

REFERENCES

1. Shin E-S, Ann SH, Singh GB, et al. OCT-defined morphological characteristics of coronary artery spasm sites in vasospastic angina. *J Am Coll Cardiol Img* 2015;8:1059-67.
2. Gertz SD, Uretzky G, Wajnberg RS, Navot N, Gotsman MS. Endothelial cell damage and thrombus formation after partial arterial constriction: relevance to the role of coronary artery spasm in the pathogenesis of myocardial infarction. *Circulation* 1981;63:476-86.
3. Gertz SD. Vascular damage and thrombosis from spasm. *N Engl J Med* 1979; 300:197.

THE AUTHOR REPLIES:



We would like to express our admiration of the remarkable experiment by Gertz et al. (1) 35 years ago and agree with their findings wholeheartedly. Their animal study proved that endothelial damage and thrombus formation occurred just at the proximal site of partial obstruction without reduction in coronary flow based on the electron microscopy findings. They reported that for this reason, vasospasm could cause not only angina pectoris but also acute myocardial infarction (AMI) and furthermore suggested that the possibility that atherogenesis could start at the site of spasm because of endothelial damage.

In our study (2), which was an in vivo study, we presented optical coherence tomography findings in study subjects who had >90% diameter stenosis during spasm and had symptoms of angina accompanied by electrocardiographic changes. Nevertheless, we found thrombus in only 29% of subjects. However, a luminal irregularity suspicious for plaque damage was found in 61% of subjects even when thrombus was not found. It is postulated that the prevalence of thrombus in our study compared with thrombus observed in the animal study by Gertz et al. (1) can be underestimated due to the reason itself that the resolution of optical coherence tomography is much lower than that of electron microscopy. Certainly it is highly possible that the presence of thrombus could be lowered by endogenous thrombolysis as well as pre-treatment with aspirin, clopidogrel, and heparin. Although it may look as if the degree of coronary flow reduction during spasm is neither associated with the prevalence of thrombus nor with AMI clinically, this could be due to the small number of subjects (Table 1). We are in the process of finalizing our next study on the comparison of thrombus and plaque erosion at coronary spasm sites and nonspasm sites in patients with suspicious vasospastic angina using optical coherence tomography. In this study, all thrombi were observed in the areas with plaques, and thrombus was also observed at the nonspasm sites. In fact, however, thrombus was

TABLE 1 Prevalence of Thrombus in Vasospastic Angina

	Thrombus		p Value
	Present (n = 23)	Absent (n = 57)	
DS during spasm, %	91.6 ± 9.7	94.1 ± 9.3	0.290
DS after nitroglycerin, %	25.4 ± 22.5	23.3 ± 21.2	0.694
TIMI flow grade during spasm			0.757
0	8 (34.8)	16 (28.0)	
1	2 (8.7)	3 (5.3)	
2	2 (8.7)	9 (15.8)	
3	11 (47.8)	29 (50.9)	
AMI (n = 11)	5	6	0.487

Values are mean ± SD or n (%).

AMI = acute myocardial infarction; DS = diameter of stenosis; TIMI = Thrombolysis In Myocardial Infarction.

found 4 times more frequently at spasm sites than at nonspasm sites. Although endothelial damage and thrombus were found at the proximal stenosis sites due to arterial constriction in the animal study, the cause-and-effect relationship is not clear in the in vivo study. The effects that spasm has on the natural history of plaque are a future research subject of great interest to us.

Eun-Seok Shin, MD*

*Department of Cardiology
Ulsan University Hospital
University of Ulsan College of Medicine
877 Bangeojinsunhwan-doro
Dong-gu
Ulsan 682-714
South Korea
E-mail: sesim1989@gmail.com

<http://dx.doi.org/10.1016/j.jcmg.2016.01.002>

Please note: Dr. Shin has reported that she has no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Gertz SD, Uretzky G, Wajnberg RS, Navot N, Gotsman MS. Endothelial cell damage and thrombus formation after partial arterial constriction: relevance to the role of coronary artery spasm in the pathogenesis of myocardial infarction. *Circulation* 1981;63:476-86.
2. Shin E-S, Ann SH, Singh GB, et al. OCT-defined morphological characteristics of coronary artery spasm sites in vasospastic angina. *J Am Coll Cardiol Img* 2015;8:1059-67.

Characterizing the Hyperemia-Induced Mechanical Stress Acting on the Plaque



I read with great interest the article in *JACC* by Choi et al. (1), who provided an innovative characterization of the hemodynamic force acting on individual plaques in a series of patients. By applying computational fluid dynamics in coronary computed

tomography angiographic data, these investigators quantified the “axial plaque stress” (i.e., the hemodynamic stress acting on the longitudinal direction of stenotic lesions) and related that force to geometric lesion features.

A critical parameter in the elaborate characterization performed by the investigators is the assumption of hyperemic blood flow in all their computational fluid dynamics analyses. By applying boundary conditions of high blood flow, axial plaque stress values in this study actually represent the peaks in axial tensile stress that are induced by the hyperemia-triggered blood pressure drop over a lesion. According to fluid mechanics principles, the pressure drop across a stenosis results from the sum of the following: 1) viscous (frictional) losses along the entrance (entrance effects) and mostly at the throat of the stenosis; and 2) inertial (kinetic energy) losses downstream secondary to the sudden lumen expansion that creates zones of flow separation and recirculation. Both losses (primarily inertial) are rapidly augmented with increasing blood flow rates and are maximized under conditions of hyperemic blood flow. The nonlinear increase in inertial losses with increasing flow rates causes the pressure gradient on the upstream portion of an idealized symmetrical lesion (upstream vs. downstream morphology) to be significantly greater than that on the downstream portion of the lesion, and thus a net axial force that acts on the plaque from upstream to downstream governs under hyperemic conditions, as also shown in Figure 1 of the article (i.e., upstream axial plaque stress is higher than downstream stress) (1).

In contrast, under conditions of resting flow, the pressure gradient would be similar in the upstream and downstream portions of a symmetrical lesion, thus resulting in “neutralization” of the opposite-acting axial stresses in the upstream and downstream regions. Because the absolute rate of blood flow is critical for the value of axial plaque stress and the dominance of either net antegrade or retrograde axial plaque force, Choi et al. (1) could also investigate the relationship of the predicted axial plaque stress (including the pattern of the stress distribution) with the absolute rate of hyperemic flow, which, of note, is not known but is variably estimated for each patient according to a model used by these investigators.

The application of hyperemic blood flow for computing the peaks in axial plaque stress distribution also has important implications for the mechanism of the plaque rupture that one presumably intends to predict by using the proposed biomechanical approach. Hyperemic blood flow occurs during physical exertion, and thus axial plaque stress could

be helpful in predicting exertion-triggered acute coronary syndromes but may not be relevant in predicting cardiac events at resting conditions (e.g., predicting myocardial infarctions or deaths at rest). Those events at resting conditions may be a result of sudden blood pressure surges translating into sudden peaks of local tensile stress acting perpendicularly to the endothelial surface (i.e., particularly related to the radial component of hemodynamic stress).

Finally, another issue I would like to raise is that hyperemic flow conditions have a great impact on the computed wall shear stress. Mean values of wall shear stress in the article were >10 Pa ($= 100$ dynes/cm²) in both upstream and downstream regions of the lesions studied (1). This value is much greater than the expected range of wall shear stress magnitude observed in arteries (2). Although the association of low shear stress (<1 to 1.5 Pa) with atherosclerosis development or progression and high-risk plaque features (vs. moderate or high shear stress) is well documented both in experimental models and in clinical studies (3), the pathophysiological implications of very high shear stress are not known. The transient peaks of the entire wall shear stress distribution that may occur under hyperemic blood flow conditions warrant further investigation.

Michail I. Papafaklis, MD, PhD*

*Michailideion Cardiac Center, Medical School
University of Ioannina
Stavrou Niarchou Avenue
Ioannina 45100
Greece

E-mail: m.papafaklis@yahoo.com

<http://dx.doi.org/10.1016/j.jcmg.2015.11.017>

Please note: The author has reported that he has no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Choi G, Lee JM, Kim HJ, et al. Coronary artery axial plaque stress and its relationship with lesion geometry: application of computational fluid dynamics to coronary CT angiography. *J Am Coll Cardiol Img* 2015;8:1156-66.
2. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999;282:2035-42.
3. Cheng C, Tempel D, van Haperen R, et al. Atherosclerotic lesion size and vulnerability are determined by patterns of fluid shear stress. *Circulation* 2006;113:2744-53.

THE AUTHORS REPLY:



We thank Dr. Papafaklis for his interest in our study (1). Dr. Papafaklis suggested the need for further investigation on axial plaque stress distribution at