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 anterograde 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/cm^2) 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.

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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

resting condition on the basis of the reasoning that the hyperemic blood flow inherently triggers a large pressure drop across the lesion. The motivation of using hyperemic blood flow in our study was to apply clinically validated boundary conditions for the analysis of axial plaque stress in relation to legion geometry. However, we fully agree with Dr. Papafaklis' opinion and acknowledge that further simulation studies with resting and exercise conditions can provide more insight on plaque rupture during various clinical situations.

Dr. Papafaklis also raised an important issue on the role of radial component of the hemodynamic stress. It is true that both radial and axial components of hemodynamic force can act as triggers for plaque rupture. However, a previous study showed that the axial component was dominant in clinically relevant stenosis (2). It is well known that most ruptures in minimal lesions are clinically silent, and stenosis severity and plaque burden are the key determinants of future cardiovascular events in patients with coronary artery disease (CAD).

The last issue was on the level of wall shear stress (WSS) in our study, a level higher than that of previous studies. The reason is the difference in boundary condition (resting vs. hyperemic) and lesion severity. We believe that the high WSS in our study suggests the possible link between high WSS and acute coronary events. Several recent studies demonstrated the negative influence of very high WSS on CAD. It was reported that high WSS could induce thinning of plaque cap by promoting metalloproteinase activity, smooth muscle cell apoptosis, and decreased matrix synthesis (3). Samady et al. (4) showed that lesions exposed to high WSS were more likely to transform into vulnerable plaques. Very high WSS is also reported to be associated with platelet activation (5). Nevertheless, we think that a pathophysiological implication of high WSS in patients with CAD certainly needs further investigations.

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Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults: An Alternative Explanation

We read with interest the work by de Marvao et al. (1). We congratulate the investigators on the novel insights into ventricular remodeling from their extensive 3-dimensional computational analysis of 1,258 cardiac magnetic resonance studies. However, we would like to raise several points for discussion.

The investigators excluded subjects with self-reported cardiovascular disease. Subclinical hypertrophic cardiomyopathy (HCM) and genetic predilection to HCM, although likely to be rare, warrant consideration especially because hypertensive subjects with asymmetric thickening have higher incidence of HCM (2). A normal resting electrocardiograph and family history would have been additive in excluding incidental HCM. There is no mention of tissue characterization with late myocardial gadolinium enhancement, which can be a useful discriminator of causes of left ventricular (LV) hypertrophy. This is particularly important because the finding of regional myocardial function being diminished in regions that exhibit the greatest hypertrophy conflicts with previous work by Puntmann et al. (3), which demonstrated increased deformation in regions of increased wall stress in hypertensive heart disease and the opposite in HCM.

Baseline exercise activity level is another important variable to consider. Asymmetric LV thickening (segmental thickness ≥13 mm and >1.5-fold the