

EDITORIAL COMMENT

Morphological Characteristics of Coronary Arteries in Patients With Vasospastic Angina

Another Form of Atherosclerosis?*

Amir Lerman, MD,[†] Taek-Geun Kwon, MD, PhD,[†] Lilach O. Lerman, MD, PhD[‡]



Vasospastic angina (VSA) is a variant form of angina in which chest pain typically appears without provocation, is accompanied by transient ST-segment elevation, and usually resolves spontaneously or with rapid-acting nitroglycerin. Although VSA usually occurs in angiographically normal or near-normal coronary arteries, intravascular ultrasound studies (IVUS) have demonstrated early atherosclerosis, characterized by noncalcific plaque with negative remodeling (1,2), in vasospastic lesions. However, because of its relatively low resolution, it is challenging to use IVUS to discriminate the specific lesion characteristics responsible for vasospasm.

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Optical coherence tomography (OCT) is a high-resolution imaging modality capable of evaluating intimal thickening and microstructures, including thrombus and macrophages, in atherosclerotic plaques. In this issue of *JACC*, Shin et al. (3) report the use of OCT to evaluate the morphological characteristics of the culprit site in patients with spasm-induced acute coronary syndrome (ACS). Most spasm sites had atherosclerotic plaques, and two-thirds showed lumen irregularity without thrombus. Plaque erosion, defined by the presence of thrombus with or without lumen irregularity overlying intact fibrous cap on multiple adjacent OCT image slices, was detected in more than one-fourth of spasm sites.

Thus, this study challenges the notion that coronary spasm occurs in normal coronary arteries and underscores the need for additional novel imaging modalities in patients presenting with ACS and non-obstructive coronary artery disease.

VSA is typically caused by focal spasm of a major epicardial coronary artery, resulting in a severe obstruction to flow. Coronary vasospasm can present with several clinical features, including variant angina, ACS, syncope, and sudden cardiac death. Notably, Shin et al. (3) enrolled patients presenting with ACS for OCT and provocation tests. A previous OCT study demonstrated that intraluminal thrombi and intimal erosion were frequently found in patients with vasospasm-induced ACS (4). The present study further supports that vasospasm is associated with vascular intimal injury, including intimal disruption and erosion. In fact, this intimal injury and thrombus formation at the vasospasm site may be caused by endothelial dysfunction, leading to severe vasoconstriction. Histology has also demonstrated that intimal injuries such as neointimal hyperplasia, thrombus formation, and intimal hemorrhage are frequently found in patients with VSA, which links vasospasm to vascular injury and plaque progression (5). However, although intimal erosion and thrombus may cause ACS, the plaque characteristics of vasospastic lesions differ from those of ACS lesions. Virtual histology-IVUS showed that vasospastic lesions have a lower plaque volume, containing a smaller necrotic core and dense calcium, compared with culprit lesions in patients with unstable angina (6).

Although the pathogenesis of coronary vasospasm has not been fully elucidated, vascular smooth muscle hyperreactivity and endothelial dysfunction are considered key factors. Hypercontractility of coronary smooth muscle is associated with increased receptor activation. Shimokawa et al. (7,8)

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From the [†]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; and the [‡]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

demonstrated that Rho kinase, which participates in regulation of vascular smooth muscle contractility, is associated with hyperreactivity and vasospasm. In addition, this hyperreactivity may be associated with increased smooth muscle cell mass. Tanaka et al. (9) showed that vasospastic lesions had a larger medial area and thickness, and an intimal bump (projection into the lumen) by medial contraction frequently occurred even before spasm provocation. Intimal bump and lumen irregularity resulting from medial contraction might represent hyperreactivity of coronary smooth muscle and a distinctive morphological feature of vasospastic lesions. Consistent with this notion, the current study reports lumen irregularity in more than two-thirds of spasm-inflicted segments (3).

Endothelial dysfunction has also been implicated in VSA. Intracoronary acetylcholine infusion usually induces vasodilation in a coronary artery with an intact endothelium by releasing nitric oxide. Conversely, arteries with dysfunctional or disrupted endothelium often respond with vasoconstriction as a result of direct activation of muscarinic receptors on vascular smooth muscle cells (10). Interestingly, acetylcholine injection can induce coronary spasm in patients with VSA (11), which implies epicardial endothelial dysfunction. However, coronary spasm is a relatively rare condition compared with endothelial dysfunction. Furthermore, in contrast to vasospastic lesions that are characterized by intimal erosion and irregularity, in early coronary atherosclerosis OCT has identified macrophages and intraplaque neovessels in segments with epicardial endothelial dysfunction, which suggests that inflammation and neovascularization may contribute to the abnormal vascular reactivity and plaque progression (12). These different lesion characteristics might explain why VSA is relatively uncommon.

Although Shin et al. (3) have well demonstrated intimal erosion and irregularity at spasm sites, all study subjects had ACS, and imaging of the segments adjacent to the vasospastic segments was not performed. A recent report showed that intimal tear, erosion, and intraluminal thrombi were more frequent in patients with spasm-induced ACS than in those with chronic stable VSA (13). Intimal erosion and thrombus may not be universal findings in

patients with VSA. In addition, some patients did not undergo a provocation test, especially patients presenting with acute myocardial infarction. Although these patients showed spontaneous vasoconstriction that was relieved by intracoronary nitroglycerin injection, vascular injury such as intimal tear and erosion can induce vasoconstriction unrelated to vascular smooth muscle hyperreactivity. Therefore, a cause-and-effect relationship is unclear in these patients.

One of the important clinical implications of this study relates to future therapy and management of these high-risk patients. The percentage of smokers in the current study is alarmingly high and illustrates the need for a more aggressive smoking cessation program in these patients. Moreover, OCT findings of intimal erosion and thrombus suggest the potentially beneficial effect of antiplatelet therapy (perhaps better with dual-antiplatelet therapy), especially in patients presenting with ACS. Currently, American College of Cardiology/American Heart Association guidelines recommend calcium channel blockers and long-acting nitrates and suggest HMG-CoA reductase inhibitors (statins) as useful drug therapy for VSA (14). Further studies are needed to evaluate the efficacy of antiplatelet therapy in this specific patient group. In addition, this study demonstrates the persistence of intimal irregularity by medial contraction even after intracoronary nitroglycerin injection. Hence, vasodilators may have little effect on vascular smooth muscle hyperreactivity, resulting in medically intractable VSA. New therapeutic targets, possibly like Rho-kinase inhibitors, should be evaluated (8).

In conclusion, Shin et al. (3) have demonstrated morphological characteristics of coronary plaques such as erosion, thrombus, and medial contraction in patients with vasospasm-induced ACS. A large-scale prospective study is needed to evaluate the role of novel imaging for decision making in patients with ACS and abnormal vascular reactivity.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Amir Lerman, Division of Cardiovascular Disease and Department of Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: lerman.amir@mayo.edu.

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