We would like to express our gratitude to Drs. Li and Gillard for giving us their honest comments regarding our article (1). The key points of their criticism were: 1) we have to recognize the inherent limitations of computational fluid dynamics; and 2) we should consider the degree of stenosis, pressure distribution across the stenosis, as well as in-plaque stress, all of which may be more important in plaque rupture. We agree entirely with these comments.

Any kind of computational analysis, especially for life systems, requires many assumptions and hypotheses. To ensure its validity, all we can examine is the correspondence between the calculated results and the real-world data. The location of shear stress concentration obtained by our program, which is commercially available, corresponded almost exactly to the real location of plaque rupture. It may be true that the maximum shear stress should be at the location of the maximum stenosis; however, it comes to effect only if the cross-sectional lumen is circular or uniform in shape. The lumen shapes we analyzed were much more complicated, having non-negligible side branches, and the top of plaque hill usually did not correspond to the maximum stenosis. Furthermore, shear stress is dependent on not the peak value but the maximum “derivative” of flow velocity with respect to the distance from the vessel wall. Even if our data did not indicate the real shear stress, our method can still be useful for predicting the future rupture point.

Regarding other critical factors in plaque rupture, such as wall-distending pressure, the degree of stenosis, and in-plaque stresses, we responded to the previous letter to the editor (2). In addition to their work in 2006 (3), we also published an article in the Journal in 2005 (4) demonstrating the importance of fibrous cap thickness, lipid core, and calcification in plaque rupture. Wall-distending pressure or in-plaque stress may be much more important in driving the plaque rupture, because the degree of shear stress is very small compared with such forces. Therefore, we think that the local elevation of shear stress might become a trigger rather than a major driving force of plaque rupture. When one attempts to tear a thin paper into 2 parts, just stretching the paper is not sufficient. However, if one makes just a tiny cut in an edge of the paper, it will tear it very easily. We think that the local elevation of shear stress might form such a tiny cut-line, which may be derived from the modification of endothelial cell functions.

In our study (1), we demonstrated just such a statistical relationship between shear stress and plaque rupture. We are under the impression that plaque rupture is a multifactorial multiprocess as well as multi-interaction phenomenon that is deterministic in some ways and stochastic in others.

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Local Blood Pressure Rather Than Shear Stress Should Be Blamed for Plaque Rupture

A recent article (1) published in the Journal corroborates the hypothesis that shear stress triggers fibrous cap rupture. In 20 patients with considerable lumen narrowing (maximum area reduction of 80 ± 7%), ulcerative plaque rupture preferentially occurred in areas with locally high wall shear stresses (WSS), estimated by means of computational modeling. However, the authors of this study do not answer the basic question of whether local WSS distribution is indeed related to plaque rupture.

Hemodynamics is an interplay between pressure, flow, and morphology. The study by Fukumoto et al. (1) mainly considers the interaction between flow and morphology under steady-state conditions. Compared with an unaffected site, the increase in WSS around a plaque can be estimated to be a factor of 10 assuming simple circular geometries. For a normal WSS of 0.6 Pa (2), the mean WSS within the stenosis will remain <10 Pa, which might be too low to initiate plaque rupture directly, as acknowledged by the authors.

The article does not fully appreciate the influence of local blood pressure within a stenosis, although this pressure was calculated as well. Let us consider the hemodynamics in the vicinity of a stenosis (3), where in a steady-state situation the sum of potential energy (local blood pressure) and kinetic energy (local blood velocity) is constant (Bernoulli equation): an increase in velocity induced by geometry decreases local pressure (3). An area reduction of 80% converts to an increase in velocity by a factor of 5, and the

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associated pressure decrease will be 1.1 kPa (8.4 mm Hg), which is 100 times greater than the WSS. In the longitudinal direction, the pressure gradient across the wall also goes down by 8.4 mm Hg and is partially restored distal to the stenosis.

Now let us assume that the vasa vasorum function properly (4). Then, within the arterioles supplying the plaque, blood pressure highly depends on the blood pressure proximal to the stenosis, despite frictional losses along the arterioles. Because of high stenotic blood flow velocities, not only a high WSS but also a substantial pressure gradient develops across the wall towards the lumen. This situation is opposite to normal conditions where the transmural pressure gradient is directed outward.

Pulsatile conditions aggravate the situation. High-grade stenoses cause strong pulse wave reflections, increasing the proximal pulse pressure by almost a factor of 2. The pulsatile transmural pressure and the longitudinal pressure gradient into the stenosis contribute to (position-dependent) wall and plaque deformation. Because of the fragility of plaque structures (5), this deformation will very likely contribute to cap rupture. The pressure gradient across a plaque may contribute to the release of thrombogenic material into the lumen.

Wall shear stress plays an important role in atherogenesis but is merely coincidental with plaque rupture. The combination of high velocities due to lumen narrowing, the vasa vasorum, plaque composition, and structure and pressure wave reflection induce longitudinal and transmural pressure gradients and plaque deformation, contributing to plaque rupture. A small residual lumen generates high inward pressure gradients and inward “bleeding.”

First of all, we would like to express our deep appreciation for the sincere academic criticism of Dr. Hoeks and colleagues. Key points of their criticism were: 1) our study (1) did not answer the basic question whether local wall shear stress distribution is indeed related to plaque rupture; 2) we did not fully appreciate the influence of local blood pressure within a stenosis; and 3) the combination of high velocities due to lumen narrowing, the vasa vasorum, plaque composition and structure, and pressure wave reflection mainly contribute to plaque rupture. We do not have any critical arguments against their points.

Actually, we also had recognized the importance of such factors before our article was published. We previously reported the importance of in-plaque stress concentration in plaque rupture (2). The major driving force of plaque rupture is related to wall-distending pressure, tensile in-plaque stresses, inward pressure gradients, and inward bleeding. As they pointed out, we showed just a statistical relationship between local elevation of shear stress and future rupture point. However, the research of the direct cause-effect relationship between some local situations and plaque rupture is substantially difficult. The reasons are as follows:

1. Because the prevalence of plaque rupture is relatively low (approximately 3% per year), a prospective study to clarify the direct trigger or predictor of plaque rupture is quite a long way off.
2. According to fracture mechanics, there are several kinds of material fracture. The initiation of some types of fracture, such as fatigue breakdown or time-dependent fracture, does not necessarily require great values of stress, which should overcome the strength of the material.
3. As Dr. Hoeks and colleagues suggested, there are quite a few factors that we have to consider as a determinant of plaque rupture. It has been documented that vulnerable plaques can frequently be observed in the nonculprit segments in patients with acute coronary syndrome. It is not yet fully understood in such cases how or why a particular plaque ruptured among many vulnerable plaques. Therefore, it can be speculated that plaque rupture is a rather stochastic phenomenon. If plaque rupture is not a deterministic process, a direct, single cause of plaque rupture might not exist.

Our study was not intended to clarify the main player in plaque rupture but rather to propose that shear stress, the value of which is very small, might not be a negligible factor in the initiation of plaque rupture or in the prediction of its future rupture point. We expect further thorough investigations of the plaque rupture mechanism.

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