SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

The Role Of Endothelial Dysfunction In Coronary Artery Disease And Implications In Therapy

Originally presented by: PETER GANZ, MD

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Endothelial dysfunction is a first and constant feature of the atherosclerotic process. Endothelial dysfunction can be demonstrated even in apparently normal coronary arteries when vasoconstriction is observed in response to acetylcholine. Lipid lowering, especially when coupled with antioxidant therapy, can result in improved endothelial dysfunction and may, in part, explain a beneficial clinical effect observed after only 6-12 months of treatment. More recent evidence suggests that ACE inhibitors may also improve endothelial dysfunction.

In a presentation at a satellite symposium at the 46th Annual Scientific Session in Anaheim, California, on March 15, 1997, Dr. Peter Ganz (Director of Cardiovascular Research, Cardiac Catheterization Laboratory, Brigham & Women's Hospital, Boston, MA) discussed the importance of the endothelium in coronary artery disease. Due to its strategic location, positioned as the interface between the flowing blood and the underlying vessel wall, the endothelium serves as a primary mediator of any blood-associated effects in the initial development of atherosclerosis.

The Atherosclerotic Plaque

Atherosclerosis is the result of a complex interaction between blood elements, disturbed flow, and vessel wall abnormality and involves several pathologic processes: inflammation, with increased endothelial permeability, endothelial activation, and monocyte recruitment; growth, with smooth muscle cell proliferation, migration, and matrix synthesis; degeneration, with lipid accumulation; necrosis, possibly related to the cytotoxic effect of oxidized lipid; calcification/ossification, which may represent an active rather than a dystrophic process; and thrombosis, with platelet recruitment and fibrin formation.[1]

Atherosclerotic plaques typically consist of a lipid-rich core in the central portion of the eccentrically thickened intima (Fig. 1a). The lipid core is bounded on its luminal aspect by a fibrous cap, at its edges by the "shoulder" region, and on its abluminal aspect by the base of the plaque. The central, lipid-rich core of the typical lesion contains many lipid-laden macrophage foam cells derived from blood monocytes. Once they reside within the arterial wall, these cells imbibe lipid, which accounts for their foamy cytoplasm. These foam cells can produce large amounts of tissue factor, a powerful coagulant that potently stimulates thrombus formation when in contact with blood.[1,2]

The integrity of the fibrous cap overlying this lipid-rich core fundamentally determines the stability of an atherosclerotic plaque. Rupture-prone plaques tend to have thin, friable fibrous caps (Fig. 1a). Plaques not liable to precipitate acute myocardial events tend to have thicker fibrous caps to protect the blood compartment in the arterial lumen from contact with the underlying thrombogenic lipid core (Fig. 1b).

Role of Endothelium in the Atherosclerotic Process

Endothelial cells interact with cellular and soluble factors present in the blood as well as in other layers of the vessel wall. Until recently, the endothelium was thought of as only a passive barrier between the blood and vessel wall. However, it is now clear that the endothelium is metabolically active and plays a dynamic role in the regulation of normal vascular biology, in the repair of the arterial wall following injury, and in the pathogenesis of atherosclerosis. The endothelium produces and

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Figure 1a: The "Vulnerable" Atherosclerotic Plaque

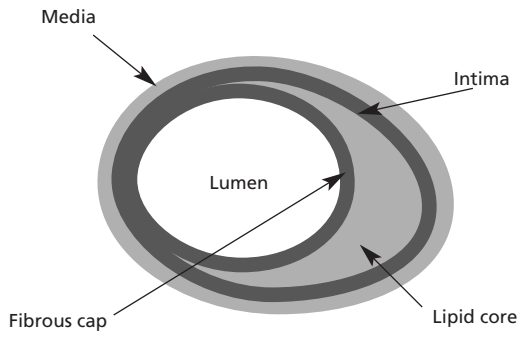
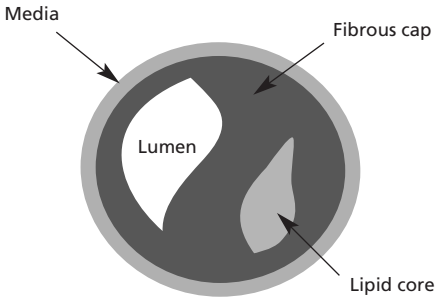


Figure 1b: The "Stable" Atherosclerotic Plaque



Adapted from Libby P.[2]

releases numerous substances that not only affect vascular tone, but also exert antithrombotic, anti-inflammatory, and growth inhibitory functions (Fig. 2). One of the most important mediators released by the endothelium is nitric oxide (NO). NO plays a central role in the prevention of atherogenesis. Adequate basal levels of NO prevent platelet adhesion and the release of platelet-derived growth factor, one of the most potent growth-promoting mitogens known. This action indirectly interferes with atherogenesis. Basal levels of NO also prevent expression of leukocyte adhesion molecules or chemo-attractants, such as monocyte chemotactic protein. Healthy basal levels of NO also prevent oxidation of low-density lipoproteins (LDL) by scavenging reactive oxygen substances, which oxidize LDL particles. However, oxidized LDL depresses the function of the NO synthase pathway, further reducing NO production.

Consequences of endothelial dysfunction that can initiate or contribute to the atherosclerotic process are: (1) abnormal control of vascular tone, (2) increased platelet adhesion, (3) increased leukocyte adherence and transmigration, (4) reduced promotion of growth inhibitors, (5) excess production of growth promoters, and (6) increased lipid deposition.

Assessment of Endothelial Function

Acetylcholine (ACh) is an endothelium-dependent, muscarinic, cholinergic agonist. In response to ACh, normal vessels dilate, through the release of NO. However, atherosclerotic vessels constrict in response to ACh, since its direct vasoconstrictor effect on muscarinic receptors in smooth muscle cells overrides the decreased NO effect in atherosclerotic vessels (Fig. 3). Ludmer et al[3] were the first to recognize the paradoxical vasoconstriction induced by ACh in atherosclerotic human coronary arteries. They demonstrated that ACh produced dose-dependent dilatation in normal arteries. However, in atherosclerotic arteries, ACh led to dose-dependent constriction of the stenotic, pre-stenotic, and post-stenotic, coronary artery segments. Ludmer et al[3] concluded that paradoxical vasoconstriction induced by ACh represents a defect in endothelial vasodilator function. Gordon et al[4] extended these findings further by demonstrating that angiographically normal arteries usually dilated during supine bicycle exercise (or in response to acetylcholine) compared with controls. However, arteries with irregularities or stenoses generally constricted in response to either exercise or ACh. The normal dilatation was thought to represent flow-mediated vasodilatation in response to an increase in coronary flow and sympathetically mediated effects on the endothelium. Subsequent work by Hess and colleagues[5,6] has shown that hypertension and hypercholesterolemia impair exercise-induced responses, particularly in the smooth segment.

Figure 2: The Normal Endothelial Cell

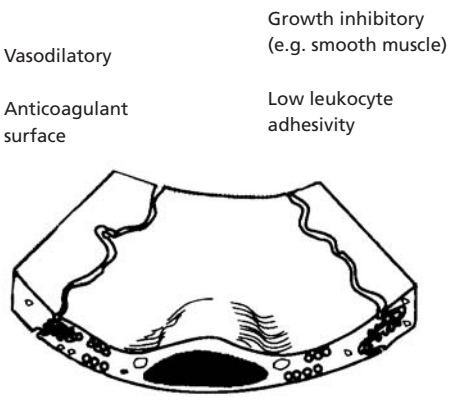
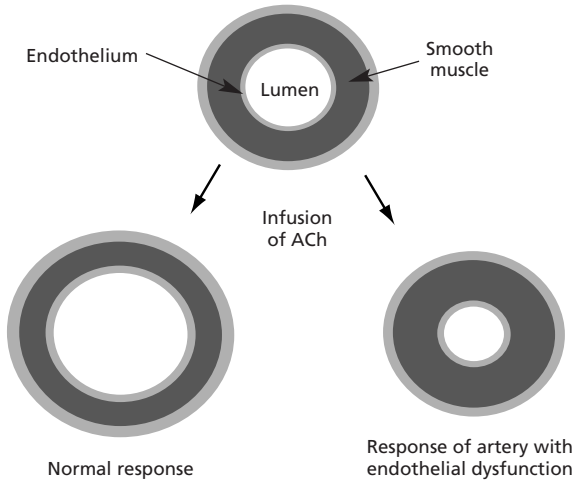


Figure 3: Acetylcholine (ACh) and Endothelial Response



Stylized representations of endothelial responses. After a coronary artery is infused with acetylcholine, the artery dilates in the absence of disease, reflecting normal endothelial cell function (left). In contrast, arteries constrict in the presence of hypercholesterolemia and/or atherosclerosis, reflecting endothelial cell dysfunction (right).

Impaired endothelial vasodilatation also appears to affect the coronary microcirculation (the resistance as compared to the conduit vessels). For example, Egashira et al[7] demonstrated impaired endothelial dilatation of the coronary microcirculation in patients with normal coronary arteries but with evidence of myocardial ischemia as detected by myocardial lactate production. Indeed, these patients show a paradoxical decrease in coronary blood flow during increased metabolic demand as well as exercise-induced thallium perfusion defects indicative of myocardial ischemia.[8] These findings suggest a crucial role for endothelium-dependent vasodilatation of coronary resistance vessels in coupling metabolic demand and coronary blood flow. Finally, Quyyumi et al[9] have recently established that coronary blood flow regulation during increased myocardial demand is largely mediated by NO.

Therapeutic Interventions to Improve Endothelial Dysfunction

The treatment of endothelial dysfunction that has been studied most is cholesterol lowering. Leung et al[10] studied 25 men who had hypercholesterolemia but no angiographic evidence of coronary atherosclerosis. Subjects received treatment with a cholesterol-reducing diet and cholestyramine for six months. No control group was evaluated. Between baseline and follow-up, the mean total serum cholesterol level fell by 28.7% and the mean LDL-cholesterol level dropped by 35.6%. Treatment normalized the response of coronary artery disease to acetylcholine, suggesting that reducing serum cholesterol can reverse endothelial dysfunction.

Treasure et al[11] performed a randomized, double-blind study of lovastatin with a lipid-lowering diet versus placebo in 19 subjects with atherosclerosis. After six months of therapy, the lovastatin-treated subjects showed significantly less vasoconstriction to acetylcholine than the placebo group ($p=0.013$), as measured by quantitative coronary angiography. As lipid-lowering therapy and diet had reduced total serum cholesterol by 31% in the treatment group, these investigators concluded that cholesterol-lowering therapy significantly improved endothelium-mediated responses in the coronary arteries.

Anderson et al[12] randomized 49 subjects with atherosclerosis to diet, lovastatin, and cholestyramine (the LDL-lowering group) or lovastatin and probucol, a potent antioxidant (LDL-lowering/antioxidant group). Coronary artery vasomotion in response to an intracoronary infusion of acetylcholine was assessed at baseline and after one year of treatment. Those subjects randomized to diet showed no improvement in coronary vasomotor responses and those receiving the LDL-lowering regimen had modest improvement compared with the diet group ($p=0.08$). Subjects randomized to the LDL-lowering/antioxidant regimen displayed significant improvement in endothelial function ($p<0.05$ versus the diet group). These results suggested that the addition of the antioxidant provided an important and additive effect to LDL lowering.

Recently, Mancini et al[13] showed that angiotensin-converting enzyme (ACE) inhibition improved endothelial dysfunction in normotensive patients with coronary artery disease who did not have significant hyperlipidemia. In a double-blind, randomized, placebo-controlled study of quinapril, 40 mg daily, the treated group showed significant net improvement in response to incremental concentrations of acetylcholine after six months of therapy ($p=0.002$). The Trial on Reversing Endothelial Dysfunction (TREND) study suggests that the benefits of ACE inhibition are likely due to attenuation of the contractile and superoxide-generating effects of angiotensin II and to the enhancement of endothelial cell release of NO secondary to diminished breakdown of bradykinin.

Summary

The best treatment of endothelial dysfunction (and its related NO deficiency) includes aggressive risk-factor modification (better diabetic control, discontinuation of cigarette smoking, treatment of hypertension and hyperlipidemia, estrogen replacement therapy in postmenopausal women). The role of other agents, such as calcium channel blockers, ACE inhibitors, nitrates, and antioxidants should become more clearly defined as further studies evaluate these therapies in endothelial dysfunction.

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