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PATHOGENESIS OF HIGH-ALTITUDE PULMONARY EDEMA[1]

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ABSTRACT. Madison strain Sprague-Dawley rats were exposed to low barometric pressures of 294 and 236 torr, or 8.5% oxygen at normal pressure for 8-10 hours. This resulted in an increase of pulmonary artery or right ventricular systolic pressure from 30.5 to 49 torr. Ultrastructural studies of the lung showed evidence of stress failure of pulmonary capillaries including disruption of the capillary endothelial layer, alveolar epithelial layer, or all layer of the wall, red blood cells (RBCs) and edema fluid in the alveolar wall interstitium, proteinaceous fluid and RBCs in the alveolar spaces, and fluid-filled protrusions of the endothelium into the capillary lumen. These appearances are consistent with the ultrastructural changes we have previously described in rabbit lung when the capillaries are exposed to high transmural pressures, strongly suggesting that the pathogenesis of HAPE is stress failure of pulmonary capillaries.

Key Words: stress failure of pulmonary capillaries, pulmonary hypertension, high-permeability edema.

RESUMEN. Ratas Sprague-Dawley de la especie Madison fueron expuestas a baja presión barométrica de 294 y 236 torr, o 8.5% de oxígeno a presión normal por 8-10 horas. Esto resultó en un aumento de la presión de la arteria pulmonar y de la presión sistólica ventricular derecha de 30.5 a 49 torr. Los estudios ultraestructurales del pulmón mostraron evidencia de una insuficiencia por stress de los capilares pulmonares que incluyen una interrupción de la capa endotelial capilar, la capa epitelial alveolar, o todas las capas de la pared, eritrocitos y edema en el intersticio de la pared alveolar, fluido proteináceo y eritrocitos en los espacios alveolares, y protrusiones llenas de líquido del endotelio en la luz de los capilares. Estas características son consistentes con los cambios estructurales que previamente hemos descrito en pulmones de conejos cuando los capilares son expuestos a altas presiones transmurales, lo que fuertemente sugiere que la patogénesis de HAPE es una insuficiencia por stress de los capilares pulmonares.

Palabras Claves: Insuficiencia por stress, Capilares pulmonares, Hipertensión pulmonar, Edema.

INTRODUCTION

The pathogenesis of high-altitude pulmonary edema (HAPE) remains obscure. We have recently proposed that HAPE is due to damage to the walls of pulmonary capillaries as a result of very high wall stresses caused by increased capillary transmural pressures (West et al., 1991; West and Mathieu-Costello, 1992). These high capillary pressures are the result of uneven hypoxic pulmonary vasoconstriction as originally proposed by Hultgren (1969). Extensive studies in our laboratory have shown that raising the capillary transmural pressure in rabbit lung causes ultrastructural damage to the capillary walls including disruptions of the capillary endothelial layer, alveolar epithelial layer, and sometimes all layers of the wall (West et al., 1991; Tsukimoto et al., 1991; Costello et al., 1992; Fu et al., 1992; Elliot et al., 1992). The result is a high-permeability of form of edema (Tsukimoto et al., 1994).

In this paper we report studies on Madison strain Sprague-Dawley rats exposed to simulated high altitude. These animals have previously been shown to develop high pulmonary artery pressures and pulmonary edema under these conditions. Ultrastructural studies of the lung showed the typical changes of stress failure of

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pulmonary capillaries, and we proposed that this is the mechanism of HAPE.

METHODS

Twenty-nine Madison strain Sprague-Dawley rats, body weigth 290-327 g, were used. Thirteen animals were exposed to a pressure of 294 torr in a low pressure chamber for 3 to 12.5 hours. Four rats were exposed to a pressure of 236 torr for up to 8 hours. Four animals breathed 8.5% oxygen for up to 8 hours, and eight animals were studied as controls. The protocols were approved by the Animal Subjects Committees of UCSD and Dartmouth Medical School.

Measurements of pulmonary artery and right ventricular pressures were carried out via implanted catheters inserted 48 hours prior to the experiment (Sardella and Ou, 1993). Pressure measurements were done immediately after taking the rats out the low pressure chamber and transferring them to a Plexiglass box where they breathed 8.5% oxygen if they had been exposed to a pressure of 294 torr, 6.6% oxygen if they had been exposed to 236 torr, or ambient room air if they were controls.

The lungs were prepared for electron microscopy by perfusion fixation with buffered glutaraldehyde as described previously (Tsukimoto et al., 1991).

RESULTS

Pulmonary artery or rigth ventricular pressures.

In all rats exposed to a low Po_2, increases in pulmonary artery or rigth ventricular pressure were seen. The mean pulmonary arterial systolic pressure in the control animals breathing air was 30.5± 0.5 (SE) torr (n=4). The animals exposed to a pressure of 294 torr, 236 torr or 8.5% oxygen had a mean pulmonary arterial or rigth ventricular systolic pressure of 49 ± 2 torr (n=15).

Macroscopic appearance of lung and light microscopy.

Blood-stained frothy fluid was seen in the trachea of 2 animals exposed to a pressure of 294 torr, and in 1 animal exposed to a pressure of 236 torr. In over half the animals exposed to hypoxia, the lungs showed various degrees of macroscopic abnormalities ranging from irregular sparse dark areas to large hemorrhagic regions.

Ultrastructural appearances of lung parenchyma.

Red blood cells were seen in the alveolar spaces as well as electron-dense granular material which represents edema fluid with a high protein concentration. There was also edema of the interstitium of the alveolar wall, fluid-filled protrusions of the endothelium into the capillary lumen, and swelling of alveolar epithelial cells. There was also clear evidence of disruptions of the capillary endothelial and alveolar epithelial layers consistent with stress failure of pulmonary capillaries (Tsukimoto et al., 1991). Red cells were seen in the interstitium of the alveolar wall indicating disruption of the capillary endothelial layer in the proximity. Figure 1 shows complete rupture of the blood-gas barrier with a red cell passing from the capillary lumen into the alveolar space.

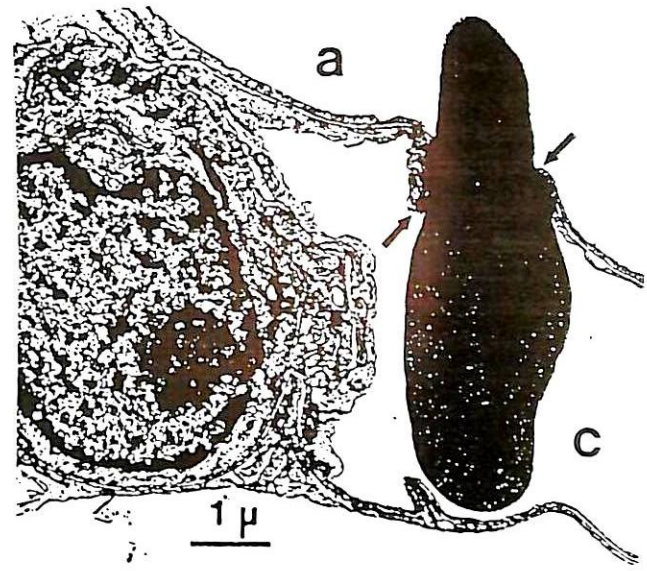

Figure 1. Electron micrograph of lung parenchyma in Madison rat exposed to 294 torr barometric pressure for 4 hours. Note complete rupture of the blood-gas barrier (arrows) with a red blood cell passing into the alveolar space (a); c, capillary. From West et al., 1995)

DISCUSSION

The hypothesis that HAPE is caused by stress failure of pulmonary capillaries fits with many features of the disease. One is the marked correlation between HAPE and pulmonary hypertension. For example, direct pressure measurements in patients with HAPE show high values (Hultgren et al., 1964). Also, patients who develop HAPE tend to have an unusually high degree of hypoxic pulmonary vasoconstriction (Hultgre et al., 1971). Finally, reducing the pulmonary arterial pressure, for example by giving the calcium channel blocker nifedipine usually causes rapid dissappearance of the edema (Oelz et al., 1989), and nifedipine is also effective in preventing HAPE in a high risk group (Bärtsch et al., 1991).

It is also known that the edema of HAPE is of the high-permeability type. Schoene et al. (1988) and Hackett et al. (1986) obtained samples of alveolar fluid by bronchoalveolar lavage in patients with HAPE and reported that fluid was of the high-permeability type with a large concentration of high molecular weight proteins and many cells. Increased concentrations of leukotriene B_4 and complement fragment C5a were also found (see below).

The combination of a hydrostatic pressure basis for HAPE and abnormalities of the capillary walls which are required for the high-permeability edema, can be explained on the basis of stress failure of pulmonary capillaries. Studies from our laboratories have shown that raising the pressure in capillaries of rabbit lung causes ultrastructural changes in the capillary disruption of the capillary endothelial layer, alveolar epithelial layer and sometimes all layer of the wall (West et al., 1991; Tsukimoto et al., 1991). We suggested that this might be the pathogenic basis of HAPE (West et al., 1991) but there were no electron micrograph studies of the lung in that disease, and it is difficult to find animal models. Evidence of ultrastructural changes similar to those reported here was found in lung of rats exposed to acute decompression in a hypobaric chamber (Mooi et al., 1978), but the mechanism was not recognized. In this study, we used Madison strain Sprague-Dawley rats because they do show a strong pulmonary pressor response to hypoxia, and some animals develop pulmonary edema (Colice et al., 1992).

The mechanism of pulmonary hypertension during acute exposure to high altitude is known to be hypoxic pulmonary vasoconstriction. Since this chiefly occurs in small pulmonary arteries (Kato and Staub, 1966), it is not immediately clear why some pulmonary capillaries would be exposed to the high pressure. The explanation is presumably that given by Hultgren (1969) who suggested that the vasoconstriction is uneven with the result that some capillaries are not protected from the increased pressure in the pulmonary arteries. This hypothesis is supported by the very patchy nature of the edema in HAPE (Hultgren et al., 1964; Vock et al., 1991) and the increased dispersion of transit times in hypoxic animal lungs (Dawson et al., 1983).

It has been suggested that HAPE may have an inflammatory basis because of the presence of inflammatory markers including leukotriene B_4, other lipoxygenase products of arachidonic metabolism, and C5a complement fragment in the lavage fluid (Schoene et al., 1988). At first sight these findings seem to argue for some other mechanism than stress failure of pulmonary capillaries. However an important feature of the ultrastructural changes in stress failure is that the basement membrane of capillary endothelial cells are frequently exposed (Tsukimoto et al., 1991). The exposed basement membrane is electrically charged and highly reactive, and can be expected to activate leukocytes and platelets. Indeed in bronchoalveolar lavage studies of our rabbit preparations, leukotriene B_4 is seen in the lavage fluid (Tsukimoto et al., 1994). Platelet activation will result in the formation of small thrombi which are a feature of the pathology of HAPE (Arias-Stella and Kruger, 1963).

If HAPE is caused by stress failure of pulmonary capillaries, the main therapeutic objective is to reduce the pulmonary artery pressure. Since the pressure is high because of hypoxic pulmonary vasoconstriction, the best way to reduce it is by rapid descent or by giving oxygen if this is available. Calcium channel blockers such as nifedipine are also effective because they rapidly reduce the pulmonary arterial pressure (Oelz et al., 1989).

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