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.

Andrei Codreanu, MD*
Pauline Ferry, MBS
Marine Beaumont, PhD
Pierre-Yves Marie, MD, PhD
*Service de Cardiologie
Centre Hospitalier de Luxembourg
4 rue Barblé
L-1210
Luxembourg
E-mail: codreanu.andrei@chl.lu

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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

time or with therapy when patients may change significantly, e.g., effusions, renal function, body composition), the bolus-only approach is reasonable; that is, if there is reduced accuracy or precision, it is outweighed by the convenience of the approach.

Steven K. White, BSc, MBChB
Thomas A. Treibel, MA, MBBS
James C. Moon, MD*
*The Heart Hospital
16-18 Westmoreland Street
London W1G 8PH
United Kingdom

E-mail: james.moon@uclh.nhs.uk

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