Endothelial dysfunction is an independent predictor of cardiovascular risk. It is found with aging, and in many conditions associated with increased cardiovascular risk such as hypertension, atherosclerosis, dyslipidemia, diabetes, obesity, smoking, and renal failure, among others. It is characterized by increased permeability, altered endothelium-mediated vasodilatation, increased vascular reactivity, platelet activation and enhanced thrombogenicity, leukocyte adhesion, and monocyte migration. In large measure it results from increased oxidative stress in the vascular wall mostly attributable to activation of vascular reduced nicotinamide adenine dinucleotide (NADPH) oxidase and uncoupling of endothelial nitric oxide synthase (eNOS). There is also increased expression of endothelin-1 (ET-1), an altered balance between the production of vasodilator and vasoconstrictor prostanoids, and induction of adhesion molecules and other proinflammatory mediators.

The degree of endothelial dysfunction has been shown to correlate with cardiovascular outcomes, and dysfunctional endothelium plays a role in the triggering of cardiovascular events. Although it involves many mediators related to vasoconstriction, vasodilatation, inflammation, and thrombosis, endothelial function was initially described in the Nobel Prize–winning discovery as consisting mainly of vasodilation induced by cholinergic agents, ultimately leading to the demonstration that NO was one of the main mediators of endothelium-dependent vasodilatation. NO is produced in the blood vessel wall mainly by eNOS, and may be scavenged by excess reactive oxygen species (ROS). Thus, the availability of NO to dilate blood vessels depends on the balance between ROS in the vascular wall and the production of NO (Figure). Physiologically, vessels are generally maintained in an NO-mediated quiescent and dilated state. In pathological situations, NO is quenched by excess ROS, generated in large part in blood vessels by vascular NADPH oxidase. In the endothelium, ROS formation is highly complex because not only is superoxide formed by activated NADPH oxidase, but eNOS also has the potential to generate ROS. In fact eNOS may produce both NO, via its oxygenase function, and superoxide through its reductase function, the latter dependent on NADPH. In oxidative states, reduction in tetrahydrobiopterin results in uncoupling of eNOS, resulting in production of superoxide by the eNOS monomer whereas the dimer, in the presence of abundant tetrahydrobiopterin, produces mainly NO. This delicate balance could exert a critical role in the ability of blood vessels to maintain normal homeostasis and remain dilated. It impacts as well on the progression of atherosclerosis, development of vulnerable atherosclerotic plaques with a tendency to rupture, and precipitation of thrombosis. Increased ROS production and a shift in balance from NO to ROS signaling represent common characteristics in vascular disease.

Preclinical evidence indicates that levels of endothelial NO depend on various factors, which include the activity and coupling of eNOS, which determine whether NO or superoxide and peroxynitrite (ONOO−) are the predominant products. Other sources of ROS, such as vascular NAD(P)H oxidase, xanthine oxidase, mitochondrial enzymes, and myeloperoxidase, as well as the dismutation of superoxide by superoxide dismutases (SOD) that leads to formation of hydrogen peroxide can also impact on the balance between NO and ROS.

In this issue of Hypertension, Lavi et al. demonstrate for the first time in a human study that endothelial function in the left anterior descending territory of the coronary circulation as evaluated during coronary angiography, in early atherosclerosis, and in the absence of obstructive coronary artery disease, coronary artery diameter in response to cholinergic stimuli is related not to the activity of eNOS and generation of NO but rather to the bioavailability of NO. The latter depends on the amount of ROS present that can transform NO to ONOO− and as well oxidize tetrahydrobiopterin to dihydrobiopterin leading to eNOS uncoupling and more ROS production. In the study of Lavi et al., individuals with endothelial dysfunction, as measured by impairment of coronary artery dilatation in response to acetylcholine, and in subjects with normal endothelial function, the effect of 1-NMMA, an eNOS inhibitor, whose blunting action on acetylcholine-induced vasodilation is a measure of NO production, and nitrotyrosine concentration, a measure of ONOO− production, were similar. In contrast, these authors demonstrate that impaired vasodilatation in response to acetylcholine correlated with increased production of F2-isoprostane across the coronary circulation (used in this study as a measure of local ROS generation) and reduced superoxide dismutase activity (an antioxidant mechanism). Interestingly, myeloperox-

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idase activity was not different, suggesting that ROS generation is probably not from leukocytes/macrophages, which characteristically possess myeloperoxidase.

Thus, in the subjects studied by Lavi et al, without obstructive coronary artery disease but with endothelial dysfunction, it appears that local superoxide generation is enhanced but NO production is conserved, whereas NO bioavailability is reduced by the increased local oxidative stress. Although eliminating myeloperoxidase and accordingly local leukocyte vascular wall infiltration as a source of increased oxidative stress in coronary arteries and modulation of NO responses, the study does not clarify what the source of ROS may be. It is known that NADPH oxidase is the most important source of superoxide in the vascular wall, and as mentioned above, other sources may also be important. In fact, the increased ROS could simply reflect decreased antioxidant capacity. Moreover, from this study it does not appear that uncoupling of eNOS or that myeloperoxidase play a role in the early stages of atherosclerosis. However, study of these effects after increasing the local concentration of tetrahydrobiopterin could help determine the former more unambiguously but may be difficult in the acute setting of coronary angiography. Which of the different superoxide dismutases is reduced is not clarified, although it is likely that extracellular SOD released from the endothelium is the most probable source. Although the mechanism for this reduction is not elucidated, there is data suggesting that in apoE knockout mice there is an initial increase and subsequent decrease of SOD activity, which may account for reduction of antioxidant defenses and increased oxidant stress in the vascular wall.

It should also be clarified that in the study of Lavi et al, only one measure of ROS was determined, namely F2-isoprostanes, which actually represents lipid peroxidation and not necessarily oxidative stress. F2-isoprostanes are an indirect index of redox state as they are formed from arachidonate by free radical-mediated oxidation. Generation of lipid peroxidation products depends not only on ROS, but also on patient lipid status, which could be important in the cohort studied in which subjects with endothelial dysfunction had a higher Framingham risk score than those with normal endothelial function.

Nevertheless, the findings Lavi et al are important because the study was carried out in vivo in humans and provides insights into early human atherosclerotic disease. The results are intriguing, and although there are limitations mentioned above, they may have therapeutic significance. Dissecting the mechanisms that contribute to reduced bioavailability of NO would facilitate development of novel therapeutic approaches that could allow increasing NO bioavailability and combating local ROS generation, the latter known to predict outcomes. This may help these subjects who suffer from angina and who may develop cardiovascular events as a consequence of either proximal epicardial or distal microvascular endothelial dysfunction.

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Disclosures

None.

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Oxidative Stress, Nitric Oxide Synthase, and Superoxide Dismutase: A Matter of Imbalance Underlies Endothelial Dysfunction in the Human Coronary Circulation

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