

Chronic Smoking and Vascular Disease: What Can we Hope for the Future?

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Chronic smoking is associated with a marked incidence of cardiovascular morbidity and mortality. Although the impact of cigarette smoke on vascular disease is probably predetermined by patients' phenotype status, smoking-induced vascular disease is strongly believed to be secondary to oxidative stress [1]. It has been demonstrated that chronic smoking is associated with high level of plasma cholesterol, vasoreactivity dysregulation, platelet aggregation disorder, and atherosclerotic plaque formation. Although the precise mechanism by which chronic smoking induces vascular disease is not completely understood, growing evidence shows that impairment of endothelial morphology and function plays a crucial role in pathogenesis of vascular disease. Oxidants, delivered by cigarette and deposited in pulmonary vessels through the systemic vasculature, activate superoxide producing enzymes within the vascular wall via oxidative stress, and might be the cause of endothelial dysfunction and dysregulation of endothelial barrier [2].

We already know that normal endothelial function and structure is a key player in the maintenance of vascular health. In healthy vasculature, endothelium forms the inner lining of blood vessels and serves as a physical barrier. Though for a long time regarded as a passive semi-permeable barrier that controls the passage of plasma, cells, and small molecules from the circulation into the tissue, the endothelium is known now as a secreting organ by producing abundant mediators to control homeostasis, inflammation, cell proliferation, and vascular tone. Therefore, endothelial dysfunction is defined as an imbalance between relaxing and contracting factors, between anti- and pro-coagulant substances, or between growth-inhibiting and growth-promoting mediators. It has been demonstrated that endothelial dysfunction is one of the earliest manifestations of vascular disease and atherosclerosis [3].

However, experimental and clinical evidence show that acute or chronic smoking could morphologically and functionally harm the endothelium. Animals exposed to cigarette smoke have severe structural alteration and impairment of vasodilator production (prostacyclin and nitric oxide [NO]) [4]. Our recent publication shows that pulmonary endothelial dysfunction has been present even in healthy smokers [5]. It becomes clear that in chronic smoking, increase of vascular oxidative stress potentially leads to dysregulation of endothelial barrier and function, increasing the risk of vascular disease.

Over recent decades, increasingly studies try to elucidate the mechanism by which the potential signaling pathways are involved in the pathogenesis of smoking-induced vascular disease and atherosclerosis. The most important is the role of endothelial nitric oxide synthase (eNO)/NO signaling pathway. This pathway acts as a key messenger in the cardiovascular system in humans. We have learned that impairment of NO bioavailability and eNOS activity may play a crucial role in the formation of atherosclerotic plaques in chronic smoking. Studies from animal models and clinical trials have demonstrated that both acute and chronic smoking could impair NO production by altering eNOS activity or NO derived from the endothelial cells [4]. Down-regulation of eNOS activity by cigarette smoke associated with impairment of endothelium-dependent vasorelaxation is significantly correlated with the risk of cardiovascular disease.

Recently, the role of the RhoA/Rho-kinase pathway in vascular disease has been demonstrated [6]. It has been shown that cigarette smoke-derived free radicals and cigarette smoke-induced oxidative stress may up-regulate RhoA/Rho-kinase (ROCK) signaling and increase vascular stiffness in smokers [7]. Specific (fasudil or Y-27632) or nonspecific (statins) Rho-kinase inhibitors could protect against vascular remodeling and atherosclerosis [8]. Long-term inhibition of Rho-kinase activity results in a regression of arteriosclerotic coronary lesions. Interestingly, RhoA/Rho-kinase signaling might accelerate vascular disease because it also down-regulate eNOS/NO activity through alteration in eNOS mRNA stability and NO bioavailability.

Unfortunately, cigarette smoke contains more than 4,000 known components, but only the role of a few components responsible for vascular disease, has been identified. Polycyclic aromatic hydrocarbons, present in the tar fraction, and butadiene, a vapor component of cigarette smoke, can accelerate atherosclerosis in experimental models. In addition, exposure to nicotine may decrease NO bioavailability and increase atherosclerosis with high doses. It is clear that the adverse effects of cigarette smoking on vascular disease is due to superoxide radicals and other reactive oxygen species (ROS). The antagonist effect of ROS on eNOS/NO signaling pathway results in the fast combination of superoxide with NO to produce peroxynitrite, thereby decreasing the basal level of NO. In addition, ROS may induce shortage of NO level and endothelial dysfunction by inducing NOS uncoupling via depletion of cofactor tetrahydrobiopterin (BH₄) or increase of superoxide production [9].

Although preliminary results from some substances have been shown capable to restore endothelial function and atherosclerotic plaque formation, smoking prevention is still the recommended strategy to reduce the risk of vascular disease in smoker for future.

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