Endothelial dysfunction and cardiovascular disease

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Summary

Healthy endothelium plays a central role in cardiovascular control. Therefore endothelial dysfunction (ED), which is characterized by an imbalance between relaxing and contracting factors, procoagulant and anticoagulant substances, and between proinflammatory and antiinflammatory mediators, may play a particularly significant role in the pathogenesis of atherosclerosis and cardiovascular disease. ED is thought to be an early physiologic event in the development of atherosclerosis, occurring before morphologic changes in the vessel wall can be detected. It is closely related to different risk factors of atherosclerosis, to their intensity and their duration. The involvement of risk factors in ED is also supported by results of intervention studies that showed regression of ED with treatment of risk factors. Further, it was shown that ED is significantly and directly correlated with the occurrence of cardiac events. The common denominator whereby different risk factors cause ED is most probably increased oxidative stress and consequently decreased bioavailability of nitrogen oxide. Endothelial dysfunction promotes atherosclerosis and probably plays an important role in the development of thrombotic complications in late stages of the disease. As ED is a key underlying factor in the atherosclerotic process, markers of endothelial abnormali-

ties have been proposed, but loss of endothelium – dependent vasodilation has become a broadly accepted indicator of endothelial dysfunction. Using these non-invasive tests it is possible to follow the dose - response of harmful effects or risk factors, and the effects of preventive procedures on vessel wall function.

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Introduction

New findings in the last decade have demonstrated that the vascular endothelium is an important regulatory organ in maintaining cardiovascular homeostasis and that endothelial dysfunction is present in several cardiovascular diseases. The endothelium, which was once thought to be a simple barrier separating blood and vessel wall, is now known to synthesize and release vasoactive substances, which contributes to local vascular regulation. Endothelial cells control vascular tone by converting angiotensin-I into angiotensin-II, inactivating bradykinin, norepinephrine and serotonin, and by secreting vasodilator substances, such as prostacyclin and nitric oxide (NO), and contracting factors such as endothelin (1).

One of the most important regulatory and vasoactive substances produced by endothelial cells is nitric oxide (NO). NO modulates vascular tone, and inhibits the interaction between blood cells and the vessel wall. In addition NO appears to be

an endogenous inhibitor of tumour necrosis factor, and the expression of proinflammatory molecules such as the vascular cell adhesion molecule (VCAM-1) and the chemoattractant protein-1 (MCP-1) (1).

Definition of endothelial dysfunction

The term endothelial dysfunction describes several pathological conditions, including altered anticoagulant and anti-inflammatory properties of the endothelium, impaired modulation of vascular growth, and dysregulation of vascular remodeling. In much of the literature, however, the term endothelial dysfunction specifically refers to an impairment of endothelium dependent vasodilation caused by decreased NO bioavailability in the vessel wall.

Risk factors of atherosclerosis and endothelial dysfunction

Endothelial dysfunction has been demonstrated in subjects with different risk factors for atherosclerosis, such as hypercholesterolemia, diabetes, hypertension and smoking, and in patients with atherosclerotic disease (coronary, peripheral arterial) (2).

Most studies on endothelial dysfunction were performed on patients with diabetes mellitus and essential hypertension. It was shown that endothelial dysfunction is an early event in type I and II diabetes and that it is related to the development and progression of diabetic vascular complications (3). In one of our studies on type I diabetic patients it was shown that impaired flow mediated endothelium dependent dilation of the brachial artery appears in subjects with microalbuminuria and that it is inversely related to its extent (4).

Deterioration of endothelium dependent vascular function was also confirmed in different forms of arterial hypertension. Arterial hypertension produces a shear stress effect on the vascular endothelial cells, and this could lead to changes in the production or release of different vasoactive substances (5).

If there exists an interrelationship between endothelial dysfunction and atherosclerosis, then the progression of the dysfunction, like the atherosclerotic process, should be related to the intensity of the individual risk factor and to the total risk of an individual subject. We demonstrated that endothelial dysfunction progresses with the duration of hypertension, diabetes or smoking. It was also shown that there exists a close relationship between the intensity of an individual risk factor or the number of risk factors present, and endothelial function (4, 6). Therefore, a dose-response relationship exists between risk factors of atherosclerosis and endothelial dysfunction.

The mechanisms whereby risk factors cause endothelial dysfunction are largely unknown. Endothelial dysfunction 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 probably cause injury to the endothelium through biochemical mechanisms. A common denominator for all conditions related to risk factors 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 superoxide 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.

Endothelial dysfunction and atherosclerosis

As NO acts as a vasodilator and inhibits platelet adherence and aggregation, smooth muscle proliferation, and endothelial cell-leukocyte interaction, a decrease in its activity may contribute importantly to the initiation and progression of atherosclerotic lesions. The consequences of mechanical or chemical damage to the endothelium by different risk factors are also several cellular processes, such as inflammation, that maintain endothelial dysfunction and promote atherosclerosis.

In recent years it has become evident that an inflammatory process is involved in atherosclerosis and there is mounting evidence that inflammation plays a role in the development of coronary heart disease. Elevated concentrations of acute phase reactants, such as C-reactive protein (CRP) and proinflammatory cytokine interleukin-6 (IL-6) were found in patients with acute coronary syndromes and peripheral arterial disease (7). CRP may play a direct role in promoting the inflammatory component of atherosclerosis and there is a close interrelationship between indicators of inflammation and endothelial dysfunction. Unfortunately, it was shown that CRP, at concentrations frequently observed in high-risk subjects, induces significant expression of adhesion molecules by human endothelial cells, which are markers of endothelial damage.

Studies also showed that an elevated CRP level is not only related to the increased levels of circulating markers of endothelial dysfunction but also to abnormal systemic endothelial vascular reactivity. Thus, the identification of elevated CRP levels as an independent predictor of endothelial dysfunction might provide an important clue to link systemic markers of inflammatory processes to atherosclerotic disease progression.

Study of endothelial dysfunction raised the question as to whether it is a cause or consequence of atherosclerosis. Endothelial dysfunction is most probably a consequence of the harmful effects of risk factors of atherosclerosis on the vessel wall. However; recent observations favour the hypothesis that endothelial dysfunction could also be a primary defect and as

such directly inherited. Irrespective of the sequence of events, endothelial dysfunction probably promotes atherogenesis through different mechanisms: increased adherence of monocytes, enhanced permeability of the endothelial layer to monocytes/macrophages and lipoproteins which then accumulate in the vessel wall. Endothelial dysfunction is also related to increased platelet adherence, and smooth muscle cell migration and proliferation - both involved in atherogenesis. Furthermore, it has been shown that endothelial dysfunction which precedes the early morphological atherosclerotic changes in the arterial wall plays an important role in the development and growth of atherosclerotic lesions, as well as in the development of ischemia and thrombosis in the late stages of the disease (8).

Endothelial dysfunction and clinical symptoms of coronary artery disease

Endothelium-mediated relaxation is impaired in atherosclerotic human coronary arteries, shifting the balance in favour of vasoconstriction in response to a variety of stimuli such as exercise, mental stress, and cold exposure. In addition to impairment of flow mediated dilation of the epicardial conductance vessels, in atherosclerosis the vasodilator function of the coronary resistance vessel is adversely affected. A defective endothelium-mediated vasodilator function may therefore potentiate known trigger mechanisms of myocardial ischemia and thereby induce a mismatch between myocardial oxygen supply and demand. Even through the changes in luminal diameter produced by inappropriate vasoconstriction of the epicardial vessel in response to sympathetic activation are usually less than 30 %, such an increase in the arterial tone might be enough to convert a subcritical stenosis into a critical one with an ensuing decrease in blood flow. Impaired FMD of the resistance vessels will further reduce coronary flow reserve (5).

Endothelial dysfunction might also be related to circadian variation in transient ischemic episodes, being most frequent in the morning hours. Indeed, vascular resistance has been shown to be elevated in the morning hours.

In unstable angina pectoris, which is mostly caused by plaque rupture, a number of vasoactive substances are released into the coronary circulation, most notably serotonin and thrombin. Both substances have been shown to exert potent vasoconstrictor effects in the presence of dysfunctional endothelium. Thus, endothelial dysfunction may cause a constrictor response and importantly magnify the ischemic response in the distal vascular bed and whatever the mechanism of acute myocardial infarction, inappropriate constriction of resistance vessels distal to the site of coronary thrombosis could influence the size of myocardial necrosis. This is one of the reasons that acute events and consequences are unrelated to

stenosis severity. Further in the vascular bed of the non-infarct related arteries in the presence of endothelial dysfunction, there is also an enhanced response of resistance vessels to systemic and local neurohormonal constrictor stimuli, which could increase the extent of the ischaemia at the periphery of the infarcted area and reduce collateral flow to the infarct-related arterial bed, thus contributing to the acute impairment of ventricular function and to the extension of necrosis.

Endothelial dysfunction could also be responsible for the no-reflow phenomenon. Endothelial cells are at least as susceptible as myocytes to acute ischemic injury and reperfusion damage. This is evident from the profound loss of capacity of myocardium to be reperfused following severe ischaemia which is known as the no-reflow phenomenon. However, this inability to perfuse dead tissue compromises also perfusion of the immediately adjacent viable tissue, which is a region of "low flow" in which, despite their dilatation, many capillaries are incompetent (9).

There also exists interrelationship between endothelial dysfunction and microvascular angina (syndrome X). This clinical setting is characterized by angina-like pain and abnormal exercise ECG changes in the presence of a normal coronary angiogram. The role of endothelial dysfunction in this setting is controversial. It has been shown that patients with microvascular angina have endothelial dysfunction in the resistance vessels, possibly as a result of diminished formation of NO. However, other studies on coronary epicardial vasodilatation in patients with syndrome X were unable to find signs of endothelial dysfunction.

Therefore, endothelial dysfunction has different clinical implication. Its importance was also confirmed by study of Scächinger who found close relationship between endothelial dysfunction and the occurrence of coronary events (10).

Reversibility of endothelial dysfunction and therapeutic aspect

Different studies showed that treating risk factors results in improvement of endothelial dysfunction. It has been shown that treatment of hypercholesterolemia with different statins improves endothelial function. Further, regression of endothelial dysfunction was observed during treatment of arterial hypertension with various drugs. Several antihypertensive agents can prevent and reverse impaired endothelium-dependent relaxation in large conduit as well as in resistance arteries of hypertensive rats. In contrast, data from studies in hypertensive patients are still controversial. Calcium channel antagonists seem to mediate part of their pharmacological effect by increasing endothelial NO - production with consequent improvement of endothelial function. Angiotensin-converting enzyme (ACE) inhibitors, beyond inhibiting the renin-angiotensin system, diminish the inactivation of bradykinin,

thus leading to an augmentation of NO release. In the forearm circulation, on the other hand, treatment with captopril and enalapril or cilazil failed to improve vasodilatation to muscarinic agonists, while lisinopril selectively improved the vasodilating response to bradykinin. Further, the available data underlie the role of endothelial dysfunction and the potential benefit of ACE inhibition in the field of ischaemic heart disease. ACE inhibition of kininase inhibits the breakdown of bradykinin resulting in increased release of NO, consequently pathological vasoconstriction is prevented and vasodilation of the coronary arteries occurs (11).

We also observed improvement of endothelial dysfunction during physical training of patients with cardiac insufficiency and the polymetabolic syndrome. Further improvement of endothelial dysfunction was registered during growth hormone replacement in growth hormone deficient patients (12). All these data show that endothelial dysfunction is reversible and by treating risk factors it is possible to improve it and to restore vascular function.

References

1. Drexler H. Factors involved in the maintenance of endothelial function. *Am J Cardiol* 1998; 83: S1-S4.
2. Drexler H, Horning B. Endothelial dysfunction in human disease. *J Mol Cell Cardiol* 1999; 31: 51-60.
3. Schiekofer S, Balletshofer B, Andrassy M, Bierhaus A, Nawroth PP. Endothelial dysfunction in diabetes mellitus. *Semin Thromb Hemostas* 2000; 26: 503-11.
4. Poredoš P, Kek A. Relation of blunted dilation of the brachial artery in insulin-dependent diabetes mellitus to microalbuminuria. *Am J Cardiol* 2000; 86: 364-7.
5. Žižek B, Poredoš P, Vide_nik V. Endothelial dysfunction in hypertensive patients and in normotensive off-spring of subjects with essential hypertension. (Scientific letter). *Heart* 2001; 85: 215-6.
6. Poredoš P, Orehek M, Tratnik E. Smoking is associated with dose-related increase of intima-media thickness and endothelial dysfunction. *Angiology* 1997; 50: 201-7.
7. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000; 148: 209-14.
8. Kuo L, Davis MJ, Cannon MS, Chilian WM. Pathophysiological consequences of atherosclerosis extend into the coronary microcirculation. Restoration of endothelium-dependent responses by L-arginine. *Circulation Res* 1992; 70: 465-6.
9. Hearse DJ, Maxwell I, Saldanha C, Gavin JB. The myocardial vasculature during ischemia and reperfusion: a target for injury and protection. *J Mol Cell Cardiol* 1993; 25: 759-800.
10. Motz W, Vogl M, Rabenau O et al. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms. *Am J Cardiol* 1991; 68: 996-1003.
11. Higashi Y, Sasaki S, Nakagawa K, Ueda T, Yoshimizu A, Kurisu S et al. A comparison of angiotensin-converting enzyme inhibitors, calcium antagonists, blockers and diuretic agents on reactive hyperemia in patients with essential hypertension: a multicenter study. *J Am Coll Cardiol* 2000; 35: 284-91.
12. Pfeifer M, Vrhovec R, Žižek B, Prezelj J, Poredoš P, Clyton RN. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *J Clin Endocrinol Metabol* 1999; 84: 453-7.