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

opposing wall) has been described in 2.2% of healthy, young adult army recruits by cardiac magnetic resonance, rising to 10% following a period of physical training (4).

In addition, the study demonstrates a relationship between systolic blood pressure (BP) and cardiac remodeling. de Marvao et al. (1) suggest that rising BP might have a much earlier impact on cardiac structure than previously recognized, implying the former drives the latter while acknowledging this cannot be proven in their cross-sectional observational study design. However, there is another theoretical explanation that warrants consideration. The underlying driver for the hypertensive state may actually also be exerting a direct influence on the myocardium. Elevated sympathetic nerve activity is recognized as a potential etiology in some hypertensive subjects and can be measured by muscle sympathetic nerve activity level. Seravalle et al. (5) recently investigated muscle sympathetic nerve activity in optimal, normal, and high-normal BP subjects. They found that muscle sympathetic nerve activity was significantly higher in subjects with high-normal BP than in those with normal and optimal BP. This neurogenic alteration may be implicated in the progression to established hypertension. In parallel, it could also drive asymmetric LV changes owing to the denser sympathetic innervation of the interventricular septum relative to the lateral wall.

The relationship between BP and cardiac remodeling is likely to be complex. Time spent at a certain elevated blood pressure, rather than just the absolute systolic BP level, as well as nocturnal dipper and nondipper status, are also likely to be important factors. Differences in these variables, not investigated in the current study, may help explain why de Marvao et al. (1) were only able to demonstrate weak correlation between systolic BP and LV mass in prehypertension subjects and actually no significant correlation in subjects with hypertension.

Finally, we agree that we still have much to learn about hypertensive heart disease, but the advanced cardiac magnetic resonance post-processing techniques described by de Marvao et al. (1) have the potential to contribute greatly to our understanding of hypertensive heart disease and beyond.

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THE AUTHORS REPLY:

We thank Dr. Rodrigues and colleagues for their interest in our paper (1). Our data would support the accumulating evidence that left ventricular hypertrophy is not required to maintain normal systolic function under the increasing stress of rising systolic blood pressure. Longitudinal studies have shown that increased wall thickness is associated with a subsequent progression to hypertension, and we agree that the mechanisms that regulate left ventricular mass, including neurohumoral processes, have yet to be fully determined (2). With regard to the statement relating to “subclinical” and “genetic predilection” to hypertrophic cardiomyopathy and the need for electrocardiograms and family history, we would like to reassure Dr. Rodrigues and colleagues that all participants had normal resting 12-lead electrocardiograms and no family history of hypertrophic cardiomyopathy (or other inherited cardiac conditions). Perhaps unique to our study, we have sequenced all clinically relevant and research-implicated inherited cardiac condition genes in this cohort and, though preliminary, we have no evidence to suggest that genetic variation in hypertrophic cardiomyopathy genes contributed to the phenotypes described in our paper. We have also taken exercise into account, and indeed there is a relationship