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Circulating microparticles from a rat model of pulmonary arterial hypertension induce endothelial dysfunction

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Année	2009
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Titre du colloque	Archives of Cardiovascular Diseases
Volume	102, Suppl. 1
Auteur	Tual-Chalot, Simon [1], Guibert, Christelle [2], Savineau, Jean-Pierre [3], Andriantsitohaina, Ramaroson [4], Martinez, Maria Carmen [5]
Résumé en anglais	Pulmonary arterial hypertension (PAH) is a rare and severe disease characterized by an increase of pulmonary vascular resistance and right heart failure. Chronic hypoxia induces PAH, which is accompanied by functional (endothelial dysfunction, increased vasoconstriction) and structural (thickening of media) changes in pulmonary arteries. However, the mechanisms of these alterations remain unsolved. Among biological hallmark of this disease, level of circulating microparticles (MPs), small vesicles of plasma membrane released during cell activation and apoptosis, is increased in PAH patients. Although MPs can act as biological vectors of endothelial dysfunction, their role in PAH are not elucidated yet. We studied circulating MP effects on endothelial function during hypoxic PAH. Male Wistar rats were exposed or not to chronic hypoxia (3 weeks, 0.5 atmosphere) and normoxic or hypoxic MPs were isolated from peripheral blood and characterized by flow cytometry. Endothelial cells from rat normoxic aorta or pulmonary arteries were incubated for 24 h with MPs. We studied also effects of in vivo treatment of MPs on vasomotricity, for this, normoxic or hypoxic MPs or vehicle were i.v. injected into rats, and 24 h after, endothelial function were studied. Levels of circulating MPs from hypoxic rats was twice than MPs from normoxic rats (1568 Â± 174 vs 852 Â± 80 MPs/Âµl of plasma). In vitro treatment of endothelial cells with hypoxic MPs reduced NO production both in aortas and pulmonary arteries ; these effects were associated with enhanced phosphorylation of endothelial NO-synthase at their inhibitory site. By contrast, O2- production was increased only in endothelial cells from pulmonary arteries. In vivo injection of normoxic or hypoxic MPs into rats impaired to the same extent the endotheliumdependent relaxation induced by acetylcholine in aorta. Although pulmonary arteries from rat treated either with normoxic or hypoxic MPs displayed reduction of endothelium-dependent relaxation to carbachol compared to control, the deleterious effect of hypoxic MPs was greater than normoxic MPs. These data provide evidence that hypoxic circulating MPs induce in vitro and in vivo endothelial dysfunction by increasing oxydative stress and by decreasing NO production.
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