Editorial

Hypoxia and the heart

The heart can be exposed to hypoxia in several circumstances including pulmonary disease, pulmonary embolism, aspiration, during cardiac arrest, and at high altitude. In patients with chronic pulmonary diseases there may be severe hypoxia on exercise and during sleep.[1 2] The mechanisms of nocturnal hypoxia are complex, and include reductions in alveolar ventilation and mismatching of ventilation and perfusion.[3 4] Hypoxia in these patients leads to secondary pulmonary hypertension and cor pulmonale.[5 6] Patients with sleep apnoea syndromes, either obstructive or central, also have episodes of nocturnal hypoxia.

There have been few studies of the effects on the heart of arterial hypoxaemia as distinct from myocardial ischaemia. It is likely that the effects differ: first, arterial hypoxaemia is generalised whereas myocardial ischaemia is usually localised; and secondly, the cellular metabolism of ischaemic myocardium differs from that of perfused but hypoxic myocardium.[7 8]

The effects of hypoxia on myocytes are similar to those in other cells. There is a decline in ATP concentrations and increased glucose uptake and anaerobic glycolysis, the resulting pyruvate being largely converted into lactate and alanine.[8] During hypoxia without ischaemia there is a sustained increase in glycolytic flux with less intracellular acidosis than occurs during ischaemia.[8] Hypoxia also causes less mitochondrial damage, and the rate of ATP synthesis recovers more rapidly after a period of non-ischaemic hypoxia than after ischaemia.[9 10]

Unlike localised myocardial ischaemia, hypoxaemia will also affect the heart via direct and reflex effects on other sites in the circulation. Hypoxia acts directly as a vasodilator especially in the coronary and cerebral vessels, and stimulation of the carotid body chemoreceptors causes reflex vasoconstriction of the splanchnic, muscle, pulmonary, and cutaneous beds, with either vasodilation or no net effect in the coronary and cerebral beds.[11]

Direct effects of hypoxaemia on pump function

Although there have been many studies on the effects of hypoxia on isolated hearts and muscle preparations in vitro there are few reports in humans or intact animals. Observations on those who travel to high altitude are therefore of interest: P_{O_2} is 150 mm Hg at sea level but only 80 mm Hg at 14 000 feet. Typically the resting heart rate increases acutely, but returns to slightly above pre-ascent values in one to two days.[12] Stroke volume gradually decreases over 5–10 days to 20% below pre-ascent values.[13] Echocardiography shows a decrease in left ventricular end diastolic and end systolic diameters, while the ejection fraction and other indices of contractility remain normal.[14] Cardiac output increases acutely and then decreases over the next 2–5 days to a steady state some 20% below resting cardiac output at sea level.[12] During exercise at a given submaximal work rate, cardiac output is approximately 20% below that during exercise at the same work rate at sea level.[15]

From the observation that echocardiographic indices of contractility remain normal, it has been argued that the decrease in stroke volume represents a physiological adaptation rather than impaired myocardial function.[14] The reduction in cardiac output may be secondary to improved oxygen delivery to the tissues caused by an increased haematocrit and adaptive changes in haemoglobin-oxygen binding.

In chronic hypoxic lung disease the function of left heart is usually normal as judged by left ventricular ejection fraction, pulmonary wedge pressure, and cardiac output.[16–18] When coronary disease coexists, however, hypoxia together with carbon dioxide retention and acidosis may precipitate left ventricular failure.[19] In postmortem studies of patients dying of chronic cor pulmonale, thickening and patchy fibrosis of the left ventricular myocardium are common.[20 21] Left ventricular function may also be affected in chronic airflow limitation by the wide swings in intrathoracic pressure and by hypertrophy of the right ventricle.[22 23]

In patients with sleep-disordered breathing there may be episodes of acute hypoxaemia, during which cardiac output is reduced[24] and pulmonary wedge pressure may increase.[25] In obstructive sleep apnoea these changes may be the result of the changes in intrathoracic pressure rather than hypoxaemia.[26] Acute severe hypoxaemia also occurs in adult respiratory distress syndrome, fat embolism, and pulmonary embolism, and is often associated with severe depression of cardiac output, but in these conditions hypoxaemia is only one of many pathophysiological changes.

Effects of hypoxaemia on coronary blood flow

Experiments in healthy individuals showed that breathing hypoxic gas mixtures considerably increased coronary blood flow: a reduction of the inspired concentration of oxygen to 10% led to a doubling of coronary flow as the coronary arterial oxygen content was reduced.[27] After ascent to high altitude, coronary blood flow shows a small acute increase, and then decreases over 7–10 days to 25% below pre-ascent values, while the coronary arteriovenous difference in oxygen content increases.[28] It is thought that this results from increased unloading of oxygen in the capillaries caused by a rightwards shift in the haemoglobin-oxygen binding curve which occurs as an adaptation to high altitude. Myocardial oxygen consumption remains unchanged or decreases slightly.[28]

Changes in coronary flow have not been reported in relation to hypoxaemia in other clinical situations. In animal experiments it seems that hypoxia causes dilatation of coronary microvessels that is mediated by prostaglandins rather than by an endothelium-derived relaxant factor.[29]

Effects of hypoxaemia on electrophysiology

Hypoxia in healthy individuals does not seem to cause arrhythmias either when a hypoxic gas mixture is breathed[27] or at high altitude,[12] unless ascent to high altitude results in acute mountain sickness with pulmonary oedema. In contrast, brief episodes of hypoxaemia during sleep apnoea are associated with various arrhythmias including prolonged sinus pauses, atrial fibrillation, transient atrioventricular conduction block, multifocal ventricular extrasystoles, and non-sustained ventricular tachycardia.[30–33] The mechanisms of arrhythmogenesis are

not clear,[34] and although there is a close correlation between the level of hypoxaemia and the occurrence of ventricular extrasystoles,[35] other factors including hypercapnia and autonomic changes may contribute to arrhythmias.[36] Indeed, ventricular arrhythmias may occur during sleep in subjects without apnoea,[37] and may be related to the nocturnal reduction in mean heart rate.[38] The arrhythmias associated with sleep apnoea are improved or abolished when patients with obstructive sleep apnoea are treated by tracheostomy[39] or when obese patients lose weight.[40 41] Patients with severe chronic left ventricular failure may also show episodes of oxygen desaturation during sleep. Although the severity of hypoxaemia is less than in hypoxic lung disease, some of these episodes are associated with arrhythmias[42 43] and might relate to the increased risk of sudden death in this condition.[42]

Hypoxic pulmonary vasoconstriction

Hypoxia is a potent stimulus to pulmonary vasoconstriction, but the relation of pulmonary vascular resistance to hypoxia is complex. First it is non-linear: studies of healthy individuals showed that pulmonary vascular resistance increased particularly rapidly when Po_2 was $\leqslant 8$ kPa.[44] Second, the response to hypoxia varies widely between individual subjects,[45] and an individual's pulmonary vascular reactivity may determine his risk of developing cor pulmonale at altitude or with chronic lung disease.[46] Some of those who reside at altitudes of 10 000 feet or above develop pulmonary hypertension and features of right ventricular strain, but many do not.[47]

In chronic hypoxic lung disease other factors besides hypoxic pulmonary vasoconstriction may be important in the development of pulmonary hypertension. The rate of rise of pulmonary artery pressure in these patients is variable[6] and long-term oxygen therapy has only a small effect on pulmonary hypertension.[48 49] Recent evidence from necropsy studies also suggests that hypoxic pulmonary vasoconstriction may be less important: abnormalities of the intima and development of longitudinal muscle in the media were noted in these patients.[50 51] These changes may be caused by repeated stretching and distortion of the small pulmonary vessels; whereas hypoxia causes circular muscle hypertrophy. Emphysematous destruction of the pulmonary vascular bed can also increase pulmonary artery pressure.[52] Hypoxia causes secondary polycythaemia, further increasing pulmonary vascular resistance to a small extent.[53 54]

The mechanisms of cor pulmonale in severe chronic hypoxic lung disease are probably multifactorial. As well as increased pulmonary vascular resistance owing to a combination of vasoconstriction and destruction of the pulmonary vasculature, hypoxia increase renin, aldosterone, and vasopressin (anti-diuretic hormone) concentrations.[54] Together with reduced renal blood flow these lead to salt and water retention, and these changes may be more important than any direct effects of hypoxaemia on the heart in this condition.[56 57]

Conclusions

It is perhaps surprising how little is known about the effects on the heart of hypoxia as opposed to ischaemia. The cardiovascular responses of healthy individuals to hypoxia have been studied in the laboratory and during ascent to high altitudes, but the effects of hypoxia on diseased hearts are not well understood. Chronic hypoxic lung disease and sleep apnoea have many effects on the heart and circulation, and it is not known whether hypoxia itself or other mechanisms are the more important. Potentially serious arrhythmias during sleep apnoeas and in heart failure may be triggered by hypoxaemia. It is important to be aware of these effects because episodes of hypoxia occur in various conditions, and are probably underdiagnosed. It is possible that oxygen therapy will be beneficial in some circumstances but much work remains to be done.

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