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Pulmonary Venous Changes in Chronic Hypoxia

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Summary. Lung tissue from 14 normal residents of high altitude regions, 10 patients with chronic bronchitis and emphysema, and 1 patient with Pickwickian syndrome was studied with regard to the occurrence of pulmonary vascular changes. In addition to the well-known pulmonary arterial alterations, lesions in small pulmonary veins were found in the great majority of the cases. These changes, consisting of medial hypertrophy and arterialization and of bundles of smooth muscle cells within the venous intima, have not been described before in man. These findings suggest that alveolar hypoxia acts not only on small pulmonary arteries and arterioles but also on veins of small caliber, probably by inducing venoconstriction.

Key words: Pulmonary venous changes – Chronic hypoxia – High altitude – Intimal smooth muscle cells – Venoconstriction.

Introduction

Alveolar hypoxia acts as a potent vasoconstrictor on pulmonary arteries. In this respect it is irrelevant whether the hypoxia is caused by the environment, such as low barometric pressures at high altitude, or as a result of chronic obstructive lung disease or diseases of the thoracic cage. Eventually chronic hypoxia may cause elevation of pulmonary arterial pressure and right ventricular hypertrophy.

The accompanying changes in the pulmonary arteries are fairly characteristic for hypoxic pulmonary hypertension (Hicken et al., 1965; Wagenvoort and Wagenvoort, 1973) but little attention has been paid to the pulmonary veins under these circumstances. Our observation that alterations in pulmonary veins and venules occur regularly in individuals with chronic alveolar hypoxia, in residents of high altitude areas, as well as in patients with chronic bronchitis and emphysema, has been the incentive for the present study.

Material and Methods

For this study we used blocks of lung tissue from 14 individuals who had lived at high altitude regions in various parts of the world. Of them, 5 were residents of Leadville, Colorado (altitude: 3,300 m). The others were inhabitants from the Andean mountains, 6 from Peru and 3 from Bolivia (altitude: 4,000–4,800 m). The age of these individuals varied from 16 to 60 years with an average of 37 years. Most of them died from accidents and at autopsy gross pathology of lungs or heart was absent except for the regular occurrence of moderate degrees of right ventricular hypertrophy.

Moreover, we used lungs from 10 patients who died as a result of chronic bronchitis and emphysema with right ventricular hypertrophy. The average age of this group was 55 years. Finally, the lungs of 1 37-year-old male patient with Pickwickian syndrome was studied.

Histologic sections of the paraffin-embedded blocks of lung tissue were stained with hematoxylin and eosin, Lawson's elastic-van Gieson stain, and Perl's iron stain. Since in a previous study (Wagenvoort and Wagenvoort, 1973) the changes in the pulmonary arteries and arterioles were investigated in part of this material, the current study paid special attention to the pulmonary veins and venules. In the available material from high altitude residents all pulmonary veins and venules were screened, in the patients with chronic bronchitis those in four blocks of lung tissue in each individual. In four cases serial sections were studied.

As controls we used histologic sections of lung tissue, prepared in the same way, from 20 individuals of the same age group, not suffering from heart or lung disease and in whom the lungs were judged normal.

No attempt was made for exact morphometrical assessment of medial and intimal thickness of the veins, since in the adult the collapsed state of these vessels makes such measurements unreliable (Wagenvoort, 1970). Postmortem injection of the vessels may restore the circular cross section but at the same time tends to produce an irregular and unpredictable distension which makes assessment of diameter and wall thickness even more hazardous. We preferred, therefore, to use a semiquantitative assessment, taking care that the sections of hypoxia cases and of controls were mixed so that their nature was unknown to the investigator.

Results

The muscular pulmonary arteries possessed a media which was either normal or mildly hypertrophied, but the number of arterioles of an external diameter smaller than 70 μ, (which were muscularized), thus showing a distinct muscular media, was significantly increased. Moreover, in all cases of chronic bronchitis and in all but two of the high altitude cases there was a characteristic development of longitudinal smooth muscle fibers within the intima of the small arteries and arterioles.

The pulmonary veins exhibited medial hypertrophy and arterialization. The term arterialization implies that the elastic configuration of the veins is changed in such a way that, at least over part of its circumference, a distinct internal and external elastic lamina is formed instead of the haphazard arrangement of elastic fibers in the normal venous wall (Wagenvoort, 1970). In this respect the vein may resemble a pulmonary artery.

Distinction between pulmonary arteries and veins presented problems only when their caliber decreased below approx. 100 μ, when the association of the vessels with bronchioli and interlobular fibrous septa, respectively, became lost. Even then recognition was often possible, although sometimes it was necessary to trace the vessels in serial sections to establish their contact with larger

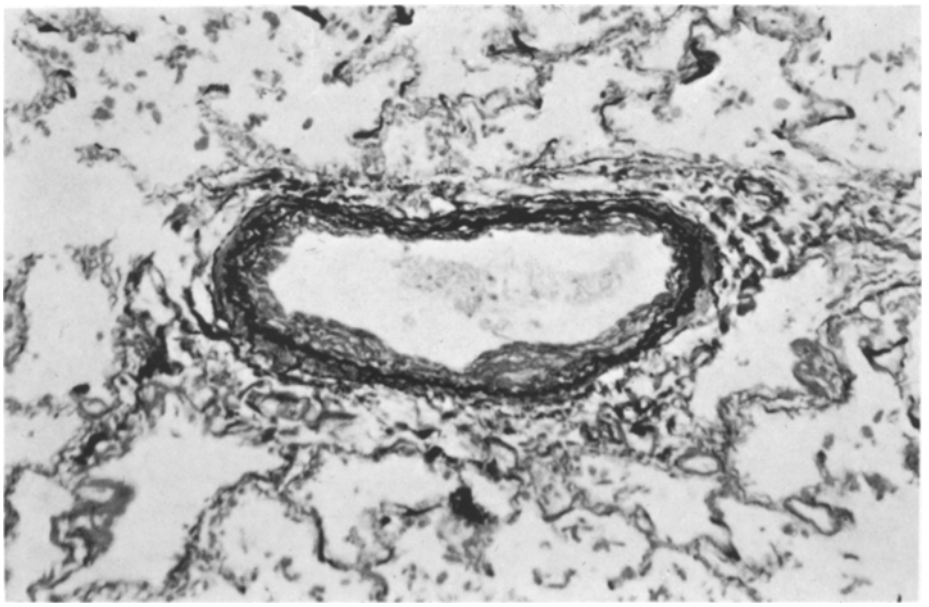

Fig. 1. Small pulmonary vein in a boy aged 16 years, a normal resident of Andes at altitude of 4,500 m. There is distinct medial hypertrophy and arterialization of venous media and intimal fibrosis (Elastic-van Gieson, × 140)

and more distinctive vessels. If identification as arteriole or venule was not possible, vessels were disregarded.

Medial hypertrophy and arterialization of small pulmonary veins (Fig. 1), usually of a caliber of less than 150 μ, were found in the majority of the patients, while they were absent in the controls. In only three of the high altitude residents were the veins judged normal in this respect. These changes were pronounced in five of the high altitude residents, in four of the bronchitis patients, and in the patient with Pickwickian syndrome. In the remaining patients these lesions were mild to moderate. In all instances thickening of the media appeared to be due mainly to increase of smooth muscle cells in this layer.

Intimal fibrosis of pulmonary veins was found in all cases, but this is a feature which is also regularly observed as an age change. It was, however, severe and distinctly more marked than in the controls in seven of the high altitude residents, in five of the bronchitis patients, and in the one patient with Pickwickian syndrome.

Moreover, the development of intimal smooth muscle bundles arranged in a longitudinal direction was noted in small pulmonary veins, in the same way as observed in the arteries and arterioles. Sometimes these muscle bundles formed small eccentric or crescent-shaped patches, but in some cases the venous cross section contained concentric layers of these muscle cells (Fig. 2). Isolated smooth muscle cells within patches of intimal fibrosis also occurred regularly. In serial sections it appeared that these bundles usually extended over considerable dis-

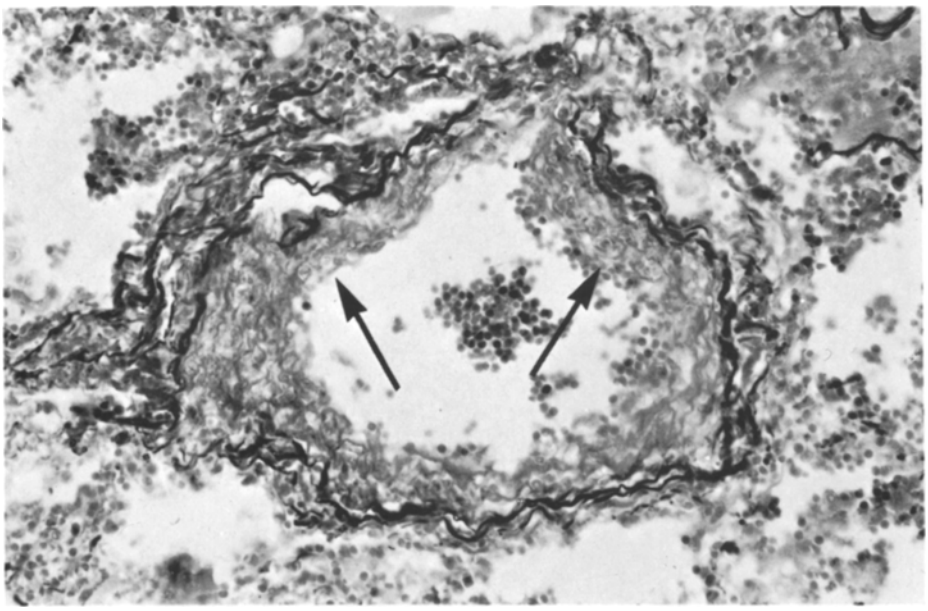

Fig. 2. Small pulmonary vein in a man aged 25 years, a normal resident of Andes at altitude of 4,500 m. Marked circumferential thickening of intima is composed largely of bundles of smooth muscle cells (*arrows*) (Elastic-van Gieson, ×230)

tances. Pulmonary veins containing longitudinal smooth muscle were observed in six high altitude residents, in seven of the bronchitis patients, and in the case of Pickwickian syndrome.

Discussion

In chronic hypoxia constriction of lung vessels is the most important factor in elevating the resistance in the pulmonary circulation and the available evidence suggests that vasoconstriction takes place at a precapillary level (Bergofsky, 1974). Morphologic data are also consistent with constriction of small muscular pulmonary arteries and arterioles since these vessels in particular show medial hypertrophy and muscularization, while they often contain longitudinal smooth muscle bundles in the intima, usually in a reduplication of the internal elastic lamina (Hicken et al., 1965; Hasleton et al., 1968).

Additional constriction of postcapillary vessels in states of hypoxia has been suggested by Kuida et al. (1963) on the basis of hemodynamic studies in cattle with brisket disease. On the other hand, it was shown that while the pulmonary arterial pressure rises gradually with increasing alveolar hypoxia in human individuals, the wedge pressure remains unaffected (Westcott et al., 1951; Estes et al., 1957). This has been taken as an indication that there is no response of pulmonary veins to hypoxia.

Naeye (1965) described increase of smooth muscle in the walls of pulmonary veins in cattle raised at high altitude and postulated that venous constriction might occur in addition to arterial constriction in these instances. So far in the human no changes in pulmonary veins have been reported to our knowledge.

The results of the present study indicate that chronic hypoxia, whether due to low barometric pressures at high altitude, to chronic bronchitis, or to Pickwickian syndrome, does not only affect the small pulmonary arteries and arterioles but may also produce changes in pulmonary veins, particularly in those of small caliber, even though these alterations are less consistently present and less pronounced than in small arteries. Medial hypertrophy and arterialization with increase of vascular smooth muscle tissue may well result from a prolonged increase of tone in these veins. In the individuals reported in this study, there was no indication of left cardiac failure or of valvular disease, which could account for these pulmonary venous lesions. The presence of longitudinal smooth muscle bundles in the intima, well known in small pulmonary arteries and arterioles of patients with hypoxic pulmonary hypertension, has not been described in pulmonary veins. As in the arteries and arterioles, their significance is unknown. It is striking, however, that they were predominantly found in veins of small caliber.

Although vasoconstriction of pulmonary arteries in chronic hypoxia is well established, the mechanism by which this constriction is brought about is unknown (Fishman, 1976). Histamine derived from perivascular mast cells has been implicated in its production, while a direct effect of the alveolar oxygen tension on the walls of small arteries has also been suggested. Either of these mechanisms could apply to the smallest pulmonary veins and venules, even though the anatomical relation of the arterioles to the alveolar air spaces is somewhat closer than that of the venules.

Our findings suggest that alveolar hypoxia does influence the small pulmonary veins, probably in the sense of constriction with vascular changes as a long-term result. Since these alterations are less consistent and milder than in the arteries, they may fail to produce significant changes in the pulmonary arterial wedge pressure of individuals thus affected.

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