to this, another study using thallium-201-labeled single photon emission computed tomography (SPECT) imaging showed that the attenuating effect of caffeine on a myocardial perfusion defect size using a standard adenosine dose (0.14 mg/kg/min) disappeared when the dose was increased by 50% (0.21 mg/kg/min) (3).

Indeed, as suggested by Dr. Hage and colleagues, we found a negative linear association between stress MBF and serum caffeine concentration similar to that of MBF reserve. We agree that a decline in MBF reserve was most likely due to the observed decrease in stress MBF (−0.06 [ml/g/min]/[mg/l]; 95% confidence interval [CI]: −0.10 [ml/g/min]/[mg/l] to −0.04 [ml/g/min]/[mg/l]; $p < 0.0001$), rather than increasing rest MBF (0.005 [ml/g/min]/[mg/l]; 95% CI: −0.002 [ml/g/min]/[mg/l] to 0.012 [ml/g/min]/[mg/l]; $p = 0.13$). Furthermore, we can confirm that the negative linear association between MBF reserve and serum-caffeine shown in Figure 1B (1) did not change significantly when excluding results from 2 outliers with serum-caffeine level above 20 mg/l. In support of this, we found a range of different serum-caffeine levels between individuals receiving the same caffeine dose. This may be due to differences in caffeine metabolism among individuals (4). Therefore, even though our results may suggest that a scan could be performed 1 h after ingestion of 100 mg or less of caffeine, this may vary among individuals. In our opinion a potential solution to the caffeine dilemma could be point-of-care measurement of serum-caffeine level with an immediate result and a predefined cutoff level for whether or not to proceed with a scan. In accordance with our results showing a mean caffeine level of 2.1 mg/l, corresponding to 100 mg of caffeine 1 h before scan, with no significant change in MBF reserve, a serum-caffeine level of approximately 2 mg/l could be a suitable cutoff. However, these results would need further investigation, including studies using standard assays for measuring caffeine concentration.

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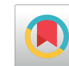
T1 Mapping for Cardiac Allograft Rejection



Cardiovascular imaging is a promising approach for detecting cardiac allograft rejection and reducing unnecessary endomyocardial biposies. We congratulate Imran et al. (1) for their study of T1 mapping. The study pointed out the excellent negative predictive value of T1 time (derived from the mid-left ventricle level) for detecting rejection noninvasively in their 34 cardiac allograft recipients. Repeated endomyocardial biopsies were used mainly during the first year after heart transplantation, which is a relatively riskier period for rejection. Native T1 values are known to increase with both intracellular and extracellular signal resulting from fibrosis, inflammation, edema, or necrosis and extracellular volume fraction to increase mainly by extracellular expansion which are all typical features of rejection.

This study confirms and complements the previous findings by Sade et al. (2), which also showed the excellent sensitivity and negative predictive value of quantitative T1 mapping to detect acute cellular rejection. In that study, the authors proposed a strategy to risk-stratify patients and to guide biopsies selectively by incorporating the information from T1 mapping into clinical follow-up for tissue characterization and strain quantification for functional assessment to reliably define rejection-related myocardial damage. Both strain quantification and T1 mapping were performed from the entire left ventricle. T1 time ≥1,090 ms, extracellular volume ≥32%, and global longitudinal strain had very high sensitivity and negative predictive value, suitable for screening and confidently ruling out grade ≥2R after the first year

of heart transplantation. Careful interpretation of those cutoff values and the values obtained by Imran et al. (1) is crucial because the definition of rejection is a “moving target” in the context of graft aging and healed rejections. Complete return to baseline values after resolution of grade 2R is not unanimous and smoldering deterioration of the graft occurs over the years (3). Therefore, the cutoff (>1,029 ms) to define cardiac allograft rejection derived within the first year after transplantation may not be the best discriminative cutoff value in the following years. In addition, previous data demonstrated that “normal” T1 and T2 measurements are higher after transplantation than those in healthy volunteers due to subclinical structural and functional alterations of transplantation-related damage and improve over time (4). This is in contrast with the data presented by Imran et al. (1). Primary graft failure is also an important confounder to consider, particularly when endomyocardial biopsy is normal despite symptoms of heart failure. The study by Imran et al. (1) seems to include all patients after heart transplantation regardless of potential confounders such as systemic infections and primary allograft failure. Imran et al. (1) did not take into account either the imprecision introduced by the correlated repeated observations potentiating the effect of the predictive value of T1 mapping cutoff values. It would have been appropriate either to include 1 rejection per patient and see how the values evolved after resolution of rejection or to use a predictive model that accounts for the correlation structure of the repeated observations.

The judgement stated by the authors as “T1 mapping did not reflect fibrosis” is an interpretation not sufficiently supported by their results, which are derived from the midventricular level, given the patchy nature of rejection, and contrasts with the worldwide successful detection of fibrosis by T1 mapping in a variety of diseases with pathological confirmation (5). If T1 times were to reflect edema rather than fibrosis, one would expect complete normalization of T1 times after resolution of rejection. However, follow-up data are lacking, except for 6 patients in whom pre-rejection values were not presented for comparison. The study did not include T2 measurements to assess edema, and extracellular volume quantification was not enough either.

In conclusion, the result of the study by Imran et al. (1) generates a hypothesis regarding the promotion of T1 mapping alone during the first year after heart transplantation to exclude cardiac allogarft rejection; however, the level of evidence presented is not robust enough to prove it.

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THE AUTHORS' REPLY:

We thank Dr. Sade and colleagues for their interest in our research. Their recent work in T1 mapping demonstrating excellent sensitivity and negative predictive value of quantitative T1 mapping in the detection of acute cellular cardiac allograft rejection after the first year of transplantation (1) nicely complements our research exploring T1 mapping in the first year after transplantation (2). Native T1 mapping has evolved as a highly reproducible modality not only to diagnose edema in acute myocarditis and myocardial ischemia but also to track its recovery post-treatment (3,4), making the imaging technique ideal for diagnosing the inflammation and edema associated with cardiac allograft rejection.

Although the work by Dr. Sade and colleagues is complementary, the T1 cutoff value they have suggested for the diagnosis of clinically significant rejection (International Society for Heart and Lung Transplantation grade ≥2) is substantially higher