steno sis. (1). The Hypertension Genetic Epidemiology Network (HyperGEN) Study Group conducted a genome-wide linkage scan on aortic valve sclerosis (2) that deserves to be discussed. This HyperGEN cohort was a substudy of a larger National Heart, Lung, and Blood Institute program, the Family Blood Pressure Program, designed to search for hypertension/blood pressure genes. The authors reported familial aggregation of aortic valve sclerosis with a sibling recurrence risk ratio of 2.3 and identified many linkage signals throughout the genome, suggesting the multilocus nature of aortic valve sclerosis. However, their results also highlighted the challenge of collecting samples of a sufficient size to study this disease. Major research resources were invested in the HyperGEN cohort to phenotype and genotype 1,871 patients. However, in the end, only 41 patients with isolated aortic valve sclerosis from families with at least 2 affected siblings were informative for the genetic linkage analyses. The authors also recognized the limitation of their ascertainment scheme that was based on hypertension to identify genetic loci influencing aortic valve sclerosis. Accordingly, recycling data from larger studies conducted on related traits provided a cost-effective way to identify new leads. However, studies specifically designed to study calcific aortic valve disease are likely to be more powerful and are clearly warranted.

By addressing study design and focusing on genomic approaches that are likely to be more successful, we should re-emphasize the need for genome-wide association scans on case-control studies. The identification of genes of complex diseases by this approach was considered one of the scientific breakthroughs of the year in 2007 (3). In contrast, genome-wide linkage studies have been used extensively in the past and have proven to be very productive to identify genes for monogenic traits. However, limited success has been reported for complex diseases (4), and a good example is the results from the Family Blood Pressure Program (5). Even in studies in which strong linkage peaks were originally identified, positional cloning attempts to find the causal genes responsible for the linkage signals have often been disappointing (4). Hence, the article by Bella et al. (2) is certainly worth mentioning, but the results of this study also provide an impetus for the design and realization of future genomic studies with a population and methodology that are more suitable for a complex disease such as calcific aortic valve stenosis.

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Plaque Rupture: Plaque Stress, Shear Stress, and Pressure Drop

We read with interest the article by Fukumoto et al. (1) in a previous issue of the Journal. They used 3-dimensional intravascular ultrasound and computational fluid dynamics (CFD) to study wall shear stress (WSS) distribution in arteries with ruptured plaques. Their results showed that there are local elevations of WSS concentrations at proximal sites in the plaques and that these correspond to the rupture sites.

We want to emphasize that WSS is calculated as blood viscosity multiplied by the derivative of flow velocity with respect to the distance from the vessel wall (τ = η × ∂u/∂y). Flow velocity varies along the stenotic artery across the plaque as the lumen narrows. Generally, the maximum WSS should be at the location of the maximum stenosis, where the velocity is the highest and the lumen diameter is the smallest. There should not be any local elevation of WSS concentration if the lumen surface is smooth and there are no bad mesh elements. The use of image-based CFD can often cause problems with the geometry reconstruction and mesh generation. WSS is largely dependent on the geometry. Therefore, any effort to improve the model reconstruction and mesh generation is useful to improve the accuracy of the WSS calculation.

Pressure distribution across the stenosis is not shown in the article (1); it is not clear how pressure boundary condition was given in this study, but it is thought to be more important for plaque vulnerability. There is a pressure drop across the plaque because of the stenosis. According to the Bernoulli principle, this increased blood velocity produces a lower lateral blood pressure acting on the plaque. Thus, a pressure gradient build-up is created across the plaque that could rupture it. Any increase in systemic pressure or increase in the narrowing of the lumen would further increase the velocity through the narrowed lumen and increase the pressure drop. Furthermore, the magnitude of the pressure drop is much higher than the WSS. It can be tens to hundreds of times the magnitude of WSS for different degrees of stenosis.

Plaque stress (stress within the plaque) may be a more important factor when the mechanism of plaque rupture is considered. The arterial wall continuously interacts with hemodynamic forces, which include WSS and blood pressure. Plaque stress is the result of external hemodynamic forces. Plaque rupture itself represents structural failure of a component of the diseased vessel, and it is therefore reasonable to propose that the biomechanical properties of atheromatous lesions may influence their vulnerability to rupture. Recognizing which features contribute to this increased vulnerability may improve risk stratification and allow aggressive interventions to be targeted at patients with plaques that are prone...
to rupture. Therefore, when we model the mechanical process of plaque rupture, we need to look at the plaque stress and compare plaque stress with plaque material strength limit. We previously used a blood flow and plaque interaction model and demonstrated that fibrous cap thickness is critical to plaque stability (2). In this study, we also found that plaque stress in often higher at the shoulder regions at the proximal part of the plaque, and this is where plaque rupture can often be found.

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Reply

First of all, we would like to express our deep appreciation for the sincere academic criticism of Drs. Li and Gillard. 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 Drs. Li and Gillard 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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