Endothelin
Key to Coronary Vasospasm?

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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 that repeatedly affects the same coronary vascular segment either spontaneously or after provocation. Thus, a local dysfunction of the blood vessel wall at the site of spasm must be involved. Accordingly, alterations of local neurogenic control, vascular smooth muscle, the endothelium, or blood cells have been implicated.

For years, research interest has focused on a local hyperresponsiveness 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 provoku-
able 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 cor-
onary spasm, however, do have a higher incidence of
Raynaud’s phenomenon, migraine, and ocular vaso-
spasm than those without the disease.19,20 Also, resis-
tance in passing an intra-arterial catheter is often
noted in these patients, indicating a systemic vaso-
spastic diathesis.16

Therefore, does endothelin simply induce a vascu-
lar hyperresponsiveness to various stimuli rather than
being the true cause of vasospasm? If so, increased
endothelin levels might be an essential but not suffi-
cient 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 vasocon-
strictor stimuli.21,22 Threshold concentrations of en-
dothenlin-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 mecha-
nism 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
abulminally 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 provok-
able vasospasm? The production of endothelin can be
stimulated by receptor-operated mechanisms activ-
ated by adrenaline, angiotensin II, arginine vasopres-
sin, thrombin, transforming growth factor β, or inter-
leukin-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,25 a reduced local
formation of endothelin-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 conclu-
sion. 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 re-
leased from coronary segments prone to spasm, a
decreased washout of the peptide during spasm and
dilution by blood draining from the nospastic seg-
ments 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 ther-
apy. In patients with coronary vasospasm, calcium
antagonists and nitroglycerin have proved to be
highly effective.1,28 Conflicting results have been re-
ported as to the effects of calcium antagonists on
endothelin-induced contractions.15 Although in vari-
ous 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 con-
tractions induced by serotonin and norepinephrine
are prevented by calcium antagonists of the dihydro-
pyridine type.23 Nitroglycerin, SIN-1 (the active me-
tabolite of molsidomine), and the endogenous nitrate
endothelium-derived relaxing factor are all highly
effective in reversing endothelin-induced contrac-
tions, 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 cal-
imium antagonists and nitrates in this syndrome.

What do we learn from these most recent devel-
opments 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 recep-
tor 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 predis-
posing 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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