higher values seen at 24 h provide evidence of activated or damaged vascular endothelium.

In combination, these data suggest that heavy exercise at altitude alters lung barrier permeability with alveolar-capillary injury, resulting in leakage of RBC and infiltration of inflammatory cells into the alveolar space.

MCAF/MCP-1 Protein Expression in a Rat Model for Pulmonary Hypertension Induced by Monocrotaline*

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Monocrotaline (MCT) administration is known to chronically cause medial thickening in the pulmonary arteriole as well as fibrotic changes in alveolar septum. However, the mechanisms of cell-mediated injury induced by MCT are rarely investigated. The expression of monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 (MCAF/MCP-1), a potent chemoattractant and activator of monocytes, has been reported to be increased in pulmonary fibrosis. We, therefore, investigated the localization of MCAF/MCP-1 protein expression and the role of MCAF/MCP-1 in the pathogenesis of MCT-induced pulmonary hypertension and pulmonary fibrosis in rats.

Eighty adult male Sprague-Dawley rats were subcutaneously injected with 60 mg/kg of MCT, followed by killing at 2, 6, and 48 h, and 7, 14, 21, and 28 days after administration. Hematoxylin-eosin staining and immunohistochemical staining by MCAF/MCP-1 polyclonal antibodies, as well as a specific antibodies against macrophage were successively performed. MCAF/MCP-1 contents in bronchoalveolar lavage fluid (BALF) and sera were also measured by a sandwich ELISA.

MCAF/MCP-1 protein expression that was mainly detected in alveolar macrophages reached enzyme-linked immunosorbent maximal levels 21, whereas the levels of MCAF/MCP-1 protein in sera and BALF were the highest on day 7 (202±53 (untreated)–1254±652 (7th day)/pg/ml) and day 14 (0±0–2365±1797 pg/ml), respectively. The degree of MCAF/MCP-1 protein expression correlated with the progression of pulmonary hypertension and right ventricular/left ventricular plus septum weight ratio.

These results suggest that MCAF/MCP-1 may be involved in the development of MCT-induced pulmonary hypertension.

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Pulmonary Endothelial Dysfunction Following Chronic Left Lung Autotransplantation*

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Left lung autotransplantation (LLA) results in significant abnormalities in pulmonary vasoregulation and a chronic increase in pulmonary vascular resistance. The goals of the present in vitro study were the following: (1) to assess the effects of LLA on the pulmonary vasorelaxant response to the sympathetic β-adrenoceptor agonist, isoproterenol; and (2) to identify the locus of dysfunction in the signal transduction pathway responsible for the attenuated pulmonary vasorelaxant response to isoproterenol post-LLA.

Size and position-matched pulmonary arterial rings were isolated from the right (control) and left (LLA) lungs of 12 dogs 1 to 5 months post-LLA. The rings were suspended for isometric tension recording and precontracted. With the endothelium intact, the maximal pulmonary vasorelaxant response to isoproterenol was reduced (p<0.02) to 57±9% in LLA rings compared to 87±3% in control rings. The concentration-effect curve for choloro toxin (Gs protein activator) was shifted to the right in LLA rings compared to control without altering the maximal response, and the IC50 (log mg/L) was increased (p<0.01) in LLA rings (-1.50±0.09) compared to control (-1.88±0.11). In contrast, the vasorelaxant responses to forskolin (adenylate cyclase activator) and dibutyryl cyclic adenosine monophosphate (cAMP) were similar in intact control and LLA rings. In endothelium denuded rings, the maximal vasorelaxant responses to isoproterenol were reduced (p<0.01) to approximately 25% in both control and LLA rings. In denuded rings, choloro toxin, forskolin, and dibutyryl cAMP caused 100% vasorelaxation in control and LLA rings, and the IC50 values for these agonists were similar in control and LLA rings. Isoproterenol increased (p<0.05) tissue cAMP to the same extent (fivefold) in control and LLA rings with or without endothelium. In contrast, isoproterenol increased (p<0.05) tissue cyclic guanosine monophosphate (cGMP) only in endothelium intact rings. Moreover, the isoproterenol-induced increase in cGMP was reduced (p<0.05) approximately 50% in LLA rings compared to control rings.

These results indicate that isoproterenol-induced pulmonary vasorelaxation involves both an endothelium-dependent and a vascular smooth muscle component. Moreover, the attenuated vasorelaxant response to isoproterenol post-LLA is due to an endothelial defect involving the cGMP signal transduction pathway.

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