T1 Mapping for Myocardial Extracellular Volume Measurement by CMR

Bolus Only Versus Primed Infusion Technique

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OBJECTIVES The aim of this study was to determine the accuracy of the contrast "bolus only" T1 mapping cardiac magnetic resonance (CMR) technique for measuring myocardial extracellular volume fraction (ECV).

BACKGROUND Myocardial ECV can be measured with T1 mapping before and after contrast agent if the contrast agent distribution between blood/myocardium is at equilibrium. Equilibrium distribution can be achieved with a primed contrast infusion (equilibrium contrast-CMR [EQ-CMR]) or might be approximated by the dynamic equilibration achieved by delayed post-bolus measurement. This bolus only approach is highly attractive, but currently limited data support its use. We compared the bolus only technique with 2 independent standards: collagen volume fraction (CVF) from myocardial biopsy in aortic stenosis (AS); and the infusion technique in 5 representative conditions.

METHODS One hundred forty-seven subjects were studied: healthy volunteers (n = 50); hypertrophic cardiomyopathy (n = 25); severe AS (n = 22); amyloid (n = 20); and chronic myocardial infarction (n = 30). Bolus only (at 15 min) and infusion ECV measurements were performed and compared. In 18 subjects with severe AS the results were compared with histological CVF.

RESULTS The ECV by both techniques correlated with histological CVF (n = 18, r^2 = 0.69, p < 0.01 vs. r^2 = 0.71, p < 0.01, p = 0.42 for comparison). Across health and disease, there was strong correlation between the techniques (r^2 = 0.97). However, in diseases of high ECV (amyloid, hypertrophic cardiomyopathy late gadolinium enhancement, and infarction), Bland-Altman analysis indicates the bolus only technique has a consistent and increasing offset, giving a higher value for ECVs above 0.4 (mean difference ± limit of agreement for ECV <0.4 = −0.004 ± 0.037 vs. ECV >0.4 = 0.040 ± 0.075, p < 0.001).

CONCLUSIONS Bolus only, T1 mapping-derived ECV measurement is sufficient for ECV measurement across a range of cardiac diseases, and this approach is histologically validated in AS. However, when ECV is >0.4, the bolus only technique consistently measures ECV higher compared with infusion. (J Am Coll Cardiol Img 2013;6:955–62) © 2013 by the American College of Cardiology Foundation

Expansion of the myocardial extracellular volume is ubiquitous in cardiac disease, whether as focal scar, diffuse fibrosis, through infiltration in amyloidosis, or edema (1). Extracellular volume expansion might represent a key intermediate phenotype preceding cardiac morbidity and mortality. Recent developments in T1 mapping by cardiac magnetic resonance (CMR) have permitted its noninvasive quantification. This new biological parameter has the potential to provide new mechanistic insights into health and disease states (2,3) and might have the ability to detect early disease, guide therapy, and/or predict outcomes (4).

T1 mapping measures myocardial longitudinal magnetic relaxation, and this can be performed before and after a standard gadolinium-based contrast agent. The contrast agent distributes between cells embedded in the interstitium between cells (extracellular space) and blood plasma such that the relative pre- and post-contrast signal changes measure the myocardial extracellular volume fraction (ECV) (Fig. 1). However, this assumes that a steady-state equilibrium of gadolinium contrast agent exists between blood and myocardium. This can be established by the administration of a primed slow intravenous contrast infusion—a technique known as equilibrium contrast cardiac magnetic resonance (EQ-CMR) (5)—but it is time consuming and adds clinical complexity. One alternative is that at sufficient time after a single contrast bolus, a dynamic equilibrium might exist (6,7)—principally because contrast flux between tissue compartments is faster than renal excretion—allowing the equivalent ECV measurement. This clinically straightforward approach is highly attractive. However, concerns about the "bolus only" approach have been raised (8), and although the technique provides short-term prognostic information (4), it is not validated histologically and has not been tested in distinct disease groups.

We hypothesized that the bolus only technique would be good enough to measure ECV across a range of cardiac diseases. To achieve this we compared our results with 2 independent techniques: firstly, with histology, specifically collagen volume fraction (CVF) (%) in severe aortic stenosis (AS); and secondly, the infusion technique, EQ-CMR.

METHODS

Bolus only and infusion ECV measurements were performed and compared with histological CVF in 18 subjects with severe AS and in a population of 147 subjects with a range of different diseases. In conditions with late gadolinium enhancement (LGE) where the ECV is high, these areas were considered separately.

Patients with atrial fibrillation or a contraindication to contrast CMR examination were excluded from the study. The research received approval from the local research ethics committee, and all participants provided written informed consent.

The study population consisted of:

1. Normal healthy subjects (n = 50, median age 48 [range 24 to 88 years], 51% male) were recruited through advertising within the hospital, university, and general practitioner surgeries. All normal subjects had no history or symptoms of cardiovascular disease or diabetes. Four subjects had been prescribed statin therapy for hypercholesterolemia (primary cardiovascular prevention), but no other normal healthy subject was using any cardiovascular medication. All subjects had a normal blood pressure (defined as <140/90 mm Hg), 12-lead electrocardiogram, and clinical CMR scan.
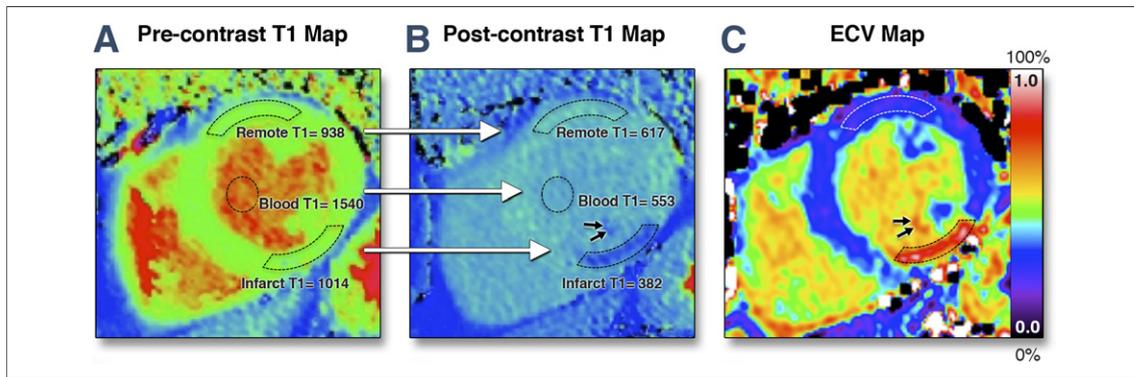
Figure 1. Calculation of ECV From Pre- and Post-Contrast T1 Maps

The extracellular volume fraction (ECV) was calculated with regions of interest drawn pre- **(A)** and post-contrast **(B)** agent with the equation: myocardial $ECV = (1 - hematocrit) \times (\Delta R1_{myocardium}/\Delta R1_{blood})$, where $R1 = 1/T1$. Two post-contrast maps exist: 1 at 15 min post-bolus; and 1 at equilibrium. In the future, pixel-by-pixel ECV maps will be constructed automatically online **(C)** (19). Here, the ECV of this chronic inferior infarct was high at 0.82; remote myocardium was 0.28 (infusion result). Infarction of part of the inferior papillary muscle is highlighted **(small black arrows)**, with an intermediate ECV of 0.65. The **large white arrows** indicate the change in T1 values following contrast administration. The T1 values are given in milliseconds.

2. Hypertrophic cardiomyopathy (HCM) patients (n = 25, median age 54 years [range 21 to 75 years], 76% male). All patients met previously described diagnostic criteria (9). Eighty percent of patients had an asymmetrical septal hypertrophy pattern with the remainder apical predominant hypertrophy. The mean maximal wall thickness (from CMR steady-state free precession short-axis assessment) was 20 ± 4 mm. Patients were found to have LGE in a variety of locations, such as at the right ventricular insertion points or the left ventricular apex. LGE was absent in 4 patients. In 10 patients LGE was present on pre- and post-contrast T1 maps, allowing ECV measurement in both HCM LGE zones and HCM remote zones.

3. Severe AS patients (n = 22, median age 72 years [range 46 to 84 years], 73% male). All patients had undergone clinical evaluation and echocardiography for diagnosis and were listed for surgical aortic valve replacement.

4. Cardiac AL amyloidosis patients (n = 20, median age 62 [range 41 to 76 years], 75% male). All patients had disease proven by noncardiac biopsy. Cardiac involvement was ascertained through echocardiography, supported by a Mayo clinic classification score of 2 or 3 (10).

5. Chronic myocardial infarction patients (n = 30, median age 61 years [range 37 to 75 years], 87% male). Studies were performed at not <6 months after an acute ST-segment elevation myocardial infarction with complete culprit artery occlusion—Thrombolysis In Myocardial Infarction

flow grade 0 (culprit lesions: 11 left anterior descending artery; 11 right coronary; and 8 circumflex artery). The infarct zone was identified by routine LGE imaging. Remote myocardium was defined as nonenhancing myocardium outside of the infarct zone.

CMR protocol. The EQ-CMR primed infusion technique uses the contrast agent Gadoterate meglumine, (gadolinium-DOTA, marketed as Dotarem, Guerbet S.A., Paris, France) at a dose of 0.1 mmol/kg for the bolus and up to an additional 0.1 mmol/kg for the infusion, started after a 15-min delay at 0.0011 mmol/kg/min for a minimum of 30 min (5). This meant T1 measurements could be made precontrast agent, at 15 min (dynamic equilibrium time) post-contrast agent bolus and at infusion, for 2 ECV calculations. The scanner used was a conventional cardiac-enabled magnetic resonance imaging scanner (1.5-T Avanto, Siemens Medical Solutions, Ehrlangen, Germany). The T1 mapping sequence employed was shortened look locker inversion recovery (ShMOLLI). The ShMOLLI T1 mapping was applied as previously described (11), allowing for standard cardiac planning adjustments. A complete set of sequence parameters are available online (12).

Analysis. The ShMOLLI sequence T1 maps were generated with a previously published algorithm (11). A single region of interest (ROI) was then drawn for each of the 4 required parameters: myocardial T1 estimates and blood T1 estimates before and after gadolinium contrast administration. Myocardial T1 was measured in the basal to mid septum of a routinely planned 4-chamber acquisition,
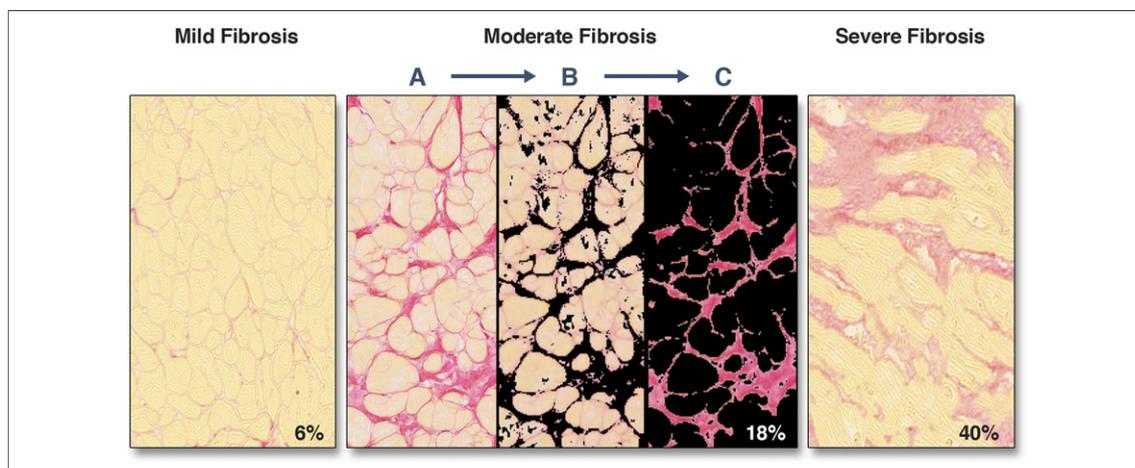
Figure 2. Histology of an Intra-Myocardial Biopsy Sample in 3 Patients With Severe Aortic Stenosis

Picrosirius red stains collagen (fibrosis) red/pink, and counter stains myocytes yellow **(A)**. Collagen volume fraction (%) was calculated by automated subtraction of these 2 color stains, which also thresholds out slicing artifact (seen in **B**) leaving collagen alone **(C)**.

avoiding areas of LGE, except in amyloid (where the ROI was drawn irrespective of the ill-defined presence/absence of LGE), HCM, and myocardial infarction (where ROIs were drawn around the LGE zone itself, and the remote nonenhancing zone in the short axis) (Fig. 1). Blood T1 was assessed in the LV cavity blood pool in all subjects, avoiding the papillary muscles. An ROI in the septum was chosen, because this corresponds with the site of previous histological validation (5) and the site of biopsy in this study.

All analyses were performed blinded to the technique of ECV measurement. A hematocrit was taken in all subjects immediately before each CMR study. The ECV was calculated with each method as: myocardial ECV = $(1 - \text{hematocrit}) \times (\Delta R1_{\text{myocardium}}/\Delta R1_{\text{blood}})$, where R1 = 1/T1.

Histological validation. Histological sampling and analysis was performed in 21 patients with severe AS listed for surgical aortic valve replacement as previously described (5). In summary, an intra-operative deep myocardial biopsy (Tru-Cut type biopsy needle) was taken from the basal LV septum, stained with picrosirius red, and photographed at high-power magnification (200×) (Fig. 2). The CVF (%) was automatically quantified over an average of 12 high-power fields with a purpose-written macro in ImageJ (13). All samples were analyzed (A.S.F.) blinded to the CMR findings and ECV values. One biopsy specimen was excluded from analysis in accordance with pre-specified exclusion criteria: 1) extremes of patchy fibrosis (n = 1); and 2) presence of LGE at the site of the biopsy (n = 0). In addition, 2 samples were further

excluded, because they were deemed to be superficial and included mainly endocardial tissue. One patient did not undergo sampling, because more than 6 months had elapsed between the CMR study and the operative procedure. These 4 patients excluded from histological correlation were included in the comparison of bolus technique with EQ-CMR.

Statistical analysis. All data were normal and expressed as mean ± SD. Correlation between continuous variables was assessed with Pearson's test. Comparison of the strength of correlations was performed as described by Steiger (14), with a freely available online computer program (15). The differences between the 2 ECV techniques and the relationship to the mean were compared with Bland Altman plots, with limits of agreement quoted as ±1.96 SD. Comparison of differences was assessed with T tests: unpaired for the means of ECV above and below 0.4; and paired for the comparison of differences in means between bolus only and infusion techniques. Analysis was performed with SPSS version 21 (SPSS, Chicago, Illinois). A statistical significance level of <0.05 was used.

RESULTS

Histological validation. All biopsies were uneventful. The mean histological CVF of the 18 biopsies was 17 ± 8% (range 5% to 40%). The ECV by both techniques correlated well with histological CVF ($r^2 = 0.69$, p < 0.01 vs. $r^2 = 0.71$, p < 0.01, p = 0.42 for comparison) (Fig. 3) and did not differ statistically. In keeping with previously published histological correlation (16), we also found correlation with post-contrast T1 values and CVF (bolus
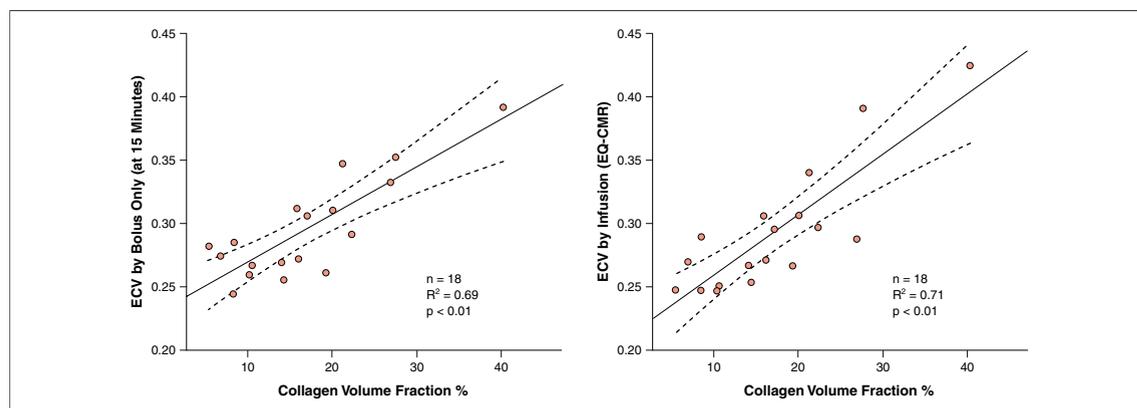
Figure 3. Correlation With Histological Collagen Volume Fraction in Severe Aortic Stenosis

Both the bolus only technique (at 15 min) and the infusion technique (equilibrium contrast cardiac magnetic resonance imaging [EQ-CMR]) correlate well with collagen volume fraction. The **dashed lines** represent 95% confidence intervals. ECV = extracellular volume fraction.

only r^2 = 0.21, p = 0.04, and infusion r^2 = 0.26, p = 0.03), but these were statistically inferior to the ECV correlation by either technique.

ECV comparison. Across health and disease, there was strong correlation between ECV as measured by bolus and infusion techniques (r^2 = 0.97) (Fig. 4). More importantly, in high ECV diseases (amyloid, the late enhancing myocardium in HCM, and the infarct zone of myocardial infarction), there was a consistent and increasing offset on Bland-Altman analysis (r = 0.56, p < 0.001), with the bolus technique measuring higher ECV than the infusion technique (Fig. 4). An iterative analysis of difference showed that, as ECV increased (at 0.05

intervals) above 0.4, a natural cutpoint was observed between the high ECV diseases (amyloid, LGE in HCM, and infarction) and all other conditions (mean difference ± limit of agreement for ECV <0.4 = −0.004 ± 0.037 vs. ECV >0.4 = 0.040 ± 0.075, p < 0.001; and across the cohort as a whole 0.015 ± 0.061). Mean T1 values pre- and post-contrast agent with the bolus only and infusion techniques are given in Table 1.

DISCUSSION

This is the first study to validate the bolus only technique against histology. The correlation with
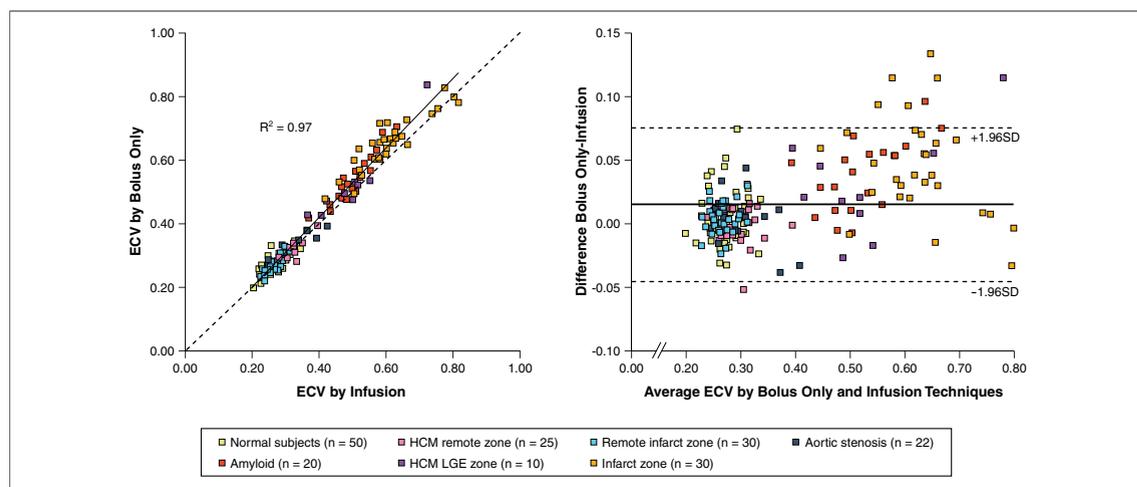
Figure 4. Correlation and Bland-Altman Analysis of Comparison Between Bolus Only and Infusion Techniques Across Health and Disease

There is an offset toward higher extracellular volume fraction (ECV) values in those diseases where the ECV >0.4, and this increases with increasing ECV (amyloid, hypertrophic cardiomyopathy [HCM] late gadolinium enhancement [LGE], chronic infarct zones). The **dashed lines** denote the line of identity in the scatterplot and the mean ± 1.96 SD in the Bland-Altman plots for all subjects combined.

Table 1. Mean T1 Values Pre- and Post-Contrast Agent With Bolus Only and Infusion Techniques

	Normal Subjects (n = 50)	HCM Remote Zone (n = 25)	Severe AS (n = 22)	Amyloid (n = 20)	HCM LGE Zone (n = 10)	Infarct Zone (n = 30)	Remote Infarct Zone (n = 30)
Blood							
Pre-contrast	1,530	1,519	1,558	1,597	1,498	1,532	1,532
Post-contrast bolus only (at 15 min)	496	501	508	590	498	513	513
Post-contrast infusion	512	506	465	525	477	447	447
Difference post-contrast bolus only infusion	−16*	5	43†	65†	21*	66†	66†
Myocardium							
Pre-contrast	968	997	997	1,137	1,058	1,026	947
Post-contrast bolus only (at 15 min)	600	589	603	539	463	411	601
Post-contrast infusion	613	592	575	509	460	381	560
Difference post-contrast bolus only infusion	−13†	−3	28†	30†	3	30†	41†

Values are in milliseconds. *p < 0.05; †p < 0.01.

AS = aortic stenosis; HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement.

CVF was similar to that with the infusion technique (0.69 vs. 0.71) and did not differ statistically. When compared with infusion-derived ECV (EQ-CMR), the bolus only approach seems to be equivalent provided that the disease under study has an ECV below 0.4. Above this (amyloid, LGE areas of HCM and chronic myocardial infarction) the bolus only approach consistently and increasingly provides a higher ECV. The clinical significance of this is yet to be explored.

These findings are important, because an ECV measurement with a bolus only technique is extremely easy to incorporate into routine clinical practice—a single breath-hold, here of approximately 8 s, before and after the contrast agent administration is all that is required (a total of 6 breath-holds for a 16-segment ["whole-heart"] approach). The approach might also be generalizable to other organs (17) and computed tomography with iodinated contrast agents (18). Given the potential importance of ECV as a biomarker representing interstitial expansion, this result goes some way to justifying clinical use. In scenarios where highly accurate ECV measurement is paramount (serial follow-up or research setting), a tailored technique could be employed: for example, with the advent of online, real-time, motion-corrected, and co-registration ECV map generation (shown in Fig. 1) (19,20), the ECV could realistically be measured at 15 min, and if found to be over 0.4, an infusion could be commenced, and the ECV could be re-measured with EQ-CMR.

There is now a family of CMR techniques that use T1 mapping (1). Native or pre-/non-contrast T1 mapping techniques measure a composite signal from both myocytes and interstitium but can detect T1 elevation in disease (fibrosis [21], infarction [22], and amyloid [23]). A single post-contrast T1 measurement has been used to measure change in myocardial signal (16,24), but this approach has been criticized for its lack of correction for confounding variables (4). Our data support this, suggesting a significantly lower r^2 (0.21 vs. 0.71 with infusion) when post-contrast T1 values are correlated with CVF. Three techniques advance on this susceptibility to confounders (by a single post-contrast T1 assessment), by measuring the ratio of the blood and myocardial signal change post-contrast agent with correction for hematocrit to derive myocardial ECV. These remove kinetics effect in different ways, leaving signal change dependent only on contrast volume of distribution: 1) the logistic and time demanding primed infusion technique (EQ-CMR) (5); 2) a multiple measurement technique to derive the slope of the blood/myocardial contrast dynamics (25); and 3) the bolus only technique, which assumes a dynamic equilibrium occurs with sufficient delay post-bolus, because blood/myocardial exchange rate constants are much faster than other effects that influence blood gadolinium concentration (such as renal excretion). This dynamic or "pseudo-equilibrium" technique was explored here: its simplicity gives it maximum potential clinical utility. Earlier work in healthy volunteers or patients with modest ECV increases has demonstrated either little drift in ECV with time post-bolus (0.6%) (6) or up to 10% over 40 min (8). Further work is needed to clarify this. It might be that such a time dependency is unimportant in many clinical scenarios. For infarction, however, contrast equilibration does not seem to be established in acute infarct zones when complicated by

microvascular obstruction. In chronic infarction, there is evidence that equilibration can be reached after 20 min (with a higher dose of contrast agent: 0.2 mmol/kg) (26,27).

Currently, disease-orientated T1 mapping research is fast-developing, but to date, little technical validation has been presented of the bolus only approach, either in disease—particularly those with high ECV values and enhancing myocardium—or with histological validation with single breath-hold T1 mapping. Here, we emphasize a difference in measuring high ECV diseases.

Study limitations. We do not yet know which precise experimental details are important for bolus only T1 mapping. Here, a single contrast bolus (not split, as might be used in perfusion protocols) at 3 ml/s of a single contrast agent Dotarem (Gadoterate meglumine) at 0.1 mmol/kg with post-contrast T1 map at 15 min was performed. Bolus delivery rate, dose, contrast agent, and timing of post-contrast imaging might have modifying effects and must be investigated systematically. It might be that in diseases with ECV >0.4 simply waiting longer or giving a larger dose might reduce this difference. Furthermore, the data here do not necessarily support either approach for serial measurement, for example, as a surrogate endpoint in a clinical trial. In this situation, where other major changes might be occurring in body composition or hematocrit or renal function and where over time these could

influence, systematically, the residual pharmacokinetic effects, the infusion approach is theoretically less confounded, but this is unproven. The key parameter for clinical trials and detecting differences will be the reproducibility of the respective measures. Lastly, this study provided biopsy data in only 1 disease, and we used only 1 T1 mapping sequence, ShMOLLI. Despite these limitations, these data advance the field of ECV measurement and provide substantial justification for the simplification of ECV methodology in this implementation of the bolus only technique. Further technical development work will be required before a comprehensive model of bolus only ECV measurement is available, accounting for all potentially relevant parameters.

CONCLUSIONS

A bolus only, T1 mapping-derived ECV measurement is sufficient for ECV measurement across a range of cardiac diseases, and this approach is now histologically validated in AS. However, when ECV is >0.4, the bolus only technique consistently measures ECV higher, compared with infusion.

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