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Endothelial dysfunction in conduit arteries and in microcirculation. Novel therapeutic approaches

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ABSTRACT

The vascular endothelium not only is a single monolayer of cells between the vessel lumen and the intimal wall, but also plays an important role by controlling vascular function and structure mainly via the production of nitric oxide (NO). The so called "cardiovascular risk factors" are associated with endothelial dysfunction, that reduces NO bioavailability, increases oxidative stress, and promotes inflammation contributing therefore to the development of atherosclerosis. The significant role of endothelial dysfunction in the development of atherosclerosis emphasizes the need for efficient therapeutic interventions.

During the last years statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, antioxidants, beta-blockers and insulin sensitizers have been evaluated for their ability to restore endothelial function (Briasoulis et al., 2012). As there is not a straightforward relationship between therapeutic interventions and improvement of endothelial function but rather a complicated interrelationship between multiple cellular and sub-cellular targets, research has been focused on the understanding of the underlying mechanisms. Moreover, the development of novel diagnostic invasive and non-invasive methods has allowed the early detection of endothelial dysfunction expanding the role of therapeutic interventions and our knowledge.

In the current review we present the available data concerning the contribution of endothelial dysfunction to atherogenesis and review the methods that assess endothelial function with a view to understand the multiple targets of therapeutic interventions. Finally we focus on the classic and novel therapeutic approaches aiming to improve endothelial dysfunction and the underlying mechanisms.

Contents

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ADMA, asymmetrical dimethyl arginine; ARBs, angiotensin-receptor antagonists; BH_4, tetrahydrobiopterin; CAD, coronary artery disease; DDAH, dimethyl arginine dimethyl aminohydrolase; ED, endothelial dysfunction; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cells; FMD, flow mediated dilation; GTP, guanosine-5′-triphosphate; LDLs, low density lipoproteins; L-NMMA, NG-monomethyl-L-arginine; NADPH, nicotinamide adenine dinucleotide phosphate-oxidase; NO, nitric oxide; NOS, nitric oxide synthase; oxLDLs, oxidized low density lipoproteins; ROS, reactive oxygen species; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

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1. Introduction

The vascular endothelium is a monolayer of cells between the vessel lumen and the vascular smooth muscle cells. It plays a pivotal role in the regulation of vascular function and structure by releasing various biochemical mediators, such as nitric oxide (NO) and prostacyclin (Tousoulis et al., 2012). A growing list of factors, including the so called "cardiovascular risk factors", such as hypertension, hypercholesterolemia, smoking, diabetes mellitus, congestive heart failure, hyperhomocysteinemia and aging process itself, are associated with impaired endothelial function (Siasos et al., 2012). Endothelial dysfunction (ED), observed in these conditions, is characterized by decreased NO bioavailability and increased oxidative stress. As a result, ED promotes inflammation, oxidation of lipoproteins, platelet aggregation and thrombus formation and thus contributes to the development of atherosclerosis (Fig. 1).

Over the last years vascular endothelium has emerged as a new therapeutic target in cardiovascular disease. Several therapeutic approaches are currently available, targeting both synthesis and production of NO in human vascular endothelium, such as statins, angiotensin converting enzyme inhibitors, and thiazolidinediones and others are still under investigation (Table 1). Nevertheless, the impact of treatments in endothelial function is not constant while the underlying mechanisms are sometimes unknown. Moreover, there is a discrepancy between the achieved endothelial improvement and clinical outcome, thus further complicating the evaluation of treatment effects.

In the current review we present the available data concerning the contribution of endothelial dysfunction to atherogenesis and review the methods that assess endothelial function with a view to understand the multiple targets of therapeutic interventions. Finally we focus on the classic and novel therapeutic approaches aiming to improve endothelial dysfunction and the underlying mechanisms.

2. Pathophysiology of endothelial dysfunction

It is well established that vascular endothelium has a pivotal role in the modulation of vascular function and structure mainly via the formation of NO (Luscher &Barton, 1997). More specifically, NO causes vasodilatation and is responsible for the balance of endothelium-derived contracting factors, such as endothelin-1 and thromboxane A2, thus regulating the vascular tone (Vita, 2002). Besides this, it also inhibits platelet aggregation, inflammation, vascular smooth muscle cell migration and proliferation, and leukocyte adhesion and exerts antioxidant effects. Thereby, many pathophysiological states evoke endothelial dysfunction mainly by reducing endothelium-dependent vasodilation (Tousoulis, Charakida & Stefanadis, 2006; Antoniades, Antonopoulos, Bendall & Channon, 2009).

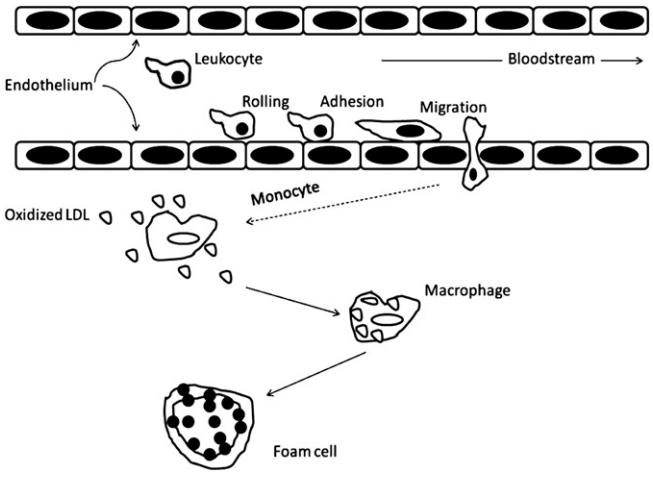

Fig. 1. The role of endothelium in atherosclerosis. From adhesion and migration of leukocytes in sub-endothelial layers and the transformation of tissue macrophages in atherosclerotic foam cells.

Table 1
Classic and novel therapeutic approaches aiming to improve endothelial function.

Agent	Impact on endothelial function
Statins (W. Sun et al., 2006), (Matsuno et al., 2004)	↑ eNOS expression ↓ NF-kB, AP-1 and HIF-1 pathways ↓ endothelial cell apoptosis
Angiotensin converting enzyme inhibitors (Imanishi et al., 2008)	↑ NO bioavailability
Folic acid/5-methyltetrahydrofolate (Antoniades, Antonopoulos, Tousoulis et al., 2009), (Antoniades, Shirodaria et al., 2006)	↑ eNOS coupling by BH_4 stabilization ↑ vascular BH_4 bioavailability
Thiazolidinediones (Hwang et al., 2005), (Calnek et al., 2003)	↑ eNOS activity and expression ↓ endothelial cell apoptosis ↓ NADPH & iNOS related oxidative stress
Arginase antagonists (Torondel et al., 2010)	↑ NO production
Endothelium-specific GTP cyclohydrolase overexpression (Zheng et al., 2003)	↑ BH_4 deficiency ↑ NO production by endothelial cells
Epoxide hydrolase inhibitor (D. Zhang et al., 2012)	↑ NO bioavailability

eNOS: endothelial nitric oxide synthase; NO: nitric oxide; BH_4: tetrahydrobiopterin; HIF-1: hypoxia-inducible factor-1; AP-1: activator protein-1; NF-kB: nuclear factor-kappa B; GTP: guanosine triphosphate; NADPH: nicotinamide adenine dinucleotide phosphate. ↑: increase/improve; ↓: decrease/inhibit.

ED plays a key role in the development of atherosclerosis and cardiovascular risk factors are highly associated with impaired endothelial function (Tousoulis, Koutsogiannis et al., 2010; Tousoulis, Papageorgiou et al., 2010; Tousoulis et al., 2011). More specifically, ED is caused by an increase in reactive oxygen species (ROS) generation and a reduction of NO bioavailability in vascular endothelium, either by decreasing its synthesis and/or by increasing its oxidative inactivation (R. Lee et al., 2012).

Due to the increased oxidative stress there is a decrease in NO bioavailability mediated by diverse mechanisms. Initially, superoxide anions react with existing NO producing peroxynitrite and thus reduce the concentration of NO (Channon, 2004). In addition, ROS reduce the production of NO by reducing the enzymatic activity of endothelial nitric oxide synthase (eNOS), the enzyme responsible for NO's synthesis (Guzik et al., 2002). In the vascular endothelium, NO is synthesized from L-arginine by eNOS via the transport of electrons to L-arginine. In order for this to happen, eNOS has to be bound to an essential cofactor, which is tetrahydrobiopterin (BH_4). This is known as "coupling" of eNOS (Cunnington &Channon, 2010). Without BH_4 eNOS becomes "uncoupled" and electrons are transported to oxygen instead of L-arginine generating superoxide rather than NO (Alp et al., 2003). In atherosclerosis, BH_4 levels are decreased because of their oxidative degradation by peroxynitrite and superoxide (Antoniades, Shirodaria et al., 2007). This reduction of BH_4 leads to eNOS "uncoupling" and so eNOS instead of synthesizing NO produces superoxide. This in turn reacts with existing NO to produce peroxynitrite and both of them cause further oxidation and depletion of BH_4 and thus enhance even more the oxidative stress and the reduction of NO bioavailability in vascular endothelial cells (Channon, 2004). Another mechanism responsible for the reduction of NO is via the regulation of asymmetrical dimethyl arginine (ADMA) levels. ROS reduce the enzymatic activity of dimethyl arginine dimethyl aminohydrolase (DDAH), which is crucial for the catabolism of ADMA, and up-regulate gene expression of protein methyl transferases, enzymes responsible for the transformation of L-arginine to ADMA. As a result, ROS induce an increase in ADMA levels. As it has been shown, ADMA inhibits and causes "uncoupling" of eNOS and thus an increase in ADMA levels is highly associated with a decrease in NO levels (Landmesser et al., 2004). Furthermore, ROS can down-regulate gene expression of eNOS and thus reduce even more NO