18.3.1 Respiratory function tests 3956 G.J. Gibson

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18.3 Clinical investigation
of respiratory disorders CONTENTS 18.3.1 Respiratory function tests 3956 G. J. Gibson 18.3.2 Thoracic imaging 3970 Susan J. Copley and David M. Hansell 18.3.3 Bronchoscopy, thoracoscopy, and tissue biopsy 3992 Pallav L. Shah 18.3.1 Respiratory function tests G. J. Gibson ESSENTIALS Respiratory function tests are used in diagnosis, assessment, and prognosis and in monitoring the effects of treatment of various re- spiratory conditions. Their use as a diagnostic tool is in recognizing patterns of abnormality which characterize particular types of disease; they are also used to quantify the severity of functional disturbance or to locate the likely anatomical site(s) of disease (airways, alveoli, or chest wall). The commonly applied tests are most conveniently classified as (1) tests of respiratory mechanics, (2) carbon monoxide uptake, (3) arterial blood gases and acid–base balance, and (4) exercise. Tests of respiratory mechanics Spirometers record the volume of air that is displaced from the lungs in tidal breathing or with forced inspiratory and expira- tory manoeuvres. This allows measurement of the tidal volume, inspiratory capacity, forced expiratory volume in 1 s (FEV1), and vital capacity. Residual volume remains in the lungs after full ex- piration. Total lung capacity represents the volume of air in the lungs after full inspiration—the sum of vital capacity and residual volume. Residual volume cannot be measured by spirometric methods: inert gas dilution and whole-body plethysmography are the two main clinical methods used for the measurement of absolute lung volume. Forced expiratory tests are simple to perform, do not require com- plex equipment, and are relatively independent of the effort applied by the patient. The characteristic feature of diffuse airway obstruction is a slowing of the rate of expiration, so that the ratio of FEV1 to forced vital cap- acity (or FEV1 to vital capacity) is reduced, which defines an ‘ob- structive’ ventilatory defect. In the alternative ‘restrictive’ pattern of ventilatory function, total lung capacity is reduced and both FEV1 and vital capacity are reduced in approximate proportion. Measurement of FEV1 and vital capacity is not sensitive to local- ized narrowing of the central airway: airflow during forced expiration and inspiration should be examined as maximum flow–volume curves if this is suspected. Measurements of respiratory muscle function are indicated in evaluation of patients with various neuromuscular diseases. Carbon monoxide uptake Carbon monoxide (CO) diffusing capacity (DLco) or transfer factor (TLco)

is widely used as a simple test of the integrity of the alveolar capillary membrane and the overall gas-exchanging function of the lungs. Arterial blood gases and acid–base balance The primary measurements made by modern blood gas analysers are the arterial partial pressures of oxygen (Pao2) and carbon dioxide (Paco2), and hydrogen ion concentration [H+] or pH. A reduction in Pao2 can occur by various mechanisms, but in dis- ease the commonest is mismatching of alveolar ventilation (V’A) and perfusion (Q’). Respiratory failure is defined in terms of the arterial blood gas ten- sions as a reduction in Pao2 below 8 kPa (60 mm Hg) at sea level, either without (‘type I’) or with (‘type II’, ‘ventilatory failure’) CO2 retention. The ratio of Pao2/FIo2 is widely used in the assessment of pa- tients with severe oxygenation problems: in acute lung injury, a value greater than 300 (Pao2 in mm Hg, FIo2 as a fraction) indicates

18.3.1 Respiratory function tests 3957 relatively mild hypoxaemia, while a value of less than 100 represents very severe disturbance of gas exchange. Abnormal acid–base disturbances are traditionally classified as one of four types: respiratory acidosis and respiratory alkalosis— where the primary disturbance is reduced or increased CO2 excretion, respectively—and metabolic acidosis and metabolic alkalosis—where the primary disturbance is increased or decreased [H+], respectively. A mixed picture is frequently seen. The likely cause(s) of metabolic acidosis are usefully classified in terms of the ‘anion gap’, which is calculated simply by subtracting the concentrations of the most abundant anions in blood (chloride and bicarbonate) from the most abundant cations (sodium and potassium). Exercise Formal cardiopulmonary exercise testing usually involves controlled exercise on a bicycle ergometer or treadmill. The commonest in- dications are evaluation of breathlessness or exercise intolerance (particularly when breathlessness appears out of proportion to ab- normality demonstrated by other investigations), evaluating prog- nosis and monitoring of patients with congestive cardiac failure, and preoperative assessment for prediction of morbidity and mortality. Introduction Respiratory function tests are used in diagnosis, assessment, and prognosis and in monitoring the treatment of various respiratory conditions. In the diagnosis of specific diseases, respiratory function tests—like functional tests of other organs—inevitably have limita- tions. Their use as a diagnostic tool is usually in recognizing patterns of abnormality which characterize particular types of disease, as well as identifying the likely anatomical site(s) of disease (airways, alveoli, or chest wall). In addition, they are commonly used to quantify the severity of functional disturbance The commonly applied tests are most conveniently classified as: (1) tests of respiratory mechanics; (2) carbon monoxide uptake; (3) arterial blood gases and acid–base balance; and (4) exercise. Measurements made during sleep are de- scribed elsewhere (see Chapter 18.5.2). Tests of respiratory mechanics Mechanics of breathing The volume of air in the lungs at the end of tidal expiration at rest (functional residual capacity—FRC) represents the ‘neutral’ volume of the thorax, that is, the volume pertaining when the respiratory muscles are inactive (as also during anaesthesia with muscle par- alysis). Expansion of the lungs above FRC is achieved by contrac- tion of the inspiratory muscles (predominantly the diaphragm), while normal resting tidal expiration is essentially passive, with the driving force provided by elastic recoil of the lungs. The main ex- piratory muscles are those of the abdominal wall; their contraction increases abdominal pressure which is transmitted to the thorax. In health the expiratory muscles become active when ventilation is in- creased markedly, as on exercise, or during coughing when a high intrathoracic pressure aids the clearance of airway secretions. Measurements of ventilation Measurements of tidal breathing (tidal volume, respiratory fre- quency) are rarely made in the resting awake subject, other than recording respiratory rate as part of clinical examination. Measurement of ventilation is,

however, of importance in patients receiving ventilatory support, during detailed exercise testing, and during sleep investigations. During exercise testing, ventilation is usually obtained by electrical integration of airflow measured at the mouth, but this approach is impracticable for prolonged monitoring (such as during sleep) and the application of a mouthpiece and nose clip may itself disturb the pattern of resting breathing. Less intrusive methods of varying complexity are available, based on measuring external movement of the chest wall (ribcage and abdomen). Most are at best semiquantitative. They include the traditional mercury/ rubber tube stethograph (measuring chest circumference), mag- netometers (diameter), and the inductance plethysmograph (cross- sectional area). To obtain an estimate of ventilation, measurements of both ribcage and abdominal motion are required, together with an appropriate calibration procedure using a spirometer. The more complex technique of optoplethysmography, which is largely a re- search tool, uses several small reflectors on the chest and abdomen illuminated by infrared light, with the reflected signals captured and processed electronically to allow three-dimensional reconstruction of dynamic chest wall volume, for example, during exercise testing. Elastic properties of the lungs and chest wall In principle the mechanical function of the respiratory system can be characterized by the compliance (‘stiffness’) of the lungs and chest wall and the resistance of the airway. In practice, however, neither lung compliance nor airway resistance is commonly measured dir- ectly in clinical testing. For measurement of lung compliance, the pressure required to distend the lungs can be obtained by recording oesophageal pressure, which equates to pleural pressure. In clinical investigation, the elastic properties of the lungs are usually inferred from measurements of lung volumes, because lungs which are un- usually stiff and poorly compliant (as in pulmonary fibrosis) are usu- ally shrunken and reduced in volume, while lungs with abnormally high compliance (as in emphysema) are easily distensible and are associated with increased total lung capacity. The traditional sub- divisions of lung volume are illustrated in Fig. 18.3.1.1 and typical changes seen in disease in Fig. 18.3.1.2. The elasticity of the total respiratory system (i.e. lungs and chest wall together) is sometimes measured in intubated patients re- ceiving positive pressure ventilation, with acute respiratory distress syndrome (ARDS), for example. Sophisticated ventilators allow pre- cise measurement and computation, and monitoring of respiratory mechanics in this way has been shown to improve prognosis by al- lowing optimal ventilation strategies to be devised. Airway and respiratory resistance Direct measurement of airway resistance requires estimation of the pressure difference along the airway, between the alveoli and mouth. The various techniques available for estimating alveolar pressure in- clude oesophageal pressure monitoring, body plethysmography, and transient interruption of airflow. The plethysmographic method can be combined with measurement of lung volumes (see next section, ‘Measurements of lung volume’.). It requires the subject to make gentle panting efforts both with and without an occlusion at the

 mouth, while seated in a body plethysmograph. With the interrup- tion method, mouth pressure during transient occlusion is assumed to equal the alveolar pressure immediately prior to occlusion. The technique tends to underestimate airway resistance. It is used more often in paediatric than adult practice as it requires little cooperation from the subject. Airway resistance varies with lung volume, falling as volume in- creases due to an expanding effect of more negative pleural pres- sure and the increased tension in the lung tissue surrounding the intrapulmonary airways. Resistance (RAW) is often expressed as its reciprocal conductance (GAW), which in turn can be divided by the lung volume at which it is measured (specific airway conductance, SGAW) to allow for variations in volume. Resistance is dominated by the narrowest part of the airway, which in the healthy subject is the upper airway (trachea and

larynx). Although more peripheral air- ways are smaller individually, the great increase in their number with sequential branching creates a much larger overall cross-sectional area. Since chronic airway disease usually has its greatest impact on peripheral airways, plethysmographic measurements of airway re- sistance are not sensitive to the earlier stages of disease. An alternative and increasingly popular method for evaluating respiratory resistance is by forced oscillation. This involves super- imposition of a small oscillating pressure and airflow at the mouth during tidal breathing. The frequency of oscillation is varied and computerized analysis of the consequent pressure and flow signals allows calculation of respiratory resistance, which includes elements related to lung tissue and chest wall, as well as the airway. The tech- nique has the advantages of portability and simplicity of use, with little cooperation required from the subject. In clinical practice, however, airway function is most commonly assessed by tests based on forced expiration. Measurement of lung volume A spirometer records only the air which can be displaced from the lungs and not their absolute volume, because the unmeasured re- sidual volume (RV) remains in the lungs after full expiration. The maximum volume expired after a full inspiration (or inspired after a full expiration) is known as the vital capacity (VC). while the total lung capacity (TLC) represents the volume of air in the lungs after full inspiration—the sum of VC and RV (Fig. 18.3.1.1). Two main clinical methods are used for measurement of absolute lung volume—inert gas dilution and whole-body plethysmography. Inert gas dilution The subject breathes a gas mixture containing an inert marker gas, usually helium, from a closed circuit. The helium equilibrates grad- ually with the gas in the lungs so that its concentration falls progres- sively and stabilizes once mixing is complete. In a healthy individual this occurs in 5–10 min, but in patients with diffuse airway disease, such as asthma or chronic obstructive pulmonary disease, the test gas is distributed very unevenly, equilibration is much slower, the endpoint is less definite and, consequently, lung volume is likely to be underestimated. The lung volume which is measured is that in the lungs when the subject was connected to the circuit (usually FRC). After disconnection from the rebreathing circuit, the subject in- spires fully and the volume inspired (inspiratory capacity, IC) added to FRC gives TLC (Fig. 18.3.1.1). In patients with moderate or se- vere airway disease, uneven distribution of the inspired gas and poor mixing in the lungs result in underestimation of lung volumes. Whole-body plethysmography The subject sits within a large airtight rigid chamber and makes gentle breathing efforts against a shutter, which closes the airway at the mouth. According to Boyle’s law (pressure × volume = a con- stant), as intrathoracic pressure falls during an inspiratory effort, the air in the lungs is rarefied and lung volume increases by a small amount. This, in turn, causes the pressure in the plethysmograph TLC IC FRC RV VC FEV1 VT 1s Fig. 18.3.1.1 Subdivisions of lung volume illustrated by spirometric recording of volume against time during tidal breathing for three breaths, followed by maximal inspiration and then maximal forced expiration, before returning to tidal breathing in a normal subject. FEV1, forced expiratory volume in 1 s; FRC, functional residual capacity; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity; VT, tidal volume. Note that TLC = FRC + IC = VC + RV. Pulmonary fibrosis COPD Severe obesity Normal Respiratory muscle weakness 0 50 100 150 Volume % predicted TLC TLC FRC RV VC Fig. 18.3.1.2 Patterns of lung volumes in disease. Overall height of bars represents total lung capacity (TLC) as % predicted; shaded areas show relative sizes of residual volume (RV); horizontal solid line shows functional residual capacity (FRC); vital capacity (VC) is represented by open bars. Dotted lines refer to normal TLC, FRC, and RV.

 to increase. The converse occurs during expiratory efforts and the thoracic gas volume can be calculated from the pressure changes re- corded. Total lung

capacity and residual volume are then derived by full inspiration and expiration immediately on opening the shutter. This method measures the volume of any air spaces within or without the lungs that share pressure changes during breathing efforts, hence poorly ventilated areas of lung (or even those totally unventilated, such as a bulla) are included. Abnormalities of lung volumes An increase in TLC occurs in most patients with symptomatic dif- fuse airway obstruction. A large increase is characteristic of emphy- sema, but is not specific for this condition. Increases are also seen in asthma, even in relative remission. A pathological reduction in TLC occurs in several conditions (Table 18.3.1.1), not only lung diseases such as pulmonary fibrosis, but also extrapulmonary conditions af- fecting the pleura, thoracic skeleton, or respiratory muscles, conditions which—along with severe obesity—all potentially impede full lung expansion (Fig. 18.3.1.2). Patients with airway disease develop marked increases in RV and FRC, and the latter (or more strictly, the end expiratory lung volume) increases further on exercise, a phenomenon known as dynamic hy- perinflation. Although this is a useful adaptation for such patients as breathing over a higher tidal volume range allows ventilation to in- crease on exertion, maintaining higher lung volumes requires more work by the inspiratory muscles, and hyperinflation contributes significantly to the dyspnoea which such patients develop on exertion. The extent of dynamic hyperinflation can be assessed by monitoring inspiratory capacity during exercise and having the subject inspire periodically to full inflation and then return to tidal breathing. Tests of forced expiration Spirometry The strengths of forced expiratory tests include the simplicity of both the manoeuvre and equipment required, and also the relative inde- pendence of the measurements of the effort applied by the patient. Forced expiratory tests are, however, effort-dependent to the extent that a preceding full inspiration is required, but during forced expir- ation the larger intrathoracic airways are subjected to dynamic com- pression by the surrounding pleural pressure. The net result is that, provided a modest expiratory effort is applied, increasing the effort merely compresses the airway further and produces no increase in flow. This effort independence is more marked as forced expiration proceeds, and is also more marked in patients with airway obstruction than in healthy subjects. Maximum expiratory flow is more dependent on effort at higher than at lower lung volumes (i.e. closer to full inflation). As peak ex- piratory flow (PEF) is attained very rapidly at the start of forced ex- piration, this measurement is therefore more effort-dependent than the forced expiratory volume in 1 s (FEV1), which effectively inte- grates flow over a large proportion of the expired volume. PEF is measurable with a simple peak flow meter and is often used at home by patients with asthma to monitor their characteristically varying respiratory function. The most commonly used index of mechanical function of the lungs is the 1 s forced expiratory volume (FEV1)—the volume ex- pired forcefully in 1 s following complete inspiration (Fig. 18.3.1.1). This is usually obtained together with the forced vital capacity (FVC), the maximum volume expired during a forced expiration. In healthy subjects the FVC is effectively the same as VC, but in patients with airway disease the FVC is often appreciably less than the true (‘relaxed’) VC obtained if the subject is encouraged to expire com- pletely without excessive initial effort. The characteristic feature of diffuse airway obstruction is a slowing of the rate of expiration, so that the ratio of FEV1 to FVC (or FEV1 to VC) is reduced. This defines an ‘obstructive’ ventilatory defect. In the ‘restrictive’ pattern of ventilatory function, both FEV1 and FVC are typically reduced in approximate proportion but, strictly, a re- strictive defect implies that TLC is reduced and this cannot be diag- nosed confidently by spirometry alone. In patients with symptomatic diffuse airway obstruction the FVC and VC are usually reduced, but the reduction is proportion- ally less than that in FEV1. Although a reduced ratio of FEV1 to (F) VC indicates the presence of airway obstruction, it is a poor guide to severity, which is better assessed by comparing the FEV1 alone with its predicted

value. An obstructive spirometric pattern is seen in asthma, chronic obstructive pulmonary disease, and widespread bronchiectasis, while a restrictive ventilatory pattern is seen in nu- merous conditions (Table 18.3.1.1). A further feature of diffuse airway obstruction is an increase in RV and in the ratio RV/TLC, but the latter is less specific than a re- duced FEV1/VC ratio as it also occurs in some patients with cardiac disease or respiratory muscle weakness. Combined obstructive (low FEV1/VC) and restrictive (low TLC) defects may be seen if dual pathology is present. Sometimes TLC may be within the normal range due to opposing influences with, for example, lung fibrosis tending to reduce it and airway obstruc- tion to increase it. Maximum flow–volume curves Measurement of FEV1 and FVC is the best way of identifying the diffuse airway narrowing of chronic obstructive pulmonary disease or asthma, but is less sensitive to localized narrowing of the central airway. If the latter is suspected, it is particularly helpful to visualize airflow obtained during forced expiration and forced inspiration in the form of maximum flow–volume curves, which relate instantan- eous flow to volume expired and inspired (Fig. 18.3.1.3). The maximum expiratory flow–volume curve has a characteristic shape, with an early peak that is equivalent to the PEF obtained with a peak flow meter. Maximum expiratory flow then declines progres- sively as volume is expired. In young healthy subjects (Fig. 18.3.1.3a), Table 18.3.1.1 Common causes of reduced total lung capacity Intrapulmonary Surgical resection of lobes/lung Pulmonary collapse Consolidation Pulmonary oedema Interstitial fibrosis Extrapulmonary Pleural effusion Pleural thickening Pneumothorax Ribcage deformity (e.g. scoliosis) Respiratory muscle weakness Severe obesity

 the descending limb of the curve approximates a straight line, while in older normal subjects (Fig. 18.3.1.3b), maximum expiratory flow is less, particularly at lower lung volumes, and the curve becomes concave to the volume axis. In patients with diffuse intrathoracic airway obstruction (such as chronic obstructive pulmonary disease or asthma) the pattern is qualitatively similar to that of ageing, but greatly exaggerated, with expiratory flow reduced more markedly as lung volume declines (Fig. 18.3.1.3d). The shape of the flow– volume curve does not distinguish between different causes of dif- fuse airway narrowing and so cannot allow the distinction of asthma from chronic obstructive pulmonary disease or emphysema. In prin- ciple, measurements of maximum expiratory flow in the latter part of forced expiration should be more sensitive to milder degrees of airway narrowing. In practice, however, indices such as maximum flow after 75% of the FVC has been expired (FEF75) have proved disappointing because the very wide normal range seriously reduces their discriminating power. Another widely used measurement is the average maximum flow over the middle two-quarters of expir- ation (FEF25–75, formerly known as maximum mid-expiratory flow). Again, however, the value of this index is seriously compromised by its wide variation in the healthy population and also by its depend- ence on VC, such that reductions are seen with both obstructive and restrictive ventilatory defects. The maximum inspiratory flow–volume curve has a more sym- metrical appearance than the expiratory curve. In patients with dif- fuse airway narrowing there is an overall reduction in maximum inspiratory flow, but little change in shape (Fig. 18.3.1.3d). In pa- tients with a restrictive ventilatory defect caused, for example, by pulmonary fibrosis, the volume displaced is reduced but absolute flows are little affected (Fig. 18.3.1.3c). Characteristic features are seen in patients with localized nar- rowing of the central airway, with the pattern depending on whether the narrowing is extra- or intrathoracic. Extrathoracic narrowing (Fig. 18.3.1.3e), such as occurs with subglottic tracheal stenosis or upper tracheal tumours, has a relatively greater effect on maximum inspiratory than expiratory flow (this corresponds to the predomin- antly inspiratory timing of the stridor of

upper airway narrowing). Maximum expiratory flow is also affected, but unlike chronic ob- structive pulmonary disease or asthma, the effects are most marked at higher lung volumes, often producing a virtual ‘plateau’ of expira- tory flow in the first part of forced expiration. If the central airway is narrowed within the thorax (e.g. lower trachea or carina) a similar plateau of expiratory flow, often with a small initial peak, may be seen, but maximum inspiratory flow is relatively less affected (Fig. 18.3.1.3f). These differing patterns can be quantified in terms of various ratios, such as that of maximum expiratory to inspiratory flow at 50% of VC, or the ratio of PEF (markedly reduced with upper airway obstruction) to FEV1 (proportionally less reduced). Such derived in- dices should be interpreted in light of the overall shape of the curves. The ‘plateau’ of maximum expiratory flow seen with upper airway obstruction has implications for the shape of the forced expiratory spirogram (volume vs. time). On the spirogram, flow is represented by the gradient of the curve and therefore a plateau on the flow–volume curve implies a ‘straight’ (rectilinear) appear- ance of the spirogram over the same volume range. Such an ap- pearance should therefore raise the possibility of a narrowing of the central airway, rather than the more common diffuse airway obstruction seen with asthma and chronic obstructive pulmonary disease (Fig. 18.3.1.4). Respiratory muscle function Forcible static inspiratory and expiratory efforts against a closed airway allow measurement of maximum expiratory and inspira- tory pressures (PE max, PI max). In general, the expiratory (pre- dominantly abdominal) muscles perform most effectively at high lung volumes and the inspiratory muscles (predominantly the diaphragm) at lower volumes. PE max is therefore usually meas- ured after full inspiration and PI max at FRC or RV. Unfortunately, the normal ranges for these tests are wide and some patients find difficulty in performing the manoeuvres, which are by definition completely effort-dependent. Alternatively, inspiratory muscle strength can be assessed during a forceful sniff, with the pres- sure measured in the nose via an occluded nostril. Many (though not all) patients find this easier than performing maximum static inspiratory manoeuvres, so the maximal sniff technique may give more reproducible results. Many laboratories ask patients to per- form both maximum inspiratory tests and report the numerically greater result. These measurements all assess the global strength of the inspiratory or expiratory muscles. More specific information on dia- phragmatic function requires measurement of transdiaphragmatic pressure using pressure-sensing devices in both oesophagus and stomach—a specialized investigation available in only a few centres. VImax (a) (b) (c) (d) (e) (f) Volume VEmax VImax VEmax Fig. 18.3.1.3 Schematic maximum expiratory and inspiratory flow– volume curves in: (a) normal young adult; (b) normal older adult; (c) patient with pulmonary fibrosis and reduced FVC; (d) patient with moderately severe chronic obstructive pulmonary disease showing overall reduction in maximal flow but particularly in $\dot{V}E$ max, at lower lung volumes; (e) patient with subglottic (extrathoracic) tracheal stenosis showing markedly reduced $\dot{V}I$ max at all volumes and reduced $\dot{V}E$ max at higher volumes; (f) patient with central intrathoracic (e.g. carinal) tracheal narrowing showing similar plateau of expiratory flow to (e) but greater reduction of $\dot{V}E$ max than of $\dot{V}I$ max.

 A simple indirect index of disproportionate diaphragmatic weakness or paralysis is a large (>25%) reduction in VC in the supine compared with the erect posture. However, isolated bilateral diaphragmatic par- alysis or severe weakness is very uncommon, and most patients with respiratory muscle weakness have disease affecting all the muscles. Causes include not only primary neuromuscular diseases such as myopathies, muscular dystrophies, motor neuron disease, and my- asthenia gravis, but also drug treatment (corticosteroids), several endocrine and connective tissue disorders, and cachexia from what- ever

cause. Respiratory muscle weakness is often an important factor preventing weaning from assisted ventilation. Respiratory muscle function in diagnosis Measurements of respiratory muscle function are indicated in the evaluation of patients with various neuromuscular diseases, condi- tions in which they have been shown to have important prognostic value. They are also helpful in confirming or excluding muscle problems in those with otherwise unexplained dyspnoea and in pa- tients with a restrictive ventilatory defect in whom the cause of the lung volume reduction is not apparent on clinical and radiographic grounds. Interpretation may be complicated in patients with airway obstruction (such as chronic obstructive pulmonary disease or asthma) because the associated hyperinflation of the lungs itself im- pairs inspiratory muscle function. Maximum expiratory pressure is not affected by hyperinflation, however, and can be used as a guide to the presence of true muscle weakness in this situation. Carbon monoxide uptake Carbon monoxide (CO) diffusing capacity (DLco) (also known as transfer factor, TLco) is widely used as a simple test of the integrity of the alveolar capillary membrane and the overall gas exchanging function of the lungs. It has good sensitivity but poor specificity, as impairment can result from several pathological processes (Table 18.3.1.2). In the commonest method, the subject inspires fully a gas mix- ture containing a very low concentration of CO and the rate of uptake of gas is measured during breath-holding for 10 s. The most important determining factor in most conditions is the effective surface area of alveoli available for gas exchange. Consequently DLco is reduced, for example, after resection of the lung, but also with widespread emphysema, in which normal-sized alveoli are replaced by much larger air spaces, with a consequently greatly diminished area. DLco is also reduced when there is loss of the ‘effective’ alveolar volume (VA) in which the test gas is distrib- uted (see next section on interpretation). Other factors affecting the DLco include the haemoglobin concentration and disease involving the pulmonary capillaries. The transfer coefficient (Kco), which is obtained along with DLco, represents the uptake of CO per litre of ‘effective’ alveolar volume, that is, Kco = DLco/VA. The ‘effective’ alveolar volume is measured simultaneously by an inert gas (such as helium) in the inspired gas mixture. This represents the alveolar volume relevant to that inspir- ation (i.e. the volume with which the inspired gas equilibrates during the 10 s breath-hold), hence if there is uneven ventilation, VA is less than the true alveolar volume (i.e. less than TLC). (a) Volume expired (litres) Time (seconds) 6 5 4 3 2 1 1 2 3 4 5 6 0 1 2 3 4 5 6 (b) Volume expired (litres) 6 5 4 3 2 1 0 Time (seconds) Fig. 18.3.1.4 Schematic spirograms of two patients with airway obstruction and similar FEV1. (a) Diffuse intrathoracic airway narrowing (chronic obstructive pulmonary disease or asthma). Note that forced expiration is continuing after 6 s. (b) Upper airway narrowing with ‘straight’ spirogram which corresponds to plateau of flow in earlier part
of expiration in Fig. 18.3.1.3e. Table 18.3.1.2 Common causes of reduced carbon monoxide diffusing capacity (transfer factor) Pulmonary diseases COPD/emphysemaa Asthma (with severe airway obstruction) Pneumonectomy Pulmonary fibrosisa Sarcoidosis Pulmonary vascular diseasea Cardiac diseases Pulmonary oedemaa Mitral valve diseasea Congenital right-to-left shuntsa Systemic diseases Anaemiaa Renal failurea Hepatic cirrhosisa Rheumatoid disease Systemic sclerosisa Systemic lupusa COPD, chronic obstructive pulmonary disease. a Kco usually also reduced.

 Kco is typically normal or increased after lung resection, when both DLco and VA are reduced. It is usually normal (or sometimes mildly increased) in asthma, where any reduction in DLco is due only to maldistribution of ventilation secondary to airway nar- rowing. By contrast, DLco is reduced in widespread emphysema not only due to

maldistribution of inspired gas, but also because even in the relatively better ventilated parts of the lung the gas exchanging surface area is diminished, hence Kco is also reduced. Some of the diseases associated with low DLco and Kco are listed in Table 18.3.1.2. In some conditions Kco and, less commonly, DLco may be high (Table 18.3.1.3). Both increase with an increase in red blood cells in the lungs due to increased capillary blood volume, alveolar haemorrhage, or polycythaemia. Kco is also increased if, at full inflation, the density of pulmonary capillaries per unit alveolar volume is greater than normal. This occurs most commonly in patients with extrapulmonary volume restriction (e.g. muscle weakness), when the density of pulmonary capillaries is unusually high in relation to the (restricted) TLC at which the measurement is made. Interpretation of respiratory function tests Reference values The results of respiratory function tests should be compared with reference values obtained in an appropriate healthy popu- lation. The main factors determining the results of most tests in the normal population are sex, age, body size (usually de- fined by height), and ethnicity. Worldwide, more than 300 ref- erence equations for spirometric volumes have been published, but none is universally applicable. To date, the most commonly used in Europe have been summary equations published origin- ally in 1993. However, these take no account of ethnicity and it has been conventional for readings from nonwhite individuals to apply a proportional reduction to predicted values of spirometric and static lung volumes, most commonly multiplying by 0.88. Variation due to ethnicity is gradually being incorporated, for in- stance, in the third National Health and Nutrition Examination Survey (NHANES III) equations now recommended for use in North America, and in those derived by the ongoing Global Lung Function Initiative of the European Respiratory Society (see ‘Further reading’). Normal or abnormal? After standardizing for the variables mentioned in the previous section, most lung function measurements are distributed normally in the healthy population. Classification of ‘normal’ or ‘abnormal’ is best done in terms of the number of standardized residuals by which a given measurement deviates from the mean predicted value (z score). With this approach, a z score ranging from –2 to + 2 would encompass 95% of a normally distributed population and –1.645 to + 1.645 encompasses 90%. When evaluating spirometric results, the need is to identify a unidirectional abnormality (e.g. a low, ra- ther than high, FEV1). It is therefore conventional to regard z values outside the 90% confidence intervals as ‘abnormal’. Thus, a z value more negative than –1.645 represents the lower fifth percentile of the normal range (i.e. only 1 in 20 of the healthy population would be expected to have a result below this value). The choice of this level is of course a compromise between sensitivity and specificity, and should not be regarded as an absolute ‘cut-off’ which will accurately classify every individual. One contentious point of interpretation is the definition of a ‘normal’ ratio of FEV1 to FVC, which is important because airway obstruction is defined by this metric. A ratio less than 0.7 is com- monly used as the cut-off that indicates airway obstruction. This has the advantage of simplicity, and it is used in some diagnostic criteria for identifying chronic obstructive pulmonary disease (COPD), but it ignores the normal age-related decline of the ratio. Since many healthy elderly individuals have values less than 0.7, its use as a blanket cut-off between ‘normal’ and ‘abnormal’ results in significant overdiagnosis of COPD in populations older than 60 years. Conversely, a value of FEV1/FVC of 0.7 in a 25-year-old would be very abnormal, hence use of this arbitrary value also risks failure to recognize significant airway obstruction in young adults. The alternative, and preferred, approach is to use appropriate refer- ence data for the FEV1/FVC ratio to define the limits of normality with which to compare the z score in the same manner as for other measurements. The test results should be examined for internal consistency and interpreted in the light of the clinical and radiographic information

available. A number of characteristic patterns of abnormality of spirometry, lung volumes, and CO diffusing capacity are recognized (Table 18.3.1.4). Arterial blood gases The primary measurements made by modern blood gas analysers are the arterial partial pressures of oxygen (Pao2) and carbon di- oxide (Paco2), and hydrogen ion concentration [H+] or pH. The alternative, commonly used, method of assessing oxygenation is by pulse oximetry, which estimates arterial oxygen saturation (Sao2). An oximeter has the advantage of allowing continuous monitoring, but it provides no information on Paco2. Easy to use transcutaneous electrodes for estimating Paco2 are becoming more widely available. Table 18.3.1.3 Conditions producing increased carbon monoxide diffusing capacity and/or Kco ↑ DLco ↑ Kco Asthma Sometimes + Pneumonectomy – + Extrapulmonary restriction Pleural disease – + Ribcage deformity – + Respiratory muscle weakness – + Obesity – + Left-to right-shunts + + Polycythaemia + + Lung haemorrhage +a +a a May be an increase from an initially reduced value (e.g. Goodpasture’s syndrome).

18.3.1 Respiratory function tests 3963 Haemoglobin–oxygen dissociation curve The general relation between the oxygen partial pressure in blood and haemoglobin saturation is defined by the oxygen–haemoglobin

dissociation curve (Fig. 18.3.1.5). The position of the curve is in- fluenced by the prevailing pH, temperature, and Pco2, as well as by the concentration of 2,3-diphosphoglycerate (2,3-DPG) in red cells. Approximate values for normal arterial and resting mixed venous Po2 and saturation are shown in Fig. 18.3.1.5. One clinically

useful ‘landmark’ is a saturation of 90% which, with a normally positioned curve, represents a Po2 of approximately 8 kPa (60 mm Hg). Also shown in Fig. 18.3.1.5 is the P50, that is, the Po2 at a saturation of 50%, which for normal adult haemoglobin is approximately 3.5 kPa (27 mm Hg). This is measured in vitro and used to

characterize ab- normal haemoglobin molecules associated with increased (low P50) or decreased (high P50) affinity for oxygen. Ventilation–perfusion mismatching A reduction in Pao2 can occur by various mechanisms (Table 18.3.1.5). In disease, the commonest is mismatching of alveolar ventilation (V’A) and perfusion (Q’). Even in

healthy lungs, distribution of both ventilation and perfusion is uneven, due mainly to gravity. In dis- ease, these relatively small effects are outweighed by unevenly distributed pathological changes affecting the distribution of venti- lation or perfusion or both. Alveoli with greater than average V’A/Q’ have higher than average

local Po2 and lower Pco2 (i.e. closer to those of inspired air). Conversely, alveoli with lower than average V’A/Q’ have lower Po2 and higher Pco2, that is, closer to the values in mixed venous (pulmonary arterial) blood. Within a single al-veolus, complete equilibration of local gas tensions usually occurs, but in different pulmonary

capillaries the gas tensions reflect those of the alveoli which they subtend. For CO2 the effects of high V’A/ Q’ and low V’A/Q’ areas on the final arterial Pco2 approximately cancel out, so that the arterial Pco2 is close to the average value in all the capillaries draining the alveoli. With oxygen, however, blood draining alveoli with high V’A/Q’ (and

therefore relatively high local Po2) cannot compensate for the areas with low V’A/Q’ (and low Po2). This arises mainly because of the shape of the oxygen dissoci- ation curve: the relatively flat upper part of the curve implies that increasing Po2 adds very little to oxygen saturation or concentration (content). Consequently,

mixed pulmonary venous (and therefore systemic arterial) blood has an appreciably lower Po2 than would be found in mixed alveolar air. An approximate assessment of the overall effects of V’A/Q’ mismatching on arterial oxygenation and Pao2 is given by cal- culation of the alveolar to arterial oxygen pressure gradient (P(A –

a)o2 = PAo2 – Pao2). This requires estimation of the average alveolar Po2 (PAo2), which depends on the inspired Po2 (PIo2) and the average alveolar Pco2 (PAco2). For the reasons discussed earlier, alveolar and arterial Pco2 (unlike Po2) are virtually the same. The alveolar Po2 is given approximately by: PAO PIO PaCO 2 2 2 0 8

− / . (Equation 18.3.1.1). The PIo2 breathing room air at sea level (moistened and warmed to body temperature) is approximately 20 kPa (150 mm Hg). In normal young subjects the upper limit for P(A – a)o2 is about 2 kPa (15 mm Hg). This limit increases with age and in healthy subjects aged Table 18.3.1.4 Common patterns of abnormal lung volumes and carbon monoxide diffusing capacity Condition FEV1 VC FEV1/VC RV TLC D L co K co COPD/emphysema ↓↓ ↓ ↓ ↑↑ ↑ ↓↓ ↓ Asthma ↓↓ ↓ ↓ ↑↑ ↑ → → or ↑ Interstitial lung disease ↓ ↓ → → ↓ ↓↓ ↓ or → Extrapulmonary volume restriction ↓ ↓ → ↑ or → ↓ → ↑ Pulmonary vascular disease → → → → → ↓↓ ↓↓ Combined pathology (e.g. COPD + interstitial fibrosis) ↓↓ ↓ ↓ ↑ or → → or ↓ ↓↓ ↓↓ COPD, chronic obstructive pulmonary disease. →, normal; ↓, moderately reduced; ↓↓, markedly reduced. 100 100 (mm Hg) 0 25 25 5 10 (kPa) Po2 50 c v b a Saturation (%) 50 75 75 Fig. 18.3.1.5 Normal haemoglobin–oxygen dissociation curve relating saturation to PO2. Point a represents normal arterial values (PO2 90 mm Hg, 12 kPa; SaO2 98%) and v¯ normal resting mixed venous values (Pv¯O2 40 mm Hg, 5.3 kPa; SaO2 75%). Also shown are the PO2 (approx. 60 mm Hg, 8 kPa) corresponding to 90% saturation (point b) and the P50 (point c), that is, PO2 corresponding to 50% saturation (approx. 27 mm Hg, 3.5 kPa). Table 18.3.1.5 Mechanisms of arterial hypoxaemia Mechanism Cause Low inspired Po2 Altitude (including air travel) Hypoventilation Neuromuscular diseases Drugs depressing ventilatory drive V’A/Q’ mismatching All pulmonary diseases Anatomical shunt Intracardiac right-to-left shunt Pulmonary arteriovenous malformations Limitation of oxygen diffusion Pulmonary fibrosis (on exercise)

section 18 Respiratory disorders 3964 60–70 years may be as high as 4.7 kPa (35 mm Hg). Unfortunately, interpretation of the P(A – a)o2 is complicated by the fact that its relation to the severity of V’A/Q’ mismatching is not constant. For a given degree of V’A/Q’ mismatching, the P(A – a)o2 increases as the alveolar Po2 increases. It therefore increases if the inspired oxygen is increased or if Paco2 falls (see Equation 18.3.1.1). Alternative indices which relate more predictably to the severity of V’A/Q’ mismatching are the ratios of arterial to alveolar Po2 (a/A Po2), and of arterial Po2 to the inspired oxygen fractional con- centration (Pao2/FIo2). The former is normally greater than 0.75 and changes little as FIo2 increases, whereas the more traditional P(A – a)o2 difference increases. The ratio of Pao2/FIo2 is widely used in assessment of patients with severe problems of oxygen- ation. For example, in acute lung injury a value greater than 300 (Pao2 in mm Hg, FIo2 as a fraction) indicates relatively mild hyp- oxaemia, while a value of less than 100 represents very severe dis- turbance of gas exchange. Estimation of ‘anatomical’ shunt The dependence of P(A – a)o2 on inspired oxygen is exemplified by the effects of breathing pure oxygen. This is sometimes used as a test for the presence of anatomical right-to-left shunting, since the effects of V’A/Q’ mismatching on Pao2 are effectively eliminated by breathing pure oxygen: even in diseased lungs, nitrogen is gradually ‘washed out’ of all the alveoli and the only remaining cause of arterial hypoxaemia is the anatomical shunt via channels which bypass the lungs, or through the capillaries supplying any alveoli that are to- tally unventilated. Although prolonged breathing of 100% oxygen encourages alveolar atelectasis which would exaggerate the shunt, in practice the technique is often helpful in investigating the causes of hypoxaemia. The usually quoted normal upper limit for the ‘ana- tomical’ shunt measured in this way is 5% of the cardiac output. In terms of the Pao2, a value greater than 500 mm Hg (>73 kPa) is usu- ally achieved. Respiratory failure Respiratory failure is defined in terms of the arterial blood gas tensions as a reduction in Pao2 below 8 kPa (60 mm Hg) at sea level, either without (‘type I’) or with (‘type II’) CO2 retention. Hypercapnic (type II) respiratory failure is also known as venti- latory failure. The causes of type I respiratory failure are legion and include virtually all diseases which

can affect the alveoli or the airways, either primarily or secondarily (e.g. cardiac failure). Hypercapnic (type II) respiratory failure is most commonly due to severe chronic airway disease. Less often it results from reduced ventilation as, for example, with severe respiratory muscle weakness or scoliosis. The mechanisms of elevation of Paco2 in type II respiratory failure are twofold. Sustained 'pure' hypoventilation— reduction in overall ventilation resulting in hypercapnia—is rare. It is seen with inadequate performance of the respiratory 'bel- lows' (e.g. in neuromuscular disease, or because of reduced drive to breathe in the unconscious subject). Much more commonly, as in chronic airway disease, the 'effective' alveolar ventilation is re- duced as a consequence of mismatching of ventilation and per- fusion. In this situation, there is often a considerable amount of ineffectual or wasted ventilation ('physiological dead space') and consequently in such patients the total ventilation is often greater than normal, even in the presence of hypercapnia. Acid–base balance The carriage of CO2 by the blood and its excretion by the lungs to- gether constitute one of the two homeostatic mechanisms for regu- lating the acid–base status of the body. Owing to the ease with which CO2 excretion can normally be increased, the lungs are able to adjust acid–base balance much more rapidly than the kidneys. The carbonic acid association/dissociation equation is: CO H O H CO H HCO 2 2 2 3 3 + ⇔ ⇔ + + − (Equation 18.3.1.2). This defines the chemical relation between the three variables, Pco2, hydrogen ion concentration [H+], and bicarbonate concentra- tion [HCO3–]. If two are measured, the third is readily calculated. Hydrogen ion concentration is usually expressed as pH, its nega- tive logarithm to the base 10. This has the dubious advantage of expressing a very small numerical value as a more easily accessible number, but the pH scale is deceptive as it obscures the fact that the hydrogen ion concentration in blood and the changes seen in disease are exquisitely small in comparison to other commonly measured ions. Thus, a normal arterial pH of 7.4 represents [H+] of 40 × 10–9 mol/litre (i.e. approximately 1 millionth the concentration of other ions, which are usually expressed in units of 10–3 mol/ litre). Doubling [H+] to 80 × 10–9 mol/litre or halving it to 20 × 10–9 mol/litre are equivalent to reducing pH to 7.1 or increasing it to 7.7, respectively (since the log10 of 2 is c.0.3, and pH is the negative log10 of [H+], 0.3 is simply subtracted from, or added to, the normal value of 7.4 if [H+] is multiplied or divided by 2). Abnormal acid–base disturbances are traditionally classified in terms of these variables as four types (Table 18.3.1.6 and Fig. 18.3.1.6), but combined disturbances are frequently seen. The more common causes of each are given in Table 18.3.1.7. Respiratory acidosis and alkalosis In respiratory acidosis the prime event is accumulation of CO2 due to inadequate or ineffective ventilation. This causes the equilibrium of Equation 18.3.1.2 to shift to the right, generating hydrogen and bicarbonate ions. An immediate increase in bicarbonate concentration is dictated by this chemical relationship and not by the physio- logical response, which occurs subsequently. The vast majority of hydrogen ions produced are buffered by proteins and the increase in [HCO3–] (measured in 10–3 mol/litre) is actually very much greater than the measured increase in hydrogen ion concentration (10–9 mol/litre). Conventionally the effects of acute respiratory acid- osis are distinguished from those of chronic respiratory acidosis, Table 18.3.1.6 Types of acid–base disturbance Arterial [H+] pH Paco2 [HCO3 –] Respiratory acidosis: Acute ↑↑ ↓↓ ↑ ↑ Chronic ↑ ↓ ↑ ↑↑ Respiratory alkalosis ↓ ↑ ↓ ↓ Metabolic acidosis ↑ ↓ ↓ ↓ Metabolic alkalosis ↓ ↑ ↑ or → ↑ →, normal; ↓, moderately reduced; ↓↓, markedly reduced; ↑, moderately increased; ↑↑, markedly increased.

 which results after several hours or days. This follows renal retention of even more bicarbonate, which in turn tends to correct the pH towards normal (Table 18.3.1.6). In respiratory alkalosis, the primary event is increased CO2 ex- cretion resulting from

hyperventilation, so that both [HCO3–] and [H+] fall (pH rises), but, again, most of the change in [H+] is buffered. Metabolic acidosis and alkalosis In metabolic acidosis [H+] rises (pH falls) and [HCO3–] falls. The physiological response (hyperventilation) is so rapid that acute and chronic phases are not distinguishable. Any tendency for Paco2 to rise (equilibrium of Equation 18.3.1.2 shifted to the left) is more than offset by the increased drive to breathe resulting from production of acid, and the measured effect is a reduction in Paco2. The likely cause(s) of metabolic acidosis are usefully classified in terms of the 'anion gap', which is calculated simply by subtracting the concentrations of the most abundant anions in blood (chloride and bicarbonate) from the most abundant cations (sodium and po- tassium). The difference represents other anions (mostly protein and inorganic phosphate) normally present in blood. An increase above the normal anion gap therefore implies an excess of other anions as- sociated with metabolic acidosis (e.g. lactate, ketoacids). In metabolic alkalosis there is an increase in [HCO3–] and a re- duction in [H+] (pH increases). The measured result is somewhat variable due to opposing influences: any increase in Paco2 tends to stimulate breathing, but the reduced acidity tends to inhibit it. In subjects with healthy lungs, the net effect is often maintenance of Paco2 in the high normal range, unless the alkalosis is profound (e.g. as seen with vomiting due to pyloric stenosis and severe deple- tion of acid). However, in patients with chronic airway disease and pre-existing or incipient hypercapnia, an increase in Paco2 occurs more readily. This is particularly relevant to patients with chronic obstructive pulmonary disease receiving treatment with diuretics and corticosteroids, both of which tend to produce a metabolic alkalosis. Other acid–base indices Several other indices of acid–base status have their advocates. Standard bicarbonate, base excess and deficit, and total buffer base are often derived when blood gases are measured by automated equipment. They are obtained by titration of the blood in vitro to specified standard values of pH and/or Pco2. Indices such as standard bicarbonate and base excess are used mainly to distin- guish 'respiratory' and 'metabolic' components of an acid–base dis- turbance, but in this context the 'metabolic' component comprises not only a primary metabolic disturbance, but also renal compen- sation for a primary respiratory disturbance. Consequently, in a Fig. 18.3.1.6 Relations of pH and [H+] to PCO2 in acid–base disorders. Bands indicate the expected ranges in uncomplicated respiratory (acute and chronic) and metabolic disorders. Isopleths represent corresponding estimates of arterial [HCO3 –] (× 10–3 mol/litre). Values outside these bands indicate intermediate or combined disturbances. For example: patient a with an acute exacerbation of chronic obstructive pulmonary disease has an 'acute-on-chronic' respiratory acidosis (PaCO2 10.6 kPa, pH 7.24, [H+] 58 × 10–9 mol/litre, [HCO3 –] 34 × 10–3 mol/litre); patient b with both respiratory and circulatory failure has a combined respiratory and metabolic acidosis (PaCO2 8 kPa, pH 7.04, [H+] 95 × 10–9 mol/litre [HCO3 –] 15 × 10–3 mol/litre). Table 18.3.1.7 More common causes of acid–base disturbance Disturbance and site of disease Cause Respiratory acidosis Cerebral Drugs (sedatives, hypnotics, anaesthetics) Raised intracranial pressure Primary alveolar hypoventilation (very rare) Spinal cord Trauma Motor neurons Motor neuron disease, poliomyelitis Peripheral nerves Guillain–Barré syndrome Motor endplate Myasthenia gravis, neuromuscular blocking agents Respiratory muscles Myopathies, dystrophies Ribcage Scoliosis, trauma, thoracoplasty Lung parenchyma ARDS, pulmonary oedema (severe), interstitial fibrosis (very advanced) Airways COPD, asthma (severe), upper airway obstruction (very severe) Respiratory alkalosis Cerebral Anxiety, central neurogenic hyperventilation (very rare), drugs (aspirin) Pulmonary Pulmonary fibrosis, pneumonia, pulmonary embolism, asthma, pulmonary oedema Iatrogenic Mechanical overventilation Metabolic acidosis Increased anion gap Ketoacidosis, uraemia, lactic acidosis, drugs (aspirin), poisons (ethylene

glycol) Normal anion gap Renal tubular acidosis, severe diarrhoea Metabolic alkalosis Severe vomiting Pyloric stenosis Iatrogenic Diuretics, corticosteroids, bicarbonate infusion ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

section 18 Respiratory disorders 3966 respiratory acidosis, an increased standard bicarbonate indicates a degree of chronicity. Conversely, the severity of acidaemia in a hypercapnic patient is a useful practical index of the 'acute' com- ponent of an acute-on-chronic respiratory acidosis and is widely used, for example, when deciding on the need for noninvasive ventilation. Another simple and frequently available index of acid–base status is the venous 'bicarbonate' concentration (strictly total CO2 con- tent), which is often obtained routinely when electrolytes are meas- ured. A raised value is seen with primary metabolic alkalosis, but in patients with respiratory disease it may also be a useful clue to unsuspected ventilatory failure. 'Strong ion' approach The analysis of acid–base balance presented in the previous section is oversimplified. A more comprehensive (but more complex) ap- proach based on the principles of physical chemistry was proposed by Stewart and subsequently developed by others. This focuses on the factors that independently determine [H+], reducing the emphasis on [HCO3–], as both are regarded as dependent variables. According to this analysis, there are three independent variables controlling acid–base balance: the Pco2; the 'strong ion difference' (SID); and the total weak acid concentration (a weak acid is one which is partly dissociated rather than completely ionized). SID is the difference be- tween the charge of the strong (completely dissociated) cations and anions in plasma and is determined largely by [Na+] + [K+] – [Cl–]. A higher value of SID reduces acidity (higher pH). The weak acids in blood are predominantly proteins, particularly albumin, with a small contribution from inorganic phosphate. This approach defines six rather than four primary acid–base dis- orders. Respiratory disturbances remain as before, but metabolic acidosis and alkalosis can each be either of two types, resulting from increases or decreases either in SID or total weak acid concentration. Decreasing SID or increasing [weak acid] produces acidosis, while increasing SID or decreasing [weak acid] produces alkalosis. In practice, the strong ion approach is of most value in under- standing complex metabolic disturbances, as commonly occur in patients receiving intensive care. In particular it highlights the important role of albumin concentration: since albumin is a weak acid, a reduction in its concentration has an alkalinizing effect, such that a metabolic acidosis resulting from a reduction in SID may be underestimated or concealed in patients with hypoalbuminaemia. Again, it is well recognized that infusion of large volumes of normal saline can result in an acidosis; in terms of the strong ion theory, this is readily explicable as due to a reduction in plasma SID as plasma [Cl–] increases proportionally more than [Na+]. An important de- terminant of SID is renal function, in particular the regulatory ef- fect of the kidneys on plasma chloride concentration. Thus, in 'renal compensation' for a respiratory acidosis, the strong ion approach emphasizes increased excretion of chloride (rather than retention of bicarbonate); this increases plasma SID and therefore reduces acidaemia. Exercise testing The increased supply of oxygen to, and removal of carbon dioxide from, exercising muscles depends on the coordinated responses of the cardiovascular and respiratory systems. The efficiency of this process requires the integration of several factors, with the respiratory muscles, lungs, chest wall, pulmonary circulation, heart, systemic circulation, blood and limb muscles all contrib- uting. Functional defects in any one (or more) of these are likely to impair overall efficiency and limit the exercise ability of the individual. Normal physiological responses to exercise Metabolic response In healthy individuals, muscle metabolism during moderate ex- ercise generates ATP mainly via aerobic pathways, but with more strenuous exercise the delivery of oxygen to the muscles is insuf- ficient to support completely aerobic metabolism,

and anaerobic metabolism—which produces CO2 without consuming oxygen—is increasingly important and results in the production of lactic acid. During aerobic exercise, the respiratory quotient (RQ, i.e. the ratio of CO2 produced to oxygen consumed) in the muscles varies from 0.7 to 1.0 (averaging about 0.9), depending on the substrate(s) util- ized. This value increases as anaerobic metabolism increases. The ratio of CO2 production (V’CO2) to oxygen consumption (V’O2) measured at the mouth is termed the respiratory exchange ratio (R). R and RQ are identical in a completely steady state, but under the conditions of most exercise tests, their values are likely to differ to some extent. The ‘anaerobic threshold’ (AT) is defined as the level of V’O2 at which the onset of anaerobic metabolism is detected. However, anaerobic metabolism does not ‘switch on’ abruptly, but increases gradually as exercise becomes more strenuous. The true maximum oxygen uptake is measured only once a plateau value is reached despite further increases in workload, a situation achieved only in very fit healthy individuals. Although in progres- sive exercise it is more correct to use the terms ‘symptom-limited V’O2 max’ or ‘peak V’O2 max’, the term ‘V’O2 max’ is used here be- cause of its common use in clinical testing. Ventilatory response During progressive exercise, both ventilation (V’E) and V’CO2 in- crease with V’O2, initially in linear fashion, but—at higher levels of exercise as anaerobic respiration increases—the lactic acid gen- erated stimulates ventilation further. Consequently, both V’E and V’CO2 increase disproportionately to V’O2 (Figs. 18.3.1.7, 18.3.1.8a), though the relation of V’E to V’CO2 is close to a straight line. The increasing ventilation during progressive exercise results from increases in both tidal volume and breathing frequency, with the former dominating at lower levels of exercise until it approaches a plateau level (determined by respiratory mechanics), after which further increases are achieved by increasing frequency alone. Cardiovascular response Cardiac output also increases progressively on exercise in relation to V’O2, but the relationship is slightly curvilinear, with a diminishing rate of increase at higher workloads. During mild exercise, increases in stroke volume and heart rate both contribute. Stroke volume, however, approaches a maximum at a relatively low level of exercise, and subsequent increases in cardiac output depend on a more rapid heart rate. The increased stroke volume is due partly to an increase in venous return and partly to a larger ejection fraction. The oxygen

18.3.1 Respiratory function tests 3967 provided to the exercising muscles increases relatively more

than the cardiac output because they extract a greater proportion of the oxygen in arterial blood than at rest. The ‘oxygen pulse’, defined as the V’O2 divided by the heart rate, represents the volume of oxygen extracted by the metabolizing tissues per beat, and is sometimes used as an indirect estimate of stroke volume An

abnormally high slope of the relationship between heart rate and V’O2 usually implies a small stroke volume. Limits
to progressive exercise
Maximum heart rate (beats/min) declines with age and is commonly predicted using one of two simple equations, either: 220 −age in years or 210 0 65 − × ( ) age in years . .

Each gives similar values for subjects under the age of 40 years, but the second tends to be more accurate in older healthy individuals. For predicting maximum ventilation, the equation for predicting maximum voluntary ventilation (MVV) from FEV1 is often used:

MVV FEV l min

× 1 35 / . In general, in healthy individuals the

maximum oxygen uptake on exercise is determined by the capacity of the circulation to supply oxygen to the exercising muscles, rather than by the ventilatory system. At the breaking point of a progressive exercise test, healthy individuals approach their predicted maximum heart rate, while they usually reach only 50–75%

of their ventilatory capacity so that, normally, there is an appreciable ‘ventilatory reserve’. In most pa- tients with lung disease, the maximum attainable ventilation is reduced and this determines their exercise capacity. However, in patients with moderate or severe airway obstruction (e.g. COPD) the maximum exercise ventilation may

exceed that predicted from FEV1 and a more realistic maximum is predicted approximately by the formula: Maximum exercise ventilation 20 min

× + [ ] / . FEV l 1 20 Values of maximum ventilation and maximum heart rate during progressive exercise are often used as guides to the main factor(s) limiting exercise and in directing attention to disease of the respira- tory or circulatory systems as the likely main cause of breathlessness in the individual patient. The limits to exercise are, however, often 60 40 20 0 1 2 V'E (Lmin–1) V'O2 (Lmin–1) Fig. 18.3.1.7 Relationship of oxygen consumption (V’O2) to ventilation (V’E) during exercise. Fig. 18.3.1.8 (a) Relationship of oxygen consumption (V’O2) to CO2 production (V’CO2) during exercise: the gradient of the line changes at the anaerobic threshold (AT). (b) Relationship of the ‘ventilatory equivalent’ for oxygen (V’E divided by V’O2 (i.e. the ventilation ‘required’ for each litre of oxygen consumed) against V’O2 during exercise: the nadir value is taken as the AT.

section 18 Respiratory disorders 3968 multifactorial; for example, comorbid cardiovascular disease as well as deconditioning (unfitness) contribute to the breathlessness of many patients with respiratory disease. Indications for exercise testing Exercise tests may be performed for diagnostic, prognostic, or thera- peutic indications, or for objective assessment of exercise ability (Table 18.3.1.8). However, apart from using exercise to provoke exercise-induced asthma (see next section on exercise tests), the diagnostic role of exercise tests is limited. Types of exercise test Simple walk tests Exercise tests vary considerably in complexity and in the number and types of measurements made. Simple self-paced tests of walking dis- tance, most commonly in 6 min, aim to mimic the real-life situation and are widely used for global assessment of disability and for docu- mentation of exercise-related oxygen desaturation. Desaturation is seen in some (but not all) patients with advanced chronic obstructive pulmonary disease, and also in those with interstitial lung disease or pulmonary vascular disease. Walk tests are used to identify patients who might benefit from the use of ambulatory oxygen, which is in- dicated only if repeat testing while breathing oxygen improves SpO2, as well as breathlessness and/or performance. Walk tests are

insensitive to mild disease and there is a signifi- cant learning effect, as well as dependence on motivation and encouragement. An alternative to the self-paced test is the shuttle walk test in which the walking speed is increased each minute; this gives more reproducible results than the 6 min walk and is more akin to laboratory-based tests of maximum performance. Cardiopulmonary exercise tests Formal testing involves controlled exercise on a bicycle ergometer or treadmill. Use of a bicycle is less prone to movement artefacts, and exercise is easier to standardize as the external work rate is more readily quantified, but cycling is less familiar to many middle- aged patients and it puts relatively more strain on the leg muscles. A treadmill allows more natural exercise but is less convenient for use with a mouthpiece and nose clip, and sometimes more difficult for the patient. The subject's bodyweight has more effect on V'O2 while walking on a treadmill than when seated on a bicycle and, in practice, a bicycle ergometer is preferred by most pulmonary func- tion laboratories. The electrocardiograph (ECG) is monitored throughout and the commonly made measurements include work rate (usually in Watts), heart rate, blood pressure, minute ventilation, tidal volume, breathing frequency, V'O2, V'CO2, end-tidal PO2, and PCO2 (PETO2, PetCO2) and oxygen saturation by oximetry. Arterial blood gases are rarely measured directly in clinical testing; arterialized earlobe capillary sampling is sometimes used but requires experience to obtain valid samples. PETO2 and PETCO2 are sometimes used as surrogates for alveolar gas tensions, but—while this assumption may be valid in healthy individuals—it does not hold in patients with sig- nificant lung disease. The degree of breathlessness at each workload can be assessed using simple self-rating scales (visual analogue scale or Borg scale). After a few minutes for acclimatization and resting measure- ments, the workload is increased progressively by a constant amount, usually between 10 and 30 Watts depending on the subject's likely capacity, with periods of 1–3 min at each level. The subject, wearing a nose clip and breathing via a mouthpiece, exercises until no longer able to continue because of discomfort or until halted by the investigator. Measurements are averaged over the final 15–30 s of exercise at each workload, or breath-by-breath using appropriate computer software. Due to technological advances, breath-by-breath measure- ments are increasingly common, but are inevitably more 'noisy' than averaged data, and from the large number of measurements a po- tentially bewildering array of graphical displays can be constructed. Several issues should be borne in mind when interpreting the re- sults of cardiopulmonary exercise tests. These include the reason for performing the test, relevant clinical information, and the results of other cardiac and respiratory investigations, the technical quality of the test, including a subjective assessment by the operator of ef- fort (especially if the predicted physiological limits have not been reached), and why the patient discontinued exercise (e.g. whether due to breathlessness, leg discomfort, or chest pain). It is reasonable to assume that the subject has exercised maximally if any of pre- dicted V'O2 max, ventilation, or heart rate has been reached. Although several algorithms for interpretation have been pro- posed, there is no general consensus. The most commonly used indices include both maximal values measured at the end of exer- cise, and submaximal values recorded as workload increases. The former comprise the change in SpO2 compared to the resting value and peak ventilation, heart rate, and V'O2 (V'O2 max). V'O2 max is often 'normalized' by dividing by bodyweight, but this does not correct fully for weight as lighter individuals have higher weight– corrected values than obese individuals. Submaximal indices can be evaluated in many different ways, most commonly by plotting them against the simultaneous V'O2 or V'CO2 as an indication of the 'metabolic load' (Figs 18.3.1.7, 18.3.1.8). The externally measured work rate (in Watts) can be used as an alternative, but the relation between V'O2 and workload varies between individuals of differing bodyweight. Obesity adds to the 'cost' of exercise such that the graph of V'O2 versus work rate is displaced upwards in

obese people (i.e. to a higher V’O2 for a given work rate), although the slope of the rela- tionship is not affected. The anaerobic threshold can be measured by direct monitoring of blood lactate concentration, but more commonly it is estimated indirectly by recognizing a ‘break point’ in graphical displays of various indices plotted against V’O2. The most commonly used are the plots of V’CO2 against V’O2 (Fig. 18.3.1.8a) and the ‘venti- latory equivalent’ for oxygen (V’E divided by V’O2, i.e. the venti- lation ‘required’ for each litre of oxygen consumed) against V’O2 Table 18.3.1.8 Indications for exercise testing Diagnosis Assessing unexplained breathlessness Identifying factors limiting exercise Identifying exercise-induced asthma Assessment Objective assessment of exercise capacity Monitoring progress and effects of treatment Prognosis Heart failure Preoperative evaluation Treatment Ambulatory oxygen assessment Planning rehabilitation

 (Fig. 18.3.1.8b). With the former ‘V slope’ method, linear regres- sions are fitted to each of the two phases of the relationship and the point of intersection of the two straight lines is taken as the AT. With the latter ‘ventilatory equivalents’ method, the decreasing ventilatory equivalent during modest exercise subsequently in- creases as anaerobic metabolism provides an additional stimulus to ventilation and the nadir value is taken as the AT. The AT is defined as the V’O2 at which the inflection points occur and is expressed as a percentage of the predicted value of V’O2 max (%V’O2 max predicted). The two values obtained are likely to differ somewhat and, if both are measured, the average is usually reported. Rather than interpreting the AT literally, it is more appropriate to regard it as a pragmatic way of recognizing a disproportionate increase in ventilation and the effects of this on gas exchange during progres- sive exercise. In healthy sedentary individuals, its value is typically 50–60% of V’O2 max predicted. It has been suggested that, in patients who cease exercise prema- turely because of symptoms, the AT, as a submaximal index, is an effort-independent measurement that can assist clinical decision- making. However, since the AT is reduced in a broad range of clin- ical conditions, it has little discriminatory ability between different diseases. As with V’O2 max, a reduced value is rather nonspecific (Table 18.3.1.9). Clinical uses of cardiopulmonary exercise tests Typical patterns of abnormality are shown in Table 18.3.1.9, but it should be noted that there is considerable variation and overlap be- tween diagnostic categories. Of note, the findings in unfit (decon- ditioned) normal subjects are qualitatively similar to those of heart failure, and it can be difficult to distinguish mild cardiac impairment from lack of fitness. In practice, the commonest indications for detailed cardiopul- monary exercise tests are evaluation of breathlessness or exercise intolerance (particularly when simpler tests have not revealed a diagnosis or breathlessness appears out of proportion to the ob- jective evidence of abnormality on other investigations), evaluating prognosis and monitoring of patients with congestive cardiac failure (including assessment for transplantation), and preoperative assess- ment (aiming to predict morbidity and mortality of patients under- going lung resection or other major surgery). Most conclusions about the clinical value of cardiopulmonary exercise tests are based on observational studies and consensus rather than randomized trials, and in some studies the prognostic value of the results has not been compared with that of simpler tests such as spirometry. The best evidence for the value of cardiopulmonary exercise tests in assessing prognosis is in patients with chronic heart failure, where studies have consistently shown that a useful threshold for V’O2 max is 14 ml/min/kg bodyweight. Lower values are associated with a rapidly diminishing survival rate. Other indices, in particular V’E/ V’CO2, also have strong prognostic value in this population. Values of V’O2 max less than 10 ml/min/kg are widely accepted as a strong indication for heart transplantation, which may also be considered with values between 10 and 14 ml/min/kg. Management of patients with lung cancer is often complicated by compromised respiratory function due to coexistent COPD, hence

preoperative risk assessment is particularly important in this popu- lation. Assessment may include cardiopulmonary exercise tests as a guide to the likelihood of serious complications after lung resection, with values of V’O2 max less than 15 ml/min/kg predicting a high complication rate. In this clinical situation, however, simpler tests of respiratory function such as spirometry and DLCO also have useful prognostic value. Consequently, some guidelines suggest that car- diopulmonary exercise tests be limited to patients with borderline resting function. The position of cardiopulmonary exercise tests in preoperative assessment for other major surgery is less clear. Some evidence sup- ports its use for risk assessment before major noncardiopulmonary surgery, but a recent systematic review of patients being assessed for repair of an abdominal aortic aneurysm or other major vascular surgery cautioned that the paucity of evidence did not justify its routine use. Exercise-induced asthma The identification of exercise-induced asthma has rather different requirements. During exercise, most subjects with asthma show bronchodilatation, and those who have exercise-induced asthma develop bronchoconstriction after exercise. Of course, many pa- tients with asthma become unduly breathless during exercise, but in most this is due to the increased work of breathing associated with a degree of pre-exercise airway obstruction, or to deconditioning, rather than to exercise-induced bronchoconstriction. In susceptible individuals, the intensity of exercise necessary to provoke asthma is relatively high, and consequently exercise-induced asthma is rele- vant mainly to children and young adults. It is demonstrated opti- mally after exercising for at least 5 min at a constant rate, chosen to increase ventilation to around 50% maximal or to increase heart rate to around 80% maximal. FEV1 or peak flow should be measured be- forehand and for up to 30 min afterwards. Table 18.3.1.9 Typical patterns of abnormality seen in cardiopulmonary exercise testing Condition Maximal indices Submaximal indices V’O2 max HR max Ventilatory reserve SpO2 a V’E/V’CO2 slope AT Unfitness/deconditioning ↓ → or ↓ → → ↑ or → → or ↓ COPD ↓ ↓ ↓ or 0 variable ↑ or → → or ↓b Interstitial lung disease ↓ ↓ ↓ ↓ ↑ → or ↓ Heart failure ↓ → or ↓ → → ↑ ↓ Pulmonary vascular disease ↓ → → ↓ ↑ ↓ Key: ↓ reduced; → normal or unchanged; ↑ increased. a compared to resting value; b if severe may not be achieved.

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