Physiology of breathing I

Jane Ward

The main function of the respiratory system is gas exchange. The lungs also break down microthrombi arriving from the veins, and have several metabolic actions, including the activation of angiotensin I to angiotensin II and the breakdown or deactivation of substances (e.g. 5-hydroxytryptamine, bradykinin, noradrenaline, acetylcholine, some drugs).

The respiratory system contains a branching system of airways leading to the alveolar region. Moving towards the periphery, each generation of airways divides to give approximately double the number in the previous generation. The first 16 generations (trachea, bronchi, bronchioles) do not take part in gas exchange and, together with the nose, pharynx and larynx, form the anatomical dead space. These conducting airways are important for speech as well as warming, humidifying and filtering inspired air. Gas exchange occurs in the thin-walled alveoli found in the respiratory bronchioles (generations 17–19) and alveolar ducts and sacs (generations 20–23).

Lung volumes and ventilation

Figure 1a shows the spirometer trace when a subject breathes quietly and then takes a maximal breath in and out.

- Tidal volume (V_T) is the volume of a breath in and out.
- Vital capacity (VC) is a maximum tidal volume.
- Residual volume (RV) is the volume left in the lungs after a maximal expiration.
- Total lung capacity (TLC) is the volume in the lungs at the end of a maximum breath in.
- Functional residual capacity (FRC) is the volume at the end of a normal expiration.

Capacities are volumes comprising two or more volumes, whereas volumes are indivisible. Typical values in a young male of average height are shown in Figure 1a.

The range of normal lung volumes is large, and measurements must be compared with predicted values from nomograms that take into account the subject's age, sex and height. The trace in Figure 1a illustrates FRC, RV and TLC, but these volumes cannot be measured from this trace because all the gas in the lungs cannot be emptied into the spirometer; their measurement requires helium dilution or body plethysmography.

Ventilation (or minute volume) is the volume of air breathed in or out each minute. Some of the ventilation goes to the anatomical dead space and does not take part in gas exchange. In disease (e.g. pulmonary embolism), there may also be alveoli that are ventilated but not perfused, and these non-gas-exchanging regions form alveolar dead space. Alveolar ventilation is the volume of gas taking part in gas exchange each minute. In health, the anatomical dead space is about 150 ml and there is no alveolar dead space. With a typical resting V_T of about 500 ml and a respiratory frequency of 15 breaths per minute, the resting minute ventilation is 7500 m/minute and alveolar ventilation is 5250 ml/minute ((500 – 150) × 15). If dead space is increased, normal gas exchange is possible if minute ventilation is increased sufficiently.

FRC: at about 3500 ml, the FRC is quite large compared to the 350 ml of fresh gas reaching the alveolar region with each resting V_T This results in quite stable concentrations of alveolar gas, with only small respiratory cycle fluctuations in the partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2).

In health, at FRC, the inspiratory and the expiratory muscles are relaxed and the volume within the lungs is determined by the elastic properties of the lungs and chest wall. Like all elastic structures, the lungs and chest wall have their own natural resting positions, which they adopt when no forces are acting on them. This is seen when the chest is opened: the lungs recoil to a small volume and the chest wall expands to about 1 l larger than its volume at FRC (Figure 1b). In the intact person, the inward recoil of the lungs and the outward recoil of the chest wall create a subatmospheric ('negative') pressure in the intrapleural space between them. FRC is the volume at which the two recoils balance and intrapleural pressure at this point is about –0.5 kPa.

FRC in disease **–** FRC is reduced in lung fibrosis. The stiff lungs have abnormally high elastic recoil, which balances with the recoil of the chest wall at a lower lung volume. In emphysema, tissue destruction reduces the elastic recoil of the lungs and FRC is increased. FRC is little changed in restrictive disease caused by weakness of respiratory muscle because the elastic forces are normal, and this helps distinguish it from restrictive disease caused by lung fibrosis.

FRC can also be increased by air trapping. This occurs when airway resistance is high (e.g. in chronic obstructive pulmonary disease, during a severe asthma attack). Expiration is slow and the patient must breathe in before breathing out fully, leading to a rise in FRC.

Respiratory muscles and the mechanism of normal breathing

To hold lung volume above or below FRC requires active muscle work to alter the transmural (alveolar–intrapleural) pressure gradient across the lungs. Work is also needed during the breath to create a pressure difference along the airways to generate airflow.

The main muscles of inspiration are the diaphragm supplied by the phrenic nerve (C3, 4, 5) and the external intercostal muscles supplied by intercostal nerves (T1–12). At times of increased inspiratory work, the scalene, sternomastoid and, with the arms fixed, the pectoral muscles, aid inspiration by raising the ribs. Contraction of these muscles increases chest volume and intrapleural pressure becomes more negative. This increases the pressure gradient across the lung, expanding it. As the alveoli expand, alveolar pressure falls, drawing air into the lungs.

In quiet breathing, expiration occurs by passive recoil of the lungs and intrapleural pressure becomes less negative than in inspiration, but remains below zero. Reducing lung volume below

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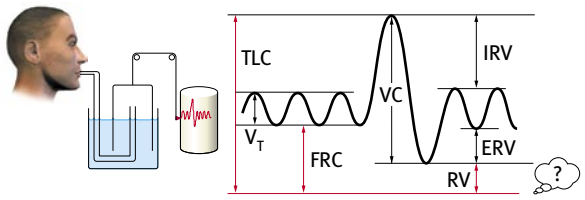
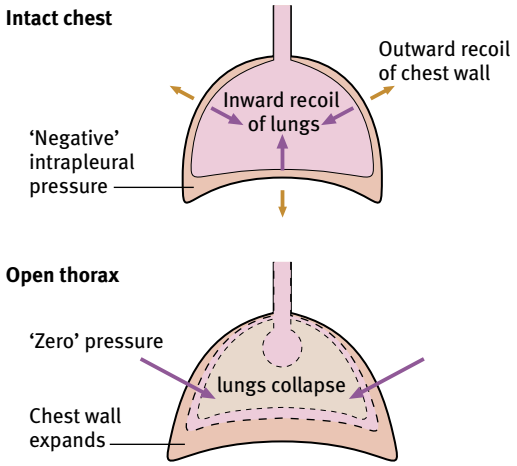
a Lung volumes and ventilation



Tidal volume (V_T) (at rest)	500 ml
Vital capacity (VC)	5500 ml
Inspiratory reserve volume (IRV)	3300 ml
Expiratory reserve volume (ERV)	1700 ml
Residual volume (RV)	1800 ml
Functional residual capacity (FRC)	3500 ml
Total lung capacity (TLC)	7300 m

The subject breathes from a water-filled spirometer to produce a volume versus time trace that illustrates some of the important lung volumes. The fourth breath is a maximum inspiration followed by a maximum expiration. The volumes shown in red cannot be measured this way because the subject cannot empty his lungs into the spirometer and hence the position of the zero line is unknown. All volumes depend on height, age and sex.

b Functional residual capacity



Functional residual capacity (FRC) is the volume left in the lungs at the end of a normal breath out when all the respiratory muscles are relaxed. At FRC, the inward recoil of the lungs exactly balances the outward recoil of the chest wall and a negative pressure is created between them. The lungs shrink and the chest wall springs out when the chest is opened.

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FRC, breathing out rapidly, and coughing, involve the expiratory muscles. The most important of these are the abdominal wall muscles, which raise abdominal pressure, pushing the diaphragm back into the chest. Intrapleural pressure can rise to 8 kPa or more with maximum expiratory effort.

Muscles of breathing in disease: transection of the cervical cord above C3 interrupts the connection between the brain stem and the respiratory muscles, resulting in apnoea. Transections of the lower cervical cord spare the phrenic nerve and allow diaphragmatic breathing, which is usually adequate. Specific damage to the phrenic nerves leads to diaphragmatic weakness or paralysis. Breathing using the intercostals and accessory muscles of inspiration may be adequate if the patient is upright, but if the patient lies down or is submerged in water, pressure from the abdominal organs makes expanding the chest more difficult, and leads to breathlessness. A paralysed diaphragm is pulled up into the chest during inspiration, causing the anterior abdominal wall to move inwards ('paradoxical breathing'). In normal breathing, descent of the diaphragm raises abdominal pressure and the abdominal wall moves out with the chest.

Hyperinflation (e.g. in chronic obstructive pulmonary disease), flattens and shortens the diaphragm and reduces its effectiveness as an inspiratory muscle.

Resistance to breathing

The amount of work that the respiratory muscles must do to achieve ventilation depends on the elastic resistance to stretch (stiffness) of the lung, and on the resistance to airflow of the airways (RAW, see below). In health, both of these resistances are low, but increases in these resistances are common; they increase the work of breathing and are common causes of dyspnoea.

Elastic resistance and compliance: the resistance to stretch of the lungs arises from elastin in the lung parenchyma and from the surface tension forces at the air–fluid interface of the alveolar lining fluid. High elastic resistance means stiff lungs or, alternatively, lungs with low compliance. Once stretched, stiff lungs have an increased tendency to return (recoil) to their resting position.

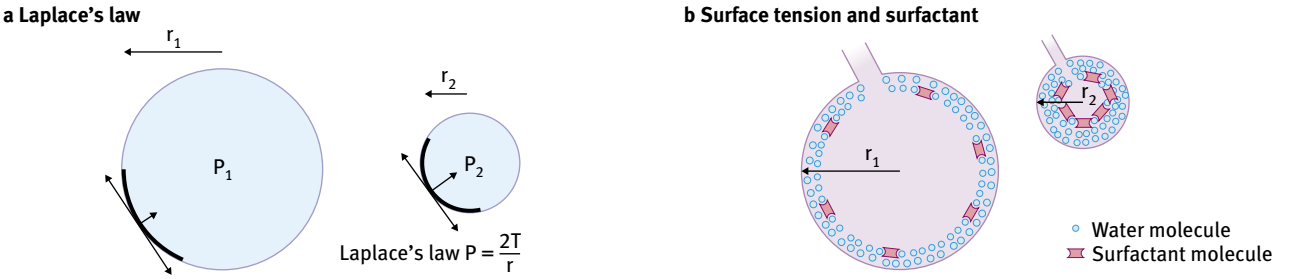
Surface tension and surfactant – surface tension forces are responsible for more than one-half the elastic resistance of normal lungs, and this would be even higher if it were not for surfactant (mixture of phospholipids and apoproteins produced by type II alveolar cells) in the alveolar lining fluid. Surfactant in alveolar lining fluid lowers the surface tension to about 20 mN/m, compared to about 70 mN/m for an air–water interface in its absence.

Surfactant makes the lungs more compliant and also helps prevent the instability that is inherent in a system of bubbles connected to each other and the atmosphere. The surface tension force acting along the liquid–air interface of a bubble resolves partly tangentially and partly inwards, towards the centre of the bubble (Figure 2a). The inward component raises pressure within the bubble and is greater when the radius of the bubble is small. Laplace's law predicts the pressure, P, within a bubble of radius r in a fluid with surface tension T:

$$P = 2T/r$$

when there is one air–fluid interface (as in the alveolus).

During expiration, this law predicts that pressure in the alveoli rises progressively as their radii fall, speeding up emptying and



The length of the thick black line represents the surface tension (T) at the air–fluid interface. Its value is the same in the two bubbles but, in the small bubble, a larger proportion of the tension resolves inwards, so that $P_2 > P_1$. The smaller bubble would empty into the larger bubble if these two bubbles were connected.

Surfactant in the alveolar lining fluid lowers the surface tension and it does this more effectively in small alveoli because surfactant molecules float at the surface. As r falls, T falls even more, helping to prevent the alveolus from collapsing.

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producing a positive-feedback cycle that leads to alveolar instability and collapse. However, the phospholipids of surfactant float on the surface and their surface concentration increases as the surface area decreases (Figure 2b), making them more effective at lowering surface tension as the alveoli shrink. The fall in surface tension more than offsets the effect of the fall in radius, helping to prevent alveolar collapse.

Type II alveolar cells start to function effectively only in the last one-third of pregnancy, and surfactant deficiency is common in premature babies, causing neonatal respiratory distress syndrome. Surfactant deficiency gives rise to increased work of breathing, low FRC and areas of alveolar collapse.

Lung compliance – the stiffness of the lungs is usually assessed by measuring lung compliance (C_L), which is the increase in volume for each kPa increase in the pressure gradient distending the lung (P = alveolar pressure – intrapleural pressure, Figure 3a):

$$C_L = \frac{\Delta V}{\Delta P}$$

Volume is measured using a spirometer. Intrapleural pressure is assumed to equal oesophageal pressure (usually measured from an oesophageal balloon attached to an external pressure transducer). The alveolar pressure can be assumed to be zero by using measurements of volume and intrapleural pressure only when no air is flowing. The subject breathes in and out in small steps and simultaneous measurements of intrapleural pressure and volume are taken at each step to construct the static pressure–volume loop (Figure 3b).

Static lung compliance is the slope ($\Delta V/\Delta P$) of the expiratory curve where it is steepest in the region just above FRC. A typical value in a young male of average size is about 1.5–2.0 l/kPa. The pressure–volume curve flattens near TLC and RV, where lung compliance is reduced.

Compliance of the chest wall and total respiratory system – in normal inspiration, the chest wall must also expand from its equilibrium position and its elastic resistance must also be overcome by the respiratory muscles. Low compliance of the chest wall causes respiratory problems (e.g. when the skin of the chest wall is badly scarred). It is rarely measured clinically, but its value in normal subjects is similar to that of lung compliance (about 2 l/kPa). The total compliance of the whole respiratory system (about 1 l/kPa) can be found from the following relationship:

1/total compliance = 1/chest wall compliance + 1/lung compliance

Compliance of the chest wall and the total respiratory system are difficult to measure in conscious subjects because all chest wall muscles must be completely relaxed. In anaesthetised paralysed subjects, total compliance (i.e. the volume by which the lungs expand divided by the positive pressure applied to achieve this) is easily estimated.

Indirect tests of abnormal lung compliance – swallowing oesophageal balloons is neither pleasant nor convenient, and lung compliance is not often directly measured. Abnormal lung compliance can be deduced from indirect measurements, particularly lung volumes and forced expiratory spirometry (see below).

Compliance in lung disease – compliance is reduced in lung fibrosis and in surfactant deficiency (e.g. neonatal respiratory distress syndrome). Tissue destruction reduces the resistance to stretch and static lung compliance is increased in emphysema. In asthma, the alveolar tissue is normal and lung compliance is usually unaffected. However, in a severe attack, air trapping may raise FRC considerably and compliance may then fall as tidal breathing encroaches on the flatter part of the pressure–volume relationship near to TLC.

RAW: airflow down a tube or series of tubes depends on the pressure difference driving the flow and the resistance of the tube or tubes.

Flow = $\Delta P/R$

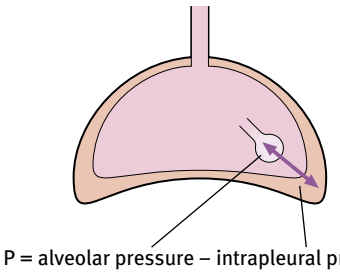
For the whole respiratory system, ΔP = alveolar pressure – mouth pressure, and R is the total resistance of all the airways, RAW.

The resistance to laminar flow of a fluid through a smooth tube depends on the length of the tube (l), its radius (r), and the viscosity of the fluid (η) as described by Poiseuille's equation:

$$\text{Resistance (R)} = \frac{8\eta l}{\pi r^4}$$

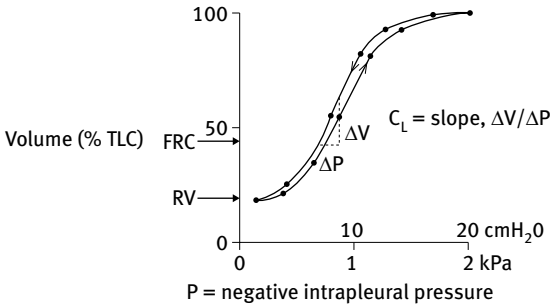
a Lung compliance

$$\text{Lung compliance} = \frac{\text{change in lung volume}}{\text{change in transmural pressure gradient}} = \frac{\Delta V}{\Delta P}$$



P = alveolar pressure – intrapleural pressure

b Static pressure–volume loop



P = negative intrapleural pressure
(measured with breath held i.e. alveolar pressure = 0)

The static pressure–volume loop is a plot of lung volume against the pressure gradient across the lung (negative intrapleural pressure). The subject breathes in and out in small steps from residual volume (RV) to total lung capacity (TLC). The inspiratory and expiratory curves are slightly different and this 'hysteresis' is common when any elastic body is stretched.

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Halving the radius increases the resistance of a tube by 16-fold. The same principles apply in airways and the resistance of individual airways increases towards the periphery as their size decreases. The number of airways in parallel with each other increases at each level of branching. The more airways there are in parallel with each other, the lower the net resistance of the generation as a whole. Within the lungs, the highest airway resistance is at generation 2–5. In the respiratory system as a whole, the nose, pharynx and larynx usually contribute more than one-half of the total resistance. The resistance of the nose is especially high and a change to mouth breathing is often necessary when ventilation is increased.

Factors affecting airway resistance

Airway smooth muscle **–** in health, there is a small basal tone in the bronchial smooth muscle which can be increased by inflammatory mediators (e.g. histamine, prostaglandins, leukotrienes) and reflexes (e.g. when airway irritant receptors are stimulated). The muscle is supplied by parasympathetic cholinergic nerves, which act on muscarinic receptors to cause bronchoconstriction. There are few sympathetic fibres to the airways, but circulating adrenaline dilates bronchial smooth muscle via β_2 receptors. Airways are also supplied by non-cholinergic, non-adrenergic bronchoconstrictor and bronchodilator nerves.

Dynamic compression of airways **–** to increase airflow rate, appropriate changes in alveolar pressure are brought about by lowering or raising intrapleural pressure using inspiratory or expiratory muscles. During forced inspiration, increased effort by the inspiratory muscle increases inspiratory airflow at all lung volumes between RV and TLC (Figure 4a, lower traces). During forced expiration, increased expiratory effort increases airflow at the start of the breath when the lungs are close to TLC but the flow fails to increase as the effort level is increased at lower lung volumes (Figure 4a, upper traces).

This 'effort-independent airflow' occurs because the increased intrapleural pressure compresses the intrathoracic airways, increasing airway resistance (Fig. 4b, lower half)—a phenomenon termed 'dynamic compression of airways'. During a forced expiratory manoeuvre, the medium-sized bronchi can be seen (through a bronchoscope) to flutter open and closed. Increased intrapleural pressure initially collapses these airways, which open again as airway pressure builds up behind the collapse. Once open, air flows, airway pressure falls, and the cycle repeats itself.

Maximum effort flow–volume curves in airway obstruction and restrictive disease are shown in Figure 5a.

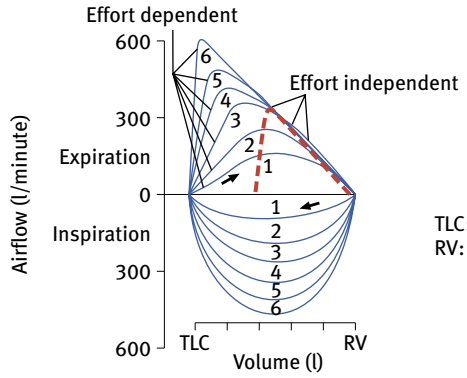
Airway resistance in common respiratory diseases: in asthma, the airways are hyperresponsive and bronchoconstriction and inflammation narrow airways, increasing resistance to airflow. In chronic bronchitis, increased airway resistance is caused mainly by hypertrophy of the bronchial epithelium and mucus glands. In pure emphysema, the airways are not directly affected, but the reduction of alveolar tissue reduces the outward pull supporting the airways, making them more susceptible to collapse during expiration.

Dynamic compression of airways is accentuated in all these conditions. The musical expiratory sounds (wheezes/rhonchi) generated in the lungs of patients with asthma and chronic obstructive pulmonary disease are probably caused by air flowing through fluttering airways. In very severe asthma, flow may be too low to generate sound and the chest becomes silent.

Assessing airway resistance: airway resistance can be measured using several techniques. The most established is the body plethysmograph, which is bulky and expensive. A typical value for RAW in healthy adults is 0.15–0.2 kPa/l/second. For most clinical purposes, indirect tests of airway resistance are adequate and more convenient. Many of these are based on forced expiration and they detect the increased susceptibility to dynamic compression seen in obstructive pulmonary disease. They use simple and widely available equipment for which normal values are well established.

Forced expiratory spirometry **–** the subject breathes in to TLC and breathes out as hard and fast as possible into a spirometer to produce a trace of volume expired against time (Figure 5b). The commonest measurements made from this trace are forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). In normal subjects, these volumes should fall within the normal range predicted for the subject, after consideration of age, sex and height, and the forced expiratory ratio (FER = FEV_1/FVC) should be > 0.75.

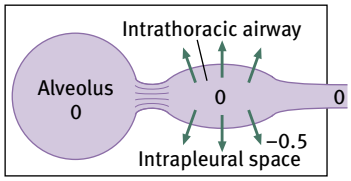
a Effect of effort on inspiratory and expiratory airflow



TLC: Total lung capacity
RV: Residual volume

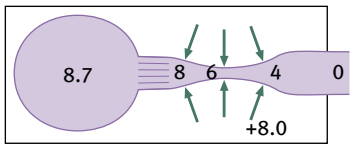
Flow–volume curves produced as a normal subject breathes in and out between total lung capacity (TLC) and residual volume (RV) with six different levels of effort. Curve 6 represents the subject's maximum effort flow–volume (MEFV) curve (see Figure 5a). The expiratory airflow achieved near the start of the breath out is affected by the effort used but, towards the end of the breath, at low lung volume, airflow is independent of effort. The red dashed line shows a maximum expiratory effort from partly filled lungs and it shows that the peak flow achieved depends on the initial volume as well as the effort.

b Effect of interpleural pressure on the intrathoracic airways



Beginning of inspiration

The negative intrapleural pressure helps to hold the airways open before and during inspiration and during normal expiration



During forced expiration

The large positive intrapleural pressure compresses the airways during forced expiration

Pressures values in kPa (1 kPa = 7.5 mmHg)

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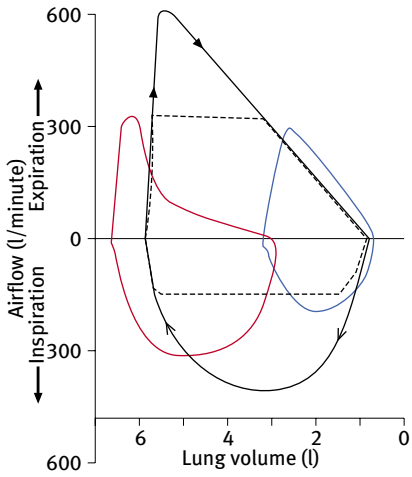
a MEFV curves in different lung conditions



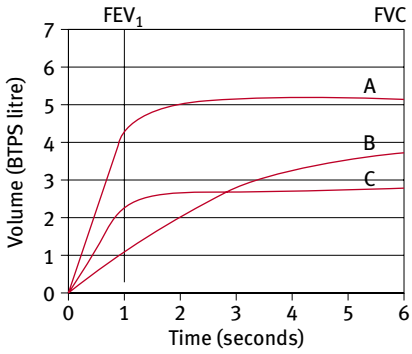
— **Normal**

— **Obstructive disease of smaller airways**. Note the concave appearance of the forced expiratory curve; forced inspiratory flow affected less than forced expiratory flow.

--- **Obstruction of the upper airway** (e.g. tracheal stenosis). Note the flat-topped flow–volume curve; forced inspiratory flow affected as much as expiratory flow.

— **Restrictive lung disease**. Note that low peak flow rates are related to low volume.

b Forced expiratory spirograms in restrictive and obstructive pulmonary disease



Traces from three subjects of same age, sex and height.
A = Normal respiratory system (FEV_1, FVC and FEV_1/FVC all normal)
B = Obstructive airway disease (FEV_1⇓⇓, FVC⇓or normal and FEV_1/FVC⇓)
C = Restrictive lung disease (FEV_1⇓, FVC⇓ and FEV_1/FVC normal)

BTPS: At body temperature and ambient pressure, and saturated with water vapour; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.

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Forced expiratory spirometry helps distinguish between restrictive lung disease in which the main problem is restricted expansion of the lung (e.g. lung fibrosis, muscle weakness) and obstructive pulmonary disease (e.g. asthma, chronic obstructive pulmonary disease) in which airway resistance is increased. In obstructive disease, expiration is slow, giving a low FEV_1 and FER < 0.75. FVC may be normal or reduced, but any reduction is proportionally less than for FEV_1. In restrictive disease, FEV_1 and FVC are reduced to a similar extent, so FER is normal (i.e. >0.75).

Peak expiratory flow – simple, inexpensive peak flowmeters record the maximum momentary flow during a forced expiration from TLC. A single peak flow reading cannot reliably distinguish between restrictive and obstructive lung disease because, as well as airway resistance, its value is also affected by lung volume. Lung recoil at any given volume is increased in lung fibrosis, which might be expected to speed up expiratory airflow but, because the starting lung volume is low, peak flow is often reduced. The main use of peak flow is in the monitoring the fluctuations of a disease (e.g. asthma) after the diagnosis has been made. ◆

Dyspnoea

Dyspnoea (breathlessness) is not a single sensation but a group of different sensations such as air hunger, increased effort or work of breathing, a feeling of suffocation and chest tightness, and these components vary in different conditions. It also occurs in normal subjects (e.g. during heavy exercise). There is no single mechanism or receptor group that can explain dyspnoea in all situations and diseases but, in many cases, a mismatch between outgoing motor signals to the respiratory muscles and incoming afferent information from lungs and chest wall appears to be important. ◆

FURTHER READING

Hughes J M B, Pride N B. *Lung function tests*. London: W B Saunders, 1999.

Lumb A B. *Nunn's applied respiratory physiology*. 5th edition. Oxford: Butterworth-Heinemann, 2000.

Ward J P T, Ward J, Wiener C M, Leach R M. *The respiratory system at a glance*. Oxford: Blackwell Publishing, 2002.

West J B. *Respiratory physiology—the essentials*. 7th edition. Philadelphia: Lippincott Williams and Wilkins, 2004.

