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ESSENTIALS Chronic respiratory failure describes a clinical state when the ar- terial Po2 breathing air is less than 8.0 kPa, which may or may not be associated with hypercapnia (defined as Pco2 more than
6.0 kPa (45 mm Hg)). Four processes cause arterial hypoxaemia due to inefficient pulmonary gas exchange—ventilation–perfusion (V/Q) mismatch, hypoventilation, diffusion limitation, and true shunt, with the most important of these being V/Q mismatching. The arterial CO2 is increased by inadequate alveolar ventilation and/or V/Q abnormality. A wide range of disorders can cause chronic respiratory failure, with the commonest being chronic obstructive pulmonary disease, interstitial lung diseases, chest wall, and neuromuscular diseases and morbid obesity. Diagnosis—the detection of mild/moderate hypoxaemia rests on an awareness of the possibility rather than any specific clinical finding. Central cyanosis may be apparent when there is an increase in the circulating deoxygenated haemoglobin to approximately 5 g/dl, but this is an unreliable clinical sign. Measurement of arterial blood gases is required, preferably when the patient is breathing air. Fingertip oxim- etry is now ubiquitous and is a valuable screening tool Management—the treatment of stable chronic respiratory failure involves: (1) making a firm diagnosis; (2) correction of the underlying disorder (when possible); (3) increasing the inspired oxygen con- centration; and (4) increasing alveolar ventilation. The benefits of regular oxygen treatment on breathlessness are marginal and there are no data to suggest that the severity or subsequent progres- sion of breathlessness is influenced by chronic oxygen treatment. Regular ‘continuous’ treatment with oxygen of patients with chronic obstructive pulmonary disease and stable hypoxaemia (Pao2 <7.3 kPa (55 mm Hg)) prolongs life. NIV prolongs admission free survival in patients with COPD who remain hypercapnic two weeks after an admission with acute hypercapnic exacerbation. Noninvasive nasal positive-pressure ventilation has generally superseded other methods of providing chronic mechanical ventilatory support, but the

patient–mask interface remains a significant problem in some cases. Introduction Although respiration is ultimately a biochemical process involving the generation of ATP, the term ‘respiratory failure’ is used more loosely to describe the failure of gas exchange within the lung to maintain arterial blood gas homeostasis. Defining normal blood gas tensions is harder than it may appear initially, as Pao2 falls with age and the extent of this is debated. The most commonly applied formula to describe this is: PaO2(kPa) = 13.86 [0.036 age(years)]. Thus, a Pao2 of 10.6 kPa may be abnormal in a man of 24 years but a ‘normal’ value in a woman of 80. Subnormal levels of arterial oxygenation are described as hypoxaemia, whereas arterial CO2 ten- sions, which do not show similar age dependence, are considered to be hypercapnic when they exceed 6.0 kPa (45 mm Hg). Respiratory failure is defined primarily in terms of hypoxaemia and is arbitrarily considered to be present when the arterial Po2
(at sea level) is less than 8.0 kPa (60 mm Hg). It need not be accom- panied by hypercapnia, but when this develops it leads to acidosis due to the accumulation of carbonic acid by the Henderson–Hasselbalch equilibrium. If the acidosis is not rapidly progressive, and in the presence of intact renal compensatory mechanisms that generate bicarbonate ions, it becomes ‘chronic’—a compensated state where the arterial pH returns to normal. In summary, chronic respiratory failure describes a clinical state when the arterial Po2 breathing air is less than 8.0 kPa, which may or may not be associated with hypercapnia, but is accompanied by a normal arterial pH and has been present for several days or more. This definition emphasizes the physiological determinants of gas exchange that characterize the problem. Unlike some other forms of organ system failure, such as car- diac or hepatic failure, the clinical symptoms and signs of chronic respiratory failure are relatively undramatic, but its development is equally significant, both as a marker of disease progression and in producing serious complications beyond those normally seen with the underlying disease. This chapter reviews the causes, clinical features, and assessment of chronic respiratory failure, as well as specific means of treatment. 18.15 Chronic respiratory failure Michael I. Polkey and P.M.A. Calverley

18.15 Chronic respiratory failure 4283 However, to do so logically requires some understanding of the principles underlying the development of this condition, as well as the factors relevant to the selection of the threshold values used in defining this state. Physiological determinants of blood gas tensions In health there is a predictable fall in the partial pressure of oxygen from that in the room air to that in mixed venous blood. This re- flects the effect of diluting room air with resident gas in the alveoli, the efficiency of pulmonary oxygen exchange, and the consump- tion of oxygen by metabolizing tissues. Conversely, there is a pre- dictable increase in the amount of CO2 added to the circulation and subsequently removed from the lungs during expiration. This simple system is reliant on a range of physical processes that differ somewhat for oxygen and CO2. Within the lungs, gas transport is largely by convective bulk transport, and in the alveoli by diffusion. In the blood oxygen combines with haemoglobin, which augments transportation to the tissues where diffusion is the final process in- volved. By contrast, CO2 transport begins with diffusion from rela- tively high tissue concentrations and is buffered in solution in the blood. This complex mechanism can be deranged in some predict- able ways that are discussed next. Analysis of pulmonary gas exchange In the last 30 years the analysis of pulmonary gas exchange has been revolutionized by the use of the complex multiple inert gas elimination techniques in research laboratories around the world. This gives a relatively complete description of the distribution of gas exchange abnormalities within the lungs. However, for an understanding of the general principles involved in disease states the traditional three-compartment model is easier to follow. This assumes that

alveolar air within the lungs is either ideally matched to pulmonary arterial blood flow within the pulmonary capillary bed or is totally mismatched, meaning that either the ventilation– perfusion (V/Q) ratio is unity (ventilation without perfusion— physiological dead space, VD) or zero (perfusion without ventilation—shunt effect). The physiological dead space includes a component due to dilution of the resident gas in the airways, the anatomical dead space, while the shunt fraction incorporates the very small amount of cardiac output (<1%) not passing through the pulmonary capillary bed. Hypoxaemia The principal mechanisms leading to arterial hypoxaemia are shown in Table 18.15.1. Individuals resident at altitude (e.g. in the high Andes or Himalayas), experience significantly lower in- spired oxygen tensions than those at sea level and in these cir- cumstances even individuals with normal lungs can develop clinically significant hypoxaemia, especially during sleep. Even minor degrees of respiratory impairment in these circumstances can produce dramatic changes in blood gas tensions and the early onset of cor pulmonale. Conversely, people with established hyp- oxaemia at sea level can occasionally experience worsening symp- toms when travelling by air, where cabin pressurization is 75% of atmospheric. However, in clinical practice, this is relatively infrequent. Four processes cause arterial hypoxaemia due to inefficient pul- monary gas exchange: • V/Q mismatch • hypoventilation • diffusion limitation • true shunt Ventilation/perfusion mismatching Much the most important cause of arterial hypoxaemia is V/Q mismatching. In many diseases where minute ventilation is in- creased, the additional inspired gas is distributed to well-perfused areas of the lungs, but when the opposite occurs and perfusion exceeds effective ventilation (low V/Q states), arterial Pao2 falls. At first this might seem surprising as most diseases associated with V/Q imbalance are of patchy distribution and compensa- tion from areas of high V/Q ratios might be expected. However, this does not occur because of an important feature of the oxy- haemoglobin dissociation curve (Fig. 18.15.1), whose sigmoid shape means that well-perfused parts of the lung cannot increase the arterial oxygen saturation of the blood leaving them beyond Table 18.15.1 Determinants of a reduced arterial oxygen tension Inspired oxygen concentration Reduced at altitude and iatrogenically Pulmonary factors V/Q mismatching Alveolar hypoventilation Diffusion limitation Arteriovenous shunts Extrapulmonary factors Increased oxygen uptake Reduced mixed venous Po2 Low cardiac output Reduced mixed venous Po2 Reduced pulmonary capillary transit time Reduced end-capillary Po2 Oxygen saturation (%) 100 80 60 40 20 0 Partial pressure of oxygen (mm Hg) v 0 20 40 60 80 100 a Fig. 18.15.1 The haemoglobin–oxygen dissociation curve. (a) Partial pressure of oxygen of 8 kPa (60 mm Hg), which is the definition of arterial hypoxia. (v) Partial pressure of oxygen of 5.3 kPa (40 mm Hg), which is typical of mixed venous blood. Note that once the Pao2 falls below 8 kPa small further falls dramatically decrease the arterial oxygen saturation.

section 18 Respiratory disorders 4284 100%, hence the saturation of the

pulmonary venous blood must fall if low V/Q areas are present. Clinical examples of this process might include pulmonary embolus, where the lung is ventilated but not perfused, or pneumonia where the lung is perfused but cannot be ventilated. Alveolar hypoventilation The second important mechanism contributing to arterial hypox- aemia is

alveolar hypoventilation, where the supply of fresh oxygen is globally reduced because of generally inadequate minute ventila- tion. This process often coexists with V/Q mismatching and tends to exacerbate it. In some situations, such as during exercise, total mi- nute ventilation may lie within the normal range but can still be

in- appropriately low for the subject’s metabolic requirements, thereby leading to hypoxaemia. Anatomical shunting and diffusion limitation

Anatomical shunting and diffusion limitation are less important mechanisms for hypoxia. The former occurs predominantly with intrapulmonary arteriovenous

malformations. Congenital cardiac anomalies such as ventricular septal defects with reversed flow are often lumped in with this problem, although technically they are extrapulmonary in origin. The failure to increase Pao2 to more than 40 kPa (300 mm Hg), even when exposed to 100% oxygen, is diagnostic. Diffusion limitation has gone

in and out of fashion as an explanation for arterial hypoxaemia. It was initially believed to be important in many diseases, the assumption being that passive diffusion of oxygen was reduced to the point where equilibration with haemoglobin during red-cell transit of the pulmonary capil- laries was incomplete. Detailed studies with

modern techniques of gas exchange analysis have shown that this is seldom the case, except for small falls in arterial oxygen tension at maximum levels of performance in elderly athletes. Recent data suggest that dif- fusion limitation contributes to some of the resting and most of the exercise-induced hypoxaemia in some forms

of interstitial lung disease. Although it is not the sole explanation of arterial hypoxaemia, the degree of hypoxaemia can be worsened when the mixed venous arterial oxygen tension is significantly reduced as occurs in low car- diac output states or conditions where peripheral oxygen consump- tion is increased. Hypercapnia

Analysis of the pulmonary causes for changes in arterial CO2 tension is much simpler, the relevant relationship being: PaCO K VCO VA 2 2

× / , where Vco2 is the CO2 production by the body, VA is the alveolar ventilation, and K is a constant. Alveolar hypoventilation It is easy to see that inadequate alveolar ventilation, due to either low

total alveolar ventilation or an inability to increase VA in re- sponse to an increase in metabolic CO_2 production, will increase the arterial CO_2. Alveolar ventilation is influenced by a range of factors, reflecting the balance of the intrinsic capacity of the venti- latory pump and the demands placed on it (Fig. 18.15.2). Ventilation/perfusion

abnormality The second important mechanism for hypercapnia is V/Q abnormality, although here the important component is the increased physiological dead space. This can be seen by a rearrangement of the earlier equation to: PaCO K VCO V V V D T 2 2 1

× × / (/), where VD/VT is the ratio of the physiological dead space to the tidal volume and V is the total minute ventilation. An increase in VD occurring when V/Q ratios are high can lead to an increase in CO2 tension. Rather surprisingly, low V/Q units are much less important in producing CO2 retention than they are in producing hypoxia since CO2 transport from the blood to the alveolar gas is linear (Fig. 18.15.3). This means that in areas of normal V/Q ratios an increase in overall minute ventilation will increase CO2 elimination and compensate for the CO2 that is not excreted from areas of reduced perfusion. Combined effects In most cases of chronic respiratory failure with CO2 retention, both alveolar hypoventilation and ventilation/perfusion abnor- mality operate and the patient is unable to sustain the high overall levels of ventilation needed to maintain CO2 tension within the normal range. An important compensatory mechanism in the

trade-off be- tween the increased chemical drive to breathing and the mechanical limitations on ventilation is the breathing pattern. In both chronic obstructive and restrictive lung disease, a rapid shallow breathing pattern is adopted to minimize respiratory discomfort while maintaining minute ventilation. However, the relative fall in tidal volume further worsens the VD/VT ratio and can itself contribute to CO2 retention. Some of these problems are resolved when the buf- fering capacity of the blood rises as compensation for respiratory acidosis occurs. Special circumstances As already noted, residence at altitude and exercise pose particular problems for gas exchange and may induce temporary respiratory failure. There is now a wealth of data indicating that similar changes Ventilatory failure Respiratory muscle pump Load Capacity Sleep CNS drive Fig. 18.15.2 Alveolar ventilation reflects the balance of the intrinsic capacity of the ventilatory pump and the demands placed on it. A reduced respiratory drive, particularly during sleep, reduces alveolar ventilation but does not produce significant hypercapnia.

18.15 Chronic respiratory failure 4285 can occur during sleep. All healthy people show an approximately 15% reduction in minute ventilation in the transition from wakeful- ness to stable nonrapid eye movement (REM) sleep, and this may be greater still in phasic REM sleep. The ventilatory responses to both hypoxia and hypercapnia decline as sleep deepens and upper airway resistance rises, especially in those who snore. Despite this the blood gas tensions vary little in health during sleep, but dramatic abnor- malities can develop during periods of repetitive upper airway ob- struction (see Chapter 18.5.2), or when coexisting neuromuscular weakness leads to excessive dependence on muscle groups whose activity declines with sleep (see next). Persistent nocturnal hypoxaemia can ‘feed forwards’ to contribute to daytime hypoxaemia in patients with otherwise normal lungs by its adaptive effect on chemoreceptor responsiveness. This occurs in a few people with obstructive sleep apnoea, but its relevance to most patients with this disease is debatable, usually being noted when there is coexisting severe obesity (see next). Gas transport to the tissues Oxygen delivered to the tissues depends on the oxygen saturation of arterial blood (Sao2), the haemoglobin concentration (Hb), and the cardiac output (CO), related as follows: Oxygen delivery

1.34 /100 . ( ) 2 2 ( ) DO CO Hb SaO

× × × ( ) This is influenced only indirectly by the effectiveness of gas ex- change. Since oxygen delivery is the clinically relevant outcome of oxygenation, decisions about when and how much to intervene therapeutically will be influenced by this variable. Small changes in saturation become clinically more important in individuals with impaired cardiac function and/or reduced haemoglobin concentra- tion, and a higher Sao2 should be maintained. In general, there is little to be gained by increasing Sao2 to the high 90s, especially as this may cause secondary CO2 retention in some diseases. As is clear from Fig. 18.15.1, desaturations below 90% only occur when the ar- terial oxygen tension is below 8.0 kPa (60 mm Hg), and this is also influenced by certain other factors that determine the position of the dissociation curve (Table 18.15.2). This provides the rationale for

the choice of 8.0 kPa as the cut-off point for the onset of respira- tory failure. Causes of chronic respiratory failure The principal causes of chronic respiratory failure are summarized in Box 18.15.1, with the commonest causes discussed next. Chronic airflow limitation This term covers the most important cause of chronic respiratory failure, chronic obstructive pulmonary disease (COPD), but is also relevant to diseases such as chronic bronchial asthma, which is now excluded from the definition of COPD, and bronchiectasis, where airflow obstruction is a frequent finding as the disease ad- vances. In all these conditions there is a reduction in the forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio below 70% and a reduction in the FEV1, which is commonly below 35% predicted before chronic respiratory failure is noted clinically. In chronic airflow limitation hypoxaemia is the earliest abnor- mality and largely due to V/Q mismatching. Attempts at relating these changes to structural patterns of airway and alveolar disease in COPD have proved unsuccessful. As lung mechanics worsen (commonly when FEV1 falls below 1.5 litres or 35% of the pre- dicted value), arterial CO_2 increases. This has been related to the development of inspiratory threshold loading (PEEPi) with the onset of chronic hyperinflation, but the degree of CO_2 retention varies between subjects suggesting that individual variations in chemoresponsiveness/perception of ventilatory load contribute to this process. There is no predictable relationship between the se- verity of impaired lung mechanics below the thresholds indicated and the degree of hypoxaemia or hypercapnia, and many patients who maintain arterial CO_2 tensions within the normal range de- velop acute CO_2 retention during exacerbations of their disease. These changes can be relatively short lived and the hypercapnia kPa 0 600 4 400 200 Concentration (ml/l) 50 100 Partial pressure (mm Hg) 12 8 0 0 O_2·CO O_2 CO CO_2 Blood Plasma Fig. 18.15.3 Concentration of oxygen (O_2), carbon monoxide (CO), and carbon dioxide (CO_2) in blood and plasma at differing partial pressures of these gases. Table 18.15.2 Important facts about the oxygen dissociation curve Pao_2 = 100 (13.3), Sao_2 = 97.5% Normal values for arterial blood Pao_2 = 80 (10.7), Sao_2 = 96% Lower limit for normal arterial blood Pao_2 = 60 (8.0), Sao_2 = 89% Dissociation curve changes shape Pao_2 = 40 (5.3), Sao_2 = 75% Mixed venous blood, or severe arterial hypoxaemia Increased temperature, Pco_2, acidosis, 2,3-DPG shifts the curve to the right and vice versa Reduces O_2 uptake from pulmonary venous blood but increases O_2 delivery in the tissues 2,3-DPG, s-diphosphoglycerate in red cells; Sao_2, arterial oxygen saturation. Figures for Pao_2 are mm Hg (kPa).

 resolves by the time of discharge. Coexisting left ventricular impair- ment reduces cardiac output and increases venous admixture, which can cause severe hypercapnia and acidosis, which none the less re- spond rapidly to appropriate treatment. Patients with COPD in association with persistent hypercapnic respiratory failure have a worse prognosis than those with intermit- tent hypercapnia during exacerbations (Fig. 18.15.4). The pattern in chronic asthma and bronchiectasis appears similar to COPD, indicating that lung mechanics rather than individual pathology dictates the severity of the gas exchange disorder. Interstitial lung disease Despite the wide range of primary pathologies covered by the term ‘interstitial lung disease’, they present with a relatively stereotyped physiological picture. A restrictive physiological disorder (FEV1/ FVC >75% with a reduced absolute FEV1 and FVC) is usual, although patients with sarcoidosis commonly show airways involvement and can present with severe airflow limitation or a mixed physiological pattern. Near normal spirometry can be seen with significant exer- cise limitation and exercise-induced oxygen desaturation in some patients where COPD and interstitial lung disease coexist. Typically, resting gas exchange is relatively preserved in interstitial lung disease until late in the course, whereas exercise-induced desaturation is an early finding,

often seen when spirometric changes are unimpressive. Studies using the multiple inert gas technique have described a bimodal pattern of V/Q distribution, with some areas of lung having normal V/Q relationships and others relatively little ventila- tion (increased physiological shunting), a situation which worsens during exercise. A few patients with severe interstitial lung disease develop CO2 retention and cor pulmonale in the terminal phase of their illness. The physiological mechanisms underlying this are poorly studied, but are probably similar to those in COPD. Chest wall and neuromuscular disease Here the underlying lung structure and potential for gas exchange are unimpaired, but the ability to maintain adequate alveolar ventilation Box 18.15.1 Causes of chronic hypoxaemia alone or with hypercapnia With normal or low PaCO2 Pulmonary diseases • Obstructive ventilatory disorders - COPD - Chronic asthma • Mixed ventilatory disorders - Bronchiectasis - Sequelae of tuberculosis • Interstitial lung disorders - Idiopathic pulmonary fibrosis - Pneumoconiosis - Sarcoidosis - Extrinsic allergic alveolitis • Pulmonary vascular diseases - Pulmonary vascular hypertension - Chronic or acute pulmonary thrombosis - Arteriovenous malformations Nonpulmonary diseases • Severe heart failure • Right to left cardiac shunt • Hepatopulmonary syndrome With hypercapnia Pulmonary diseases • Obstructive ventilatory disorders - COPD • Mixed ventilatory disorders - Bronchiectasis - Sequelae of tuberculosis Nonpulmonary diseases • Dysfunction of respiratory centres (e.g. central congenital hypoventi- lation syndrome) • Obesity hypoventilation syndrome • Depressant drugs • Lesion of brainstem • Neuromuscular diseases - Poliomyelitis - Amyotrophic lateral sclerosis (syn. Motor Neurone Disease) - Myasthenia gravis - Muscular dystrophies, polymyositis - Metabolic respiratory muscle weakness (e.g. hypothyroidism, adult onset Pompe disease) • Chest wall deformities - Kyphoscoliosis - Ankylosing spondylitis - Chest trauma - Thoracoplasty • Limitation of chest wall movement - Massive obesity - Pleural thickening • Obstructive sleep apnoea COPD, chronic obstructive pulmonary disease. 40 100 80 60 Cumulative percentage Interval (years) 20 0 1 2 3 4 5 11% 26% 33% 0 2.2 2.1 1 Fig. 18.15.4 Survival after index admission in three groups of patients with COPD who had similar initial spirometry. Group 1 never exhibited CO2 retention; group 2.1 retained CO2 during the admission but this resolved; group 2.2 had persistent arterial hypercapnia. Based on data from Costello R, et al. (1997). Reversible hypercapnia in chronic obstructive pulmonary disease: a distinct pattern of respiratory failure with a favorable prognosis. Am J Med, 102, 239–44.

18.15 Chronic respiratory failure 4287 is reduced. This can be due to increased chest wall stiffness, as in kyphoscoliosis, or reduced inspiratory muscle force, as in neuro- muscular disease. In this latter group the reduction in maximum inspiratory pressure can be global, such as in Duchenne muscular dystrophy, or more specific, such as isolated diaphragmatic weak- ness, where gas exchange abnormalities may only be present during specific sleep stages. Significant abnormalities of gas exchange at rest only occur with advanced disease and not in every patient. Alveolar hypoventilation is the dominant mechanism of both hypoxaemia and hypercapnia, although secondary changes such as pulmonary microatelectasis may contribute an element of V/Q mismatching. Assessing exercise hypoxaemia is difficult in these patients due to their generalized muscle weakness. However, sleep- related oxygen desaturation, particularly during REM sleep when the inspiratory system is most dependent on diaphragm function, is a common finding in patients with mild daytime hypoxaemia due to chest wall problems or neuromuscular diseases. Occasionally these changes are dramatic, but in boys with muscular dystrophy the presence of transient hypoxaemic episodes was no better guide to prognosis than was measurement of the vital capacity (Fig. 18.15.5). Arterial CO2 tensions often lie in the high normal range, daytime

hypercapnia only being seen in advanced disease. Obesity–hypoventilation syndrome As obesity becomes more prevalent in developed countries, so the incidence of the ‘obesity–hypoventilation’ syndrome rises. This con- dition is characterized by waking hypercapnia and mild hypoxemia in the absence of factors known to cause CO2 retention. Overnight polysomnography shows marked and sustained hypoventilation, with a rise in the CO2 retention throughout the night. Many of these patients have coexisting obstructive sleep apnoea with repetitive upper airway obstructions, which worsens both their hypoxemia and sleep disruption. However, the arterial oxygen tension before sleeping may still be low, with a waking saturation below 90% as a result of closure of the dependent airways during tidal breathing and a consequent worsening of the V/Q relationships. Nonpulmonary disorders Patients with stable congestive cardiac failure often show mild re- ductions in Pao2 and a normal or low Paco2 due to premature airway closure secondary to pulmonary oedema. Some patients with severe liver cirrhosis develop the so-called hepatopulmonary syndrome, with otherwise unexplained hypoxaemia due to V/Q mismatching and true anatomical shunting through arteriovenous communica- tions in the pulmonary circulation. A rare, but often overlooked, clinical cause of extrapulmonary hypoxia is the post-pneumonectomy syndrome in which anatomical change inherent to the surgery causes opening of a patent foramen ovale with consequent right to left shunting Morbidly obese individuals can develop hypoxaemia and hypercapnia due to profound nocturnal hypoventilation and chemoreceptor resetting. Rather more common are the problems of patients with severe obstructive sleep apnoea who develop day- time hypoxaemia and hypercapnia secondary to recurrent noc- turnal upper airway obstruction and oxygen desaturation. Careful review of these ‘Pickwickian’ patients may shows coexisting hypothyroidism or obstructive lung disease, and this diagnosis should be suspected in any patient with COPD with significant re- spiratory failure and an FEV1 greater than 1.5 litres. Correction of the sleep apnoea by nasal continuous positive airway pressure can produce significant improvement in daytime blood gases, but in most patients with obstructive sleep apnoea no significant abnor- malities of waking gas exchange are seen. Pulmonary vascular disease This is an uncommon cause of hypoxaemia, and at the time of diag- nosis CO2 retention is rare. Rather variable changes in DLco are re- ported, but as pulmonary hypertension becomes more advanced, exercise and resting hypoxaemia develops, a significant component being secondary to the reduced cardiac output and increase in mixed venous oxygen tension. See Chapter 16.15.2 for further discussion. Assessment of chronic respiratory failure The diagnosis of mild/moderate hypoxaemia rests on an awareness of the possibility rather than any specific clinical finding. Impair ment of concentration and memory can be demonstrated when the arterial Po2 is below 8.0 kPa, but these features are extremely non- specific. Although tempting to ascribe to hypoxaemia, the principal 50 100 75 25 min SaO2 (%) Survival (months) 0 r =0.62 0 25 50 75 100 2.0 1.5 1.0 0.5 0.0 Vital capacity (litres) r =0.65 Survival (months) 0 25 50 75 100 Fig. 18.15.5 Survival of boys with respiratory failure due to neuromuscular disease plotted against minimum arterial oxygen saturation recorded during sleep and vital capacity. Based on data from Phillips MF, et al. (1999). Nocturnal oxygenation and prognosis in Duchenne muscular dystrophy. Am J Respir Crit Care Med, 160, 198–202.

 cause of breathlessness in these patients is usually the underlying disease. Reduction of peripheral chemoreceptor activity by supple- mentary oxygen can be beneficial, but this is usually secondary to a fall in minute ventilation rather than to any specific ‘dyspnogenic’ effect of hypoxia itself. Hypercapnia is equally nonspecific, with headache the most com- monly attributed symptom. There are no good data to support this in compensated

respiratory failure, although a generalized degree of vasodilatation is seen in some patients with CO_2 retention, which may be accompanied by a large-volume pulse and warm peripheral extremities. On examination, central cyanosis may be apparent as a bluish dis- coloration of the mucous membranes associated with an increase in the reduced circulating haemoglobin to approximately 5 g/dl, but this is an unreliable clinical sign in some ethnic groups and in the presence of artificial illumination. Chronic hypoxaemia can lead to secondary polycythaemia due to increased renal secretion of erythropoietin. This may be exacer- bated if the patient is also a heavy smoker. The resulting increase in haemoglobin concentration contributes to a ruddy complexion, which increases the ability to detect cyanosis clinically. When right heart failure develops the jugular venous pressure may be elevated, and ankle swelling develops as CO_2 retention worsens. The principal diagnostic steps are listed in Box 18.15.2. Measure ment of arterial blood gases, preferably breathing air, is the most reliable way of diagnosing chronic respiratory failure, although the widespread availability of fingertip oximetry provides a useful screening measure. Substantial hypoxia is unlikely where the SpO_2 breathing room air is 94% or more. Measurement of fingertip SpO_2 during a corridor walk or stair climb can be a useful bedside screen for exercise-induced hypoxia. Arterialized earlobe gases are an ac- ceptable alternative to an arterial sample in the management of chronic respiratory failure and may be less painful for some patients. If an arterial (or arterialized) blood sample is taken when a patient is breathing supplementary oxygen, it is essential to record at what inspired concentration: without this information the Pao_2 simply cannot be interpreted sensibly. Patients with chronic airflow limitation treated with broncho- dilators nebulized in oxygen may show unexpectedly high Pao_2 for some time after this treatment. Noninvasive measurement of arterial oxygen saturation using pulse oximetry can be used to screen indi- viduals at risk of chronic respiratory failure and to monitor patients in hospital or overnight, but it is no substitute for assessing blood gas tensions to make the diagnosis correctly. Management of chronic respiratory failure Managing stable chronic respiratory failure involves several steps: 1 Making a firm diagnosis 2 Correcting the underlying disorder (when possible) 3 Increasing the inspired oxygen concentration 4 Increasing alveolar ventilation Making a firm diagnosis This is essential for rational management. It is important to re- member that more than one process may contribute to the devel- opment of chronic respiratory failure (e.g. poor left ventricular function due to cardiac disease and COPD together). The relative importance of each factor should be determined. Correction of the underlying disorder In general, treatment of the primary pathology improves both V/Q relationships and hence oxygenation, and respiratory system mechanics, which increases ventilatory capacity and lowers the $Paco_2$. In patients with COPD this usually involves administration of inhaled bronchodilators and corticosteroids (see Chapter 18.8), but marked improvement is the exception rather than the rule in patients where chronic respiratory failure has developed. Medical therapy tends to be ineffective by the time chronic respiratory failure has developed in interstitial lung disease and the neuro- muscular disorders. Specific pulmonary vasodilator treatment has been used to treat pulmonary hypertension, with most evidence of improvement seen after infusion of prostacyclin in primary pulmonary hyper- tension, and this field is rapidly evolving (see Chapter 16.15.12). Attempts to improve gas exchange in secondary pulmonary hypertension by the use of inhaled nitric oxide, a specific pul- monary arterial vasodilator, have been disappointing, and resting gas exchange has usually deteriorated rather than improved after this treatment. There is no specific treatment for most neuromuscular diseases or the abnormalities of the thoracic skeleton which produce chronic respiratory failure. Dramatic weight loss after bariatric surgery is possible in patients with obesity–hypoventilation. Increasing the inspired oxygen concentration Hypoxaemia secondary to V/Q mismatch or global

hypoventilation is relatively easily corrected by supplementary oxygen. In chronic airflow limitation and especially COPD, where respiratory time constants for gas exchange are long, it may take 30 min before a new steady state is reached when breathing relatively low concen- trations of oxygen. Monitoring of blood gases should be adjusted accordingly. In the chronic stable state, treatment with oxygen is given to pre- vent or reverse the chronic consequences of hypoxaemia. The bene- fits of regular oxygen treatment on breathlessness are marginal and there are no data to suggest that the severity or subsequent progres- sion of breathlessness is influenced by chronic oxygen treatment. Almost all data about oxygen therapy in chronic respiratory failure are based on observations in hypoxaemic COPD, treatment in other conditions being offered by analogy with this more common problem. Box 18.15.2 Diagnostic steps in detecting respiratory failure 1 Consider the possibility—see Box 18.15.1 2 Look for central cyanosis and other clinical signs, measure fingertip oximetry 3 If the probability is high or unanticipated signs are present, measure arterial blood gases while breathing air 4 If it is not possible to measure arterial blood gases on air, note the in- spired oxygen concentration 5 Blood gas tensions can change with the clinical state of the patient and measurements need to be repeated when this happens 6 Noninvasive pulse oximetry and capnometry is useful for monitoring progress but cannot diagnose acidosis

18.15 Chronic respiratory failure 4289 Long-term oxygen therapy Two well-performed randomized clinical trials have shown that regular treatment of patients with COPD and stable hypoxaemia (Pao2 <55 mm Hg) prolongs life (Fig. 18.15.6a). These data sug- gest that patients using more oxygen (the ‘continuous’ limb of the Nocturnal Oxygen Therapy Trial Group) do better than either the United Kingdom Medical Research Council treatment group or the North American patients using oxygen only at night. A more re- cent Polish study found no benefit when patients with COPD with a Pao2 of 7.3–8.8 kPa were treated with oxygen at home for 15 h/day (Fig. 18.15.6b), emphasizing that chronic oxygen therapy is only of value when the oxygen saturation falls below 90%. These studies showed that progression of secondary pulmonary hypertension can be halted by regular oxygen treatment and sec- ondary polycythaemia can be corrected. However, secondary polycythaemia in COPD is influenced by the amount of carboxy- haemoglobin from cigarettes, and patients who continue to smoke do not show a fall in red-cell mass or packed cell volumes with oxygen treatment. Neuropsychological effects of chronic hypoxaemia have been described and may be improved by regular oxygen treatment, although the evidence for this is limited. Most authorities consider therapeutic venesection is indicated when the haemoglobin exceeds 175 g/litre with a packed cell volume greater than 55%. Oxygen therapy during exercise Giving oxygen during exercise increases performance and par- ticularly endurance in patients with COPD who are relatively normoxaemic, as well as those with resting hypoxaemia. Again, carbon monoxide from cigarette smoking reduces this response, and whether oxygen desaturation during exercise is necessary for the benefit to occur has not been conclusively established, although it is used as a reimbursement criterion for portable oxygen in North America. Delivery of oxygen Oxygen concentrators are the most cost-effective way of delivering oxygen for near-continuous use. These devices have proved reliable and safe; they use the ability of zeolite cells to separate nitrogen from room air and so generate an oxygen-enriched inspirate. Portable battery-operated concentrators are now available, which can im- prove patients’ quality of life by enhancing their mobility. Liquid oxygen has the advantage of allowing relatively easy refilling of port- able oxygen units for use during exercise. Oxygen masks are the most accurate way of delivering oxygen, with a range of inspired concentrations (24, 28, 35%) available. However, these are easily dislodged during sleep, and plastic nasal prongs with a long extension pipe offer an easier system for use in

the home. Occasional patients, especially those with severe interstitial lung disease, may have difficulties obtaining a Pao2 greater than 8.0 kPa with these systems. Transtracheal oxygen delivery may have a role here, but early enthusiasm for this has been tempered by problems with cannula occlusion, infection, and bleeding. A variety of oxygen-conserving devices that deliver oxygen only during inspiration have been developed: these increase the time be- tween refills of portable oxygen equipment as well as having finan- cial advantages in some healthcare systems. Improving alveolar ventilation Mechanical methods These are potentially valuable ways of reducing arterial CO_2 in dis- orders like COPD and can increase arterial oxygen tension as well, especially in conditions such as neuromuscular disease where hypo- ventilation predominates. The use of tank respirators in neuromuscular weakness has now been superseded by the development of noninvasive nasal positive- pressure ventilation (NIPPV), which is normally only needed at night. This therapy is used increasingly in the management of acute- on-chronic respiratory failure in patients where the primary problem is ventilatory, without coexisting pneumonia/acute lung injury. Its chronic use arose from the belief that respiratory muscle fatigue was an important cause of CO_2 retention in COPD and the empirical ob- servation that gas exchange and survival were better in patients with kyphoscoliosis treated with night-time cuirass ventilation. Newer 100 (a) 80 40 Cumulative survival (%) 0 Time (years) 60 20 1 2 3 4 5 6 0 (b) 1.0 0.8 0.2 0.5 0.3 12 24 36 48 60 72 84 96 Long-term oxygen therapy Controls Cumulative survival (%) Survival (months) 0 0.7 Nocturnal oxygen therapy trial-oxygen 24 h/day Nocturnal oxygen therapy trial-oxygen 12 h/day MRC trial-oxygen 15 h/day MRC trial-control (no oxygen) Fig. 18.15.6 The effect of regular domiciliary oxygen on survival in COPD. Panel (a) combines data from the MRC and NIH oxygen trial in the United States of America: survival was greatest in those receiving oxygen for 24 h/day. Panel (b) is based on the study of Gorecka et al. for COPD patients with a Pao2 between 7.3 and 8.5 kPa who were treated with oxygen or normal medical therapy: there was no survival benefit in the oxygen treated group, confirming the importance of the 7.3-kPa threshold in selecting patients for this therapy.

 studies have shown that respiratory muscle function is well pre- served in COPD when allowance is made for the muscle shortening secondary to pulmonary hyperinflation. Chronic obstructive pulmonary disease Several trials of NIPPV in stable hypoxaemic but normocapnic COPD have reported relatively unimpressive results. In studies con- fined to those with persistent hypercapnia, randomized controlled trials have as yet failed to provide unanimous evidence of efficacy of this approach. A recent multicentre UK trial (HOT-HMV) has demonstrated that NIV (in addition to oxygen) tripled admission- free survival compared with oxygen alone. This finding was in con- trast to prior studies but important differences in HOT-HMV was were selection of patients who remained hypercapnic 2 weeks after an index admission with acute hypercapnic respiratory failure, and the use of a high pressure ventilation strategy. Kyphoscoliosis Significant symptomatic and blood gas improvements with NIPPV have been demonstrated in patients with kyphoscoliosis, but again no randomized clinical trial data are available. At present, it appears unlikely that trials will be set up, given the significant and sustained symptomatic benefits seen clinically. Muscular weakness The only study to report prospective data on muscular dystrophy found no effect of regular NIPPV on survival in normocapnic patients, but use of this therapy as supportive treatment in the terminal phases of advanced muscular dystrophy appears to be as- sociated with prolonged survival. A carefully constructed random- ized control trial has shown improvements in survival and quality of life with NIPPV in patients with motor neuron disease who are free from bulbar problems. However, it is always important in the face of progressive disease

such as muscular dystrophy or motor neuron disease that the patient should be fully informed of the complications of NIPPV and the fact that it is unlikely to influ- ence the underlying progression of the condition. Provided a good dialogue between patient, carer, and physician is established, then reasonable decisions about the use of this ethically difficult treat- ment are still possible. Types of ventilator support Although volume-cycled ventilation was initially preferred, most patients are now managed with a bilevel pressure-cycled patient- triggered device. This may have some advantages in obstructive lung disease, where PEEP can be added to offset static PEEPi. Adequate peak inspiratory pressure generation, certainly in excess of 20 cmH2O, is needed in both COPD and kyphoscoliosis, where total respiratory system compliance is reduced. The patient–mask interface remains a major problem, espe- cially for those with unusual craniofacial structure, where getting a comfortable mask fit without excessive tightness can be difficult. Progress should be assessed by regular blood gas measurements, and overnight monitoring of oxygenation and CO2 tensions is useful at the start of therapy. Patience and trained respiratory therapists are the best way of ensuring long-term compliance with treatment. Chronically ventilator-dependent patients In most patients with chronic respiratory failure who require ven- tilatory support the instigation of this treatment is a considered de- cision as part of the patient's ongoing management. However, for a few, chronic ventilation becomes necessary when they have pre- sented with an acute life-threatening illness which has led to ventila- tory support in the intensive care unit. Many of these patients would have previously succumbed from diseases with a poor initial prog- nosis (e.g. adult respiratory distress syndrome), but now survive to leave the intensive care unit, and inevitably some do not recover the level of lung function or independence which they had experienced before hospitalization. There is no universally agreed definition for such 'ventilator de- pendence', but a patient who requires at least 6 h/day of ventilatory support for 21 or more days meets the most widely used operational approach. Patients of this type raise important ethical, logistical, and economic issues, but it is possible to offer them a good quality of life and a reasonable prognosis if they are cared for by appropriately trained staff in specialized units. In this setting many patients can be transferred from tracheostomy-dependent ventilation to NIPPV, with a significant improvement in personal well-being and the op- tions for community care. Given the continuing developments in critical care medicine, an increase in the number of patients with chronic respiratory failure who meet these criteria appears likely. Specific pharmacological therapy Although mechanical ventilatory support is effective, it is also cumbersome, uncomfortable, and restricting, hence a drug treat- ment for chronic respiratory failure would be invaluable. Although medroxyprogesterone acetate has nonspecific ventilatory stimulant effects and can produce small falls in CO2 tension in patients with COPD, its oestrogen-like side effects limit its use. Methylxanthines like theophylline have some chemoreceptor stimulant effects, but are mainly of use for their bronchodilator and anti-inflammatory prop- erties. Almitrine bismethylate is an interesting specific peripheral chemoreceptor stimulant drug, which also modifies intrapulmonary V/Q matching and increases arterial oxygen while reducing CO2 tensions in patients with resting hypoxaemia. These properties have led to its use in parts of Europe, but it is associated with the develop- ment of peripheral neuropathy, and possibly increasing pulmonary artery pressure during exercise, which has limited its more wide- spread application. Despite the attractions of a pharmacological approach, the recog- nition that, in most diseases, the central drive to breathe is already high, mean that treatment with respiratory stimulant therapy is likely to have only limited clinical application. FURTHER READING Anonymous (1980). Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med, 93, 391–8. Anonymous (1981). Long term domiciliary oxygen therapy

in chronic hypoxic cor pulmonale complicating chronic bronchitis and em- physema. Report of the Medical Research Council Working Party. Lancet, i, 681–6.

18.15 Chronic respiratory failure 4291 Bourke SC, et al. (2006). Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized control trial. Lancet Neurol, 2, 40–7. Calverley PM, Leggett RJ, Flenley DC (1981). Carbon monoxide and exercise tolerance in chronic bronchitis and emphysema. BMJ, 283, 878–80. Calverley PM, et al. (1982). Cigarette smoking and secondary polycy- themia in hypoxic cor pulmonale. Am Rev Respir Dis, 125, 507–10. Costello R, et al. (1997). Reversible hypercapnia in chronic obstructive pulmonary disease: a distinct pattern of respiratory failure with a favorable prognosis. Am J Med, 102, 239–44. Gorecka D, et al. (1997). Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with mod- erate hypoxaemia. Thorax, 52, 674–9. Haluszka J, et al. (1990). Intrinsic PEEP and arterial Pco2 in stable patients with chronic obstructive pulmonary disease. Am Rev Respir Dis, 141, 1194–7. Iftikhar IH, Roland J (2018). Obesity hypoventilation syndrome. Clin Chest Med, 39, 427–36. MacIntyre NR, et al. (2005). The management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. Chest, 128, 3937–54. Meecham JD, et al. (1995). Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med, 152, 538–44. Ming DK, et al. (2014). The ‘anatomic shunt test’ in clinical practice; contemporary description of test and in-service evaluation. Thorax, 69, 773–5. Murphy PB, et al. (2017). Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: A randomized clinical trial. JAMA, 317, 2177–86. Olson AL, Zwillich C (2005). The obesity hypoventilation syndrome. Am J Med, 118, 948–56. Phillips MF, et al. (1999). Nocturnal oxygenation and prognosis in Duchenne muscular dystrophy. Am J Respir Crit Care Med, 160, 198–202. Powell FL, Wagner PD, West JB (2015). Ventilation, blood flow, and gas exchange. In: Broaddus VC, et al. (eds) Murray and Nadel’s Textbook of Respiratory Medicine, 6th edn, pp. 44–75. Elsevier Saunders, Philadelphia. Raphael JC, et al. (1994). Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. French Multicentre Cooperative Group on Home Mechanical Ventilation Assistance in Duchenne de Boulogne Muscular Dystrophy. Lancet, 343, 1600–4. Struik FM, et al. (2014). Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax, 69, 826–34.

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