Editorial Comment

Endothelin
Key to Coronary Vasospasm?

Thomas F. Lüscher

In 1959, Prinzmetal and colleagues described a new form of chest pain that developed at rest and very often occurred in the early morning hours. The pain was associated with ST segment elevations in the electrocardiogram and relieved by nitroglycerin. They named the syndrome “variant angina” and suggested that it was caused by a spasm of a major epicardial coronary artery.

Subsequently, coronary spasm has been documented angiographically in patients with variant angina. In addition, coronary vasomotion has been recognized as an important factor in the pathogenesis of most ischemic coronary syndromes. Although the phenomenon has been well characterized clinically and angiographically, the cause of coronary spasm remains enigmatic. Moreover, it even appears uncertain whether all increases in coronary vascular tone occurring in acute ischemic syndromes can be explained by a single factor or represent a heterogeneous entity ranging from normal coronary vasomotion in a narrowed vascular segment to “true spasm” (i.e., variant angina) with total or near-total occlusion of an angiographically normal or mildly atherosclerotic coronary artery.

See page 476

In patients with variant angina, vasospasm is a localized phenomenon of adrenergic nerves. Adrenergic nerves are unlikely to play a primary role, however, as phenylephrine and norepinephrine fail to precipitate and neither phentolamine nor prazosin consistently prevents ischemic episodes in patients with variant angina. Adrenergic nerves can accumulate serotonin at sites where platelets are activated (e.g., after intimal damage) and later release the monoamine. Because variant angina predominantly occurs at times when the sympathetic nervous system is not activated (i.e., at rest and in the early morning hours), such a mechanism is not likely to be operative in this syndrome but may play a role in certain forms of unstable angina.

Coronary spasm can be provoked with various maneuvers and pharmacological interventions. This would suggest that the defect does not involve a specific receptor or signal transduction pathway but rather a more basic mechanism regulating vascular contractility. Ergonovine, acetylcholine, and histamine are substances known to provoke vasospasm in most of the patients with variant angina. All of these substances have complex effects in the coronary circulation. Indeed, coronary arteries contain specific receptors on vascular smooth muscle and the endothelium that are activated by these substances.

In this issue of Circulation, Toyo-oka et al report increased venous and coronary sinus levels of endothelin-1 in patients with variant angina and provokable coronary vasospasm at angiography. In patients with clinical symptoms consistent with variant angina but nonprovokable vasospasm, the venous levels of the peptide were in the normal range. Immediately after its discovery, the 21-amino acid peptide endothelin has attracted great interest, particularly in this context. Endothelin is one of the most potent vasoconstrictor substances known and is produced in the endothelium of the blood vessel wall. Consistent with the concept that the lung plays a major metabolic role in extracting endothelin from the circulating blood, the levels of the peptide were significantly lower in the coronary sinus than in the systemic venous blood of the patients without provokable vasospasm studied by Toyo-oka et al. In contrast, in patients with variant angina and provokable coronary vasospasm, the venous and coronary sinus levels of endothelin did not differ significantly. This indicates that in these patients, either less endothelin is extracted during passage through the pulmonary circulation or, more likely, greater amounts of endothelin are produced in the coronary vascular bed. Surprising is the finding that not only the coronary sinus but also the venous...
endothelin levels were almost twice as high in provokable than in nonprovokable patients, particularly as coronary spasm is thought to be a local defect of specific coronary vascular segments rather than a systemic disease of the circulation. Patients with coronary spasm, however, do have a higher incidence of Raynaud’s phenomenon, migraine, and ocular vasospasm than those without the disease.19,20 Also, resistance in passing an intra-arterial catheter is often noted in these patients, indicating a systemic vasospastic diathesis.16

Therefore, does endothelin simply induce a vascular hyperresponsiveness to various stimuli rather than being the true cause of vasospasm? If so, increased endothelin levels might be an essential but not sufficient factor in triggering coronary vasospasm. The measured levels of endothelin in the coronary sinus and the circulating blood per se are unlikely to exert major vascular effects. Low levels of the peptide, however, may sensitize the vasculature to vasoconstrictor stimuli.21,22 Threshold concentrations of endothelin-1 potentiate contractions to serotonin and norepinephrine in human coronary and internal mammary arteries.23 Because norepinephrine and serotonin do not affect contractions to endothelin-1 in these blood vessels, this represents a specific property of the peptide. As endothelin-1 increases the calcium sensitivity of human arteries, the peptide interferes with a fundamental intracellular mechanism involved in the contractile process.23 Are the amounts of endothelin produced in vivo in these patients sufficient to act in this way? Obviously, it is difficult to estimate the local concentrations of the peptide at the site of coronary spasm. The circulating levels measured in the coronary sinus, however, make it more likely that subthreshold concentrations of endothelin are reached. It remains possible, however, that larger amounts of the peptide are released abluminally toward the underlying vascular smooth muscle of a coronary segment prone to spasm than toward the blood vessel lumen. Certain prostanoids are differently released in the luminal and abluminal directions by endothelial cells.24

Why are the plasma concentrations of endothelin elevated in patients with variant angina and provokable vasospasm? The production of endothelin can be stimulated by receptor-operated mechanisms activated by adrenaline, angiotensin II, arginine vasopressin, thrombin, transforming growth factor β, or interleukin-1, and by the calcium ionophore A23187.17,25 In addition, physical stimuli such as ischemia and shear stress can augment the production of the peptide.26,27 Neither of these stimuli is an obvious cause of the elevated endothelin levels in patients with variant angina. As endothelium-derived nitric oxide also takes part in the regulation of endothelin production via a cyclic GMP-dependent mechanism,28 a reduced local formation of endothelium-derived relaxant factor in a diseased vascular segment could contribute to the enhanced endothelin production.

That the levels of endothelin in the coronary sinus decrease during spasm was certainly not anticipated. Although this phenomenon could not be observed in patients with spasm of the right or both coronary arteries, this group is too small to draw any conclusion. Previous studies suggest that endothelin is not stored in endothelial cells.17 In endothelial cells in culture as well as in isolated blood vessels, the peptide can be detected only after several hours of incubation, indicating that de novo protein synthesis is required.17,25 If endothelin is preferentially released from coronary segments prone to spasm, a decreased washout of the peptide during spasm and dilution by blood draining from the nonspastic segments of the coronary circulation is the most likely explanation. However, a much faster regulation of endothelin release in vivo than in vitro cannot be excluded.

A pathophysiological concept of a disease should also explain the effects of established forms of therapy. In patients with coronary vasospasm, calcium antagonists and nitroglycerin have proved to be highly effective.1,28 Conflicting results have been reported as to the effects of calcium antagonists on endothelin-induced contractions.15 Although in various isolated arteries calcium antagonists are unable to interfere with endothelin-induced contractions, they do reverse the effects of endothelin in the human and porcine coronary artery.29,30 Most likely, in blood vessels in which calcium antagonists are effective, the endothelin receptor is linked to voltage-operated calcium channels via a G protein.29 In human arteries, the potentiating effects of threshold and low concentrations of endothelin-1 on the contractions induced by serotonin and norepinephrine are prevented by calcium antagonists of the dihydropyridine type.23 Nitroglycerin, SIN-1 (the active metabolite of molsidomine), and the endogenous nitrate endothelium-derived relaxing factor are all highly effective in reversing endothelin-induced contractions, in human blood vessels also.31 Thus, a role of endothelin in the pathogenesis of variant angina would be compatible with the known effects of calcium antagonists and nitrates in this syndrome.

What do we learn from these most recent developments in vascular biology? As increased levels of endothelin sensitize vascular segments to enhance vasoconstrictor responses, the peptide may take part in the pathogenesis of coronary spasm and act as a regulator of vascular reactivity in the circulation. If so, an increased vascular endothelin production in patients with variant angina would be an essential but not sufficient step in the development of coronary spasm. Specific antagonists of the endothelin receptor or inhibitors of the synthesis of the peptide would then be most appropriate tools in the management of variant angina. However, several questions remain unanswered. First, it remains unclear what stimulates the production of the peptide in patients with variant angina. Furthermore, if endothelin acts as a predisposing factor in variant angina, the trigger mecha-
nism of coronary spasm remains unknown. Thus, we are a step further but still far from a full understanding of this complex vascular syndrome.

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References

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