Available online at www.sciencedirect.com

SCIENCE DIRECT

Vascular Pharmacology 42 (2005) 125–140

Vascular Pharmacology

www.elsevier.com/locate/vph

Review

Clinical impact of vasomotor function assessment and the role of ACE-inhibitors and statins

Folkert W. Asselbergs[a,b,*], Pim van der Harst[a,b], Gillian A.J. Jessurun[b], René A. Tio[b], Wiek H. van Gilst[a,b]

[a]*Department of Clinical Pharmacology, University of Groningen, Groningen, The Netherlands*
[b]*Department of Cardiology, University Hospital Groningen, Groningen, The Netherlands*

Abstract

Impaired endothelial function is recognised as one of the earliest events of atherogenesis. Endothelium-dependent vasomotion has been the principal method to assess endothelial function. In this article, we will discuss the clinical value of the different techniques to evaluate endothelium-dependent vasomotion. To date, there seems not to be a simple and reliably endothelial function test to identify asymptomatic subjects at increased risk for cardiovascular disease in clinical practice. Recent studies indicate that pharmacological interventions, in particular with ACE-inhibitors and statins, might improve endothelial function. However, there is no solid evidence that improvement of endothelial function is a necessity for the observed reduction in cardiovascular events by these compounds. Overall, at this moment, there is no place in clinical practice for the use of endothelial function as a method for risk assessment or target of pharmacological interventions.

Keywords: Endothelial function; Acetylcholine; Risk factors; Prognosis; ACE-inhibitors; Statins

Contents

1. Introduction

Since the discovery of the obligatory role for the endothelium in relaxing arterial smooth muscles by acetylcholine in 1980(Furchgott and Zawadzki, 1980), the

* Corresponding author. Department of Clinical Pharmacology, University of Groningen, Groningen, The Netherlands. Tel.: +31 503632810; fax: +31 503632812.
E-mail address: f.w.asselbergs@thorax.azg.nl (F.W. Asselbergs).

1537-1891/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.vph.2005.01.009

endothelium has been the focus of intensive research. Currently, the endothelium is recognised to play a crucial role in vascular homeostasis in health and is considered to be early involved in the pathophysiology of cardiovascular disease (Moncada and Higgs, 1993; Rubanyi, 1993; Ross, 1999; Davignon and Ganz, 2004; Glasser et al., 1996). The endothelium, a single cell layer of the vascular wall, has the ability to respond to physical, chemical, and neurohumoral stimuli by the production and release of a variety biological active substances, e.g. nitric oxide (NO), prostanoids, endothelin, angiotensin II, thrombomodulin, heparan sulphate, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF), adhesion molecules, and cytokines. NO, synthesised by the endothelial NO synthases, is the most investigated substance released from the endothelium and plays a pivotal role in endothelium-dependent vasodilatation and regulation of other protective functions of the endothelium. Functions of NO include regulation of vascular smooth muscle cell tonus and proliferation, blood hemostasis, vascular permeability, inflammatory response, platelet adherence and aggregation, and endothelial cell–leukocyte interaction (Rubanyi, 1993; Moncada and Higgs, 1993; Glasser et al., 1996). In addition, the endothelium has organ-specific roles that are differentiated for various parts of the body, such as gas exchange in the lungs, control of myocardial function in the heart, or phagocytosis in the liver and spleen (Vane et al., 1990). A disturbance in the integrity or function of the endothelium is called endothelial dysfunction. In this review, we will focus on endothelium-dependent vasodilatation as a measure of endothelial function (mediated predominantly by NO). We will discuss different methods of assessment, prognostic and clinical implications, and pharmacological interventions aimed at lowering blood pressure and cholesterol, in particular with ACE-inhibitors and HMG-CoA reductase inhibitors, respectively.

2. Endothelial dependent vasomotor function

Endothelial cells synthesise NO through NO synthases (e.g. eNOS) by oxidation of the amino acid L-arginine (Fig. 1).(Palmer et al., 1988) NO is thought to be the most important endothelial derived vasodilator. Required cofactors for eNOS functioning are haem, calmodulin, tetrahydrobiopterin, flavin mononucleotide and FAD, and NADPH(Marletta, 1993; Fleming and Busse, 2003; Albrecht et al., 2003). NO is continuously produced by eNOS in the healthy endothelium in certain amounts in response to shear and pulsatile stretch of the vascular wall. The production of NO can be increased by many physiological stimuli, such as hypoxia, increase blood flow or shear stress, and pharmacological stimuli such as acetylcholine, bradykinine, adenosine triphosphate, adenosine diphosphate, thrombin, serotonin, histamine, and substance P (Luscher and Vanhoutte, 1990). NO released from the endothelium in turn stimulates the soluble guanylate cyclase in the vascular smooth muscle cells, resulting in an increase

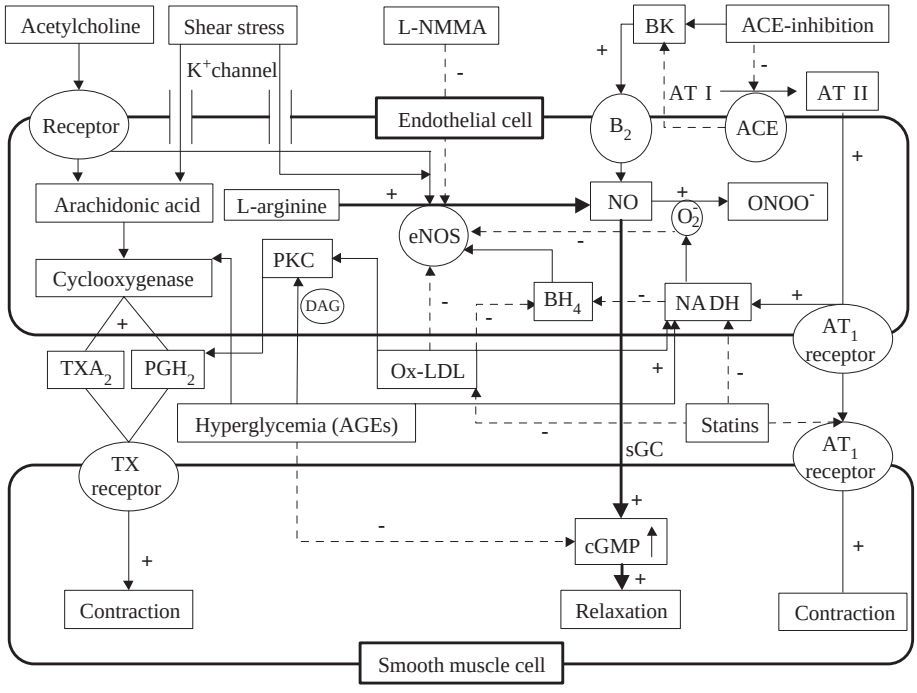

Fig. 1. Effect of acetylcholine/shear stress, ACE-inhibition, and statins on vasomotor function. BK: bradykinin, B_2: B_2-kinin receptor, ACE: angiotensin converting enzyme, AT: angiotensin, NO: nitric oxide, O_2: superoxide anion, $ONOO^-$: peroxynitrite anion, eNOS: endothelial Nitric oxide synthase, TXA_2: thromboxane A_2, PGH_2: prostaglandin H_2, PKC: protein kinase C, L-NMMA: L-N^G-monomethyl arginine, BH_4: tetrahydrobiopterin, NADH: NADH/NADPH oxidase, DAG: diacylglycerol, AGE: advanced glycation endproduct, ox-LDL: oxidised low-density lipoprotein, sGC: soluble guanylate cyclase, cGMP: cyclic guanosine monophosphate. ———— Upregulation, - - - - - -Downregulation.