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Review article

Oxygen transport in chronic hypoxic lung disease

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The evolutionary advantage of using oxygen as a final electron acceptor in the respiratory enzyme chain (now known to depend on an asymmetrical distribution of electron transport carriers on the mitochondrial membrane, thereby generating a proton gradient which drives the mitochondrial ATPase to generate ATP[1]), carries the necessity that a multicellular organism must develop both a circulation, gills or lungs, and a circulating fluid to carry the oxygen. All these evolved 500–600 million years ago, in the early palaeozoic era, when multicellular animals first became more than 1–2 mm thick.[2] Haemoglobin was a major advance, as it could hold three times as much oxygen as the earlier haemocyanin, and twenty five times more than sea water. This review considers some of the problems in provision of oxygen which are faced by patients with chronic hypoxaemia due to lung disease. It is worth noting however that life can continue, albeit at a lowly rate, and only for a short time, without oxygen, by generation of ATP by glycolysis, but this is much less efficient than aerobic metabolism. In a diving animal such as the fresh water turtle, the arterial Po_2 can drop to zero for several hours during a prolonged dive, and yet the turtle survives, as its brain can generate more ATP by glycolysis than can the brain of the non-diving mammal.[3] Furthermore, the activity of pyruvate kinase, a critical enzyme of the glycolytic pathway in mammalian cells, is increased when cells are cultured in hypoxia, as compared to similar cells grown in normoxic conditions.[4] Cells can thus adapt biochemically to chronic hypoxia. However, the fundamental problem in energy economics for a multicellular organism is to provide molecular oxygen to the cellular mitochondria at a Po_2 between 1·0–0·1 mm Hg (0·13–0·013 kPa).

"Blue and bloated"

The starting point for the cascade delivering oxygen to the mitochondria is the ambient Po_2, which for an air-breathing mammal at sea level is around 150 mm Hg (20 kPa). The major function of the lungs is to allow this abundant oxygen access to the blood, so that the arterial Po_2, again in health, is around 100 mm Hg at sea level, as this is diluted by CO_2 in the lung alveoli. Clearly this arterial Po_2 is reduced in lung disease, notably by interference with the fine balance of ventilation to perfusion amongst the 300 million alveoli, but arterial hypoxaemia also results from right to left shunts, or from global hypoventilation, when the arterial Pco_2 is also raised. Chronic bronchitis, almost always accompanied by a greater or lesser degree of centrilobular emphysema, is by far the commonest lung disease to cause chronic hypoxaemia in Britain, as a result of all three of these mechanisms. Clinically, patients with hypoxaemia due to chronic bronchitis and emphysema are usually "blue and bloated",[5] where hypoxaemia is associated with CO_2 retention, pulmonary hypertension, cor pulmonale, and secondary polycythaemia. The old idea that these "blue and bloated" patients had only chronic bronchitis, whereas patients with similar airways obstructions but relatively normal blood gas tensions ("pink and puffing"[5]) had only emphysema, is now known to be erroneous, as patients of both clinical types have some, a lot, or almost no emphysema.[6] The extent of each disease process can only be assessed with certainty when both lungs are available for pathological examination, an opportunity which only arises once in the natural history of the disease!

Sleep hypoxaemia

It has recently been recognised that "blue and bloated" patients, (who are hypoxaemic when awake), also frequently develop episodes of severe transient hypoxaemia recurrently throughout a normal night's sleep,[7] whereas such hypoxaemic episodes are both less severe and much less frequent in the "pink and puffing." Furthermore, these hypoxaemic episodes, where arterial Po_2 can fall to 25–30 mm Hg (3·5–4·0 kPa), can be associated with a further rise in the already raised pulmonary arterial pressure[7,8] and may thus contribute to the development of the sustained pulmonary hypertension which is so charac-

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teristic of the "blue and bloated" patient with cor pulmonale,[8] and which carries such a grave prognosis.[9] These transient hypoxaemic episodes are much more frequently seen during the rapid eye movement (REM) phase of sleep, but the exact mechanism is as yet undetermined. It is probable that episodic hypoventilation is important, with or without an increase in the proportion of blood shunted through the lungs (as a result of the increased cardiac output perfusing relatively poorly ventilated alveoli[10]). Whatever the mechanism, it is clear that the episodes are not due to sleep apnoea,[10] in which respiratory airflow ceases altogether for more than 10 s, on more than 10 times for each hour of sleep.[11]

In addition to pulmonary hypertension, the other major feature of the "blue and bloated" patient is secondary polycythaemia. Could this also result from profound hypoxaemia, to which he may well be exposed transiently each night? An increase in circulating haemoglobin was amongst the first of the physiological adaptations of man to high altitude which was recognised.[12] Does the bronchitic therefore mountaineer in bed?

Secondary polycythaemia

The relation between polycythaemic response, best expressed as the red cell mass, and the arterial oxygen saturation has been relatively well defined for healthy men living at altitude,[13] although some dispute the exact mathematical form of the relationship between these two variables.[14] Nonetheless it is apparent that there is a wide variation in this relation in patients with hypoxaemia as a result of chronic bronchitis and emphysema, who live at sea level. The notion that this variability could depend in part on the severity and duration of nocturnal hypoxaemia in these patients will be difficult to prove. A humoral factor mediating the increase in circulating red cells as a result of hypoxia was first proposed in 1906,[15] but was only demonstrated experimentally in 1950.[16] The chemical characterisation and reliable assay of this elusive hormone, erythropoietin, has been problematical.[17,18] Recently a new radioimmunoassay[19] of erythropoietin has been used to separate primary polycythaemia from secondary polycythaemia.[20] Erythropoietin values (measured by the same radioimmunoassay) rose at night in patients with modest hypoxaemia due to chronic lung disease,[21] whereas this rise was not seen in normoxic normal subjects. Erythropoietin concentrations (measured in this case by a fetal mouse liver system) were also raised in patients with cyanotic congenital heart disease, and concentrations rose further after venesection, indicating that the hormone output does respond rapidly to an acute hypoxaemic stimulus.[22]

The exact site of production of erythropoietin within the kidney is debated, there being some evidence that it is produced in the renal glomerulus,[23] but physiological theory would predict a site on the venous side of the circulation, at least for the sensor which detects hypoxia, and so initiates erythropoietin production. Thus in patients with high affinity haemoglobins, polycythaemia is present despite normal arterial blood gas tensions and cardiac output,[24] but in these patients the venous oxygen tension will be lower than in normal subjects.

Carboxyhaemoglobin

These observations may be pertinent to chronic bronchitis and emphysema. Cigarette smoking is widely recognised to be a major factor in causing this disease, and there is now a substantial body of evidence in support of the proteolytic theory of the pathogenesis of emphysema, which explains a potential mechanism for this association.[25] Cigarette smoke also contains carbon monoxide, cigarettes currently on the British market yielding 10–20 mg of CO per cigarette.[26] As a result cigarette smokers have a level of carboxyhaemoglobin (COHb) above 3%, and this can reach even 18% after a day's heavy smoking. These raised COHb concentrations have been related to raised haematocrit, haemoglobin concentration and red cell mass in smokers.[27] It has been known for some time that COHb reduces the P_{50} (the oxygen tension at 50% oxygen saturation on the blood/oxygen dissociation curve[30]), but it now also appears that COHb affects the shape of the dissociation curve, by reducing "n" in Hill's equation ($\log SO_2/1-SO_2$ = "n" $\log PO_2$[31]). These two effects of COHb interact in a complex way to affect blood oxygen transport, so that for a given arteriovenous oxygen content difference, the resulting mixed venous oxygen tension is less affected by a rise in COHb from 0–20% when the arterial PO_2 is low, than it is when the arterial PO_2 is normal. This arithmetic consequence of these changes in P_{50} and "n" by increasing COHb could explain why COHb has such little effect on exercise tolerance in patients who are already hypoxaemic.

The degree of secondary polycythaemia, as assessed by the red cell mass, is more closely related to the prevailing COHb concentration than it is to the arterial oxygen saturation in patients with chronic hypoxaemia.[32] This again suggests that the sensor for hypoxia whose activation stimulates erythropoietin production lies on the venous side of the renal circulation. Such a notion is further supported

by the recent observation that long term oxygen therapy[32] is only effective in reducing the red cell mass during such treatment in "blue bloaters" who give up smoking, as shown by persistently low COHb concentrations; whereas long term relief of hypoxaemia in patients who have persistently high COHb concentrations as they continue to smoke does not lead to reduction in red cell mass.[32] One can speculate that these effects of COHb on the dissociation curve could explain why there is no obvious excess mortality from coronary heart disease in patients with hypoxaemia due to chronic bronchitis and emphysema, for calculations based on the effects of increases in COHb on the P_{50} and "n", show that in the coronary circulation, with a very wide arteriovenous oxygen content difference, the coronary sinus P_{O_2} is only marginally reduced by increasing COHb, if the patient has persistent arterial hypoxaemia.

Many of these speculations, which are based upon physiological interpretations of this new data on the effects of COHb concentrations on oxygen dissociation curves, will be open to direct study if the newly described radioimmunoassay of erythropoietin lives up to its apparent promise in providing us precise analysis of this elusive hormone,[19] which could prove to be very valuable as an indicator of the body's response to hypoxaemia in life.

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