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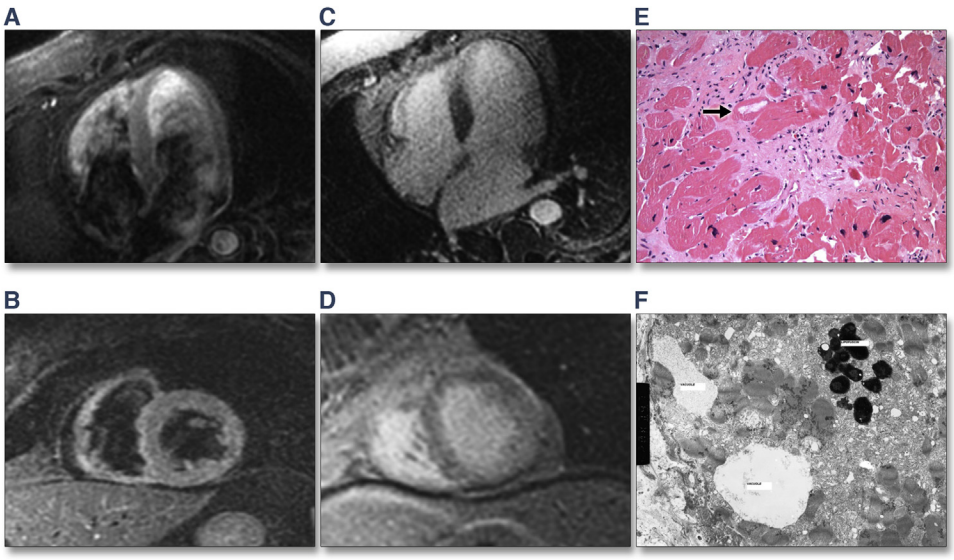
FIGURE 1 CMR Images and Biopsy Findings



(A and B) T2-weighted spin echocardiogram images in 4-chamber and short-axis views, respectively, showing diffusely increased signal intensity in the right and left ventricles. The left ventricular myocardial to skeletal muscle T2 ratio was 3:1 (normal <1.9). **(C and D)** Late gadolinium enhancement images in 4-chamber and short-axis views, respectively, showing marked diffuse biventricular hyperenhancement in a transmural pattern with sparing of the basal and mid septum. **(E)** Endomyocardial biopsy. Groups of myocytes are separated by collagen (interstitial fibrosis). Nuclei are enlarged and hypertrophic, consistent with myocardial hypertrophy. The sarcoplasm contains focal vacuoles **(arrow)**. The resected apical core showed identical findings. Hematoxylin and eosin 200×. **(F)** Electron microscopy of cardiac biopsy. Cardiac myocytes show vacuolar spaces and increased lipofuscin, consistent with cardiomyopathy due to cobalt toxicity (1). Please see Online Videos 1 and 2.

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APPENDIX For supplemental videos and their legends, please see the online version of this article.

Presence of Ischemia by FFR Without Significant Anatomic Stenosis Is Likely due to Concomitant Diffuse Disease and Not due to Impaired Vasodilation From Pharmacological Stress

The editorial (1) commenting on the paper by Park et al. (2) in the January 2015 issue of *iJACC* addressed the discordance between measured % diameter stenosis of the coronary artery disease (CAD) lesion by computed tomography angiography (CTA) and the presence of ischemia by invasive fractional flow reserve (FFR) of <0.8, and concordance with high-risk plaque characteristics by CTA (volume, low attenuation, and positive remodeling). The pathway was reviewed, from atherosclerosis leading to endothelial dysfunction and impaired vasodilation response to physiological and pharmacological stress (i.e., microvascular dysfunction [MVD]), which would add to the maximal flow limitation imposed by the

stenosis, and therefore postulated as an explanation of the increased prevalence of ischemia by invasive FFR.

However, impaired vasodilation response to pharmacological stress with adenosine during invasive FFR measurement results in a *higher measured FFR* value because a lower maximal flow rate is achieved, resulting in a lower pressure gradient across the lesion generated at the submaximal flow achieved. This is the opposite of the findings reported by Park et al. (2) in which they demonstrated a greater prevalence of ischemia as indicated by a *lower measured FFR* in the subset of patients with high-risk plaque characteristics by CTA.

In addition to stenosis severity, FFR is affected in opposite directions by MVD and diffuse CAD (DD) resulting in discordance for ischemia by coronary flow reserve (CFR) in ~40% of lesions (3). Concomitant MVD and DD both decrease CFR, but *DD decreases FFR*, whereas *MVD increases FFR*. This alters the ischemia threshold of FFR using CFR <2.0 as the reference standard, from ~0.65 in a theoretical model without DD/MVD (3) to ~0.75 to 0.8 in CAD patients (4).

Thus, if a fixed FFR ischemia threshold value of 0.8 is used as in the paper by Park et al. (2), concomitant DD will decrease and MVD increase the measured FFR value and result in discordance in opposite directions.

On the basis of this analysis, I suggest that the factor most likely responsible for the increased prevalence of ischemia by invasive FFR associated with the high-risk lesion characteristics by CTA is coexistent DD, which adds to the hydraulic resistance due to the focal stenosis and *further decreases the measured FFR*. This would increase the prevalence of ischemia by invasive FFR with the ischemia threshold fixed at 0.8. The effect of progressive increase in diffuse disease superimposed on a focal stenosis has been well characterized by Johnson et al. (3) in a theoretical model of the coronary circulation, which demonstrates the additive effect of diffuse disease to focal stenosis in *lowering the measured FFR*.

An alternative possibility is that high-risk plaque characteristics resulted in a systematic measurement error that underestimated the % diameter stenosis.

Both DD and MVD are ubiquitous, but of varying degrees in CAD patients with focal lesions, and affect measured FFR in opposite directions. Of course, neither of these 2 factors were measured in the study of Park et al. (2) to definitively explain the finding.

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REPLY: Presence of Ischemia by FFR Without Significant Anatomic Stenosis Is Likely due to Concomitant Diffuse Disease and Not due to Impaired Vasodilation From Pharmacological Stress

We thank Dr. Ramanna for his interest in our paper (1) that details the relationship of atherosclerotic plaque characteristics (APCs) and coronary ischemia by fractional flow reserve (FFR). We identified a strong and positive relationship with % aggregate plaque volume, positive arterial remodeling and low attenuation plaque (a surrogate marker for lipid-laden plaque) with coronary ischemia by FFR. Dr. Ramanna commented on the potential mechanisms associated with these findings—impaired vasodilation, diffuse atherosclerosis, and microcirculatory dysfunction—as we discussed in detail in our paper. His hypothesis is that the increased ischemia associated with APCs is due to coexistent diffuse atherosclerosis, which is certainly a potential explanation. Dr. Ramanna also believes that it is unlikely that impaired vasodilation in diseased vessels is the cause of the observed coronary ischemia, as he suggests that impaired vasodilation will reduce overall hyperemic flow and thus increase FFR values. However, any particular coronary lesion with APCs may cause local rather than global impairment in adenosine-mediated vasodilation, which will serve to increase flow proximal to the stenosis and relatively decrease flow distal to the