have all been tested and used to determine the optimal angiographic deployment projection angle (1–3). These modalities, however, remain limited by the need for iodinated contrast, which carries with it inherent risks of subsequent renal dysfunction in the elderly and high-risk TAVR patients. Recently, an integrated 3D Echo-X-Ray navigation system (EchoNavigator, Philips Healthcare, Eindhoven, the Netherlands) was employed whereby 3D transesophageal echocardiography (TEE) imaging is registered automatically in real time with live 2-dimensional fluoroscopy images acquired from the x-ray imaging system. Although use of this integrated navigation system to determine an optimal x-ray angiographic deployment projection necessitates the use of TEE during TAVR, it offers the potential to mitigate some of the contrast agent risk associated with the alternative imaging modalities. **Figure 1** demonstrates a case example using x-ray/3D TEE coregistration to accurately predict the optimal x-ray angiographic deployment projection for TAVR. Further investigation of the methods described in this case example should be validated in a larger series of patients.

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Effects of Blood T1 on Extracellular Volume Calculation

We read with much interest the recent publication by White et al. (1), assessing the accuracy of the contrast bolus T1 mapping cardiac magnetic resonance technique for measuring myocardial extracellular volume fraction (ECV). The study provides the first validation of the bolus technique against collagen volume fraction from myocardial biopsy. The bolus technique was also compared with the gold standard infusion technique in 5 representative conditions. The 2 techniques provide equivalent results, except for pathological states with an ECV >0.4, where the bolus approach consistently and increasingly overestimates the ECV value.

To date, T1 mapping has been used mainly for differentiation between healthy and disease states in clinical settings associated with an increased ECV. The technique should provide even more clinical benefit through its ability to differentiate between different degrees of pathological states associated with scar or edema in such settings as post-infarction remodeling, myocarditis, and transplant rejection follow-up. In this regard, the lower precision of the bolus technique in the ECV range of myocardial scar or edema is a matter of concern.

As suggested by the authors, a possible reason for such ECV overestimation is that renal clearance might be faster than the exchange rate between the intravascular and interstitial compartments, leading to lower $\Delta R1$ in blood compared with $\Delta R1$ of myocardium with time. This is in line with previous observations in subjects with normal or modestly increased ECV, showing small but significant changes in ECV with time using the bolus approach (2,3). This should cause a slight overestimation in the high ECV range with the bolus approach, as a limitation of the 2-compartment model, but independent of noticeable differences in blood T1 related to the underlying clinical state.

The data in the present study show some intriguing differences in blood T1 between groups. Post-contrast blood T1 is higher for bolus than for infusion in all subjects except for the healthy and the HCM-remote groups. This includes therefore all cases of high ECV (i.e., the Amyloid, HCM LGE Zone, and Infarct Zone groups in Table 1 in White et al. (1)). As such, the relative difference in blood T1 between bolus and infusion (with pre-contrast T1 as the reference) is up to 4.3 times higher in the high ECV subjects compared with the healthy or HCM-remote group. The lower $\Delta R1$ for blood with the bolus approach in

the high ECV subjects is therefore likely to contribute to the higher calculated ECV with this method. This is most striking for the HCM-LGE subgroup compared with the HCM-remote group and raises the question of whether the observed differences in blood T1 between groups do not reflect different equilibrium states between blood and myocardium according to the study groups.

Multiple factors may contribute to the higher blood T1 with the bolus approach in subjects with disease. Heart rate or flow-dependent variations in blood inversion could lower the accuracy of T1 measurement (4). Altered blood clearance through renal impairment and synovial third-space penetration of contrast may also act as confounders. More complex examinations in disease may produce lower image quality, altering intrastudy ECV reproducibility as a factor of time (5).

We are aware of the complex nature of myocardial T1 measure, of multiple factors interfering with ECV calculation and we much appreciate the transparency and completeness of data provided. We would like to know the authors' interpretation of the blood T1 data. We believe this is an issue of practical interest in a field expected to provide a key biomarker in cardiac disease in the future.

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REPLY: Effects of Blood T1 on Extracellular Volume Calculation

We thank Dr. Codreanu and colleagues for their interest in our paper (1). This study explored whether extracellular volume fraction (ECV) measurement using a bolus-only approach was equivalent to the (cumbersome and time-consuming) primed infusion protocol. If so, it takes this promising novel biomarker a step closer to routine clinical applicability (2). We confirmed no apparent detriment to the relationship with collagen volume fraction in low ECV states, but in high ECV states, the bolus-only approach measured the ECV higher.

How to scrutinize this discrepancy? First, although reasonable, it is an assumption that the primed infusion technique is the truth standard. Second, given sufficient time, the infusion approach needs no priming bolus; the blood gadolinium (Gd) concentrations will gradually rise to an infusion rate:renal clearance equilibrium. We, however, use a *primed* infusion with fixed bolus (per kilogram), fixed delay, and fixed infusion rate (per kilogram). The choice of these affects whether the 15-min T1 is higher than, equal to, or lower than the equilibrium T1. Here in high ECV states, the 15-min pseudoequilibrium T1 was higher than the infusion equilibrium (i.e., Gd blood concentrations climb to equilibrium). Possible explanations include factors that affect peak blood concentration, any of the Gd decay rate constants (blood redistribution, tissue distribution and renal function), and final resting equilibrium (renal function and body composition). Our suspicion is that high ECV patients have worse renal function and are generally leaner (thus proportionally overdosed with Gd).

Does this matter? For an infusion approach, a bolus + delay + infusion rate normogram based on pharmacodynamic/kinetic modeling, lean body mass, and renal function could be constructed, aiming for an identical equilibrium Gd concentration. Provided the T1 mapping sequence sensitivity is stable over the clinical range of T1 measured and provided Gd concentrations are not so high that relaxation of intracellular water ceases to be within the fast exchange limit, individualization is probably not necessary. Other possible approaches include serial time point measurements to create a curve (the Jerosch-Herold method) (3) and a bolus-only approach with serial measurement and ECV calculation at a fixed blood T1 or Gd concentration (rather fixed time post bolus).

It is clear we do not understand all the issues. Currently, however, our interpretation is that, excepting amyloidosis research (tracking change over