

Aging endothelium in atherothrombotic and diabetic angiopathies

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Endothelium constitutes the first line of vascular defence against atherothrombotic macroangiopathies (mainly cardiac and cerebral atherosclerosis) and diabetic microangiopathies (mainly retino- and nephro-pathies). The principal reason for endothelial dysfunction in these diseases is premature senescence of endothelium, usually subsequent to neglecting of “endotheliophilic lifestyle” (*Mc Carthy MF Med Hypothes 2004,63,719*).

Prostacyclin (PGI₂) and nitric oxide ((EDRF)NO) are two main defensive substances produced by the endothelium. Both are highly unstable, and therefore their continuous generation is the only way to ensure the safety to vascular system. PGI₂ and NO execute their actions *via* cyclic nucleotides: c-AMP and c-GMP, respectively, thus preventing blood elements (platelets, monocytes, granulocytes) from invasion on vascular wall. In that way endothelial secretagogues prevent all forms of vasculitis. i.e. formation of atheromatic plaque, plaque rupture, parietal thrombosis, microangiopathies. Consequently, continuous endothelial generation of PGI₂ and NO (as well as other protectors, e.g. t-PA, bradykinin, CO, biliverdin, SOD) protects from myocardial infarction, cerebral stroke, amputation of extremities, blindness or kidney dialysis.

We demonstrated that endothelial cells release PGI₂ and EDRF(NO) in a coupled manner (*Gryglewski RJ et al Br J Pharmacol 1986,87,685*), and that EDRF(NO) is selectively destroyed by superoxide anions (*Gryglewski et al Nature 1986,320.454*). Later, it was shown that this last reaction leads to formation of extremely toxic peroxynitrite (ONOO⁻). It inactivates PGI₂ synthase (*Schmid P et al J Biol Chem 2003,278,12813; Cirino G et al TiPS 2003,24.91*). Many of us consider peroxynitrite as a major culprit in premature ageing of endothelium. Then the endothelial dysfunction triggers arterial hypertension, atherothrombotic and diabetic angiopathies, promotes general cell senescence, tissue degeneration development of pro-cancerogenic *milieu* (*d'Alessio P Exper Gerontol 2004,39,165*). There are known several groups of cardio-vascular drugs which apart from their basic mechanism of action, in addition they correct endothelial function. For instance, ACE-Inhibitors are known as antihypertensive drugs, while Statins are used as hypocholesterolemic agents, however, both groups of drugs exert also pleiotropic endothelial action, i.e. they correct or prevent endothelial dysfunction (*Gryglewski RJ et al Ann NY Acad Sci 2001,947,229; Thromb Res 2003,110, 323*). These drugs are of special value to elderly, however, also given to youngsters with endothelial dysfunction resulted from nicotine use these drugs along with cessation of tobacco smoking may help them to recuperate from endothelial dysfunction (*Casey RG et al J Surg Res 2004,227-33*).

