lung parenchyma

(which was not observed in any of the 17 patients) and a total lung capacity less than 100% of the predicted value. In the present series, total lung capacity was measured by the body plethysmograph method, which gives larger values in patients with severe airflow obstruction than the gas dilution methods used by Burrows *et al.*, and only one patient had a value below that predicted. One other criterion was slightly modified, a sputum volume of 5 ml or more in the first hour collection being taken as equivalent to a volume of 10 ml or more over 24 hours (Miller, Tinker, and Fletcher, 1965).

ANALYSIS OF MECHANISM OF AIRFLOW OBSTRUCTION Airway calibre is determined by the interplay of the intrinsic properties of the airway wall and lumen and the extrinsic forces acting across the wall tending to distend or compress it. During quiet breathing these extrinsic forces will distend the airway. Hence airway narrowing may be caused either by intrinsic obstruction of the airway (defined as a reduced airway lumen at a standard airway distending pressure) or by loss of airway-distending forces (Dayman, 1951).

To distinguish between these two forms of airflow obstruction in life it is necessary to examine the relationship between airway size and airway-distending pressures. An overall indication of the size of the airways can be obtained by measuring airways conductance (the reciprocal of airways resistance) at low flow rates in the body plethysmograph. The value of conductance potentially provides a sensitive estimate of airway radius, since the conductance of a tube is proportional to the fourth power of its radius. Airway-distending pressures cannot be estimated so directly but theoretical and experimental studies (Butler, Caro, Alcalá, and DuBois, 1960; Mead, Takishima, and Leith, 1970; Stubbs and Hyatt, 1972) indicate that during breath-holding or breathing at low flow rates the pressure distending the intrathoracic airways is probably similar to the pressure distending the lung as a whole, which is static transpulmonary pressure. Therefore by relating airways conductance (indicating overall airway dimensions) to static transpulmonary pressure (indicating airway-distending forces) it is possible to demonstrate whether airway narrowing is due to loss of airway-distending forces or to disease of the bronchial wall or lumen itself. In practice it is preferable to measure this relationship over a range of lung volumes and to obtain the value of Δ conductance/ Δ static transpulmonary pressure (Fig. 1) rather than to rely on values close to FRC where absolute differences in conductance with contrasting mechanisms of airflow obstruction will be smaller. Δ conductance/ Δ static transpulmonary pressure is in some ways analogous to a measurement of airway distensibility and will be reduced if individual airways are stiff and indistensible. However, Δ conductance/ Δ static transpulmonary pressure will also be reduced if there is a reduction in the total number of open airways, or if primary airway disease leads to an overall reduction in airway diameters. Hence a reduced Δ conductance/ Δ static transpulmonary pressure indicates disease of the bronchial wall or lumen itself. In contrast, a normal value of Δ conductance/ Δ static transpulmonary pressure will

FIG. 1. Theoretical relationship between airways conductance and static transpulmonary pressure. Disease of the bronchial wall or lumen reduces conductance at any given value of static transpulmonary pressure and also reduces the slope, Δ conductance/ Δ static transpulmonary pressure. With loss of airway-distending forces conductance remains normal for the value of transpulmonary pressure and Δ conductance/ Δ static transpulmonary pressure is unchanged.

be found when airway narrowing is caused solely by a reduction in extrabronchial forces distending the airways.

RESULTS

The mean results of the standard tests of pulmonary function in the 17 patients are shown in Table I. The expected increase in total lung capacity and reduction in transfer factor were observed and the average mixed venous PCO_2 was very close to that predicted.

The 10 normal subjects had an average height of 1.77 metres; mean FEV_1 was 4.15 litres (109% of the predicted value) and mean TLC was 7.33 litres (106% of the predicted value). Transfer factor and mixed venous PCO_2 were not measured in the normal subjects.

SUBDIVISION INTO 'EMPHYSEMATOUS', 'BRONCHIAL', AND INDETERMINATE SUBGROUPS Six patients were placed in the 'emphysematous' group on the basis of widespread vascular attenuation on the chest radiograph. In all of them total lung capacity was greater than 120% of the predicted value, transfer factor per litre of lung volume was less than 1.40 $\text{ml min}^{-1} \text{mmHg}^{-1}$ and the mixed venous PCO_2 was less than predicted from the FEV_1 . Six patients fulfilled the criteria for the 'bronchial' group. Mean values of FEV_1 in these two subgroups were identical but there were large differences in transfer factor and mixed venous PCO_2 levels, and a smaller difference in total lung capacity (Table I). These differences correspond to those described previously (Burrows *et al.*, 1966). The remaining five patients, placed in the indeterminate subgroup, were smaller than those in the other subgroups and had somewhat less severe reduction of the FEV_1 .

TESTS OF PULMONARY MECHANICS Table II shows the results of tests of pulmonary mechanics in the normal subjects and the patients with airflow obstruction. As expected, the patients with chronic airflow obstruction had lower values of conductance and higher values of static lung compliance at functional residual capacity than the normal subjects.

Static lung compliance was greater in the 'emphysematous' than in the 'bronchial' subgroup, but the differences were small. Expiratory pressure-volume curves in the 'emphysematous' patients tended to be displaced to higher volumes and lower transpulmonary pressures than in the 'bronchial' patients but

TABLE I
MEAN VALUES OF STANDARD TESTS OF PULMONARY FUNCTION IN 'EMPHYSEMATOUS', 'BRONCHIAL' AND INDETERMINATE SUBGROUPS

Group	No.	Age (yr)	Height (m)	FEV ₁		Total Lung Capacity		Transfer Factor			Mixed Venous PCO ₂	
				Litres	% Pred.	Litres	% Pred.	ml $\text{mmHg}^{-1} \text{min}^{-1}$	% Pred.	TF/VA*	Absolute Value (mmHg)	Deviation from Pred. (mmHg)
'Emphysematous'	6	62.7	1.69	0.98	36	8.05	132	5.0	21	1.00	43.8	-8.5
'Bronchial'	6	57.2	1.71	0.98	33	7.18	115	12.3	37	3.08	58.5	+9.5
Indeterminate	5	64.8	1.61	1.10	46	7.24	136	10.4	46	2.36	47.6	-0.4
All patients	17	61.4	1.67	1.02	38	7.51	127	9.0	37	2.14	50.1	+0.2

*TF/VA = Transfer factor for CO ($\text{ml mmHg}^{-1} \text{min}^{-1}$) per litre lung volume.

TABLE II
MEAN VALUES OF MEASUREMENTS OF PULMONARY MECHANICS

	No.	Static Compliance at Functional Residual Capacity (litre cmH ₂ O ⁻¹)	Conductance at Functional Residual Capacity (litre sec ⁻¹ cmH ₂ O ⁻¹)	Δ Conductance
				Δ Static Transpulmonary Pressure
Normal subjects	10	0.30 (±0.02)	0.83 (±0.11)	0.111 (±0.013)
Chronic airflow obstruction	17	0.44 (±0.05)	0.27 (±0.03)	0.066 (±0.012)
A 'Emphysematous'	6	0.51 (±0.11)	0.33 (±0.04)	0.100 (±0.024)
B 'Bronchial'	6	0.43 (±0.09)	0.20 (±0.03)	0.038 (±0.008)
X Indeterminate	5	0.36 (±0.03)	0.29 (±0.06)	0.060 (±0.018)
P value (A v B)		N.S.	<0.05, >0.01	<0.05, >0.01

Figures in parentheses indicate 1 standard error of the mean.

there was considerable overlap and only one of the 'bronchial' patients had a pressure-volume curve entirely within the normal range (Fig. 2).

Values of conductance at functional residual capacity in the 'emphysematous' patients were significantly higher than in the patients with 'bronchial' features, although in both groups mean values were below the lower limit of normal (0.4 litre sec⁻¹ cmH₂O⁻¹). The value of Δ conductance/Δ static transpulmonary pressure was within the normal range in four of the six 'emphysematous' patients and the mean value for this 'emphysematous' group as a whole was only slightly below that found in the normal subjects. Values of Δ conductance/Δ static transpulmonary pressure were reduced in the

'bronchial' group. Two of the five indeterminate patients had normal values of Δ conductance/Δ static transpulmonary pressure.

DISCUSSION

In 1951 Dayman first suggested that two different processes—intrinsic obstruction of the airway lumen and loss of airway-distending forces—were likely to be important in airflow obstruction. Although he equated these two contrasting types of obstruction with asthma and emphysema respectively, the 'bronchial' type of airflow obstruction could also be expected to be caused by intrinsic obstruction. These two causes of airway narrowing can be distinguished by measuring the change in conductance as transpulmonary pressure is increased because the value of Δ conductance/Δ static transpulmonary pressure remains normal with loss of airway distending forces but is reduced when there is intrinsic obstruction. In the present study four of the six patients with evidence of widespread emphysema had normal values of Δ conductance/Δ static transpulmonary pressure so that in them abnormalities in conductance could be explained by loss of airway-distending forces without any need to postulate additional disease of the bronchial wall or lumen. In contrast, the six patients in the 'bronchial' subgroup had an abnormal conductance-transpulmonary pressure relationship, indicating the presence of abnormality of the bronchial wall or lumen. Although our normal subjects were considerably younger than the patients, there appears to be no change in conductance at the resting breathing level (Butler *et al.*, 1960) or in Δ conductance/Δ static transpulmonary pressure (Colebatch, Finucane, and Smith, 1973) with increasing age, so this difference should not have influenced our results.

FIG. 2. Expiratory static transpulmonary pressure plotted against lung volume (expressed as % of predicted total lung capacity). Continuous lines show the curves of the six 'emphysematous' patients, and the interrupted lines the curves of the six 'bronchial' patients. Hatched area shows the range of the curves in 10 normal subjects.

In 1960 Butler *et al.* described changes in the value of Δ conductance/ Δ static transpulmonary pressure in patients with chronic airflow obstruction but they did not use this technique to distinguish different mechanisms underlying chronic airflow obstruction. Recently, Colebatch *et al.* (1973) have found nearly normal conductance—static transpulmonary pressure curves (obtained by a different method) in patients with radiological evidence of emphysema but without chronic expectoration. These authors also state that in further unpublished experiments they found reduced values of Δ conductance/ Δ static transpulmonary pressure in patients with clinical evidence of bronchitis. Several other workers have distinguished an 'emphysematous' type of airflow obstruction on the basis of a normal value of conductance at the resting breathing level (Stevens, Orman, and Graves, 1969; Duffell, Marcus, and Ingram, 1970; Penman, O'Neill, and Begley, 1970). This criterion will underestimate the number of patients in whom loss of airway-distending forces can account for the airflow obstruction, since if static transpulmonary pressure is reduced at functional residual capacity, airways conductance will also be reduced. Only two of our emphysematous patients had values of conductance at the resting breathing level at or just above the lower limit of the normal range ($0.4 \text{ litre sec}^{-1} \text{ cmH}_2\text{O}^{-1}$, equivalent to an airways resistance of $2.5 \text{ cmH}_2\text{O litre}^{-1} \text{ sec}$), whereas four of them had normal values of Δ conductance/ Δ static transpulmonary pressure. Hence we prefer to measure the conductance/ Δ static transpulmonary pressure slope to distinguish airway narrowing due to loss of airway-distending forces.

In assessing the significance of these results, three important qualifications need to be made. First, although reductions in airway conductance during quiet breathing in emphysematous patients often can be accounted for by reductions in static transpulmonary pressure, this does not establish that the airways in these patients are anatomically normal. Considerable pathological changes can be present in the more peripheral airways without total airways conductance being greatly affected, because the larger airways play the major part in determining the value of conductance (Hogg, Macklem, and Thurlbeck, 1968). Nevertheless recent morphological studies have shown that there are only slight alterations in the number and diameters of small airways (less than 2 mm internal diameter) in emphysematous lungs when compared to control lungs fixed at a similar transpulmonary pressure (Matsuba and Thurlbeck, 1972).

Second, the present analysis of airway dimensions only applies during static or near-static conditions.

The finding that the FEV_1 was similar in the 'emphysematous' and 'bronchial' subgroups, despite differences in conductance measured at low flow rates, indicates that during forced expiration additional dynamic factors were contributing to the expiratory obstruction in the emphysematous patients. Although loss of static transpulmonary pressure will itself reduce maximum flow rates from the lung (Mead, Turner, Macklem, and Little, 1967; Pride, Permutt, Riley, and Bromberger-Barnea, 1967) in all the emphysematous patients maximum flow was reduced more than could be accounted for directly by loss of static transpulmonary pressure. The contribution of dynamic airway narrowing to airflow obstruction is discussed in detail elsewhere (Leaver *et al.*, 1973).

Third, there is often evidence of bronchial disease as well as a reduction in static transpulmonary pressure in an individual patient. In the present series we attempted deliberately to contrast subgroups with strongly 'emphysematous' or 'bronchial' features in order to study different mechanisms of airflow obstruction. Many patients cannot be placed in either of these subgroups; even when the criteria are fulfilled, complete separation of 'emphysematous' and 'bronchial' features is often not obtained. Two of the patients in the 'bronchial' group had total lung capacities of 125% of the predicted value, reduced transfer factor, and markedly increased static lung compliance, suggesting that they also had some emphysema which was not detected on the chest radiograph. These two patients largely account for the failure to obtain a clearer distinction between the pressure-volume characteristics of the lungs in the two groups. In addition all the patients with emphysema had a chronic cough, although in most the volume of sputum expectorated was very small. While chronic expectoration is not necessarily associated with functional evidence of airway narrowing, it is perhaps surprising that as many as four of the emphysematous patients had a normal conductance-static transpulmonary relationship since the combination of significant intrinsic narrowing of the airways and loss of airway-distending forces would reduce the value of Δ conductance/ Δ static transpulmonary pressure.

We conclude that, during quiet breathing, extra-bronchial factors (i.e., loss of airway-distending forces) are often of great importance in the airway narrowing of patients with radiological and functional evidence of emphysema. The recognition of the bronchial and extrabronchial contributions to airflow obstruction is likely to be of more value to physicians interested in the pathogenesis of these common and disabling diseases than to those concerned solely with everyday clinical management.

But the distinction is of practical importance to morbid anatomists using the now standard technique of inflating the lung to a pressure of 25 cmH₂O for post-mortem fixation, since this technique may completely eliminate airway narrowing in the lungs of patients who have suffered during life from airflow obstruction arising from loss of airway-distending forces.

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