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Pathophysiology of the Pulmonary Blood Vessels in Chronic Lung Disease

J. HERGET

Department of Pathophysiology, Faculty of Paediatrics, Charles University, Prague

Pulmonary hypertension is a serious complication of several chronic lung diseases (Howard 1985). The increase of the pulmonary arterial blood pressure in chronic lung damage results from the high resistance of pulmonary vessels to blood flow. Three main factors contribute:

1. Encroachment of hypertrophied vascular smooth muscle into the lumen of peripheral pulmonary arteries
2. Decreased compliance of lung vessels
3. Pulmonary vasoconstriction

The mechanisms of these changes are complex. Chronic lung diseases cause the uneven distribution of inspired gas within the lungs. The lung damage and inflammatory reaction influence the morphology and regulation of pulmonary blood vessels directly. The altered reactivity of pulmonary vasculature to the pathogenic stimuli also participate.

Effects of Uneven Pulmonary Ventilation

The regional alveolar hypoventilation, hypoxia and hypercapnia result from the local increase of airway resistance and decrease of lung compliance due to lung disease. Chronic lung hypoxia is a very potent mechanism of development of hypoxic pulmonary hypertension already known for more than 60 years (Campbell 1927). Similar effects were also found after intermittent exposure to hypoxic environment (Widimský *et al.* 1973). In rats with experimental lung emphysema, the presence of pulmonary hypertension correlated well with the level of arterial hypoxaemia (Fig. 1). It was not related, however, to the extent of emphysematous lesions in the lungs of experimental animals (Herget *et al.* 1979).

Much is known about the morphologic changes of pulmonary vessels in patients with chronic lung disease (Wagenvoort 1987) or in animals with experimental models of pulmonary hypertension (Herget and Paleček 1978). The presence of the thick smooth muscle layer in the media of peripheral intraacinar pulmonary arteries is the most characteristic feature. It is not specific, however, for the effects of chronic hypoxia and similar changes are found in all other types of pulmonary hypertension. The relative number of thickened pulmonary arteries correlates well with the severity of chronic bronchitis in patients (Scott 1976). Muscularization of pulmonary arteries is a reversible process, but the recovery takes

a long time. In experiments in rats, the smooth muscle in pulmonary arterioles was still present twenty weeks after a sojourn in a hypoxic chamber (Herget *et al.* 1978).

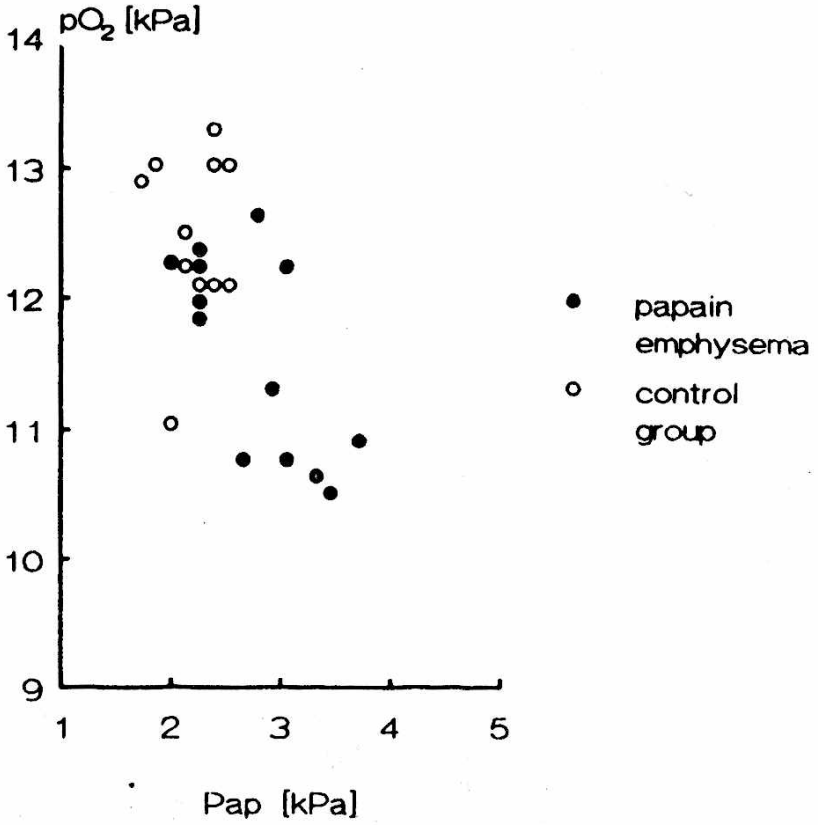

Fig. 1

The relation between the mean pulmonary blood pressure (Pap) and partial pressure of oxygen in arterial blood (PO_2) in rats with lung emphysema induced by papain lung instillation (emphysema) and in control group of rats (controls). In the group of rats with lung emphysema the pulmonary hypertension was present only in those animals with arterial hypoxaemia. The values of pulmonary arterial blood pressure and partial pressure of oxygen were measured in intact rats under urethane anaesthesia.

What stimulates the growth of the vascular smooth muscle in pulmonary hypertension? In the past, some investigators accepted the explanation that it is a result of high intravascular pressure and the muscularization of pulmonary arteries was regarded as a "work hypertrophy" of smooth muscle cells. New evidence, however, supports the hypothesis that the smooth muscle hypertrophy in intraacinar vessels is one of the causes and not the result of pulmonary hypertension. It is, at least in the part, related to the change of metabolic activity of damaged endothelial cells. Vender and co-workers (1987) in their well-designed experiments showed that hypoxic bovine endothelial cells isolated from the pulmonary artery produced a specific mitogen which stimulated the growth of the vascular smooth muscle cells *in vitro*. The production of the mitogen was not found in normoxic endothelial cells or in hypoxic and normoxic endothelial cells isolated from the aorta.

The next important mechanism in pulmonary hypertension is the increase of production of collagen and elastic fibers in the vascular wall (Stenmark *et al.* 1988). Two stimuli have been related to the augmented collagen synthesis in pulmonary arteries, namely transvascular leak of proteins (Laurent 1990) and increased wall tension (Riley *et al.* 1990). In both cases, however, the presence of endothelial cells is necessary. In experiments of Kerr and his co-workers (1987), the inhibition of collagen synthesis in hypoxic rats partly prevented the development of hypoxic pulmonary hypertension. This is in agreement with our recent experiments, where we showed attenuated hypoxic pulmonary hypertension in lathyrogenic rats (Herget *et al.* 1990) (Fig. 2). Lathyrism was induced by repeated administration of β-aminopropionitrile. This lathyrogenic agent inhibits the collagen intramolecular links and the formation of stable intermolecular aggregates. This results in the loss of tensile strength of the tissue (Tanzer 1965).

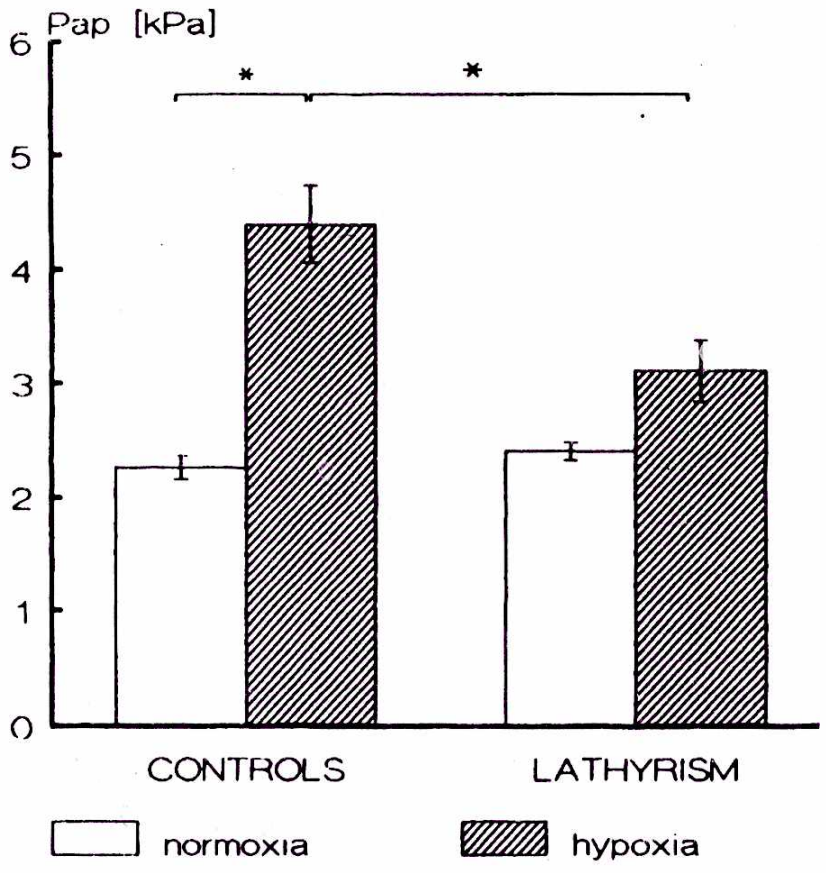

Fig. 2
Pulmonary arterial mean blood pressure (Pap) in control and lathyrogenic rats living in air or after two weeks of exposure to 10% of oxygen in isobaric hypoxic chamber. The lathyrism was induced by repeated oesophageal gavage of β-aminopropionitrile solution in young rats. The values were measured in intact rats under urethane anaesthesia. * = $P<0.05$.

Both encroachment of pulmonary vascular smooth muscle in the lumen of peripheral pulmonary arteries and the decrease of vascular compliance contribute to the increase of pulmonary vascular resistance in chronic hypoxia (Finlay *et al.* 1986, Reid 1990).

Acute hypoxia induces pulmonary vasoconstriction which has a crucial regulatory role. It opposes the effects of uneven lung V/Q relationship and therefore prevents arterial hypoxaemia due to unequalities of the distribution of inspired air (Herget and McMurtry 1985). Mechanisms of pulmonary vasoconstriction in chronic hypoxia and in chronic lung injury, however, are probably different from the mechanisms of acute lung hypoxia (Herget and Ježek 1989). They are related to the metabolic effects of lung injury as it is discussed below.

In addition, there are other consequences of the uneven V/Q distribution which may alter pulmonary vasculature in chronic lung disease. Because of the restriction of pulmonary blood flow in hypoventilated areas, the perfusion of the remaining parts of the lung increases. The cardiac output does not change much in stable *cor pulmonale*. The increased flow of blood, which often is of high viscosity due to polycythaemia, represents excessive shear stress on the endothelial surface which may also be related to the above described changes of morphology and function of pulmonary vascular smooth muscles (Rabinovitch 1987).

The possibility of direct contribution of the increase of airway resistance and the decrease of lung compliance in lung disease to the increase of pulmonary vascular resistance is often debated. In the normal vascular bed, the effects of the changes of lung mechanical properties on pulmonary haemodynamics are relatively insignificant. In pulmonary hypertension, however, the intraalveolar arteries possess smooth muscle fibers. Therefore, the part of vasculature which is exposed to the changes of alveolar air pressure and elastic lung recoil has a definite smooth muscle tone. The downstream resistance of this portion of pulmonary vasculature to blood flow is the sum of the vascular tone, alveolar pressure and elastic recoil of the lung septa. Because of the low vascular compliance in lung disease, the positive expiratory pressure may be more effective than the negative pressure during the inspirium (Wach *et al.* 1987).

Lung Inflammation

Repeated experimental lung inflammations in rats result in chronic pulmonary hypertension (Herget *et al.* 1981) (Fig. 3). The part of the increase of pulmonary vascular resistance was the result of vasoconstriction, which was not influenced by oxygen breathing but it was blocked by calcium channel antagonists.

Are there any direct effects of lung inflammation on the pulmonary vascular bed? The key structure are the different types of lung macrophages. There are two populations of these cells in the lung: alveolar macrophages and intravascular macrophages. Therefore, both sites of the pulmonary vascular wall seem to be eligible. Activated lung macrophages produce a variety of vasoactive substances and the factors which attract the neutrophils. The intravascular macrophages (Bertram *et al.* 1987) are probably even more metabolically active than their alveolar counterparts and, in addition, they produce direct intercellular junctions with the endothelial cells. The activation of lung macrophages and neutrophils have two

consequences which alter the regulation of pulmonary vasculature. Firstly, different vasoactive substances are produced which increase the vascular tone. Secondly,

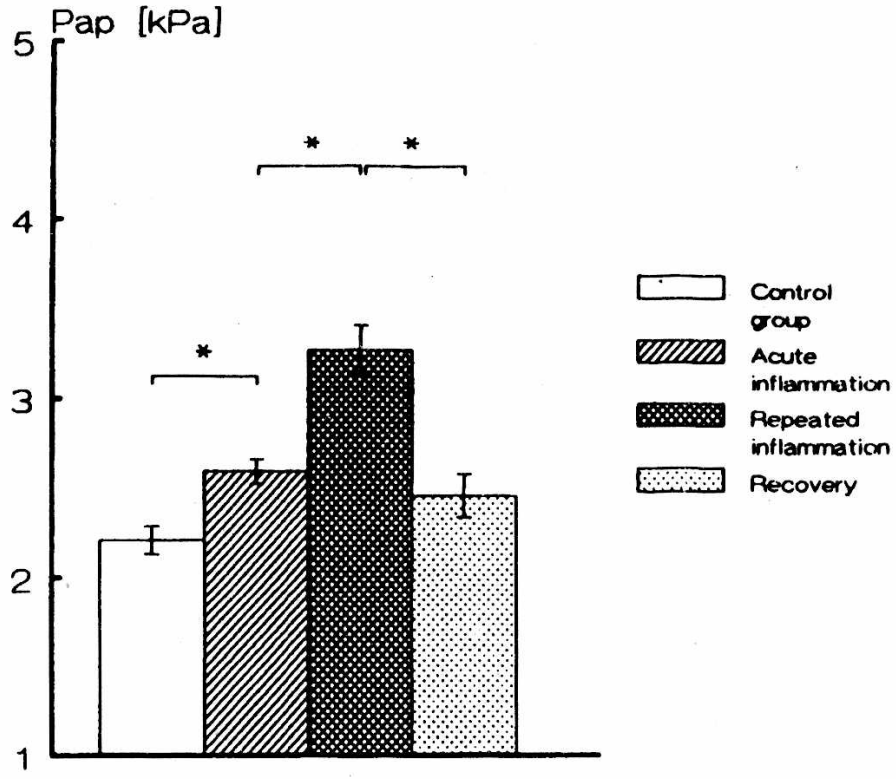

Fig. 3
Pulmonary arterial mean blood pressure (Pap) in rats after acute and repeated lung inflammations and during the recovery after repeated lung inflammations. The lung inflammations were induced by the intratracheal instillation of carrageenan. Controls = group of rats treated with saline. Acute inflammation = group of rats where pulmonary arterial blood pressure was measured 3 days after a single dose of carrageenan. Repeated inflammations = blood pressure was measured 3 days after the sixth lung inflammation. The lung inflammations were repeated at two-week intervals. Recovery = pulmonary arterial blood pressure was measured two weeks after the last, sixth, injection of carrageenan. Measurement was performed in intact rats under urethane anaesthesia. * = $P<0.05$.

macrophages and leukocytes produce substances and enzymes which injure the endothelial layer (Herget and Ježek 1989). The subsequent transvascular protein and fluid leak may impair the communication between the endothelial cells and cells in the vascular media. The morphological reconstruction of the vascular wall may be initiated, in addition to the already discussed mechanisms, also fibrinopeptides which leak in to vascular media from the blood plasma (Laurent 1990). The metabolic activity of endothelial cells is related to the regulation of pulmonary vascular tone. The endothelial damage decreases EDRF (endothelial derived relaxing factor) production (Furchgott *et al.* 1984). This mechanism may also contribute to the pulmonary vasoconstriction in chronic lung disease.

The restriction of the pulmonary vascular bed due to lung inflammation probably does not play the crucial role (Herget and Paleček 1978, Herget *et al.* 1981).

Pulmonary Vascular Reactivity

There are important differences between species and individuals in the reactivity of pulmonary vasculature to the effects of acute and chronic hypoxia. The hyperreactive groups of cattle (Weir *et al.* 1974) and rats (Ou and Smith 1983) were described. We have no information, however, about the similar interindividual variability in man.

The prominent changes in the morphology and regulation of pulmonary vasculature take place at birth. We have shown that adverse stimuli (chronic hypoxia or block of the cyclooxygenase pathway) applied at this period have permanent effects on the reactivity of pulmonary blood vessels (Herget *et al.* 1990, Slavík *et al.* 1989). Pregnant female rats were exposed to hypoxia (FIO_2 = 0.12, one week before the expected delivery) and the offsprings born in hypoxic air were kept for another week in the same environment. They were then raised in atmospheric air and when they were adult, they were exposed to chronic hypoxia again (FIO_2 = 0.1, 2 weeks). During the recovery from this period of hypoxia, the reactivity of pulmonary blood vessels to acute hypoxic challenges was measured in the preparation of isolated, ventilated, blood perfused lungs. The rats born under hypoxic conditions exhibited much greater perfusion pressure increases to mild degrees of ventilation hypoxia than the group of rats born in normoxia (Fig. 4). Similar permanent changes in pulmonary vasoreactivity were also found in the group of rats whose mothers were treated by repeated doses of indomethacine during the pregnancy (Slavík 1989).

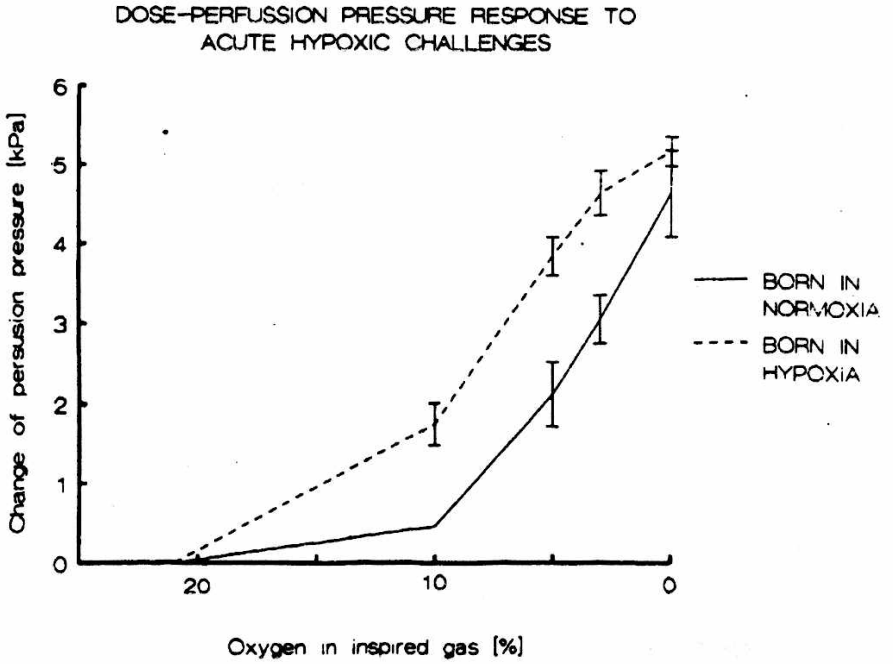

Fig. 4

The dose response of pulmonary arterial pressure to acute lung hypoxic challenges (FIO_2 = 0.1, 0.05, 0.03 and 0 O_2 + 0.05 CO_2 balanced with N_2) in the control group of rats and group of rats born in a isobaric hypoxic chamber (FIO_2 = 0.12). Before the measurement, both groups of rats were exposed for two weeks to isobaric hypoxia (FIO_2 = 0.1) and measured after two weeks of recovery in air. The experiment was performed in isolated, constant flow, blood perfused lungs.

The increased responses of pulmonary vessels to agonists were found during the recovery from different kinds of experimental lung injuries (Perkelt *et al.* 1981, Hill *et al.* 1984, Hilliker and Roth 1985).

What are the mechanisms of this increase of pulmonary vascular reactivity during the recovery from lung damage? The first possible explanation is the presence of hypertrophied smooth musculature in peripheral, intraalveolar vessels. The site of vasoconstriction shifts to the vessels of smaller diameter and therefore the comparable stimulus produces a greater increase of resistance to blood flow (Folkow *et al.* 1971). The other important factor is the metabolic state of structures in the pulmonary vascular wall. It is altered during the recovery from pulmonary vascular injury and lung inflammation. The biochemical changes in the lung vessels persist even after symptoms of lung injury have completely disappeared (Minty *et al.* 1978). The reaction of pulmonary vascular smooth muscles to different stimuli including hypoxia is influenced by basal vascular tone (Barer *et al.* 1976, Hyman and Kadowitz 1986, McMurtry 1982). Many non-specific factors may influence pulmonary vascular reactivity by increasing the basal tone of pulmonary vascular smooth muscle. There is no direct experimental data, however, concerning the pulmonary vascular tone in patients with chronic lung disease.

Pattern of Development of Chronic Lung Disease and Pulmonary Hypertension

Most of the changes induced by pulmonary vascular injury are reversible, but the reconvalescence takes a long time. The typical development of chronic lung disease associated with pulmonary hypertension is intermittent in character (Filley *et al.* 1968). The acute attacks of lung inflammation, and often of respiratory insufficiency, are alternated by recovery periods. During recovery, the pulmonary vascular reactivity is influenced by the effects of previous episodes of acute lung inflammation and also by other factors in the patient's history. The recovery of the morphological reconstruction of the pulmonary vascular wall is very slow. Therefore, each new acute exacerbation of the lung disease interacts with altered and probably hyperreactive pulmonary vascular bed.

Conclusions

Pulmonary hypertension in chronic lung disease is the result of damage of the pulmonary vascular wall by chronic hypoxia, inflammation or mechanical stress. The results of vascular injury are due to vascular smooth muscle remodelling, a decrease of vascular compliance, vasoconstriction and increase of vascular reactivity to agonists. These are direct causes of the increase of lung vascular resistance to blood flow and pulmonary hypertension. The important factor is the intermittence of the development of lung disease. Furthermore, other different factors in the patient's history may have permanent effects on pulmonary vasculature and can be related to pulmonary hypertension and its gravity in patients with lung disease.

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Reprints requests:
Prof. dr. J. Herget, Research Institute for Child Development, 2nd Medical School, Charles University, CS–150 06 Prague 5, V úvalu 84.