Hypoxia and the pulmonary circulation

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It is a singularly interesting fact that sustained hypoxia exerts diametrically opposite effects on the systemic and pulmonary circulations. In general, hypoxia has a relaxing effect on smooth muscle and it brings about vasodilatation in the systemic circulation. Native highlanders and sojourners at high altitude for many years exhibit a fall in systemic blood pressure (Heath and Williams, 1977). In sharp contrast to this, hypoxia is the most powerful pulmonary vasoconstrictor known, giving rise to increased pulmonary vascular resistance and hence to pulmonary arterial hypertension. Since the original demonstration of this in the cat by von Euler and Liljestrand (1946) there has been an impressive accumulation of supporting experimental evidence from a variety of animal species and from man and recently we have extensively reviewed these data (Harris and Heath, 1977).

Morbid anatomical associations

The constriction of the terminal portions of the pulmonary arterial tree in response to hypoxia is associated with characteristic histological changes. These may be rapidly produced in most laboratory animals by subjecting them to sustained decompression. Thus exposure to a diminished barometric pressure of 380 mm Hg, simulating an altitude of 5500 m, for five weeks will cause the pulmonary arterioles to become muscularized (Abraham *et al*, 1971; Heath *et al*, 1973). The normal pulmonary arteriole in man and most animal species has a wall consisting of a single elastic lamina. Under the influence of hypoxia, circumferentially orientated smooth muscle cells form a continuous muscle coat so that the vessel comes to resemble a systemic arteriole both in structure and in its potential for constriction (fig 1). This coat of smooth muscle is bounded on the outer side by a thick elastic lamina and on its inner aspect by a thin elastic membrane (fig 1). We shall consider the ultrastructural basis for this in a moment.

As the pulmonary arterioles become muscularized they constrict, raising pulmonary vascular resistance and pulmonary arterial blood pressure. This leads

to medial hypertrophy of the pulmonary trunk so that the ratio of the thickness of its media compared to that of the aorta increases from the normal range of 0.4 to 0.7 (Heath *et al*, 1959) to something in the range of 0.7 to 1.1 (Heath *et al*, 1973). At the same time the right ventricle undergoes hypertrophy. There is evidence to suggest that these responses of the pulmonary vasculature and right ventricle to hypoxia are modified by age and sex (Smith *et al*, 1974). We found that right ventricular hypertrophy develops to its greatest extent in the old male rat whereas the most striking degree of muscularization of the terminal portions of the pulmonary arterial

Fig 1 Transverse section of a pulmonary arteriole from a Wistar albino rat maintained for five weeks in a decompression chamber at a constant barometric pressure of 380 mm Hg, simulating an altitude of 5500 m above sea level. The normal pulmonary arteriole in the rat, as in man, has a wall consisting of a single elastic lamina. The pulmonary arteriole shown here is abnormally muscularized. A distinct media of circularly orientated smooth muscle (arrow) has formed internal to the original thick elastic lamina. On the inner aspect of the muscle layer a new thin internal elastic lamina has been laid down. The vessel now resembles a systemic arteriole and is capable of elevating pulmonary vascular resistance to give rise to pulmonary arterial hypertension and right ventricular hypertrophy (elastic Van Gieson $\times 1125$).

tree is to be found in the adult female rat (Smith *et al*, 1974).

The same histopathological changes occur in the human lung in states of chronic hypoxia such as chronic bronchitis and emphysema, kyphoscoliosis, native highlanders, sufferers from chronic mountain sickness (Monge's disease), the Pickwickian syndrome and even in children with greatly enlarged adenoids. Some years ago we coined the term 'hypoxic hypertensive pulmonary vascular disease' to describe this form of arterial pathology (Hasleton *et al*, 1968). In addition to muscularization of the pulmonary arterioles by circularly orientated smooth muscle fibres there is the development of longitudinal smooth muscle in the intima. An outstandingly important feature is the absence of occlusive intimal fibrosis. This has the important functional implication that the associated pulmonary hypertension is both moderate and almost totally reversible. A moment's consideration will show that if this were not the case, life in mountainous areas would not be possible as the indigenous population would gradually become decimated by pulmonary hypertension and congestive cardiac failure. While man at high altitude is thus protected partially in this manner, his animal companion the llama (fig 2) appears to have developed an even greater evolutionary adaptation to the environment, for the terminal portions of its pulmonary arterial tree are devoid of muscle and this species does not seem to develop right ventricular hypertrophy at all (Heath *et al*, 1974).

Ultrastructural associations

Electron microscopy of the lungs of rats developing hypoxic hypertensive pulmonary vascular disease in a decompression chamber shows that the muscularization of the pulmonary arterioles is brought about not only by vasoconstriction but by the appearance of new muscle cells (Smith and Heath, 1977) (fig 3). They appear internally to the original single thick elastic lamina of the normal pulmonary arteriole and a much thinner elastic lamina then itself appears inside the new coat of muscle (Smith and Heath, 1977, fig 3). Such ultrastructural appearances explain the disparity of the thickness of the inner and outer elastic laminae of muscularized pulmonary arterioles seen on light microscopy (fig 1).

The pulmonary circulation at high altitude

The structural alterations in the pulmonary arterial tree and the associated vasoconstriction brought about by hypoxia elevate pulmonary vascular resistance and cause pulmonary arterial hypertension. This progression of events is best shown in a situation where the effects of hypoxia *per se* are not complicated by coexisting disease of the heart or lungs. Such a situation is met in native highlanders who are exposed to the chronic hypoxia of diminished barometric pressure inherent in life at high altitude (fig 4). Thus healthy man born and living at high altitude has some degree of pulmonary arterial

Fig 2 Llamas at Rancas (4720 m) in the Peruvian Andes where the P_{O_2} of the ambient air is greatly reduced. This indigenous, high-altitude species is adapted to such environmental conditions in contrast to the Quechua Indians, who are acclimatized. Thus, unlike the Indians, the llama shows neither muscularization of its pulmonary arterioles nor right ventricular hypertrophy. It has a low haematocrit and its erythrocytes do not contain 2,3 diphosphoglycerate.

Fig 3 Electron micrograph of a muscularized pulmonary arteriole from a Wistar albino rat similar to that shown in figure 1. The inner elastic lamina is indicated by arrow I and the other elastic lamina by arrow E. Situated between the two elastic laminae are smooth muscle cells, M. There has been constriction of this muscularized arteriole so that its lumen has become occluded by the swollen endothelial cells, e. Such muscularized vessels are the essential component of hypoxic hypertensive pulmonary vascular disease (electron micrograph $\times 5000$).

hypertension at rest. Peñaloza *et al* (1962) and Sime *et al* (1963) have studied the pulmonary haemodynamics of 38 healthy adults and 32 healthy children at Morococha (4540 m) and Cerro de Pasco (4330 m) in the Peruvian Andes. In the former town the mean barometric pressure is 446 mm Hg and the atmospheric P_{O_2} 80 mm Hg, while in the latter settlement these values are respectively 455 and 90 mm Hg. They found that the highlander has

a mean pulmonary arterial pressure of 28 mm Hg compared to a level of 12 mm Hg in sea level residents at Lima. The corresponding levels of pulmonary vascular resistance are $401 \text{ dyn s cm}^{-5}$ in highlanders as contrasted to $159 \text{ dyn s cm}^{-5}$ in coastal dwellers. The pulmonary wedge pressure does not increase in those living at great elevations. In young children between the ages of 1 to 5 years the level of pulmonary arterial pressure is considerably greater. Thus Sime

Fig 4 A Quechua from Cerro de Pasco (4330 m) in the Peruvian Andes. He shows the features of acclimatization to the chronic hypoxia of high altitude with a greatly elevated haemoglobin level giving his mucous membranes a deep russet-red coloration. Such native highlanders have muscularization of the terminal portions of the pulmonary arterial tree, an elevated pulmonary vascular resistance, and right ventricular hypertrophy. So greatly elevated was the haematocrit in this man that there were fears that he was developing chronic mountain sickness (Monge's disease).

et al (1963) found the average pulmonary arterial mean pressure in seven young children to be no less than 45 mm Hg with a systolic pressure as high as 58 mm Hg. After the age of 5 years the pulmonary arterial pressure falls to adult levels. The effects of the hypoxia of high altitude on pulmonary haemodynamics are shown in a more pronounced manner on exercise. Peñaloza *et al* (1962) found that the average pulmonary arterial mean pressure rose as high as 60 mm Hg on exercise in subjects at high altitude, the systolic level being 77 mm Hg. In patients with chronic mountain sickness (Monge's disease) (fig 5), the level of pulmonary hypertension

Fig 5 A family scene at Cerro de Pasco (4330 m) in the Peruvian Andes. The husband, aged 35 years, has developed chronic mountain sickness (Monge's disease) with loss of acclimatization to the chronic hypoxia of high altitude. His haemoglobin level now exceeds 23 g/dl. Such subjects show pronounced muscularization of the pulmonary arterioles in response to the chronic alveolar hypoxia brought about by hypoventilation. They also develop more pronounced pulmonary arterial hypertension and right ventricular hypertrophy than is seen in healthy highlanders. The wife and children are not affected.

and total pulmonary resistance are higher than are observed in healthy highlanders (Peñaloza and Sime, 1971; Peñaloza *et al*, 1971). The cardiac output and pulmonary wedge pressure are not significantly different from those found in healthy highlanders.

Brisket disease

Above we noted that the response of the pulmonary circulation is closely related to the amount of muscle present in the vasculature of the lung. Thus we have seen that the llama does not respond to hypoxia

significantly, no doubt an expression of evolutionary adaptation (fig 2). The reverse situation is seen in animal species which have a naturally muscular pulmonary vasculature. Thus cattle grazing at high altitude in Utah and Colorado not infrequently develop congestive cardiac failure secondary to hypoxic vasoconstriction of their small muscular pulmonary blood vessels (Hecht *et al*, 1959). The oedema in these animals occurs particularly in the region between the forelegs and the neck, the 'brisket' of commerce, and hence the condition is commonly referred to as 'brisket disease'. Cattle are particularly susceptible to the constrictive action of hypoxia on the terminal portions of the pulmonary arterial tree since they have very muscular pulmonary arteries and arterioles (Best and Heath, 1961; Alexander, 1962). High mountain disease occurs mostly in calves taken to high altitude for the first time and this is probably related to the fact that they have the most muscular pulmonary arteries of all. Wagenvoort and Wagenvoort (1969) found that whereas in cattle over 1 year of age the medial thickness of the small pulmonary arteries is in the range of 6.2 to 16.4 per cent, in calves from one day to three months of age, the medial thickness was in the range of 13.4 to 22.6 per cent. For comparison in the normal adult human lung the range of percentage medial thickness is 2.8 to 6.8 per cent (Heath and Best, 1958). This excessive pulmonary vasoconstriction brought about by hypoxia represents one form of loss of acclimatization. It should not be regarded as a bovine form of Monge's disease which is a respiratory rather than a vascular type of loss of acclimatization (Heath and Williams, 1977).

The reversibility of hypoxic pulmonary hypertension

Since the pulmonary arterial hypertension induced by chronic hypoxia is sustained by constriction of vascular smooth muscle, without any organic basis of occlusion by intimal fibrosis, it follows that on withdrawal of the hypoxic stimulus both the pulmonary hypertension and the associated muscularization of the pulmonary vasculature regress. This has been demonstrated experimentally in rats in which hypoxic hypertensive pulmonary vascular disease has first been induced by placing the animals in a hypobaric chamber (Abraham *et al*, 1971). When calves with acute brisket disease are brought down from their summer grazing ranges to sea level, their clinical abnormalities disappear in four to six weeks (Kuida *et al*, 1963). When a patient with Monge's disease descends to sea level, or to a lower altitude, there is some immediate regression of his pulmonary hypertension, although the regression becomes more

pronounced after two months' residence at sea level (Peñaloza *et al*, 1971). It seems likely that the reduction in pulmonary arterial pressure and resistance on descent to sea level is achieved in three stages (Heath and Williams, 1977). These stages appear to apply to healthy highlanders, to patients with Monge's disease, to calves with brisket disease and to experimental rats removed from hypobaric chambers. First, there is a relaxation of pulmonary vasoconstriction formerly maintained by the chronic hypoxia. Thus administration of 35 per cent oxygen to produce an oxygen tension similar to that found at sea level will immediately reduce the pulmonary arterial pressure of highlanders by 15 to 20 per cent (Peñaloza *et al*, 1962), but by no more than this. Second, there is a progressive fall in polycythaemia. Third, and finally, there is a regression of the muscularization of the terminal portions of the pulmonary arterial tree. Thus Peñaloza *et al* (1962) found that in 11 inhabitants of Cerro de Pasco (4330 m) the average pulmonary arterial mean pressure halved from 24 to 12 mm Hg after two years' residence at sea level. In other words, short-term and partial regression of hypoxic pulmonary hypertension is effected through relaxation of pulmonary vasoconstriction. Long-term and complete regression requires loss of muscularization of the terminal portions of the pulmonary arterial tree.

The mode of action of hypoxia on pulmonary vascular smooth muscle

We must now consider how hypoxia gives rise to vasoconstriction in the lung. For a long time it has been believed that hypoxia by airway is much more effective than hypoxaemia by bloodstream in this respect. This in turn has suggested that there may be some intermediary agent lying in close approximation to the walls of the pulmonary arteries being stimulated by hypoxic air in the alveolar spaces to secrete a humoral agent which in turn directly initiates the vasoconstriction.

Mast cells and hypoxic pulmonary vasoconstriction

Mast cells have been the most recent popular candidate for the theoretical intermediary rôle in the response of the pulmonary arterial tree by hypoxia (Harris and Heath, 1977). Kay *et al* (1974) exposed rats to a barometric pressure of 380 mm Hg for a period of 20 days and found a distinct increase in the numbers of mast cells in the lungs which was related to right ventricular weight. More recently we have confirmed this observation in our own laboratory (Williams *et al*, 1977) and found that the increase in the numbers of mast cells affected those in the

alveolar septa and around blood vessels but not those around bronchi.

The significance of this hyperplasia of mast cells is not at all clear. Certainly mast cells contain a number of vasoactive substances, including 5-hydroxytryptamine and histamine (Selye, 1965). All the evidence suggests that the former is not involved in the hypoxic response (Lloyd, 1964; Bergofsky, 1974; Harris and Heath, 1977). A great difficulty in accepting histamine as the humoral mediator of hypoxic pulmonary vasoconstriction is that its effect on the pulmonary circulation has not universally been shown to be constrictor. Aviado (1965), after an extensive review of the literature, concluded that in the perfused lung histamine caused vasoconstriction while in the intact lung it caused vasodilatation. The effect of histamine has been reported to be vasodilatory in the lung of the fetal lamb (Cassin *et al*, 1964) and the neonatal calf (Silove and Simcha, 1973) both of which are highly sensitive to hypoxia. Shaw (1971) found that histamine reversed the pulmonary vasoconstriction caused by hypoxia in the rat and cat. Since the concern of medical investigators is likely to be mainly with the human pulmonary circulation it is worthy of note that in an extensive review of the literature on the pharmacology of the pulmonary circulation we found that in man the effects of histamine on the pulmonary circulation are vasodilator (Harris and Heath, 1977). Note, for example, in table I that the results of four separate studies show that the intravenous injection of histamine in both normal subjects and in patients with a variety of diseases leads to an unequivocal fall in pulmonary arterial resistance.

One has come to associate the appearance of large numbers of mast cells in the lung with subacute or chronic oedema of that organ. Thus they are to be found in the lung in large numbers in mitral stenosis and chronic left ventricular failure (Heath *et al*, 1969). They are plentiful in the lungs of rats to which *Crotalaria spectabilis* has been administered (Kay *et al*, 1967). In this situation the changes in the lung

parenchyma are reminiscent of those which occur in mitral stenosis and are characterized by persistent pulmonary oedema. When the human or rat lung is subjected to hypoxia or decreased barometric pressure, the lungs have a pronounced tendency to become oedematous. In the newcomer to high altitude this may progress from acute mountain sickness to high-altitude pulmonary oedema (Heath and Williams, 1977). Under such circumstances of incipient or sustained oedema of the lung parenchyma one would anticipate the appearance of mast cells.

The direct action of hypoxia on smooth muscle cells

The view that alveolar hypoxia is more effective than hypoxaemia in inducing pulmonary vasoconstriction and that it acts through an intermediary agent has recently been seriously questioned by Fishman (1976) who thinks the established concept ignores the fact that, because of the shape of the oxyhaemoglobin dissociation curve, the experiments underlying this notion have rarely entailed more than an exceedingly modest drop in the P_{O_2} of mixed venous blood. He thinks that a sufficient drop in mixed venous P_{O_2} would lead to pulmonary vasoconstriction and bases this opinion on evidence of the following sort. In fetal lambs whose circulations have been crossed, asphyxia of the donor causes pulmonary vasoconstriction in the unasphyxiated recipient (Campbell *et al*, 1967). Lowering the mixed venous P_{O_2} during ventilatory arrest in the isolated perfused lung elicits pulmonary vasoconstriction (Hauge, 1969). Perfusing the pulmonary artery with well oxygenated blood during hypoxia diminishes the increase in pulmonary artery pressure during hypoxia (Boake *et al*, 1959; Hauge, 1969).

Furthermore, there is evidence to suggest that alveolar hypoxia as well as hypoxaemia can act directly on the small pulmonary blood vessels (Harris and Heath, 1977). Thus the P_{O_2} of the blood in the pulmonary arterioles and even the muscular pulmonary arteries is very rapidly influenced by the com-

Reference	Dose ($\mu\text{g/kg min}^{-1}$)	Mean Pulmonary Arterial Pressure (mm Hg)		Mean Wedge or Left Atrial Pressure (mm Hg)		Pulmonary Blood Flow (l/min^{-1})		Pulmonary Arterial Resistance (dyn s cm^{-5})		No. and Type of Subjects
		Before	After	Before	After	Before	After	Before	After	
Lindell <i>et al</i> (1964)	0.1-0.3	32	36	21	28	4.6	6.5	221	114	8 MS
Bjure <i>et al</i> (1966)	0.1-0.4	12	9	6	4	8.4	10.0	62	38	2N + 2P
Lindell <i>et al</i> (1963)	0.1-0.4	30	30	21	23	4.6	6.6	156	94	4CP
Bjure <i>et al</i> (1967)	0.1-0.45	15	12	9	8	8.0	10.4	57	34	6 N♂
Bjure <i>et al</i> (1967)	0.1-0.45	15	12	7	6	6.6	9.1	86	46	5 N♀

Table I Effects of histamine on the human pulmonary circulation (after Harris and Heath, 1977)

N = Normal, P = pulmonary disease, CP = constrictive pericarditis, MS = mitral stenosis

position of the alveolar gas. If a cardiac catheter with a platinum electrode at its tip is wedged in the periphery of the pulmonary arterial tree, it is found to respond within one second when hydrogen is inhaled (Gasteazoro *et al*, 1963; Sobol, *et al*, 1963; Jameson, 1964). Since the pulmonary arterioles and possibly the muscular pulmonary arteries seem to be the site of vasoconstriction with hypoxia the fact that their contents and walls are so directly and rapidly influenced by the composition of the alveolar gas renders the existence of an extravascular intermediary no longer theoretically necessary (Harris and Heath, 1977). It becomes necessary, therefore, to explore the possibility that hypoxia exerts its effect directly on the arterial smooth muscle cell.

The primary intracellular effect of hypoxia is presumably on the activity of the respiratory chain and hence on the rate of phosphorylation of ADP to ATP. The oxygen atom acts as the ultimate acceptor of electrons in the intracellular process of oxidation of hydrogen through which the energy liberated by electron flow is converted into a biologically useful form by the phosphorylation of ADP. Cytochrome oxidase has an extremely low requirement for oxygen and the supply of oxygen to the respiratory chain does not become rate limiting for oxidative phosphorylation until P_{O_2} falls to 2-3 mm Hg. Although the oxygen has to diffuse across the cell cytoplasm, and, therefore, must be at a partial pressure above this, it has to be borne in mind that intracytoplasmic myoglobin is likely to be present to aid diffusion. Furthermore, all the alveolar and arteriolar tissues are unlikely to be subjected to a partial pressure of oxygen much below the PA_{O_2} of 100 mm Hg. Even if the intracellular P_{O_2} of oxygen-sensing cells were that of mixed venous blood (40 mm Hg) it would be unlikely to have a substantial effect on oxidative phosphorylation. Clearly somewhere in this anatomical region is a cell capable of sensing changes in P_{O_2} to which its immediate intracellular mechanisms of oxidation seem likely to be insensitive. The systemic arterial chemoreceptors appear to function under similar circumstances. In the carotid body, blood flow is enormous relative to its oxygen consumption so that the arteriovenous oxygen difference must be very small.

Since the respiratory chain is likely to be relatively insensitive to the changes of P_{O_2} to be found in the region of the alveolus, some biochemical system of amplification will be necessary. In the process of production of ATP amplification could involve high rates of ATP hydrolysis or uncoupling of oxidative phosphorylation (Harris and Heath, 1977). In the process of utilization of ATP, amplification might take place at some enzyme activity which is depen-

dent on a high ATP concentration (Harris and Heath, 1977).

Nothing appears to be known of the relative dependence on ATP of those enzyme activities in pulmonary arterial smooth muscle which might be involved in the process of contraction. In the myocardium the ATP concentration at half-maximal activity (Michaelis constant) is about a thousand times higher for the calcium-stimulated ATPase of the sarcolemma than it is for myofibrillar ATPase (Harris and Heath, 1977). In myocardium this sarcolemmal activity appears normally to be operating near its Michaelis constant under which conditions it would be particularly susceptible to small changes in ATP concentration and a mechanism of amplification would exist. An inhibition of the calcium pump would directly increase the cytoplasmic concentration of calcium ions, while an inhibition of the sodium pump would indirectly have the same effect. It is neither difficult nor unrealistic to imagine mechanisms whereby small decreases in cytoplasmic ATP concentration increase the net transport of calcium ions across the cell membrane or increase membrane permeability to calcium while remaining sufficient to sustain contractile activity. Should that happen in pulmonary arterial smooth muscle, contraction could follow the direct action of hypoxia on the muscle cells.

The genetic influence

This account of hypoxia and the pulmonary circulation has presented the reaction of the pulmonary vasculature in a rather mechanistic fashion but this is not the whole story for there is much variation in individual reaction to hypoxia. Wagenvoort and Wagenvoort (1973) carried out morphometric studies of the pulmonary vasculature of groups of highlanders from 21 to 58 years of age from Denver (1600 m), Johannesburg (1800 m), Leadville, Colorado (3300 m) and from the Peruvian Andes (over 4000 m). They found the mean medial thickness of 'muscular pulmonary arteries' at sea level to be 5.1 per cent, at moderate elevation (Denver and Johannesburg) to be 4.9 per cent, and at high altitude (Leadville and Peru) to be 6.6 per cent. However, of the eight subjects living at high altitude three showed unequivocal medial hypertrophy of the parent 'muscular pulmonary arteries' with percentage medial thickness of 8.4, 8.6 and 9.8 per cent. Hence it would appear that there is individual variation in the response of the pulmonary vasculature to hypoxia. A genetic factor also appears to influence the development of pulmonary hypertension in cattle at high altitude. The studies of Weir *et al* (1974) demonstrated that first and second

generation offspring of two groups of cattle, one susceptible to brisket disease and the other resistant to the development of hypoxic pulmonary hypertension, showed the same susceptibility or resistance to the pulmonary hypertension-producing effects of hypoxia as their forebears, on a further exposure to an altitude of 3400 m. Genetic susceptibility to pulmonary hypertension also appears to operate in man. Vogel *et al* (1962) identified one family at Leadville, Colorado, in which five children had pulmonary arterial pressures well above the mean values for that population.

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