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Endothelial dysfunction in the pathogenesis of atherosclerosis-review article

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Abstract
Healthy endothelium plays a central role in car- diovascular control. Therefore, endothelial dysfunction (ED). Which is charncterized by an imbalance between relaxing and contracting factors, procoagulant and anticoagulant substances, and between proinflmnmatory and antiint1ammatory mediators, may play a particularly significant role in the pathogenesis of atherosclerosis. Endothelial<lysfum:tion is closdy related to different rbk factors of atherosclerosis, and to 1hcir intensity and duration. The involvement of risk factors in ED is also supported by results of interventions studies that showed re-gression of ED with treatment of risk factors. Because risk factors are commonly accompanied by decreased bioavailabil-ity of nitric oxide, the common denominator whereby different risk factors cause ED is most probably increased oxidative stress. Endothelial dysfunction may promote atherogenesis through diffcrem mechanisms such as increased adherence of monocytes, macrophages, and enhanced permeability of the endothelial layer. Further, ED probably plays an important role in the growth of athcrosclerotic lesions and in the development of thrombotic complications in late stages of the disease. Be-cause ED is a key underlying factor in the athcrosclerotic pro- cess, markers of endothelial abnornrnlities have been sought. Detection of ED is based on tests of endothelium-dependent vasomotion (dilation capability of peripheral and coronary ar-teries) and on circulating markers of endothelial function (en-dothelin-1. von Willebrnnd factor, tissue plasminogcn activa-tor, p!:tsminogen activator inhibitor. and adhesion molecules). Using these tests it is possible to follow the dose response of harmful effects of risk factors, and the effects of preventive procedures on vessel wall function.

Keywords: endothelial function-atherosclerosis-vasodilation-murkers of endothelial damage

Introduction
The vascular endothelium is an important regulatory organ in maintaining of cardiovascular homeostasis. Normal endothelial function includes control over thrombosis and thrombolysis, platelets and leukocyte in-teraction with the vessel wall, and regulation of vascular tone and smooth muscle cell proliferation. One of the most important regulatory and vasoactive substances produced by endothelial cells is nitric oxide (NO). Nitric oxide modulates vascular tone, and inhibits the interac-tion between blood cells and the vessel wall. In addition, NO appears to be an endogenous inhibitor of tumor ne- crosis factor and the expression of proinflammatory mol-ecules, such as the vascular cell adhesion molecule (VCAM-1) and the chemoattractant protein-I [1].
Because healthy endothelium plays a central role in cardiovascular control, it follows that endothelial dam-age may contribute to disease states characterized by vasoconstriction, inflammation, excessive thrombus for-mation, leukocyte adhesion to vessel walls, hypertension, and atherosclerosis [2, 3].

Endothelial dysfunction
Endothelial dysfunction is characterized by an imbal-ance between relaxing and contracting factors, between anticoagulant and procoagulant mediators, or between growth-inhibiting and promoting factors. Such dysfunc-tion can result from mechanical or biochemical injury to the endothelium. Physical damage of the endothelium is mostly caused by hypertension: several other risk factors like hypercholesterolemia. Diabetes, and smoking prob-ably cause injury to the endothelium through biochemi-cal mechanisms. Therefore, vessel wall damage may re-sult in endothelial dysfunction and can be clinically manifested as thrombosis or atherosclerosis [4].

Involvement of endothelial dysfunction in atherogenesis
Endothelial dysfunction has been demonstrated in sub-jects with different risk factors of atherosclerosis, such as hypercholesterolemia [5], diabetes [6, 7], hypertension [8], smoking [9], and in patients with atherosclerotic dis-ease (coronary, peripheral arterial) [3, 10]. We demon-strated that endothelial dysfunction progresses with the duration of hypertension, diabetes, or smoking and that a dose relationship exists between the intensity of an in-dividual risk factor or the number of presented risk fac-tors and endothelial function [7, 8, 11]. Furthermore, treatment of risk factors results in improvement of en-dothelial dysfunction. It has been shown that treatment of hypercholesterolemia with different statins improves en-dothelial function [12, 13]. Regression of endothelial dys-function was observed. during treatment of arterial hy-pertension with various drugs [14] and during physical training of patients with cardiac insufficiency and polymetabolic syndrome [15]. We also observed improvement of endothelial dysfunction during growth hormone replacement in growth hormone-deficient pa-tients [16]. Therefore, a dose-response relation exists between risk factors of atherosclerosis and endothe-lial dysfunction.
The mechanisms whereby risk factors cause endothe-lial

dysfunction are largely unknown: a common de-nominator for all these conditions is probably increased oxidative stress, which has therefore been suggested as an important cause of endothelial dysfunction. Most known risk factors cause excessive production of super-oxide anions, with consequent degradation of NO before it can reach target tissues. Decreased bioavailability of NO in the presence of risk factors is most probably also caused by decreased expression of nitrogen oxide synthase activity. Because NO acts as a vasodilator and inhibits platelet adherence and aggregation, smooth muscle proliferation, and endothelial cell-leukocyte in-teraction, decreased NO activity may contribute impor-tantly to the initiation and progression of atherosclerotic lesions [2]. The consequences of mechanical or chemical damage of the endothelium by different risk factors are also several cellular processes, such as inflammation and lipoprotein oxidation, that maintain endothelial dysfunc-tion and promote atherosclerosis.

Endothelial dysfunction is most probably a conse. quence of the harmful effects of risk factors of athero-sclerosis on the vessel wall. However, recent observa-tions favor the hypothesis that endothelial dysfunction could also be a primary, directly inherited defect. Thus, some observations showed that dysfunctional endothelial NO synthase gene polymorphism is associated with some risk factors (e.g., hypertension) and is therefore not a consequence, but rather a primary abnormality [18]. This assumption is also supported by the demonstration of endothelial dysfunction in normotensive siblings of parents with essential hypertension in one of our studies [8].

Endothelial dysfunction probably promotes atherogen-esis through different mechanisms, such as increased pad-herence of monocytes and enhanced permeability of the endothelial layer to monocytes/macrophages and lipo-proteins, which then accumulate in the vessel wall. It was indicated that endothelial dysfunction is also related to increased platelet adherence and smooth muscle cell mi-gration and proliferation, both of which are involved in atherogenesis. Because one of the earliest event-, in .ath-erogenesis is the adherence of circulating monocytes to intact endothelial cells, in some cases atherosclerosis be-haves as a chronic inflammatory process. However, this presumption does not preclude involvement of endothe-lial dysfunction, which most probably initiates different pathologic processes, including inflammation.

Furthermore, is has been shown that endothelial dys-function that precedes the early morphologic atheroscle-rotic changes in the arterial wall plays an important role in the development and growth of atherosclerotic lesions, and in the development of ischemia and thrombosis in the late stages of the disease [19].

Because the endothelial vasodilator function of the microvessels is an important determinant of tissue per-fusion, microvascular endothelial dysfunction may play a particularly significant role in the pathogenesis of tissue ischemia. In advanced atherosclerosis, endothelial dys-function in the coronary arteries, especially during peri-ods of increased demand, may be manifested clinically as periodic episodes of myocardial ischemia [20].

Indicators of endothelial dysfunction

After the recognition that atherosclerosis develops over decades and therefore has a long preclinical [silent] phase before the onset of clinical symptoms, and that in this early phase changes of the arterial wall are mostly reversible and preventable, there has been considerable interest in developing diagnostic tools for detecting and monitoring early vascular changes in asymptomatic sub-jects. Because endothelial dysfunction is a key underly-ing factor in the atherosclerotic process, markers of en-dothelial abnormalities have been sought, particularly those involving disturbed endothelium-dependent vaso-motion or related cellular products [21]. Because endo-thelium. has different functions, different tests would be needed to measure several different aspects of endothe-lial dysfunction. Areas of potential interest for detection of endothelial dysfunction include circulating markers of endothelial function and tests of endothelium-dependent vasomotion. Moreover, circulating adhesion. Molecules may serve as markers of endothelial damage or atherosclerosis.

Circulating markers of endothelial function

Endothelial injury may result in the release of various factors that can be detected in the circulation and can be potentially used as markers of endothelial dysfunction.

Endothelin-1

Endothelin-1 is an endothelium-derived peptide that has powerful vasoconstrictor properties. Increased levels of endothelin-1 have been demonstrated in conditions associated with endothelial dysfunction, such as athero-sclerosis. Hypercholesterolemia, and cigarette smoking [28, 29]. Furthermore, oxidized low-density lipoprotein has been shown to stimulate endothelin-1 production and secretion [30]. Injury to vascular endothelial cells prob-ably triggers the release of endothelin-1, and therefore it has been suggested that the levels of circulating endo-thelin in plasma may represent a marker of endothelial dysfunction. Because endothelin-1 also has mitogenic properties, it may also play a role in the development of premature atherosclerosis.

Von willebrand factor

The von Willebrand factor (vWF) is a glycoprotein synthesized mainly by vascular endothelial cells. It has important functions in hemostasis, participating in the coagulation and in the formation of platelet plugs at sites of endothelial damage. Von Willebrand factor is elevated in patients with hypercholesterolemia, and reduction of total cholesterol has been shown to be associated with a reduction in vWF levels [31]. Its levels are elevated in situations characterized by vascular damage with denu-dation of the endothelium, and it has been suggested that injured endothelial cells leak vWF, leading to increased plasma levels. Recent studies have shown that elevated levels of vWF may be predictive of recurrent cardiovas-cular events in patients with known cardiovascular disease [32].

Tissue plasminogen activator and plasminogen activator inhibitor-!

Tissue plasminogen activator is a protein released by endothelial cells. It activates the reaction in which plas-minogen is converted to plasmin. Tissue plasminogen activator regulates the fibrinolytic activity of blood in balance with plasminogen activator inhibitor-I, another product of endothelial cells, serving as the primary

in-hibitor of tissue plasminogen activator. These circulating vascular endothelial markers are elevated in hypercho-lesterolemia [33]. Furthermore, prospective studies have shown that high concentrations of tissue plasminogen activator antigen in healthy men may be associated with a subsequent risk of myocardial infarction [34] and stroke [35]. Data from the Atherosclerosis Risk in Com-munities (ARIC) study have shown that increased levels of tissue plasminogen activator and plasminogen activa-tor inhibitor-are associated with subclinical carotid atherosclerosis, measured as increased intima-media thickness [36].

Therefore, the different proteins involved in hemosta-sis and synthesized by endothelial cells have been pro- posed as markers of endothelial dysfunction. The main problem is the relatively poor specificity of these mark-ers, which may hamper their use in detection or moni-toring of endothelial dysfunction.

Functional methods for studying endothelial function

No-dependent vasodi!ation

Most of the functional methods for *in vivo* endothelial testing examine the ability of the endothelium to cause va,:odilation in response to the pharmacologic and physi-ologic stimuli that increase the endothelial release of NO. *In vivo* assessment of coronary endothelial function in humans was first reported by Ludmer *et al*. in 1986 [22]. The coronary artery diameter was measured by quanti-tative angiography before and after intracoronary infu-sion of acetylcholine. The dilation capability of the coro-nary arteries was assessed using Doppler wires or cath-eters. Later, these techniques provided valuable insights into the risk factors of endothelial dysfunction in coro-nary arteries and into the role of endothelial dysfunction in preceding overt atherosclerosis [23]. The potential for reversibility of endothelial dysfunction in the coronary a11eries by therapeutic intervention has also been as-sessed by this methodology [12]. The major disadvan-tage of intra-a11erial tests is their invasive nature, which makes them generally unsuitable for routine use in sub-jects who are at risk for atherosclerosis but who have no clinical symptoms or signs of disease. Therefore, nonin-vasive or minimally invasive clinical tests of endothelial function have been developed.

Positron emission tomography is a unique method that enables noninvasive quantitation of myocardial blood flow, which is dependent on the endothelial function of macrovessels and microvessels. By measuring blood flow at rest and after pharmacologic stimulation with dipyridarnole or adenosine, it is possible to calculate the coronary blood flow reserve. In cases with impairment in coronary reactivity, the blood flow reserve is decreased and may represent an early marker of endothe-lial dysfunction and subclinical coronary athero-sclerosis [24, 25].

Endothelial function may also be tested noninvasively in the peripheral conduit arteries using high-resolution external vascular ultrasonography. In this noninvasive method, arterial diameter is measured in response to an increase in shear stress, which causes endothelium-, dependent dilatation, and an endothelium-independent ' dilatation in response to sublingual nitroglycerin. The 1 brachia! arterial dilator response to increased blood f1ow during reactive hyperemia has been shown to be mainly caused by endothelial release of NO [26], and to con-e-late significantly with coronary endothelial function and with the extent and severity of coronary athero-sclerosis [27].

Noninvasive ultrasonography has been applied widely to asymptomatic subject groups. These studies have pro-vided information on the effects of various risk factors on early atherogenesis. Because these techniques are accu-rate and relatively reproducible, serial studies may be performed including trials of reversibility of endothelial dysfunction in asymptomatic subjects at high risk of ar-terial atherosclerotic disease.

Adhesion molecules

Binding of circulating leukocytes to the vascular en-dothelium and further leukocyte migration into the sub-endothelial space are major processes in the development of atherosclerosis. These events are mediated through diverse cellular adhesion molecules that are expressed on the surface of vascular endothelial cells such as vascular cell adhesion molecule-I (VCAM-1), endothelial- leukocyte adhesion molecule (E-selectin and P-selectin), md intercellular adhesion molecule-I (ICAM-1). Circu-lating soluble forms of these adhesion molecules have been detected in plasma. The origin and function of these circulating soluble adhesion molecules are unclear, but they most likely arise from endothelial cells [37].

Several studies have suggested that circulating adhe-sion molecules may serve as markers of endothelial dam-age or atherosclerosis. The ARIC study showed that E-selectin and ICAM-1 are associated with carotid artery intima-media thickness and are independent predictors of incident coronary artery disease [36]. This study also showed higher levels of ICAM-1 in smokers. Squadrito *et al*. [38] observed higher levels of circulating ICAM-1 and E-selectin in patients with acute myocardial infarc-tion. Increased levels of plasma P-selectin have been observed in cases of unstable angina [39], myocardial infarction [40], and hypercholesterolemia [41]. Elevated levels of ICAM-1 were also found in patients with pe-ripheral vascular disease [42]. Furthermore, ICAM-1 levels may predict cardiovascular event rates in appar-ently healthy men [43].

Of the risk factors, serum lipoproteins seem to be es-pecially related to the levels of circulation adhesion mol-ecules. In the study by Hackman *et al*. [44], dyslipidemia was associated with elevated levels of ICAM-1, VCAM-1, and E-selectin. Successful therapy with lipid-lowering statins significantly reduced the levels of circulating E-selectin. Therefore, these studies suggested that cell ad-hesion molecules may serve as possible markers of the efficacy of lipid-lowering therapy.

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