Small airways disease

T. B. STRETTON
M.B., F.R.C.P.

Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL

Summary

Mechanisms of disease in the small air passages of the lungs are described, their effects on lung function considered, and some of the ways in which such disease may be recognized are discussed.

Introduction

MY subject is 'Disease in the small airways'. I hope no one here today will leave with the mistaken impression that I have been describing some new kind of pulmonary disease. That is not the case. It is my intention first of all to discuss ways in which bronchi may become obstructed and then to consider possible means of investigating obstruction in small airways at a stage when this is not clinically overt.

In recent years much has been learned about the lungs: about lung growth during childhood and adolescence; about the normal values for FEV₁ and vital capacity at different ages, and the gradual rate of decline in both of these indices of lung function in later life; and about the more rapid rate of decline in FEV₁ in those thousands of patients with chronic obstructive bronchitis who attend our clinics every year.

Patients in this latter group so often already have such severe disease when they are first seen by hospital-based physicians that the presence of airway obstruction is recognizable as soon as the patient comes through the door of the consulting room. If it is not instantly recognized, it is usually evident on examination of the patient, and is confirmed with the aid of a spirometer. But what was the situation in such patients before this state of affairs was reached? Did they at one time have normal lung function? If so, did pulmonary function decline gradually or rapidly to its present state of insufficiency? If not, what physiological tests would have been capable of demonstrating the presence of functional impairment? These and many other questions readily present themselves to us, and in most cases we have no answers to them.

However, it is now increasingly recognized that obstruction of the small intrapulmonary airways may be extensive and yet not show on conventional

spirometric tests of lung function. Therefore other tests have been introduced to try to detect obstruction in small airways at a stage when the overall pulmonary resistance is barely affected. It is hoped that recognition of bronchial disease at this stage might allow treatment to be introduced whilst the condition is still reversible; this might be by stopping smoking, by regular use of bronchodilator drugs or by vigorous treatment of infection. Hence our interest, as physicians, in the small airways.

Effect of change in diameter of a bronchus on resistance to airflow

I should like to remind you at this point that with laminar airflow, such as occurs in small air passages, airflow resistance $\propto \frac{1}{r^4}$, where r = the radius of the airway. This is demonstrated in Fig. 1 which shows the end-on view of two tracheostomy tubes. The tube on the left has an airflow resistance of 0.5 cm H₂O/l/sec. The adjacent tube, which is half obstructed by inspissated bronchial secretions, has a resistance of 8 cm H₂O/l/sec. That is a sixteen-fold increase. This emphasizes the marked increase in resistance produced by a seemingly modest reduction in airway calibre.

Keeping this fundamental observation constantly in mind, I should now like to consider the factors which produce obstruction to the flow of air through the tracheo-bronchial tree.

Mechanisms of airway obstruction

These may be classified as *intrinsic*, that is, abnormalities in the bronchial wall itself or within the bronchial lumen; or *extrinsic*, that is, factors outside the bronchus which may either hold it open or may tend to squeeze it and cause narrowing of its lumen.

Examples of *intrinsic* abnormalities are shown in my next two slides; the first (Fig. 2) shows dense eosinophilic plugs in the terminal bronchioles of a patient with fatal status asthmaticus; the second (not shown here) illustrates the degree of mucosal gland hypertrophy found in chronic bronchitis. Both are important factors causing obstruction to airflow. Likewise, inflammatory bronchiolar lesions, as in

FIG. 1. End-on view of two tracheostomy tubes. The normal one on the left has an airflow resistance of $0.5 \text{ cm H}_2\text{O l}^{-1} \text{ sec}^{-1}$. That on the right was removed from a patient with copious inspissated bronchial secretions; its resistance was $8 \text{ cm H}_2\text{O l}^{-1} \text{ sec}^{-1}$.

FIG. 2. Longitudinal section of a bronchiole from a patient with fatal status asthmaticus. This is occluded by secretions containing large numbers of eosinophils.

acute bronchiolitis during infancy, can cause severe airflow obstruction. And, of course, changes in the degree of smooth muscle contraction or relaxation will alter airway calibre; in this context it may be recalled that the relative amount of smooth muscle is greatest at bronchiolar level.

Forces that operate from outside the air passages, the *extrinsic* factors, may be subdivided into (a) *static* and (b) *dynamic* forces.

(a) The former, the *static* forces, depend upon the elastic recoil of the lungs and the state of inflation of these organs. It is helpful to envisage airways being held open by forces applying traction on their outer surface, or circumference. The greater the elastic recoil of the surrounding lung tissue, the greater will be these traction forces. Thus, lung which is stiffer than normal (less compliant) will pull more on the outer walls of the air passages and hold them more

FIG. 3. Diagrammatic representation of the lungs and thorax to indicate their separate contributions to expiratory airflow. (a) Effect of pulmonary elastic recoil alone; (b) and (c) effect of increasing intrathoracic pressure to expel air from the lungs, and the generation of 'equal pressure point' (E.P.P.); (d) additional effect of airway obstruction on the intrathoracic pressures necessary to produce the same rate of airflow as in (c).

widely open than usual. Conversely, lung which is more compliant than normal, as in panacinar emphysema, will apply less traction and the small airways will tend to collapse inwards and become obstructed.

Static forces which tend to pull the airways open are greater when the lung is maximally inflated. So, at a high lung volume the airways are held widely open and at a low lung volume the reduction in the applied traction forces allows the air passages' calibre to diminish. As a corollary to this, in emphysema, the tendency for small air passages to obstruct (because of the loss of radial traction forces) can be partially offset by increasing the state of inflation of the lungs.

(b) *Dynamic* forces operating on the walls of the air passages are continuously changing during the breathing cycle and are influenced by the rate of airflow. To comprehend these forces it is necessary to introduce a few numbers to represent pressures (in cm H₂O) within a diagram of the lung.

In Fig. 3 the lungs are represented as a single alveolar space with a common airway, enclosed within the thorax. In Fig. 3a, at the end of a quiet inspiration the inspiratory muscles relax and the recoil force of the lung (+10) will serve to expel air through the airway to the exterior, where the pressure is atmospheric (0). Within the airway the gradient of pressure, from 10 at the alveolar end to 0 at the mouth, is always such as to maintain a higher pres-

sure inside the air passage than exists in the pleural space outside; this effect encourages the airway to remain patent and not to collapse. In the trachea there are, of course, cartilaginous rings to help maintain patency.

If expiration becomes an active process, rather than one that is passive and entirely due to the recoil force of the lung, a positive pressure is built up around the alveolar space and also around the air passage. This positive pleural pressure aids expulsion of air from the alveoli by compressing them, but it also compresses the airway. In Fig. 3b it can be seen that the net effect of a pleural pressure of 10, plus the alveolar recoil of 10, is an alveolar pressure of +20. Inside the air passage there is then a pressure gradient of 20 at the alveolar end down to zero at the mouth. Somewhere along the air passage the pressure inside it will be equal to the pressure in the pleural space outside. This has been called the 'equal pressure point' (E.P.P.). At all points downstream from that point, there will be a net force across the wall of the air passage tending to compress or squeeze it, until it passes beyond the thoracic confines.

If the pleural pressure is increased by blowing harder (Fig. 3c), the force of *dynamic compression* on the air passage is increased, and it can be seen that the E.P.P. moves upstream towards the alveoli. A longer segment of airway is thus exposed to the effects of dynamic compression.

Suppose, now, the situation is complicated by the

presence of intrinsic airway obstruction close to the alveoli, such that an alveolar pressure of 40 is necessary to achieve expiratory airflow (Fig. 3d). If elastic recoil is normal and the lung has not become over-inflated, a pleural pressure of 30 is of necessity generated. But this will in its turn exacerbate the degree of dynamic compression downstream from the E.P.P. Moreover, the exact location of the latter will be influenced by the site and severity of the intrinsic obstruction.

Anatomy of the airways and how they affect airflow resistance

We have long made the mistake of assuming that, because our air passages become smaller and smaller from the trachea to the respiratory bronchiole, the maximum resistance to airflow resides in the bronchioles. This is not so. On the contrary, because of the branching pattern of the bronchial tree, at each division down, the cumulative cross-sectional area of the air passages increases progressively. This is shown in Fig. 4, which is taken from Horsfield (1974). Horsfield has calculated that the cumulated cross-sectional area of the respiratory bronchioles is equivalent to a solitary airway with an area of 280 cm^2 . This may be contrasted with the cross-sectional area of the trachea: a mere 2 cm^2 (and, of course, the respiratory bronchioles lead to the alveoli with their huge surface area of $60\text{--}70 \text{ m}^2$ available for gas exchange). In consequence, the effective resistance to airflow through respiratory or terminal bronchioles is very small in comparison with that through the trachea and major bronchi. It has been shown by Macklem (1972) and his colleagues in Montreal that air passages 2 mm and less in internal diameter

FIG. 4. Functional anatomy of the airways, to show the increasing cross sectional area as one progresses from the trachea to the respiratory bronchioles (after Horsfield, 1974).

contribute only 10–20% of the total pulmonary airflow resistance. Suppose the resistance in these small airways were to double. From an initial total resistance of 100 units, of which 10 are due to the small airways, the total resistance would increase to 110 units and 20 of these would be due to the small air passages. This small change in total pulmonary resistance would excite little attention, even if it were measured with great precision. Therefore, extensive obstruction could be present in small air passages and go unrecognized using such conventional tests of lung function as the peak expiratory flow rate and FEV₁.

At this stage in the evolution of diseases which cause widespread obstruction of small airways, it is conceivable that vigorous therapy might halt or even reverse its progression, whereas this may be impossible later, by the time conventional pulmonary function tests have become abnormal. Hence, there has been a desire to develop tests which would detect the presence of obstruction in small airways at the earlier stage. I should like to mention three such tests.

(1) Frequency dependence of compliance

This is a technically difficult measurement and one that requires sophisticated and expensive apparatus. Although I am unable to make the measurement myself I should like to demonstrate what is meant by frequency dependence of compliance. If we take these two balloons and attach them to a common airway by means of a Y connector we can blow them up at different 'respiratory' frequencies. We find that the more compliant balloon always inflates to a larger volume than the less distensible balloon no matter how frequently we inflate them. That is, the combined compliance (C') of the two balloons which form our model lung does not change with faster breathing rates (Fig. 5). However, if we now apply a screw clip to introduce a resistance into the airway leading to the more compliant 'lung', we find that at higher inflation frequencies, the breaths are directed to the stiffer (less compliant) 'lung'. This is because there is insufficient time available for filling of the more distensible balloon at the higher respiratory frequency, owing to the obstruction in its airway. The combined compliance (C'') of our system of balloons is thus apparently lower at these high frequencies because we are now having to apply more pressure in order to distend the stiffer balloon so as to achieve the same tidal volume as before (Fig. 6).

The same applies to our own lungs when there is obstruction to small airways. At higher respiratory frequencies, ventilation is diverted away from obstructed to non-obstructed lung units. The latter are thereby overinflated and appear stiffer because they

FIG. 5. Two balloons of differing compliance, inflated at different frequencies, have the same combined compliance (C') at slow and fast inflation rates (see text).

FIG. 6. The same two balloons as in Fig. 5, arranged in the same order, with the stiffer balloon on the left and the more compliant balloon on the right; the airway to the latter is partially obstructed. At slow rates of inflation the combined compliance (C') is unchanged. At fast inflation frequencies their combined compliance falls (C''), i.e. there is frequency dependence of compliance. The graph illustrates this (and also shows the lack of frequency dependence in the system before the obstruction to airflow was introduced, taken from Fig. 5).

are being stretched to a greater degree. This apparent fall in compliance at high breathing rates is called frequency dependence of compliance.

(2) Closing volume

The lung may be envisaged as being supported within the thorax rather like the slinky spring that I am holding up vertically. The lower coils of this spring, supported in the palm of my left hand, are also closer together than the opened out coils at the top which I am pulling upwards with my right hand. Similarly, the lung units at the apex of the lung are relatively more distended than those at the base of the lung. The small air passages to the units at the top of the lung are therefore held more widely open than those at the base. During a deep expiration towards

residual volume, the airways get narrower and some close completely (trapping air in the alveoli lying distally). Because the air passages to the base of the lung are initially narrower than those to the apex, they are normally the first to close during a deep expiration. And they open later during the next breath in.

The lung volume at which airways begin to close is referred to as the 'closing volume' and measurement of this volume is the basis of a test designed to detect premature closure of small airways.

In principle, the measurement of 'closing volume' is done by monitoring at the subject's mouth the concentration of a marker gas throughout a slow delivery of the vital capacity. First, the subject exhales to residual volume and then inhales slowly to

total lung capacity; at the very onset of this inhalation he breathes in a bolus of the marker gas. The marker thus enters the lung at the very front of the inspirate and proceeds in highest concentration to lung units with open airways. Only later during the slow inspiration does marker gas enter units whose airways were initially closed; these units therefore contain a lower concentration of the marker. Having breathed in slowly to total lung capacity, the subject then exhales very slowly to residual volume and the concentration of marker gas at the mouth is plotted against the volume expired. An example of the kind of graph produced is shown in Fig. 7.

FIG. 7. Diagrammatic representation of a 'closing volume' record in which the marker gas concentration is plotted v. expired volume, commencing at total lung capacity on the left and ending at residual volume on the right (see text).

The graph is interpreted as follows: (1) at the onset of the breath out, expired air comes from the dead space of the air passages and the concentration of marker gas is zero; (2) there is an abrupt rise in marker gas concentration as this is washed out of the alveoli; (3) a plateau is reached, representing the average alveolar concentration of the marker; (4) near to the end of the vital capacity there is a further rise in marker gas concentration as this is finally expelled from those lung units which contained more in the first place because their air passages were open when the bolus was inspired. The volume at which this terminal rise in gas concentration occurs is the 'closing volume', i.e. many small airways have closed, although some remain patent even at residual volume.

If the 'closing volume' is increased, i.e. small airways are closing at a higher lung volume than normal, this suggests that these airways are partially obstructed. Thus, measurement of 'closing volume' might detect disease of the small airways in its earlier stages.

It has been shown that 'closing volume' increases with age, and in some normal older subjects small

airways may close even during tidal breathing. 'Closing volume' is increased in smokers, in obesity and in pulmonary oedema.

(3) Maximum mid-expiratory flow rate

If there is obstruction in small airways this is most likely to affect the rate of expiratory airflow at low lung volumes when, for reasons already discussed, the air passages are normally narrower anyway, and because of the effects of dynamic compression. Therefore, careful scrutiny of the lower part of the spirogram during the forced vital capacity manoeuvre may be more revealing than the FEV₁. One useful index of the presence of obstruction in small airways is the maximum mid-expiratory flow rate. While it is possible to derive this from the slope of the spirogram at 50% of the forced vital capacity, the measurement does call for rather more sophisticated apparatus than is usually available; it is then possible to present the rate of airflow and expired volume simultaneously as flow-volume curves on an oscilloscope.

FIG. 8. The relationship between conductance of the airways and lung recoil pressure (static transpulmonary pressure). Where there is loss of lung recoil the slope of the relationship is normal but high recoil pressures cannot be generated, even at very high lung volumes. With 'intrinsic' disease of the bronchial tree conductance is abnormally low at all transpulmonary pressures (after Leaver, Tattersfield and Pride, 1973).

Finally, I would like to make one last point. Supposing there is evidence of disease causing airways obstruction, is it possible to decide whether this is due to an 'intrinsic' abnormality of the air passages themselves? Or is it due to 'extrinsic' factors, i.e. an abnormality in the recoil pressure of the lungs? Pride and his colleagues (Leaver, Tattersfield and Pride, 1973) have made progress in this direction. By means of some very elegant and precise, though rather complex, investigations, they studied a number of patients with established airways obstruction. In these patients the transpulmonary pressure (= elastic recoil pressure which, as indicated earlier, provides a distending force by radial traction on the airways) was plotted at different degrees of lung inflation against airway conductance. (Conductance, the reciprocal of resistance, increases approximately linearly with increasing lung volume, owing to the increasing calibre of the airways.) In patients with airway obstruction due to an abnormality intrinsic to the bronchial wall, there was a clear difference in this relationship. That is, at all transpulmonary pressures the airway conductance was markedly

impaired. By contrast, in patients with impaired elastic recoil the conductance increased in a normal fashion with increasing transpulmonary pressure; but even at high lung volumes the transpulmonary pressure was low because of their disease process, and so was their airway conductance. This is illustrated in Fig. 8 which is taken from Leaver *et al.* (1973).

Unfortunately, time does not allow me to dwell further on this interesting topic but it does indicate the possibility of distinguishing between 'intrinsic' diseases of the bronchial tree and 'extrinsic' disorders capable of producing diffuse airways obstruction.

References

- HORSFIELD, K. (1974) The relation between structure and function in the airways of the lung. *British Journal of Diseases of the Chest*, **68**, 145.
- LEAVER, D.G., TATTERSFIELD, A.E. & PRIDE, N.B. (1973) Contributions of loss of lung recoil and of enhanced airways collapsibility to the airflow obstruction of chronic bronchitis and emphysema. *Journal of Clinical Investigation*, **52**, 2117.
- MACKLEM, P.T. (1972) Obstruction in small airways—a challenge to medicine. *American Journal of Medicine*, **52**, 721.