Before the recent discoveries on the functional importance of the endothelium in the regulation of vascular tone and growth as well as platelet function and coagulation, it was obvious that the intima was a major target of various cardiovascular injuries.1-5 Indeed, although endothelial cells are not denuded in diseased blood vessels (except at late stages), the morphology of the cells as well as the subintimal space does exhibit changes in hypertension, diabetes, hypercholesterolemia, atherosclerosis, reperfusion injury, and cyclosporin toxicity.

A crucial discovery by Furchgott and Zawadzki in 19806 was the fact that endothelial cells regulate the tone of the underlying vascular smooth muscle. Later on, it became clear that the mediator of endothelium-dependent relaxations was nitric oxide formed from L-arginine7-10 via the activity of a constitutively expressed enzyme, nitric oxide synthase.11-13 Hence, nitric oxide represents the endogenous nitrovasodilator, which activates soluble guanylyl cyclase in vascular smooth muscle14 and in turn causes profound relaxation by decreasing intracellular Ca2+ levels15 and dephosphorylating myosin light chains.16 The importance of this pathway in the circulation was further supported by the discovery that nitric oxide not only causes relaxation but also exerts potent inhibitory effects on platelet function17,18 and possibly on macrophages.

Functional alterations of the endothelial L-arginine/nitric oxide pathway may be important in cardiovascular disease, because a depressed activity of this protective mechanism would lead to impaired relaxation (and, in turn, vasocostriction and reduced local blood flow) and also be associated with reduced antithrombotic properties of the endothelial layer. If such dysfunction were to occur also at the resistance artery level, it could also contribute to the regulation of peripheral vascular resistance and, in turn, of the blood pressure. Earlier experimental studies demonstrated endothelial dysfunction in large conduit arteries19-21 and also in resistance arteries of hypertensive rats.22-25 Clinical studies in the forearm and coronary circulation of hypertensive subjects later confirmed that similar alterations in endothelial function also occur in patients.26-28 Interestingly, endothelial dysfunction at the resistance artery level is not restricted to hypertension but also occurs in patients with hyperlipidemia and normal blood pressure.29 Furthermore, diabetes also is associated with endothelial dysfunction in the microcirculation.30 Hence, it appears that functional changes of the endothelium are a common hallmark of several forms of cardiovascular disease and therefore a primary candidate as mediators of these disease states and also, particularly, of their complications (such as myocardial infarction and stroke).

Dysfunction of the endothelial L-arginine/nitric oxide pathway could occur at several levels, and may involve 1) altered expression of endothelial receptors, 2) impaired signal transduction mechanisms, 3) decreased activity of nitric oxide synthase, 4) reduced intracellular availability of L-arginine, 5) increased breakdown of nitric oxide formed from L-arginine, and finally 6) reduced responsiveness of vascular smooth muscle to the endogenous nitrovasodilator. Furthermore, two other possible explanations should be considered, namely, increased formation of an inhibitor of the L-arginine pathway such as asymmetric dimethyl arginine (ADMA31) or an endothelium-derived contracting factor (i.e., prostaglandin H219-32), which in the spontaneously hypertensive rat impairs endothelium-dependent relaxations to acetylcholine even in the presence of a functionally intact L-arginine/nitric oxide pathway.

In the recent literature, interest has focused on the potential usefulness of L-arginine as a therapeutic tool in vascular disease. Indeed, in porcine coronary arteries treated with oxidized low-density lipoproteins, endothelium-dependent relaxations to serotonin are impaired but can be improved if the vessels are pretreated with L-arginine53; this suggested that the intracellular availability of L-arginine and/or its receptor-operated mobilization from intracellular stores may be reduced under these conditions. Similarly, in hyperlipidemic rabbits, infusion of L-arginine in vivo improves or restores impaired endothelium-dependent relaxations.34 Furthermore, chronic therapy with L-arginine markedly reduces endothelium dysfunction and atherosclerosis in hypercholesteremic rabbits.35 Also, in hyperlipidemic patients, infusion of L-arginine either in the coronary circulation36,37 or the human forearm circulation38 restores the impaired endothelium-dependent vasodilatation to acetylcholine. These studies strongly suggest that the intracellular availability and/or mobilization of L-arginine may indeed be an early endothelial defect in hyperlipidemia and atherosclerosis. If so, L-arginine...
could serve as a therapeutic tool aiming at improving or even restoring impaired endothelial function,⁵⁹ at least in early stages of the disease process.

In a study reported in this issue of Circulation, Panza et al.⁴⁰ used L-arginine in an attempt to restore the reduced endothelium-dependent vasodilation in patients with essential hypertension. Their study certainly was stimulated by experimental research suggesting that L-arginine may abrogate salt-sensitive hypertension⁴¹ and by studies demonstrating a hypotensive effect of L-arginine in normal humans.⁴² Two major observations were made in the study by Panza et al: 1) L-Arginine infusion significantly augmented the vasodilator response to acetylcholine in normal subjects. 2) In contrast, in hypertensive patients, the infusion of the precursor of nitric oxide did not affect the response to acetylcholine, which was impaired, as in previous studies.⁶⁶,⁶⁷ Since L-arginine did not modify the response of both normotensive and hypertensive subjects to the endothelium-independent vasodilator sodium nitroprusside and infusion of D-arginine (the stereoisomer of L-arginine) did not alter the response to acetylcholine except at very high dosages, the effects of L-arginine should be specific.

The major conclusion from this study appears to be the fact that the mechanisms of endothelial dysfunction differ in various forms of cardiovascular disease. Whereas in hypercholesterolemia and early forms of atherosclerosis the intracellular availability and/or receptor-operated mobilization of L-arginine may be a primary problem, the situation differs in hypertension. Indeed, if L-arginine is ineffective in improving the impaired endothelium-dependent vasodilation in hypertensive subjects, the endothelial defect must involve either 1) reduced expression of muscarinic receptors (and possibly other endothelial receptors linked to the L-arginine/nitric oxide pathway), 2) impaired signal transduction, 3) an altered uptake mechanism of L-arginine into the endothelium, and/or 4) impaired activity of nitric oxide synthase. A reduced responsiveness of hypertensive vascular smooth muscle to nitric oxide can be excluded, because the response to sodium nitroprusside was identical in normotensive and hypertensive subjects.⁴⁰ Furthermore, it also appears unlikely that an increased production of the inhibitor of nitric oxide synthase, ADMA,⁵¹ is an important determinant. Indeed, if the endothelial production of this endogenous inhibitor of the L-arginine pathway was increased, one would expect depressed effects of L-arginine (which competes with ADMA for the enzyme) in hypertensive patients, but particularly at higher dosages, one should still see some effect.

The experimental setup of forearm plethysmography does not allow detailed and conclusive insights into all possible mechanisms. However, it would be crucial to know whether other agonists such as bradykinin or substance P, or increased blood flow, all potent activators of the L-arginine/nitric oxide pathway, also exhibit impaired responses in hypertension. Such experiments would answer the question whether in hypertension a selective defect of muscarinic receptors occurs or whether the disease process is associated with a more generalized impairment of endothelial receptors, for instance as a result of G protein dysfunction.⁴³ Indeed, in Dahl-salt hypertensive rats, hypertension not only impairs the response to acetylcholine but also that to ADP and thrombin.⁴¹ In contrast, in spontaneously hypertensive rats, endothelium-dependent relaxation to acetylcholine is reduced,⁴⁹ whereas that to thrombin is maintained.⁵⁰ Interestingly, in the coronary⁴⁴,⁴⁵ and forearm circulations⁴⁶ of hypertensive subjects and those with hypercholesteremia, flow-dependent vasodilation remains intact, although the response to acetylcholine already is abnormal. This would be compatible with the concept that receptor-operated signal transduction mechanisms are involved rather than a defect of nitric oxide synthase.

Quite a different explanation, however, would involve the possibility that an endothelium-derived contracting factor is formed in hypertensive patients, as suggested by experimental work.¹³,²² Indeed, as in spontaneously hypertensive rats, treatment of hypertensive patients with a cyclooxygenase inhibitor such as indomethacin improves endothelium-dependent vasodilatation to acetylcholine.⁴⁷ However, since inhibition of a cyclooxygenase-derived contracting factor (most likely prostaglandin H₂; see Reference 32) does not normalize endothelium-dependent vasodilation in hypertensive subjects, this strongly suggests an additional defect, which may in fact involve the L-arginine pathway as discussed above. In line with this interpretation, the effects of inhibitors of nitric oxide formation on the response to acetylcholine are attenuated in hypertension.⁴⁸

In summary, the L-arginine/nitric oxide pathway certainly has reached the clinical arena and is currently under intensive investigation in various forms of cardiovascular disease. The activity of this protective local vascular regulatory mechanism seems to be impaired in hypertension as well as other cardiovascular conditions. Additional studies are required to further delineate the exact mechanisms involved, but the present study of Panza et al.⁴⁰ strongly suggests that L-arginine, at least in hypertensive patients, may be a tool to investigate the mechanisms involved, although, in contrast to earlier suggestions,⁴¹,⁴² less promising as a remedy to treat this disease process. Hence, attempts to improve endothelial function in hypertension probably will have to focus more on the effects of antihypertensive drugs⁵¹,⁴⁹,⁵⁰ on endothelial function.

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Key Words • endothelium • hyperlipidemia • hypertension • receptors • Editorial Comments
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Circulation. 1993;87:1746-1748
doi: 10.1161/01.CIR.87.5.1746

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/5/1746.citation

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