morphological features of coronary plaque in culprit lesions.

Various pathological types of vulnerable plaques (e.g., plaque rupture, plaque erosion, and calcified nodules) can cause thrombosis with or without luminal obstruction and could lead to acute coronary syndromes, including myocardial infarction and unstable angina (2). Plaque rupture is the most common cause of coronary thrombosis, accounting for approximately 70% of fatal coronary thrombi (3). Thin-capped fibroatheroma is the characteristic morphology of rupture-prone plaques, in which a thin and inflamed fibrous cap covers a large and soft lipid-rich necrotic core, frequently with positive remodeling mitigating luminal obstruction (mild stenosis by angiography) (2). In intravascular ultrasound studies, intravascular ultrasound–virtual histology–derived thin-capped fibroatheroma lesions are independently associated with adverse cardiovascular events (4). However, little is known about the natural history of thin-capped fibroatheroma and the detailed process of vulnerable plaque rupture, because most published studies have thus far been cross-sectional analyses, and none have presented changes on serial intravascular images.

What is the mechanism responsible for rupture of vulnerable plaques? Although it is still uncertain that coronary spasm could cause plaque rupture, Wang et al. (5) provided evidence for the important role of coronary spasm in triggering vulnerable plaque rupture. Accordingly, we believe that by combining the acetylcholine provocation test for the evaluation of vasomotor abnormalities and intravascular imaging for defining plaque morphology, we can identify patients at high risk for future adverse cardiovascular events.

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"Waves of Edema" Seem Implausible

Fernández-Jiménez et al. (1) described a bimodal time course of myocardial edema in a pig model of ST-segment elevation myocardial infarction. We concur with their observations regarding a dynamic pattern in infarct zone T2, but "waves of edema" seem implausible.

We have studied myocardial hemorrhage in 245 patients with ST-segment elevation myocardial infarction (NCT02072850). In a serial imaging substudy (n = 30, 100% compliance), we observed a progressive increase in infarct zone T2 relaxation time in patients without myocardial hemorrhage, whereas in those with hemorrhage we observed a "bimodal" pattern for T2 (milliseconds) but not for edema (area-at-risk) (2). We conclude that the subacute reduction in T2 can be explained by the destructive paramagnetic effects of deoxyhemoglobin.

Myocardial hemorrhage is very common in reperfused pigs post-myocardial infarction (3). However, Fernández-Jiménez et al. (1) concluded that other myocardial states (i.e., myocardial hemorrhage) "had little effect on the results," despite finding that infarct-zone hemorrhage increased progressively to day 4 ($p = 0.02$).

They describe tissue water content on the basis of desiccation (1). This method provides no information on water distribution, and baking will also desiccate gelatinous blood clot.

Dark-blood T2 short-tau inversion recovery cardiac magnetic resonance imaging has suboptimal accuracy for imaging edema (4). Because the investigators' model involved anterior ST-segment elevation myocardial infarction (1), surface coil intensity issues may have rendered the inferoposterior ventricular wall dark and the anterior wall relatively bright.

Because of euthanasia, the initial population (n = 25) was reduced successively by 25% to 75% (1), and inevitably, results based on 5 animals are statistically

fragile. Conclusions that are based on nonrandomized, open-label drug assignment, partial blinding, and loss to follow-up of the majority should be viewed cautiously, especially when alternative explanations may be valid (2,3).

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REPLY: "Waves of Edema" Seem Implausible

We read the comments of Dr. Berry and colleagues on our recent study with great interest (1). On the basis of an imaging substudy of 30 patients with myocardial infarctions, they propose that the bimodal post-infarction T2 cardiac magnetic resonance imaging (CMR) pattern can be explained entirely by the effects of myocardial hemorrhage rather than by the existence of 2 distinct waves of edema. Interestingly, they state that patients with hemorrhages displayed a "bimodal" pattern for T2 but not for edema, an intriguing finding given that the identification of edema by CMR is based on T2.

We admire the important imaging work done by Berry's group. However, clinical studies by themselves are limited when it comes to mechanistic interpretation; despite the obvious differences from humans, pre-clinical animal models are the basis of progress in the understanding of pathophysiological mechanisms. It is also the case that desiccation remains a reference technique for water content quantification, although it is true that it does not differentiate between intra- and extracellular water components, as we have acknowledged (1,2). Using this technique, we were able to clearly demonstrate a bimodal post-infarction edematous reaction (1,3), and the dynamics of edema correlated with the observed CMR changes. We agree with Berry et al. that qualitative T2 CMR sequences have suboptimal accuracy for imaging edema, and for this reason, we included in all cases 2 quantitative T2-mapping methods, in addition to T2 short-tau inversion recovery (4). The evidence from these independent approaches, conducted in a human-like animal model, provide robust evidence that myocardial ischemia and reperfusion is followed by a genuinely bimodal edematous reaction.

We were challenged by the suggestion that "baking will also desiccate gelatinous blood clot," and we have performed new experiments to address this. Subjection of pig blood clots to the same desiccation protocol resulted in a mean water content of about 75%. If Berry et al. were correct and the edema at reperfusion (measured water content ~84% to 85%) were stable throughout reperfusion, hemorrhage could account for the measured water content values (~81% at 24 h) (1,3) only if it affects more than 40% of the infarcted region. However, hemorrhage affected "only" ~10% of the injury area at 24 h (unpublished data). In addition, if hemorrhage were the sole explanation for the bimodal T2 pattern, it would be difficult to understand why T2 and water content increased to day 4, coinciding with the peak of hemorrhage (1). These 2 lines of evidence (the extent of hemorrhage in the model and the coincidence of increased water content and T2 with peak hemorrhage) refute the interesting hypothesis proposed by Berry and colleagues.

Complex biological events seldom have single explanations, and we have consistently acknowledged (1-4) that T2 can be affected by other factors, including hemorrhage, in addition to myocardial water content. It is plausible that the observed bimodal post-infarction T2 pattern is due to at least 2 components: mainly the dynamic changes in myocardial water content and a lesser contribution from the classically described paramagnetic effect of hemoglobin denaturation (1,3).