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EDITORIAL

Effects of pulmonary vasodilators on the remodelled pulmonary arterial tree in chronic alveolar hypoxia

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It has been reported that treatment with the calcium antagonist felodipine, orally or by infusion, may be a valuable adjunct to ongoing long-term oxygen therapy for chronic obstructive lung disease [1]. These authors found in eight patients beneficial changes in both central haemodynamics and ventilation-perfusion matching. There were falls in pulmonary and systemic vascular resistance, an increase in cardiac output, a tendency to increased perfusion of hypoxic areas of lung, and an increase of total oxygen transport. It is worthy of consideration as to how a pulmonary vasodilator is thought to exert its effects on the remodelling of the pulmonary arterial tree which is known to occur in chronic obstructive lung disease. The abnormalities which develop in the pulmonary blood vessels in pulmonary emphysema, as in all states of chronic hypoxia, occur characteristically in the most peripheral portions of the pulmonary arterial tree. New accumulations of vascular smooth muscle cells are widespread in the intima of the small pulmonary arteries but they are laid down in a longitudinal orientation along the length of the vessel [2]. These have long been regarded as the result of stretching of pulmonary arteries around the abnormal air spaces in the lung but there are now grounds for doubting this and the longitudinal muscle may be a response to chronic hypoxia in the surrounding alveolar spaces as will be discussed below. When a patient with pulmonary emphysema treated on long-term oxygen therapy dies, there is ample histological evidence of recent laying down of more longitudinal muscle up to the time of death [2]. It seems appropriate to consider what effect a pulmonary vasodilator might be expected to have on longitudinally-orientated fasciculi of muscle in the intima of pulmonary arteries.

Commonly a thin layer of circularly-orientated smooth muscle forms internally to this layer of longitudinal muscle in the intima. This circular muscle extends in the form of tubes distally through the pulmonary arterioles to peter out in the walls of small muscularized arterioles and pre-capillaries [2]. As many as three of these inner muscular tubes may be found passing through one arteriole. Elastic tissue is laid down between these tubes and they persist even after a long period of oxygen therapy. How do pulmonary vasodilators affect these muscular tubes and thus influence pulmonary haemodynamics?

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The third component of the structural remodelling of the pulmonary arterial tree in the chronic alveolar hypoxia of pulmonary emphysema is the overgrowth of vascular smooth muscle cells in the pulmonary arterioles and pre-capillaries so that both become muscularized [2]. This is a process of overgrowth of smooth muscle cells rather than of vasoconstriction. Once again it is pertinent to ask how a pulmonary vasodilator might act on the smooth muscle cells extending along the pre-capillaries of the lung.

The classic view of the pathological effect of chronic alveolar hypoxia in producing vasoconstriction and muscularized pulmonary arterioles has been largely based on histological findings in experimental rats kept in decompression chambers [3]. However, it has to be kept in mind that the pulmonary vasculature of the rat is not a good model for events in man for the intima of the pulmonary arteries of this animal is particularly inactive, showing none of the various fibroelastic or muscular proliferations that characterize human pulmonary vascular pathology. If one bases one's views as to how the terminal portions of the pulmonary arterial tree respond to states of chronic hypoxia on what occurs in the rat it is not surprising that proliferations of muscle and connective tissue from the intima are given little or indeed any prominence.

The classic paper by ARIAS-STELLA and SALDAÑA [4] describing the pulmonary vasculature of the Quechua Indians of the Peruvian Andes also concentrates on muscularization of the pulmonary arterioles without any reference being made to intimal proliferations of muscle and connective tissue. However, on a recent visit to the Andes we were able to confirm that the Aymarás of La Paz show the same triad of longitudinal muscle in the pulmonary arteries, muscular tubes extending through the pulmonary arterioles, and extension of vascular smooth muscle into the pre-capillaries. The strong impression is thus gained that this combination of histological changes is an association of chronic alveolar hypoxia, be this due to disease or environment.

This type of pulmonary vascular remodelling in chronic obstructive lung disease is benign and in native highlanders it is hardly more than a marker of sustained alveolar hypoxia. There is, however, a second form of remodelling of the pulmonary arterial tree in response to chronic alveolar hypoxia which carries a much worse prognosis. This is found in the condition of subacute mountain sickness which occurs in infants of Han origin

being taken up by their Chinese parents to live in Lhasa (3,600 m), the capital city of Tibet [5]. This is a failure to establish initial acclimatization to the hypobaric hypoxia of high altitude. It is the human counterpart of brisket disease of calves seen in the mountains surrounding Salt Lake City, Utah. This form of pulmonary vascular disease in these Chinese infants carries a very poor prognosis and they die within three months of ascending to high altitude. In this disease there is an active migration of immature myocytes into the intima rather than a proliferation of mature smooth muscle cells as there is in chronic obstructive lung disease. This transformation of vascular smooth muscle cells into myofibroblasts is reminiscent of what takes place in plexogenic arteriopathy which is the organic basis for primary pulmonary hypertension [6]. In this condition, as in chronic obstructive lung disease, proliferation of vascular smooth muscle cells is as important as vasoconstriction. In passing, it may be noted that remodelling of the pulmonary arterial tree carrying a poor prognosis is to be found in at least one strain of rabbit as in man at high altitude. On a recent visit to La Paz we were asked to investigate the pathology which had led to the death of a New Zealand white rabbit which had died on a farm at 3,800 m. It also showed hyperplasia of vascular smooth muscle in its pulmonary arterioles and pre-capillaries [7].

It is intriguing to speculate how a substance slowing the development of pulmonary vascular disease in chronic obstructive lung disease works. Recently CAI and BARER [8] have demonstrated experimentally in rats kept in a normobaric atmosphere of 10% oxygen for two to three weeks a concomitant attenuation of right ventricular hypertrophy and muscularization of pulmonary arterioles when the animals were given ligustrazine. This substance comes from the root of an umbelliferous plant, *Ligustrazine wallichii franch*, which grows in the south west and north regions of China. It has been used in that country for 2,000 years in the treatment of cardiovascular disease. It appears to act by attenuating the growth of new muscle in the pulmonary arterioles. Perhaps the time has come for a broader term than 'vasodilator' to describe a substance that proves to be effective in ameliorating the remodelling of the terminal portions of the pulmonary arterial tree in chronic obstructive lung disease.

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