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NITRIC OXIDE-DEPENDENT ENDOTHELIAL FUNCTION AND CARDIOVASCULAR DISEASE

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ABSTRACT

Nitric oxide produced by three different isoforms of nitric oxide synthase (NOS) widely expressed in virtually all vascular cell types is mostly produced by the endothelial isoform (eNOS) in endothelial cells where it plays a crucial role in vascular tone and structure regulation. It also exerts an anti-inflammatory influence, inhibits platelets adhesion and aggregation, and prevents smooth muscle cells proliferation and migration. Several lines of evidence link endothelial dysfunction, characterized by decreased bioavailability of nitric oxide, with the development of many pathological conditions such as heart failure, hypertension, diabetes and atherosclerosis. This review focuses on nitric oxide-dependent endothelial dysfunction in cardiovascular diseases, its clinical detection and relevance, potential pathogenic mechanisms and possible therapies.

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INTRODUCTION

Since the discovery of the obligatory role of the endothelial cells for the relaxation induced by acetylcholine of isolated rabbit aortic rings by Furchgott in 1980 (1), there has been a wide recognition of the importance of the endothelial monolayer as a source of autocrine and paracrine mediators critical for the maintenance of vascular homeostasis. In fact, the total mass of metabolically active endothelial cells in the adult body has been evaluated between 1.5 and 2 kg thereby representing the equivalent of a major endocrine organ. Among the vasoactive mediators, nitric oxide produced by the endothelial cells is essential for the control of intravascular thrombogenicity, vascular smooth muscle tone and proliferation. Nitric oxide is also an important inhibitor of platelet aggregation, leucocyte migration including through the inhibition of the expression of adhesion molecules such as VCAM-1 or ICAM-1, as well as chemotactic factors such as MCP-1. Therefore, nitric oxide appears to be a molecule with generally protective properties by inhibiting several steps that are part of the atherogenic process, as evidenced by enhanced atherogenesis in animals in which eNOS is either chronically inhibited or genetically deleted (for review see (2)). Understandably, defects in the nitric oxide pathway have been implicated in a variety of cardiovascular disease states, including atherosclerosis and heart failure(3).

MOLECULAR DETERMINANTS OF THE NITRIC OXIDE PATHWAY

Nitric oxide is produced in a variety of tissues by one or several of the three isoforms of nitric oxide synthase

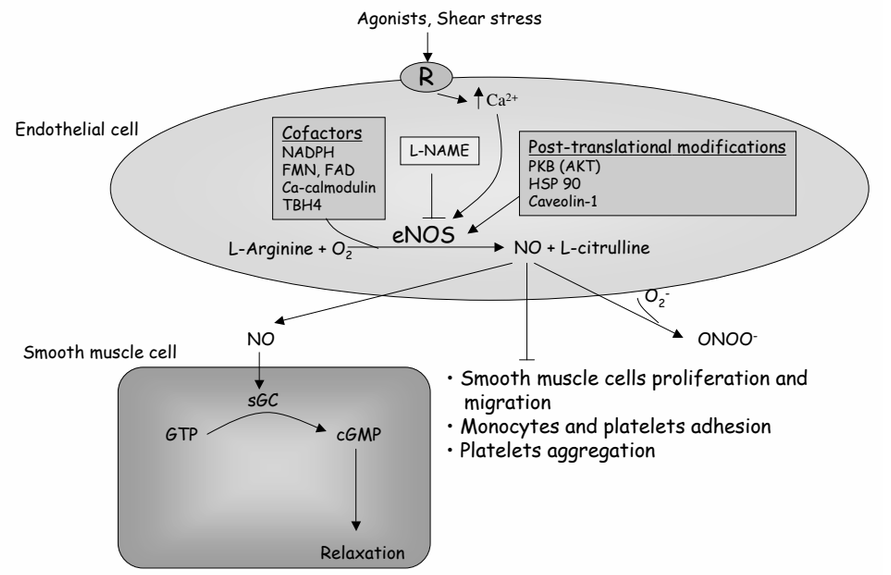
(NOS), namely the endothelial isoform (eNOS), mainly expressed in endothelial cells but also in cardiomyocytes from several species, the neuronal isoform, (nNOS) expressed in nerve cells, and the inducible isoform (iNOS), the expression of which can be induced in virtually all cell types after appropriate immune stimulation.

All three isoforms synthesize nitric oxide from the aminoacid L-arginine, yielding L-citrulline as a byproduct (Figure 1). Once produced, the labile free radical, nitric oxide is rapidly oxidized to nitrite and then nitrate and excreted into the urine(4). Whereas most of the biological actions of NO are supported by its free radical form or nitrosothiols resulting from S-nitrosylation of free thiol-containing molecules, interaction of nitric oxide with suproxide anions produces the formation of peroxinitrite, a powerful oxidant, thereby reducing the bioavailability and physiological responses mediated by nitric oxide(4).

In the vascular wall nitric oxide, once synthesized, diffuses across the endothelial cell membrane and enters the vascular smooth muscle cells to activate the soluble intracellular isoform of guanylate cyclase that catalyzes the production of intracellular cyclic guanosine 3', 5' monophosphate (cGMP) concentrations. Although cyclic GMP accounts for many of the biological effects of nitric oxide, including the control of vascular tone and platelet aggregation, nitric oxide can affect other molecular targets in a cyclic GMP-independent fashion (Figure 1). This includes haem or other iron-centered proteins, DNA and free thiol-containing proteins susceptible to S-nitrosylation as mentioned above. These reactions can affect the function of ion channels or key enzymes such as aconitase or GAPDH (for review see (3)).

Importantly, the enzymatic activity of nitric oxide synthase depends on the availability of several key cofactors including nicotinamide adenine dinucleotide phosphate (NADPH), flavine mononucleotide, flavine adenine dinucleotide, tetrahydrobiopterin (THB4) and calcium calmodulin. The latter reversibly associates with NOS through an interaction with its specific consensus calmodulin binding site to enable electron flow between the reductase to the oxygenase domain of NOS(4). The affinity of calmodulin to its binding site is sensitive to the concentration of calcium within the range of usual intracellular fluctuations of this ion, at least for eNOS and nNOS. The activating association of calcium-cal-

Figure 1 : Regulation of nitric oxide production and signal transduction pathway in endothelial cells and smooth muscle cells. *Endothelial receptor activation or shear stress induces an increase of calcium into the cytoplasm of endothelial cells, wich leads to eNOS activation and production of nitric oxide (NO) from L-arginine. This synthesis largely depends on the availability of different cofactors. Several post-translational modifications can influence the activation of eNOS. Once synthesized, NO diffuses across the endothelial cell membrane and enters the vascular smooth muscle cells to activate the soluble intracellular isoform of guanylate cyclase (sGC) that catalyzes the production of intracellular cyclic guanosine 3', 5' monophosphate (cGMP) concentrations, which induces smooth muscle cell relaxation. NO also exerts an anti-inflammatory influence, inhibits monocytes and platelets adhesion as well as platelets aggregation, and prevents smooth muscle cells proliferation and migration.*



modulin to eNOS is also influenced by other recently identified post-translational regulations, including through allosteric modulation by the chaperone protein HSP 90, changes in eNOS phosphorylation state and also negative regulation through eNOS interaction with the caveolar coat protein, caveolin (Figure 1)(5).

REGULATION OF NITRIC OXIDE PRODUCTION

As mentioned before, a continuous basal release of nitric oxide maintains resting vascular tone. Both physical forces (shear stress) and endothelial-specific receptor agonists may activate eNOS to increase nitric oxide production.

The influence of eNOS inhibition on vessel tone is more prominent in the arterial tree than in veins, especially in small resistance vessels. This can be measured from the increase in vessel tone with L-arginine analogs and NOS inhibitors in vessel rings in vitro but also from the increase in perfusion pressure in vivo. This is consistent with the development of high blood pressure in transgenic mice deficient for eNOS(6). Infusion of L-NMMA into the brachial artery also causes vasoconstriction in the human forearm vessels.

Among the most important determinants for the continuous activation of the endothelium are hemodynamic stimuli. Indeed, shear stress directly proportional to flow velocity is an important physiological stimulus increasing nitric oxide release from the endothelial lining of vessels, resulting in a constant basal nitric oxide production. Following the application of fluid shear stress to endothelial cells, nitric oxide production is enhanced twofold over basal values and is maintained as long as the stimulus is applied(7). The application of a mechanical stimulus can be transmitted through the entire cell by the cytoskeleton, which acts as a mechanoreceptor, to activate transduction cascades; specifically, the lateral zone of cell-cell adhesion is thought to be the major signal transduction site for fluid shear stress(8). Recently, a role for PECAM-1 in this transduction cascade has been suggested(8).

These initial rapid events are followed by post-translational modifications of eNOS, most notably phosphorylation of the enzyme by the serine-threonine proteine kinase B (or Akt) on a specific serine residue (Ser 1179 on human eNOS). Phosphorylation of eNOS on this residue appears to prevent the dissociation of calcium-calmodulin thereby maintaining the enzyme in its active form despite subsequent decreases in intracellular calcium. Although this secondary activation is commonly referred to as calcium-independent, it still needs the activation and binding of calmodulin which requires initial increases in intracellular calcium.

On a longer term, shear stress also activates eNOS transcription with subsequent increases in eNOS mRNA and protein abundance that sustain a stronger endothelial NO production. Conversely, decreases in shear stress consecutive to decreased flow velocity, as observed in heart failure, may explain the downregulation of eNOS expression and the impaired ability of vessels to produce NO.

Finally, many circulating autacoids may act on specific endothelial receptors coupled to eNOS activation and NO synthesis. Most of these receptor-mediated mechanisms implicate intracellular increases in calcium, although some may act through post-translational modification of eNOS such as dephosphorylation on the threonine 496 residue. It is also important to recognize that many mediators exert vasodilating actions through a combined production of nitric oxide and other endothelial-derived vasodilatory factors, such as endothelium-derived hyperpolarizing factors (EDHF) or prostanoids such as prostacycline (PGI2). Therefore, the sensitivity of peripheral vessel tone to inhibitors of nitric oxide synthase varies not only according to the species but also according to the different segments of the vascular tree, underlying differences in the relative importance of NO versus other vasodilators as physiological regulators of vessel tone.

IN VIVO ASSESSMENT OF NO-DEPENDENT ENDOTHELIAL FUNCTION

The accumulated evidence for the protective role of the nitric oxide pathway against atherogenesis underscores the need for clinical assessments of the integrity of the endothelium and of its ability to produce nitric oxide in patients. This can be done in vivo through both invasive and non-invasive approaches to assess changes in vessel diameters in response to shear stress or agonist stimulated production of endothelial derived nitric oxide (for review see (9)).

Quantitative coronary angiography can be performed during a routine cath lab evaluation of epicardial coronary artery diameters and the changes in coronary diameter in response to a intracoronary infusion of agonist such as acetylcholine. In a vessel with normal endothelial function, this usually results in an increased vessel diameter, whereas arterial segments with diseased endothelium may respond by a paradoxical va-

soconstriction (or reduced in vessel diameter), even in the absence of measurable coronary stenosis at baseline. To specifically assign the abnormal response to defects in the endothelial cells, as opposed to abnormal reactivity of the underlying vascular smooth muscle, the vessel response to acetylcholine is usually compared to changes in vessel diameter after a direct infusion of nitric oxide donors such as nitroglycerine which will result in an endothelium-independent vascular smooth muscle relaxation.

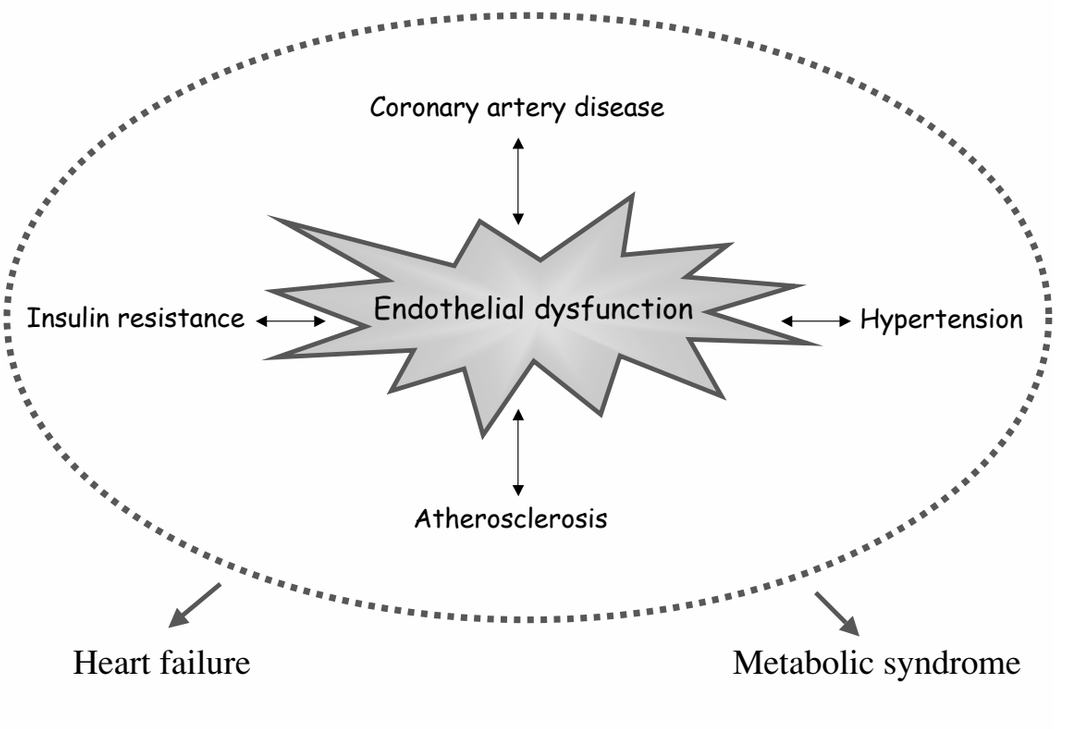
The endothelial-dependent vessel relaxation can be assessed non-invasively by ultrasonographic measurements of the changes in brachial artery diameter during flow-mediated dilatation. During this test, after the measurement of brachial artery diameter at baseline, blood flow is interrupted through the inflation of a blood pressure cuff and after deflation, physiological increases in brachial artery diameter are measured during the seconds to minutes following flow-mediated dilatation. This test of the responsiveness to increases in shear stress can be combined with more complete pharmacological characterization through the intra-arterial infusion of endothelial specific agonists or NOS inhibitors. In addition to the advantage of being non-invasive, this test has received more attention after the suggestion that it may reflect similar alterations in the endothelial function in the coronary vascular tissue. It is however sensitive to the confounding interference of many variables such as post-prandial hyperlipemia. In addition, the results with this non-invasive test may show considerable variability, unless performed by a highly experienced echographist well acquainted with the technique.

ENDOTHELIAL DYSFUNCTION IN CARDIOVASCULAR DISEASE

Defects in endothelium-dependent NO production are commonly observed in experimental models of atherosclerosis or hypertension as well as in patients with similar diseases (Figure 2)(2). This can be measured by impaired relaxation to acetylcholine in endothelium-intact vascular rings in vitro, or paradoxical vasoconstriction measured in patients with one of the techniques mentioned above.

Importantly, such defects in the endothelial function both in coronary and peripheral arterial vessels, have

Figure 2 : Endothelial dysfunction in cardiovascular disease processes. *Endothelial dysfunction precedes the development of several pathological conditions such as coronary artery disease, hypertension, atherosclerosis and insulin resistance, all of which, in turn, worsen endothelial function. Over time, these clinical conditions increase the risk to the progression towards heart failure, particularly in the context of the metabolic syndrome.*



been prospectively correlated with clinical outcomes in patients with coronary artery disease. In a recent multivariate analysis, coronary and peripheral endothelial dysfunction have been shown to be strongly and independently associated with cardiovascular events, such as cardiac death, myocardial infarction, and need for revascularization(10). Moreover, the observation that the cardiovascular events do not necessarily occur at the site where the endothelial dysfunction was detected underscores the systemic nature of endothelial dysfunction and its pivotal role in the prediction of cardiovascular events(10). In patients with heart failure, endothelial dysfunction is associated with a higher incidence of hospitalization for the decompensation of heart failure, cardiac transplantation, or cardiac death(11). In addition, improvement of systemic endothelial vasodilator dysfunction within a short time period of 8 weeks after an acute coronary syndrome is associated with significantly fewer future cardiovascular events(12). This opens the perspective to use endothelial function assessments as surrogate endpoints in future interventional trials evaluating the beneficial effect of drugs or dietary interventions targeting the endothelial NO pathway.

As mentioned above, increased vasoconstriction and defective vasodilator responses to physical stimuli are common in chronic heart failure. This probably not only reflects a reduced ability of the endothelium to produce nitric oxide (as a result of reduced eNOS expression, as clearly established in animal models) but also an increased production of vasoconstrictor agonists such as endothelin-1 or angiotensin II. The latter, in turn, accounts for an increased oxidative stress via increased generation of superoxide anions that decrease the bioavailability of nitric oxide.

Endothelial dysfunction may also be at the centre of the adverse effects of known risk factors for coronary heart disease. Hyperlipidemia, hypertension, chronic hyperglycaemia and hyperhomocysteinemia are all known to be associated with defects in endothelial-NO mediated vasodilatation. Although most, if not all, of these factors can increase vascular oxidative stress, increasing evidence from in vitro studies also suggests a direct impairment of eNOS activation by some of these factors (see below). Reduced endothelium-dependent vasodilation can be observed before the development of patent atherosclerosis in both coronary and peripheral vessels of patients with hypercholesterolemia. Causality of the lipid disorder was supported by the observation that a normal endothelium-dependent vasodilatation could be restored after several months of lipid lowering treatment, although the impact of this reversibility on coronary heart disease risk has been questioned in some studies. In high-risk patients such as those with unstable angina, however, the MIRACL trial indicates that treatment with atorvastatin, initiated during the acute phase,

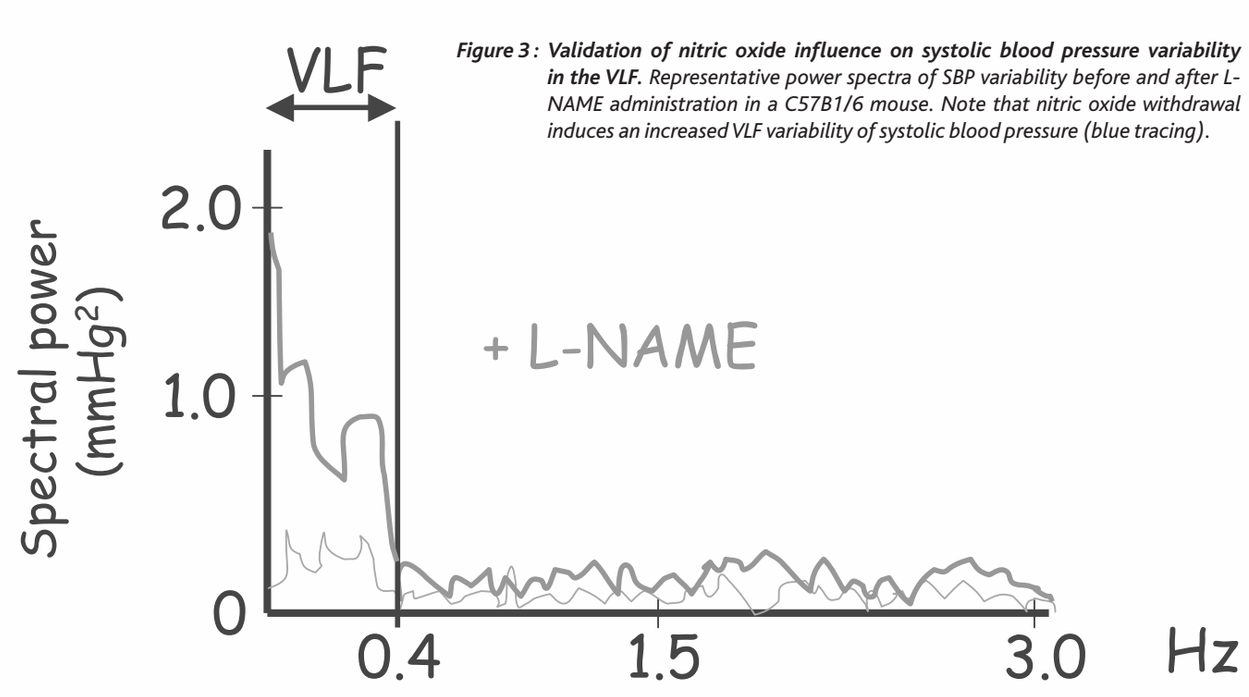


Figure 3 : Validation of nitric oxide influence on systolic blood pressure variability in the VLF. *Representative power spectra of SBP variability before and after L-NAME administration in a C57B1/6 mouse. Note that nitric oxide withdrawal induces an increased VLF variability of systolic blood pressure (blue tracing).*

reduces the risk of early, recurrent ischemic events, primarily recurrent symptomatic ischemia requiring hospitalization.(13) Moreover, the results from the PROVE-IT trial showed that among patients who had recently been hospitalized for acute coronary syndrome, an intensive lipid lowering statin regimen resulted in a lower risk to death from any cause or major cardiac event than did a more moderate degree of lipid lowering with the use of a standard dose of a statin(14). The rapidity of the clinical benefit has been suggested to be an indication of direct vascular ("pleiotropic") effects of the statin (including on the endothelium) beyond the slower alleviation of plaque lipid load resulting from systemic cholesterol reduction.

Similar alterations in basal or acetylcholine induced nitric oxide dependent relaxation have been observed in animal and human studies of hypertension. Although decreases in nitric oxide-mediated dilatation may be the result of endothelial damage from chronic high blood pressure, selective deletion of the eNOS gene results in the slow development of high blood pressure in mice(6) which would causally link defects in eNOS to the development of high blood pressure. Furthermore, endothelial NO production in response to vascular shear stress provides a short-term blood pressure buffering mechanism that, if deficient, would result in enhanced blood pressure variability. In eNOS knockout mice, the latter is significantly increased compared to WT mice(6), in a range of frequency corresponding to 0.05-0.4 Hz, previously shown to be associated with the mixed influence of neurohumoral factors in mice(15). We independently validated the influence of the NO pathway on this particular frequency band using acute inhibition of L-NAME, a non specific NOS inhibitor (Figure 3)(16). Blood pressure variability has potential clinical importance because it has been identified as an independent risk factor for cardiovascular mortality and end-organ damage independently from absolute changes in blood pressure(17). Accordingly, antihypertensive agents with known effects on endothelial NO-dependent function, such as angiotensin-converting enzyme inhibitors provide end-organ protection independently of blood pressure (BP) lowering, and reduce the risks of CV morbidity and mortality(18).

NO-dependent endothelial dysfunction may also represent the early stage of vascular disease in type 2 diabetes. This has been suggested by observations of altered flow-mediated dilatation in subjects with insulin resistance syndrome who are at risk of developing type 2 diabetes even when they are still normoglycaemic. In most studies, agonist-induced nitric oxide release and endothelial function are usually altered at later stages of the disease. Insulin resistance contributes to the induction of deleterious changes in the vascular endothelium and the lipid profile, leading to the progression of atherosclerosis. Under physiologic conditions, insulin has an anti-inflammatory and vasodilator effect through increasing the expression, but also, the activity of the endothelial NO synthase (eNOS) via the activation of the PI3 kinase pathway(19;20). When insulin resistance is established, activation of the MAP kinase pathway may be favoured, with a resulting increase in vascular inflammation and an inhibition of vasodilation(21). Thus, insulin resistance is considered as a major cause of endothelial dysfunction, which predisposes to the progression of atherosclerosis.

PPAR-γ (*Peroxisome Proliferator-Activated Receptor-gamma*) is a nuclear transcription factor implicated principally in insulin sensitivity. It is expressed in adipose tissue, liver and skeletal muscle cells, where it improves glycaemic control by increasing the peripheral utilization of glucose and promotes adipocytes differentiation for proper lipid storage in subcutaneous adipose tissue. PPAR-γ is also expressed in endothelial cells where it may exert anti-inflammatory and potentially anti-atherogenic effects(22). Thiazolidinediones, a class of antidiabetic drugs, enhance insulin sensitivity through the activation of PPAR-γ. Recent studies have shown that thiazolidinediones improve endothelial function, independently of glucose control, in patients with type 2 diabetes as well as in nondiabetic patients with cardiovascular risk factors(23;24). Likewise, using a mouse model of the metabolic syndrome, we have recently shown that weight loss caused by diet restriction improves insulin sensitivity, restores blood pressure (and its NO-dependent variability), improves cardiac function and reduces atherosclerosis(25), all of which are associated with upregulation of vascular PPAR-γ expression.

POTENTIAL MECHANISMS OF NO-DEPENDENT ENDOTHELIAL DYSFUNCTION

Theoretically, alterations in the L-arginine nitric oxide pathway may result from either reduced nitric oxide production or increased degradation of bioavailable nitric oxide. Nitric oxide production from the endothelial cells can be reduced as a result of a downregulation of the abundance of eNOS within the endothelial cells, such as observed in animal models of chronic heart failure or in the endothelial lining of vessels with advanced atherosclerotic lesions in some human studies. However, despite

unchanged abundance of eNOS, NO production can be decreased through several alterations in post-translational mechanisms. Deficiency of co-factors such as THB4 may explain reduced enzyme activity of eNOS, as observed in circumstances such as cigarette smoking, hypercholesterolemia or in animal models of genetic hypertension. In addition, the interaction of BH4 with peroxynitrite (generated from the reaction between nitric oxide and superoxide) rapidly oxidizes TBH4 and can induce eNOS uncoupling (a state in which eNOS produces radical oxidant species, ROS) and endothelial dysfunction(26). Recently, the role of TBH4 in the regulation of eNOS coupling *in vivo*, in the absence of any vascular disease, has been studied in a mouse model in which both eNOS and GTP cyclohydrolase 1 (GTPCH), the rate-limiting enzyme in BH4 synthesis, were overexpressed(27). Overexpression of TBH4 in this mouse model led to a restoration of eNOS coupling, an increased nitric oxide production and a reduced eNOS-dependent production of ROS, compared to mice with an overexpression of eNOS only.(27)

Using an in vitro model of endothelial cells exposed to human LDL-cholesterol, we found an increased uptake of cholesterol from the LDL particules and the consequent increase in intracellular free cholesterol resulted in an increased abundance of caveolin–1, a negative regulator of eNOS activity.(28) This was associated with a decreased stimulated production of nitric oxide despite unchanged abundance of eNOS. Importantly, this defect could be corrected by treatment of the cells with HMG-CoA-reductase inhibitors such as Atorvastatin that decreases intracellular cholesterol synthesis(29).

In vivo, eNOS activity may be downregulated as a result of an overproduction of endogenous inhibitors of the enzyme such as asymmetric and symmetric dimethylarginine (ADMA and SDMA) that act as competitive inhibitors of nitric oxide synthase in human plasma. These inhibitors are synthesized in human vascular endothelial cells by one of the two isoforms of protein-arginine methyltransferases (PRMTs) dimethylarginine dimethylaminohydrolase (DDAH) that have been identified and cloned so far. Recent evidence suggests that even small changes in ADMA circulating levels significantly modulate nitric oxide production. Indeed, in a mouse model in which the gene for dimethyarginine dimethylaminohydrolase (DDAH-1; the enzyme that inactivates ADMA) is overexpressed, resulting in a decreased ADMA level (of lidwoord weg), there is an increased vascular nitric oxide production leading to a decrease in blood pressure as well as systemic vascular resistance(30). Increased ADMA concentrations have been observed in patients with chronic renal failure, hypercholesterolemia, atherosclerosis and hypertension. Prospective clinical studies have suggested a role for ADMA as a novel independent cardiovascular risk factor(31). In these studies, elevated ADMA was associated with a mean three- to fivefold increase in risk of experiencing a serious cardiovascular event.(31) The list of clinical conditions associated with an increased level of these endogenous inhibitors of NOS is still growing. Finally, the use of some antidiabetic drugs, such as rosiglitazone, as well as rosuvastatin has been associated with a decrease in ADMA circulating levels(32;33).

Finally, increased oxidative stress resulting from hyperglycaemia, dyslipidemia, chronic hypertension or vascular inflammation may similarly reduce nitric oxide bioavailability, as mentioned above. The source of superoxide anions production can be either the endothelial membrane-bound NADH/NADPH oxidase or eNOS itself, when uncoupled. In the case of hyperglycaemia, it seems that activation of one or several specific isoforms of protein kinase C is a central mechanism. In addition, it is possible that some NO degradation may occur through quenching by advanced glycation end products (AGEs), which are products of non-enzymatic glycation and cross-linking of collagen proteins.

REVERSAL OF ENDOTHELIAL DYSFUNCTION : POTENTIAL THERAPIES

Following the recognition of a role for reactive oxygen species in the generation of NO-dependent endothelial dysfunction, many studies have examined the possibility to restore endothelial function with antioxidants. Despite some encouraging results in animal studies, and to a more limited extent in human patients as well, the benefit of long term supplementation with antioxidants such as vitamin C, E or beta caroten are far from being established and need to be examined further(32;34;35). In particular, the HOPE trial indicated that among patients at high risk for cardiovascular events, vitamin E has no beneficial effect on any cardiovascular outcomes(36). Some of the conflicting evidence may also be explained by the capacity of some agents such as vitamin C to produce pro-oxidant effects under certain experimental conditions.

Among the drugs commonly prescribed in cardiovascular diseases, ACE inhibitors and statins have been shown to restore or potentiate endothelial NO-dependent vasodilation. ACE inhibitors may act both through an inhibition of the generation of angiotensin II which

is known to increase superoxide anion production, and through decreasing the degradation of plasma bradykinin, a peptide agonist known to increase nitric oxide production from endothelial cells. Statins can improve the function of the L-Arginine-nitric oxide pathway by several mechanisms, including increases in eNOS expression (at least at high doses in animals), direct antioxidant effects, or post-translational modifications of eNOS that result in increased enzyme activity. The latter include enhanced eNOS phosphorylation or decreased eNOS inhibition through downregulation of caveolin expression, promoting the recruitment of the chaperone protein, hsp90 to stabilize eNOS in its active conformation. The relevance of the statins' pleiotropic effects compared with lipid lowering to their widely-established clinical benefits both in primary and secondary clinical trials of coronary and cerebral vascular disease, although still debatable in low risk patients, has received more recognition in high-risk patients. In two recent clinical studies, the effect of simvastatin(37) or atorvastatin(38) was compared to ezetimibe, an intestinal cholesterol absorption inhibitor in patients with congestive heart failure or coronary artery disease. Despite similar decreases in LDL cholesterol, both statins (contrary to ezetimibe) improved endothelial function, compatible with their beneficial effect beyond LDL cholesterol lowering(37;38).

CONCLUSION

Nitric oxide is a major physiological regulator of vascular function. It is at the centre of the vasorelaxing, antiaggregant and antiproliferative influences of the endothelium, thereby maintaining a balance against various agents with pro-atherogenic influences. Many of the known cardiovascular disease risk factors impair nitric oxide synthesis or increase nitric oxide degradation thereby producing an imbalance that may explain their pro-atherogenic influences. Several drugs can reverse the endothelial NO-dependent dysfunction and restore endothelium-dependent relaxation, as measured by both non-invasive and invasive tests in patients. Careful use of these assays to prospectively measure endothelial function as a surrogate endpoint in interventional studies will contribute to delineate the specific importance of the correction of endothelial dysfunction by these drugs as a mechanism of their beneficial effects in the prevention of atherosclerosis and acute cardiovascular events.

RÉSUMÉ

Le monoxyde d'azote produit par trois isoformes différentes de la synthétase du monoxyde d'azote, largement exprimées pratiquement dans tous les types cellulaires est surtout produit par l'isoforme endothelial (eNOS) dans les cellules endothéliales où il joue un rôle crucial dans la régulation du tonus et de la structure vasculaire. Il a également un rôle anti-inflammatoire, il inhibe l'adhésion et l'agrégation plaquettaire et prévient la prolifération et la migration des cellules musculaires lisses. Plusieurs évidences relient la dysfonction endothéliale, caractérisée par une réduction de la biodisponibilité du monoxyde d'azote, au développement de différentes conditions pathologiques telles que l'infarctus du myocarde, l'hypertension, le diabète et l'athérosclérose. Cette revue se concentre principalement sur la dysfonction endothéliale dépendante du monoxyde d'azote dans les maladies cardiovasculaires, sa détection et sa pertinence clinique, les mécanismes pathogéniques potentiels impliqués ainsi que les thérapies éventuelles.

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