

Hypoxia and the pulmonary circulation

Inder S Anand

The first description of the effects of hypoxia on the pulmonary circulation was made by Bradford and Dean in the UK exactly 100 years ago.¹ However, scientific interest in this field only began with the discovery of hypoxic pulmonary vasoconstriction in the cat by von Euler and Liljestrand² in 1946, and in man a year later in Andre Cournand's laboratory.³ Despite extensive research in this field for nearly half a century, we still do not fully understand the mechanism of hypoxic vasoconstriction or why the response of the pulmonary vasculature to hypoxia is diametrically opposite to that of the systemic circulation. Teleologically, hypoxic pulmonary vasoconstriction serves a useful purpose. It acts as a local homeostatic mechanism and, by diverting blood away from the unventilated or poorly ventilated lung, helps to maintain ventilation-perfusion homogeneity and thus arterial oxygenation. It is not surprising, therefore, to find that a similar response exists in most animal species.⁴⁻⁸

Mechanism of acute hypoxic pulmonary vasoconstriction

The mechanism by which a fall in oxygen tension is sensed and translated into vasoconstriction in the pulmonary circulation is still not fully understood. We know that pulmonary vasoconstriction is initiated within seconds of the onset of alveolar hypoxia,⁹ and that the pulmonary artery pressure gradually rises over the next few minutes. It is a remarkable coincidence that the stimulus-response curve of the pulmonary vasculature to hypoxia in humans resembles that of the carotid body chemoreceptors to acute hypoxia and of the bone marrow to chronic hypoxia.¹⁰⁻¹³ In each case the threshold of PO_2 is approximately 70–80 mm Hg. Below this value the response becomes increasingly strong. The inflection point of each of these curves is almost identical to that of the haemoglobin oxygen dissociation curve, suggesting that similar mechanisms may be involved in the sensing of oxygen in these diverse systems in the body.

Site of hypoxic pulmonary vasoconstriction

The small muscular pulmonary arteries are the major site of hypoxic pulmonary vasoconstriction. Oxygen tension of both the alveolar air and the pulmonary artery perfusate can directly influence these vessels, although alveolar hypoxia is much more effective.¹⁴⁻¹⁶ Staub and colleagues used the micropuncture technique to show that hypoxia increased pulmonary vascular resistance predominantly in

arterial segments upstream from arterioles 30–50 μ m in diameter.¹⁷ Laser technology later confirmed hypoxic vasoconstriction in small (30–200 μ m diameter) arterioles.¹⁸ How reduced oxygen tension triggers pulmonary vasoconstriction is still being investigated, but we do know that a reduction in oxygen tension in the lung depolarises resting membrane potential of pulmonary vascular smooth muscle, resulting in Ca^{2+} influx through the voltage dependent Ca^{2+} channels.¹⁹ The mechanism by which hypoxia is sensed by the pulmonary vascular smooth muscle remains unclear. For a long time a vasoconstrictive mediator has been thought to be involved. A number of potential mediators such as histamine,²⁰ serotonin,²¹ noradrenaline,²² angiotensin II,²³ vasoconstrictive prostaglandins,²⁴ leukotrienes,²⁵ reduced ATP,²⁶ and cytochrome P-450²⁷ have been investigated and excluded. The enthusiasm for a possible mediator of hypoxic pulmonary vasoconstriction has therefore waned, and there is increasing interest in the hypothesis that oxygen tension is sensed directly by the vascular smooth muscle. The possible role of K^+ channels in hypoxic pulmonary vasoconstriction has been suggested for some time,^{28,29} but the most exciting development in this field has been the finding by Weir and colleagues that hypoxia inhibits an outward K^+ current in isolated pulmonary arterial smooth muscle cells causing depolarisation of the resting membrane potential.³⁰ This could then lead to an influx of extracellular Ca^{2+} through the voltage-dependent Ca^{2+} channels and consequently to vasoconstriction. It is interesting that the type I cells in the carotid body also sense hypoxia by a similar mechanism.^{31,32} Further studies are needed to define these K^+ channels more fully, and to determine how they are modulated by hypoxia.

Effects of chronic hypoxia

The clinical effects of hypoxia are most evident in chronic hypoxic states. In addition to vasoconstriction, structural changes in the terminal portions of the pulmonary arterial tree³³ and polycythaemia³⁴ contribute to the maintenance of chronic hypoxic pulmonary hypertension. This occurs when the alveolar oxygen tension remains below the threshold for pulmonary vasoconstriction of approximately 75 mm Hg. Such a degree of chronic hypoxia is seen in conditions like chronic bronchitis and emphysema, hypoventilatory states, and in its pure form at high altitude. It is therefore interesting that an almost identical "remodelling" of the pulmonary vasculature occurs in response to alveolar hypoxia in these diverse states. In 1968 Donald Heath and his colleagues coined the

term “hypoxic hypertensive pulmonary vasculature disease” to describe this form of pulmonary vascular disease.³⁵ The most striking effect of alveolar hypoxia is muscularisation of pulmonary arterioles <70 µm in diameter which normally contain only a single elastic lamina without any smooth muscle. This distal extension of smooth muscle causes the small pulmonary arterioles to develop a distinct media with smooth muscle sandwiched between an inner and an outer elastic lamina. This was first described in Quechua Indians of Cerro de Pasco (4330 m) in the Peruvian Andes by Arias-Stella and Saldaña.³⁶ Later Heath and coworkers^{37–39} made a number of studies on Quechuas, Aymaras, mestizos, and white residents of La Paz, Bolivia (3800 m) and, while confirming muscularisation of pulmonary arterioles, found that remodelling was much more complex than had originally been envisaged by Arias-Stella and Saldaña.³⁶ Moreover, considerable individual and ethnic variations in the response to high altitude hypoxia were seen. Remodelling was more common in the Aymara and Quechua Indians than the mixed mestizos or long term white residents of La Paz. Heath *et al* also found longitudinal smooth muscle in the intima of small pulmonary arteries and development of inner muscular tubes of circularly orientated smooth muscle cells, internal to the fascicles of longitudinal muscle, lining the pulmonary arteries and arterioles.^{38,39} Similar histological changes are seen in patients with chronic obstructive lung disease at sea level,⁴⁰ but the development of longitudinal muscle and inner muscular tubes in the intima is much more prominent and occurs more frequently. The similarity of the remodelling in cor pulmonale and in the natives of high altitude suggests that it is caused by sustained alveolar hypoxia. It remains unclear, however, how pulmonary arterioles come to be muscularised. It is unlikely to be the result of work hypertrophy since these vessels have no muscle in normal subjects and hypoxic vasoconstriction occurs in vessels proximal to these arterioles. It is more likely that some smooth muscle growth factors are involved. Once pulmonary arterioles become muscularised they can constrict in response to hypoxia and vasoconstriction moves to a more peripheral site in the pulmonary vascular tree.⁴¹

Pulmonary artery pressure at high altitude

The structural changes described in the native highlanders are associated with chronic pulmonary hypertension. As stated above, however, pulmonary hypertension does not develop in high altitude residents until the alveolar oxygen tension falls below 75 mm Hg, which occurs at an altitude of approximately 2100 m.⁴² Thus the pulmonary artery pressure is normal (15 (3) mm Hg) in residents of Denver, Colorado (1600 m), borderline (19 (6) mm Hg) in Flagstaff, Arizona (2100 m), and raised (24 (7) mm Hg) in Leadville, Colorado (3100 m).¹⁰ In contrast to North American high altitude residents, the Aymaras and Quechuas of the

Andes who have lived at high altitude far longer than their American counterparts appear to develop a lesser degree of pulmonary hypertension despite being at higher altitude. Pulmonary artery pressures are normal in these subjects at 2240 m (15 (2) mm Hg)⁴³ and 2640 m (13 (3) mm Hg),⁴⁴ mildly increased at altitudes between 3700 and 4370 m (20 (3) to 23 (4) mm Hg),^{45–48} and moderately increased at an altitude of 4540 m (28 (10) mm Hg).⁴⁹ The curve relating pulmonary artery pressure and ambient oxygen tension is less steep in the Andean people than in their North American counterparts, which suggests a blunted hypoxic vasoconstrictive response. This may be a manifestation of adaptation to chronic hypoxia.

Unfortunately few data are available from the Himalayas where large populations also live at high altitude. Roy catheterised seven men at Leh, Ladakh (3600 m) who were presumably of Ladakhi origin.⁵⁰ The pulmonary artery pressure at rest was 20 (4.5) mm Hg and rose to 26 (5) mm Hg with modest exercise. The resting pressures are, therefore, almost identical to those quoted for the Andean people at similar altitude. The Andean highlanders, however, showed a greater increase in pulmonary artery pressure with similar exercise (32 (8) mm Hg). Does this mean that the Himalayan people are less reactive to hypobaric hypoxia than the Andean highlanders? Groves and coworkers have recently reported the pulmonary artery pressures in the native Tibetan highlanders of Lhasa, Tibet (3600 m).⁵¹ They found normal pressures at rest (15 (1) mm Hg, P_{iO_2} = 97 mm Hg) which did not increase significantly with further hypoxia (19 (3) mm Hg, P_{iO_2} = 62 mm Hg). Higher pulmonary artery pressures have been reported in two Chinese studies from Qinghai province in Tibet (3950 m) but it is unclear whether they studied Tibetan or Han subjects.^{52,53}

We have examined the lungs of seven Ladakhi highlanders who had never been to low altitude and who suffered accidental deaths. Their small pulmonary arteries were thin walled with no medial hypertrophy of the muscular pulmonary arteries, muscularisation of the arterioles, or any of the other changes described in the pulmonary vasculature of the Andean highlander.⁵⁴ Similar thin walled pulmonary arteries with normal pulmonary artery pressures are seen in a number of mammals indigenous to high altitude – for example, the llama,^{55,56} mountain viscacha,⁵⁷ yak,^{58,59} and snow pig.⁶⁰ Heath and Harris have suggested that this lack of pulmonary vascular remodelling and absence of pulmonary hypertension in these animals is an expression of genetic adaptation to hypobaric hypoxia.⁵⁷ By losing the property of pulmonary vasoconstriction the species finds it advantageous to avoid the harmful effects of pulmonary hypertension at high altitude at the expense of the benefits of ventilation-perfusion homogeneity. Indeed, the hypoxic pulmonary vasoconstrictive response appears to be genetically determined,⁶¹ and the loss or blunting of this response in certain species indigenous to high altitude may be explained in simple Mendelian

terms.⁶² The absence of muscularisation of pulmonary arterioles and the lack of pulmonary hypertension in the Ladakhi and Tibetan people, who come from the same ethnic stock and have lived in the Himalayas longer than their Andean counterparts,⁶³ therefore suggests that the pulmonary circulation of the native Himalayan people is remarkably well adapted to hypobaric hypoxia and perhaps better adapted than that of the Andean people.

Does this difference in the degree of adaptation of the Andean and Himalayan people really matter? Several differences in the response of these populations to alveolar hypoxia have been reported. Tibetan residents have a higher alveolar ventilation and increased ventilatory sensitivity to hypoxia than the native Andean highlanders.⁶⁴ The haemoglobin response is lower in the Himalayan than the Andean highlander.⁶⁵ These factors may explain why chronic mountain sickness is common in the Andean people but is seldom seen in the native Himalayan population, although it is frequently found amongst the Han Chinese residents of Tibet.⁶⁶

Subacute mountain sickness

The benefits of adaptation to alveolar hypoxia in the Tibetan people are best seen when they are compared with lowlanders who migrate to live permanently at high altitude. One such large experiment occurred with the Chinese occupation of Tibet in 1952 when large numbers of Chinese people of Han origin moved from mainland China to live permanently in Tibet at altitudes of 3000–4000 m. This enormous demographic change offered a unique opportunity for scientists to study the differences in the long term effects of alveolar hypoxia on people of different ethnic backgrounds.

SUBACUTE INFANTILE MOUNTAIN SICKNESS

In 1987 we went to Tibet to study the Himalayan variety of chronic mountain sickness.⁶⁶ During these studies we came across a new disease which was termed "subacute infantile mountain sickness",^{67,68} and were able to examine the records of 15 patients who had died of this syndrome. The condition was found in infants and children of both sexes aged 3–16 (mean 9) months. Of the 15 patients 14 were of Han origin and one was Tibetan. All except the Tibetan infant and a Han girl of 14 months were born at low altitude and later taken to live in Lhasa (3700 m). The average duration of their stay at high altitude was only 2.1 months. The infants presented with features of congestive heart failure including dyspnoea, cough, irritability, sleeplessness, cyanosis, puffiness of the face, and oliguria. Clinical examination revealed tachycardia, tachypnoea, cardiomegaly, heptomegaly, and rales in the chest. Chest radiography confirmed the presence of cardiac enlargement. Haemoglobin levels were not increased.

The most striking feature at postmortem examination was an enlarged heart, right ventricular hypertrophy and dilatation, and a

dilated pulmonary trunk. Histological examination of the lung was carried out by Donald Heath in Liverpool and showed changes in the pulmonary arteries, arterioles, and venules. The pulmonary arteries showed severe medial hypertrophy with crenation of the elastic laminae, suggesting vasoconstriction. There was muscularisation of the pulmonary arterioles. In contrast, the Tibetan age matched controls had thin walled pulmonary arteries and a single elastic lamina in the pulmonary arterioles. Clearly, alveolar hypoxia was responsible for the pulmonary vascular disease in these patients causing pulmonary hypertension, right ventricular hypertrophy and dilatation, and congestive heart failure. Lack of intimal proliferation, plexiform lesions, fibrinoid necrosis, or necrotising arteritis distinguished this condition from cases of primary pulmonary hypertension described in infants and children living at high altitude in Colorado.⁶⁹ In one case of subacute infantile mountain sickness, however, there was migration of myocytes from the media of small pulmonary arteries into the intima.⁶⁸ Heath has shown that such features are characteristic of early plexogenic pulmonary arteriopathy, forming the pathological basis of primary pulmonary hypertension.⁷⁰ Could this mean that the disease described in infants and children in Colorado was a late manifestation of infantile subacute mountain sickness?

The possibility of further investigating this infantile syndrome is now unlikely because, since its recognition, Han infants born at low level are no longer taken to high altitude. The incidence of the disease has therefore decreased considerably. Recent data show, however, that the arterial oxygen saturation is higher in Tibetan than Han newborn infants at Lhasa,⁷¹ suggesting that alveolar hypoventilation in the Han infants may have contributed to the pulmonary hypertension in subacute infantile mountain sickness. The rarity with which Tibetan infants develop this syndrome is another indication that the Tibetan people are adapted to alveolar hypoxia. Subacute infantile mountain sickness has not been seen in other high altitude areas. This is probably because such a large movement of lowlanders to high altitude has not occurred anywhere else. There is, however, some historical evidence that a similar condition might have affected infants born to Spanish immigrants to the Andean mining town of Potosi (4070 m) during the 16th century. The Spanish soon learned not to take their infants to Potosi until they were over the age of one year.⁷²

ADULT SUBACUTE MOUNTAIN SICKNESS

The sudden movement of large numbers of Indian troops to high altitude in the Himalayas during the 1962 India-China war was responsible for our increasing awareness of mountain-related illnesses and, in particular, of acute mountain sickness.⁷³ This experience encouraged formulation of rational acclimatisation protocols that allowed men to be deployed at much higher altitudes. The recent experience of military activity at extreme al-

titudes (>6000 m) in the Himalayas has made us aware of another syndrome called “adult subacute mountain sickness”.⁷⁴

In 1988 40 healthy soldiers (average age 22 years) stationed at extreme altitude (5800–6700 m) for an average of 18 weeks exhibited this syndrome. All were Garhwalis from the same ethnic background and were born and had spent most of their lives at an altitude of about 2000 m. They were moved to high altitude after a proper acclimatisation procedure spread over five weeks. None of them had developed acute mountain sickness. The posts they manned were snowbound with no local inhabitants or permanent settlements in the vicinity. Access to most of these areas was only possible by helicopter. The average night temperature at their posts varied from -20°C to -40°C . Their daily routine consisted of patrolling several kilometres of the slopes and other combat activities.

The illness started after the soldiers had spent an average of 11 weeks at that altitude. They developed increasing shortness of breath and oedema and later gross anasarca. Most of them responded to intermittent doses of diuretics. After an average stay of 18 weeks at extreme altitude they were finally airlifted to sea level and were investigated within three days. Most of them started spontaneous diuresis on leaving extreme altitude. Apart from features of severe congestive heart failure with oedema and ascites, they had polycythaemia (mean haematocrit 61%) and 18 had papilloedema. Chest radiography, ECG and echocardiography confirmed cardiomegaly, right ventricular hypertrophy, and dilatation, but no left ventricular enlargement or pulmonary venous congestion. Haemodynamic measurements showed mild pulmonary hypertension (mean 26 (5) mm Hg) at rest, not responsive to oxygen, which rose to an average of 40 mm Hg with mild exercise. The pulmonary wedge pressures and cardiac output were normal. All the abnormalities reverted to normal 12–16 weeks later.

The pathogenesis of this condition is not clear but a number of factors might have contributed to congestive heart failure – namely, hypoxic pulmonary vasoconstriction, structural remodelling of the pulmonary vasculature, and polycythaemia. Since none of the patients died and no histological examination of the lungs was carried out, the structural changes in these lungs are not known. Experimental data suggest that histological changes due to hypobaric hypoxia are reversible over a period of a few months.^{33,75} Similar data on humans do not exist. Other factors that might have contributed to pulmonary hypertension include the pulmonary vasoconstrictive effects of cold⁷⁶ and of exercise at extreme altitude.⁷⁷

Since the most striking finding in the adult syndrome was massive fluid retention, we decided to examine the response of the kidney and the neuroendocrine system to extreme altitude. Body fluid compartments, renal blood flow, and several plasma hormones were measured in a group of normal asymptomatic soldiers stationed at extreme altitude (>6000 m) for approximately 10 weeks.⁷⁸ The results showed

a significant increase in total body water, plasma and blood volume, and total body exchangeable sodium. Renal blood flow fell. Plasma levels of noradrenaline, aldosterone, and erythropoietin increased but the atrial natriuretic peptide and renin activity did not change. These findings suggest that salt and water accumulation seen in these normal asymptomatic subjects at extreme altitude could have resulted from mechanisms acting to reduce the renal blood flow, independent of changes in haemodynamics. Similar mechanisms could also have contributed to the pathogenesis of adult subacute mountain sickness.

Only 10–20% of subjects stationed at extreme altitude were affected by this syndrome. The factors responsible for this observation are not yet known. The cohort stationed at extreme altitude was homogenous in terms of race, age, build, and level of exertion. The incidence of the syndrome increased with altitude and with the duration of stay at extreme altitude. Interestingly, the occurrence of the disease has decreased dramatically since the adoption of measures to reduce the period of stay at extreme altitude. One factor that may be important needs to be considered. The syndrome of adult subacute mountain sickness was seen in its most florid form in only two ethnic groups: the Garhwalis⁷⁴ – as described in detail here – and six months earlier in the Gurkhas⁷⁹ on whom detailed studies could not be done. Both these populations come from submountainous areas of 2000–3000 m. It is possible that the soldiers who developed this syndrome were exposed to some degree of perinatal hypoxia. Heath has shown in experimental animals that variable exposure to perinatal hypoxia exaggerates the effects of agents inducing vasoconstrictive pulmonary hypertension in later life.⁸⁰ Whether a similar phenomenon contributed to the pathogenesis of this syndrome remains to be determined.

Both the human syndromes described here have a number of similarities with brisket disease in cattle. The length of exposure to hypobaric hypoxia required for the development of clinical features is almost identical. Hypoxic pulmonary hypertension seems to play an important part in all three conditions. The common clinical finding is one of severe congestive heart failure. The morphological changes in the lungs in brisket disease⁸¹ and in subacute infantile syndrome⁶⁷ are entirely muscular in nature. Although histological data are not available for the adult syndrome, it is likely that similar changes might be seen in this condition as well. Removal from high altitude results in complete resolution of brisket disease⁸² and adult subacute mountain sickness.⁷⁴ There is anecdotal evidence that this also occurs in the infantile syndrome. It would therefore appear that both the infantile and adult forms of the subacute syndrome are the human counterpart of brisket disease in cattle.

Even a superficial reading of this chapter will make obvious the enormous contributions that Donald Heath made to the subject of hypoxia

and the pulmonary circulation. For me it has been a great privilege to have been associated with some of his work. Over the years I have come to know Donald well. His enquiring mind, equable humour, resilient character, and transparent straightforwardness have always shown through even during the stresses of our scientific expeditions at high altitude.

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