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Heparin Effect On Pulmonary Vascular Remodeling

Pulmoner Vasküler Yeniden Biçimlenme Üzerine Heparin Etkisi

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Pulmonary vascular remodeling remains a big problem for various diseases seen in infancy. In animal models of pulmonary hypertension, administration of heparin has been shown to attenuate pulmonary vascular remodeling (1). Heparin-like molecules are thought to be therapeutically beneficial in pulmonary hypertension (2). Although it is used for its anticoagulant effect during ECMO, the anti-pulmonary vascular remodeling effect of heparin may also play a role for the recovery of ECMO patients. The anti-remodeling effect of heparin is not related to its anticoagulant properties (1).

Pulmonary vascular remodeling in pulmonary hypertension is a complex, multi factorial process that occurs with many of the physical and chemical stimuli, including shear stress, stretch and hypoxia. Structural alterations extend to the periphery of the vascular tree and includes thickening of all three layers of the blood vessel wall (adventitia, media, intima) down to the precapillary vessels. Muscularisation involves both hypertrophy and hyperplasia of smooth muscle cells, as well as increased deposition of extra cellular matrix components. Additionally, proliferation, differentiation, and migration of smooth muscle precursor cells such as pericytes and fibroblasts may contribute to this phenomenon.

Exposure of most animals to low levels of oxygen results in alveolar hypoxia and reliably causes chronic pulmonary hypertension and morphological alterations of the precapillary pulmonary vessels. Chronic hypoxic exposure of animals has been used for decades to induce pulmonary vascular remodeling. Piglets exposed to 3 days of hypoxia developed significant pulmonary hypertension and increased pulmonary vessel wall thickness with increased concentration of myofilaments within in the smooth muscle cells whereas further exposure to hypoxia for 14 days did not enhance the increase in pulmonary artery pressure and percentage wall thickness (3).

The proliferation of pericytes (smooth muscle-like cells) found in the distal pulmonary arterial microvasculature is believed to be a component of the vascular remodeling and muscularization seen in pulmonary hypertensive states. Mural vascular changes and narrowing of the vascular lumen increase the resistance to blood flow (2). In animal models of pulmonary hypertension, various drugs have been shown to attenuate pulmonary vascular remodeling (Table I) (1).

Exogenous heparin markedly inhibits smooth muscle cell proliferation in vivo after arterial injury and pulmonary vascular remodeling caused by hypoxia (2). Heparin inhibits the development of pulmonary hypertension and vascular remodeling associated with prolonged hypoxia; however, the mechanism is not completely understood. Continuous heparin infusion for hypoxic exposure has been shown to attenuate increases in pulmonary arterial pressure, right ventricular hypertrophy, and pulmonary vascular remodeling in mice. Experimental studies have shown that heparin infusion decreases the severity of hypoxia-induced vascular changes, presumably by decreasing smooth muscle hyperplasia, by an effect related to that of the sodium-hydrogen antiporter (4). Heparin inhibits the increased Na^+/H^+ exchange and the intracellular alcalinization (mediated by increased Na^+/H^+ exchange) essential to proliferation (2). Heparin induces production of p21, a potent inhibitor of cyclin-dependent kinases, thereby potentially identifying a fundamental mechanism by which heparin inhibits proliferation in smooth muscle-like cells. Heparin maintains lung pericytes in the G_0/G_1 growth phase (2). In the G_1 phase, p21 is a potent inhibitor of cyclin dependent protein kinases that are the principle regulatory proteins of cell cycle (2). Other possible mechanisms are; inhibition of the action of 5-HT and/or activation of MAPK kinase-1 (1). On the other hand, gycosaminoglycans such as heparin sulphate that are structurally related to heparin are part of the extra cellular matrix and known to regulate cell growth. Heparin at low concentration (0.03, 0.3-1.0 micrograms/ml) stimulates proliferation of normal human lung fibroblasts in culture whereas a higher concentration (100 micrograms/ml) has an inhibitory effect (5).

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Table I: Mechanisms vs. inhibitors of pulmonary vascular remodeling.

Mechanisms of PVR	Inhibitors of PVR
Mechanical Factors (pressure, stress) Hypoxia Mediators *Angiotensin II,* *Endothelin-1,* *5-hydroxytryptamine,* *Growth factors,* *Inflammatory cytokines (IL,TNF)* Tenascin-C Role of endothelium Role of serin elastase Intracellular signaling mechanisms	ACE inhibitors and receptor antagonists Endothelin antagonists and endothelin-converting enzyme inhibitors Nitric oxide Phosphodiesterase inhibitors Prostacyclin Ca^{++} channel antagonists Heparin Drugs effecting intracellular matrix Miscellaneous drugs

PVR: *Pulmonary Vascular Remodeling.*

Monocromaline ➔ Elastase & associated matrix proteinase activity ➔ Tenascin expression ➔ Medial hypertrophy & extension of muscle into distal vessels

Figure 1: Steps of chemically induced pulmonary hypertension (4).

Pulmonary hypertension, vascular changes and endothelial injury are common observations in animal models treated with monocromaline. Rats injected with the toxin monocromaline show rapid progression of structural abnormalities in PAs that result in their demise from right heart failure (4). The mechanism of induction of vascular disease is likely related to the endothelial injury (4). Increased expression of growth factors such as fibroblast growth factor has been implicated in the pathophysiology of monocromaline induced PVD (pulmonary vascular disease) (4) (Figure 1). Also, increased production of glycoprotein tenascin (extra cellular matrix component) was observed with progressive monocromaline induced PVD (4). Tenascin is associated with proteolysis of the matrix and amplifies the cells' response to growth factors (6,7). Other remodeling stimulants such as mechanical stress and serin elastase have also been suggested to increase tenascin (1). Stress unloading (Offloading the pressure by transplanting the hypertensive lung harvested from a rat following injection of monocromoline in to a normal rat) of PAs results in repression of elastase and associated matrix proteinase activity and tenascin expression, leading to apoptosis and resorption of extra cellular matrix and regression of disease (4). On the contrary, as shown by DNA staining and fluorescence-activated cell sorting analysis, heparin does not induce apoptosis in vascular pericytes (2). In contrast to the studies in hypoxic animals, heparin had no beneficial effect on PVR or pulmonary artery pressure in monocrotaline-treated rats (1). The attenuation of hypoxic pulmonary vascular remodeling by heparin is suggested to be NO mediated.

In conclusion, administration of heparin to hypoxic animals of various species has been shown to inhibit PVR (1). Heparin inhibits rat lung vascular pericyt and pulmonary vascular sub-endothelial matrix proliferation (2). Further research with pulmonary autopsies are needed to understand whether heparin acts as an inhibitor of remodeling on hypertensive human lungs in vivo or not.

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