Coronary vasoregulation, the control of coronary artery diameter and blood flow, is an important and complex physiological function in which the endothelium plays a key role. Many chemical and mechanical stimuli affect numerous endothelial cell receptors, triggering multiple signal transduction mechanisms and resulting in the release of several local activators. The net effects on coronary artery diameter and blood flow often result from opposing direct smooth muscle and endothelium-mediated actions. Nitric oxide (NO) is thought to be the predominant local endothelium-dependent vasodilator. In this issue of Circulation, Lefroy et al report the effects of intracoronary infusion of N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA), a specific inhibitor of NO synthesis, in 12 normal subjects. In the basal state, L-NMMA reduced distal coronary artery diameter and coronary artery blood flow. As previously demonstrated, intracoronary acetylcholine increased distal arterial diameter and blood flow. After L-NMMA infusion, acetylcholine (10\textsuperscript{-7} mol/L) did not increase diameter but did increase coronary blood flow. This study underscores the role of NO in the maintenance of basal arterial diameter and blood flow and, importantly, suggests that acetylcholine regulates resistance vessel diameter through a non-NO mechanism. Interpretation of clinical studies in this complex area requires an understanding of four key issues: differences in the control of arterial diameter and blood flow, stimulus concentration, site specificity, and presence of vascular disease.

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**Epicardial Versus Resistance Vessel Regulation**

In general, vasoactive stimuli tend to change coronary artery diameter and blood flow in the same direction, although different agents affect epicardial and resistance vessels in different proportions. Epacardial and resistance vessels also function interactively. In the presence of normal endothelial function, downstream-induced hyperemia results in flow-mediated vasodilatation. This response is lost in the presence of abnormal endothelial function and/or significant epicardial stenosis, resulting in vasoconstriction during exercise or hyperemia and contributing further to ischemia.

Various endothelium-dependent stimuli have different directional and quantitative effects on coronary artery diameter and blood flow. Intracoronary serotonin increases diameter and blood flow in the presence of normal endothelial function but decreases both diameter and blood flow in its absence. Ketanserin, a 5-HT\textsubscript{2} receptor blocker, administered before serotonin infusion potentiates its vasodilatory effects in normal vessels and blocks its vasoconstrictive effects in abnormal vessels. In contrast, intracoronary acetylcholine does not reduce coronary blood flow even in the presence of intense epicardial vasoconstriction associated with abnormal endothelial function. These variations result from different direct smooth muscle versus endothelium-dependent receptor effects and possibly to the release of other compensatory activators. The paper by Lefroy et al suggests the possibility that the endothelium-mediated pattern of acetylcholine response may be a result of its release of different site-specific, local activators, i.e., NO in epicardial arteries and some other substance(s) in resistance vessels.

### Site Specificity

Acetylcholine and serotonin alter distal more than proximal coronary artery diameter in the presence of both normal and abnormal endothelial function. Vascular responses in the peripheral circulation tend to be similar to those in the coronary arteries, but peripheral vascular responses may vary quantitatively. In part, this may result from differences in basal vascular "tone," which may explain quantitatively different effects of L-NMMA in the brachial artery (see below).

### Stimulus Concentration

As a result of the opposing direct smooth muscle and endothelium-dependent effects, net vasoactive stimulus action tends to be extremely concentration dependent. Progressive increases in acetylcholine and serotonin concentrations result first in epicardial vasodilatation and then vasoconstriction in the presence of normal endothelial function. Opposite dilatory and constrictor effects have been observed at different sites within the same coronary artery at selective stimulus concentrations. Whereas acetylcholine tends to produce focal spasm of coronary arteries at the site of ergonovine-induced spasm, paradoxical vasodilatation at the same site has also been observed.

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Presence of Vascular Disease

Endothelial dysfunction appears very early in the development of coronary artery disease. Initial angiographic studies demonstrated vasoconstrictor responses to acetylcholine in the presence of both mild angiographic disease and normal coronary arteries with evidence of angiographic disease elsewhere.\(^5\)\(^6\) Hypercholesterolemia may be sufficient to produce abnormal endothelial function, although subclinical atherosclerosis may be present in this instance.\(^7\) Intravascular ultrasound has revealed endothelial thickening in approximately 30% of angiographically normal coronary arteries in patients with atherosclerosis risk factors.\(^8\) This may represent the pathogenesis of angina pectoris in some patients with normal angiography, i.e., endothelial dysfunction-mediated ischemia.\(^9\) With progressive atherosclerosis, acetylcholine-induced vasoconstriction tends to decrease, partly because of increased vessel rigidity.\(^10\) This may explain the greater vasoconstrictive response to acetylcholine in distal vessels, which are generally less affected by atherosclerosis. Clinical studies of normal circulations, such as that by Lefroy et al,\(^4\) may be complicated by the presence of early atherosclerosis despite normal arteriography.

Comparison With Other Studies

NO synthesis inhibition (L-NMMA) has been reported to markedly increase coronary artery resistance in the isolated buffer-perfused rabbit heart\(^21\) compared with the mild increase observed in the study by Lefroy et al.\(^4\) This may be because of the absence of hemoglobin, a potent NO inhibitor, in the rabbit model. NO synthesis inhibition (L-NMMA) also results in a marked decrease in forearm blood flow,\(^22\) possibly because of greater basal vascular "tone." The present findings of different epicardial and resistance vessel actions\(^4\) are supported by the open-chest anesthetized dog study of Komaru et al,\(^23\) who found complete inhibition of acetylcholine-induced dilation in arteries \(>120 \mu m\) in diameter but partial inhibition in smaller vessels. In contrast, Woodman et al,\(^24\) in an anesthetized dog model, found that \(N\)-nitro-L-arginine inhibition of NO synthesis inhibited both acetylcholine-induced vasodilation and hyperemia.

Clinical Implications

This and other studies of endothelial function underscore the potential importance of dynamic epicardial and resistance vessel dysfunction in the pathogenesis of myocardial ischemia, in addition to fixed atherosclerotic stenosis. Angina with normal coronary angiography may also be caused by abnormal endothelial function in some patients.\(^19\) Traditional coronary arteriography does not evaluate both epicardial and resistance vessel vasoregulation, which could lead to substantial discordance between perceived coronary anatomy and patient functional capacity. Recently, assessment of generalized endothelial vasoactivity has been proposed as a preclinical, noninvasive means for detecting coronary and other atherosclerosis.\(^25\) The approach holds the promise of being able to detect coronary disease at a sufficiently early stage that risk factor modification may avert subsequent clinical sequelae. Confirmation of the findings of Lefroy et al\(^4\) would support the presence of a resistance vessel endothelium-mediated, non-NO pathway that might provide insight into additional mechanisms and pharmacological interventions for myocardial ischemia.

References

in patients with angina pectoris and normal coronary angiograms. 


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**KEY WORDS** · Editorials · endothelium-derived factors · vasoconstriction · vasodilation · blood flow
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