

Native T1 and Extracellular Volume Measurements by Cardiac MRI in Healthy Adults: A Meta-Analysis

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Conflicts of interest are listed at the end of this article.

See also the editorial by Dodd and Dewey in this issue.

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Purpose: To summarize the literature by performing a systematic review and pooled analysis of the data, to understand the extent of variability among studies of native T1 and extracellular volume (ECV) measurements, and to identify covariates that account for heterogeneity between studies.

Materials and Methods: PubMed, Web of Science, and Cochrane Central were searched for native T1 and ECV measurements of the left ventricle in health adult study participants. The search terms used were “T1 mapping heart,” “Native T1 heart,” and “ECV heart.” Summary means were generated with random-effects modeling. Heterogeneity was assessed by using the inconsistency factor (I^2). Subgroup analyses and meta-regression analyses were conducted to identify etiologic causes of heterogeneity.

Results: This systematic review of native T1 included 120 articles, with 5541 participants (mean age, 50 years; 51.0% men [2826 of 5541]). The pooled mean of native T1 was 976 msec (95% confidence interval [CI]: 969 msec, 983 msec) at 1.5 T and 1159 msec (95% CI: 1143 msec, 1175 msec) at 3.0 T. I^2 was 99% at both field strengths. Eighty-one articles were included in the systematic review of ECV, with 3872 participants (mean age, 52 years; 50.0% men [1936 of 3872]). The pooled mean of ECV was 25.9% at field strength of 1.5 T (95% CI: 25.5%, 26.3%) and 3.0 T (95% CI: 25.4%, 26.5%). I^2 was 94% and 90% at 1.5 and 3.0 T, respectively.

Conclusion: The pooled means of extracellular volume and native T1 measurements in healthy adult participants are summarized in this analysis. There was significant heterogeneity found among studies, highlighting the importance of standardized cardiac MRI protocols and the derivation of institution specific reference ranges.

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Online supplemental material is available for this article.

T1 mapping techniques at cardiovascular MRI are rapidly emerging as viable surrogate markers for assessing diffuse fibrosis and infiltrative processes (1–8). The current standard, endomyocardial biopsy, is prone to sampling error and confers a procedural risk (9). The advancement of T1 mapping parameters, namely native T1 and extracellular volume (ECV), stems from the need for noninvasive methods to characterize the myocardium. Extensive work has been performed by using native T1 and ECV to characterize the myocardium, and these measures demonstrated promising diagnostic and prognostic utility (10–22). A variety of factors such as differences in center-specific protocols, population studied, vendor, and pulse sequence have made specific cut-offs for native T1 and ECV difficult to define. To improve intra- and interpatient variability, the recently published parametric mapping guidelines from the Society for Cardiovascular Magnetic Resonance (23) recommends that local institutions validate a specific set of sequence parameters and that these parameters remain fixed over time. It is important to understand and quantify the magnitude and etiologic cause of the variability so that T1 mapping measurements can be reliably used in clinical and research settings.

To date there have been several studies that compare participants who have known pathologic conditions, such as hypertrophic cardiomyopathy or amyloidosis, with control participants (10,13,14,16,24–26). Although there have been some larger-scale studies that define normal ranges for a specific pulse sequence (24,26), to our knowledge there has not been a comprehensive analysis of the literature to determine what is considered normal across different studies. The primary goals of our study were to summarize the literature by performing a systematic review and pooled analysis of the data, to understand the extent of variability among studies of native T1 and ECV measurements, and to identify covariates that account for heterogeneity between studies.

Materials and Methods

Search Strategy

Two independent reviewers (M.G., a cardiology fellow with 4 years of experience, and M.S., a senior faculty member with over 15 years of experience) systematically searched PubMed, Web of Science, and Cochrane Central for articles of myocardial T1 measurements in

Abbreviations

CI = confidence interval, ECV = extracellular volume, MOLLI = modified Look-Locker inversion recovery

Summary

We evaluated normal values and variability of native T1 and extracellular volume measurements at cardiac MRI in the literature. Marked heterogeneity was found among studies, emphasizing the importance of standardizing cardiac MRI protocols.

Implications for Patient Care

- Native T1 values vary with field strength and vendor, and published cut-off values for disease need to be interpreted with caution. Extracellular volume values are similar at 1.5 T and 3.0 T and thus may be preferred for comparisons across field strengths.
- Native T1 and extracellular volume values depend in part on protocol and pulse sequence parameters. Institution should standardize MRI protocol and pulse sequences.
- Whenever possible, internal control groups should be used to derive institution-specific reference ranges for native T1 and extracellular volume values.

healthy subjects. The search terms used were “T1 mapping ‘AND’ heart,” “Native T1 ‘AND’ heart,” and “ECV ‘AND’ heart.” The search terms were used separately rather than in combination. Date limits were not placed. The initial search was performed on October 1, 2016, and the last search was performed on March 5, 2018. Abstracts were reviewed if the title of the article indicated that the study involved T1 measurements of the heart or if the applicability of the study was not made clear by the title. Reviewers further searched reference lists of eligible articles to identify any additional articles not discovered through database searches.

Study Selection

Studies were included if myocardial native T1 or ECV measurements were performed by using cardiac MRI in a study group of healthy participants. For inclusion, a study had to contain at least either native T1 or ECV data; a study did not have to contain both native T1 and ECV data for inclusion. Each study was considered for inclusion in the analysis if it included a study group of at least 10 healthy participants who were older than 18 years of age, free of any known heart disease or overt symptoms of heart disease, and free of any findings of myocardial scar on cardiac MRI. Studies that included participants who were considered low probability for heart disease or had risk factors for heart disease such as hypertension, hyperlipidemia, diabetes mellitus, or tobacco use were also included. Studies of athletes or participants who underwent cardiac MRI after exercise or following pharmacological stress were excluded. Both studies that retrospectively and prospectively recruited control participants were included. There was a large number of T1 mapping pulse sequences described in the literature. Specific techniques, defined by field strength, vendor, and pulse sequence scheme, that were used in fewer than five studies meeting the above criteria were not included in the analysis. As a result of this criterion, studies performed on GE (Waukesha, Wis) scanners were excluded. Although there were six studies found in the literature, five

different pulse sequence schemes were used in these six studies. Studies were included only if they were published in peer-reviewed journals in English; conference presentations were excluded. Discrepancies regarding inclusion were resolved by a consensus of reviewers. The included studies are shown in Tables E1 and E2 (online). This systematic review and meta-analysis was conducted in accordance with guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (27).

Data Collection

Data abstraction and study appraisal were performed by two authors (M.G. and M.S.). Because the clinical measurements of interest were native T1 and ECV in healthy participants, authors directly abstracted native T1 myocardium, native T1 blood pool, postcontrast T1 myocardium, postcontrast T1 blood pool, partition coefficient, and ECV from text and tables of fully reviewed articles.

Details of the cardiac MRI protocol used, including vendor, field strength, pulse sequence scheme, flip angle, matrix size, repetition time, echo time, interpulse delay (defined as the time between the first and subsequent inversions for modified Look-Locker inversion recovery [MOLLI] and shortened MOLLI pulse sequences), contrast agent, and contrast dose, were abstracted.

If an article presented data at different field strengths or from varied pulse sequences, each data set acquired was handled as a unique study group, even if multiple pulse sequences were applied to the same cohort of healthy participants. When data were acquired from multiple planes, data from the mid-ventricular short axis plane was abstracted.

When data were acquired both during systole and diastole, data acquired at end diastole were abstracted. If ECV values were reported at different points after contrast agent administration, values from the latest postcontrast time within 30 minutes were abstracted. Study size and demographic information was abstracted from text and tables.

Data Analysis

The summary means and confidence intervals (CIs) of native T1 and ECV were calculated by using random-effects models weighted by the inverse of the variance. Heterogeneity was assessed by using Cochran Q test; τ^2 ; and the inconsistency factor, I^2 ; with values of 25%, 50%, and 75% representing mild, moderate, and severe inconsistency, respectively. Sensitivity analyses, subgroup analysis, and meta-regression were performed to determine which variables likely affect native T1 and ECV measurements and, thus, account for some or all of the heterogeneity. Cochran Q_e test was used to assess residual heterogeneity and R^2 was used to assess the proportion of total variance that could be explained by the covariates. Small study and publication biases were examined with funnel plots and the Egger test.

Statistical analysis was performed by using software (R version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria) with the threshold for statistical significance set at α value less than .05, two-tailed level. Meta-analysis was performed by using the package *metaphor* in R.

Results

Results of the Literature Search

The database search identified 2334 articles; 1153 from PubMed (Native T1 AND Heart, 230 articles; T1 Mapping AND Heart, 571 articles; ECV AND Heart, 352 articles), 944 from Web of Science (Native T1 AND Heart, 156 articles; T1 Mapping AND Heart, 533 articles; ECV AND Heart, 255 articles), and 237 from Cochrane Central (Native T1 AND Heart, 22 articles; T1 Mapping AND Heart, 171 articles; ECV AND Heart, 44 articles). Duplicate articles were removed. The titles of the 1207 unique articles were reviewed for applicability and 380 met criteria for abstract review.

At review of the abstracts, 186 articles met the criteria for full-text review. Whereas our search included all vendors, the pooled analysis only included studies that used Philips or Siemens scanners because these were the only two vendors with adequate numbers of studies for pooled analysis. Likewise, whereas our search included all pulse sequence techniques, only two techniques, MOLLI and shortened MOLLI, were used in a sufficient number of studies to be included in the pooled analysis. Most clinical studies in the literature used either MOLLI or shortened MOLLI as the pulse sequence scheme.

Fifty-seven full-text articles were excluded because of study size, technique, or pulse sequence used, or because of incomplete data. Ultimately, 129 articles met selection criteria; 120 of the 129 articles were included in the native T1 meta-analysis and 81 of the 129 articles were included in the ECV meta-analysis (references for articles included in the meta-analysis can be found in Appendix E1 [online]). Some articles included multiple study groups that varied by the field strength, technique, pulse sequence, flip angle, contrast agent, or contrast dose used in the study. Details of the search strategy are outlined in the Quality of Reporting of Meta-Analyses Standards diagram in Figure 1.

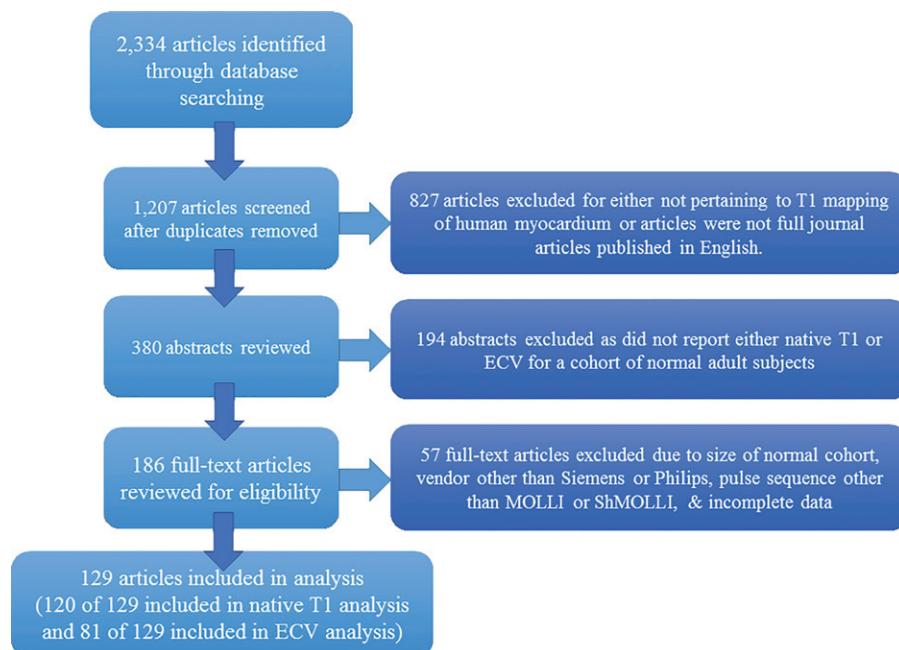


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the study review process. ECV = extracellular volume, MOLLI = modified Look-Locker inversion recovery, ShMOLLI = shortened modified Look-Locker inversion recovery.

Table 1: Results of Meta-Analysis by Subgroup

Parameter	Field Strength (T)	Technique	No. of Studies	Mean Native T1 (msec)	Mean ECV (%)
Native T1					
All vendors	1.5	All	76	976 (969, 983)	NA
Siemens	1.5	MOLLI	37	977 (969, 985)	NA
Siemens	1.5	ShMOLLI	19	954 (949, 958)	NA
Philips	1.5	MOLLI	20	994 (974, 1014)	NA
All	3.0	All	62	1159 (1143, 1175)	NA
Siemens	3.0	MOLLI	28	1192 (1171, 1214)	NA
Siemens	3.0	ShMOLLI	7	1170 (1152, 1188)	NA
Philips	3.0	MOLLI	27	1122 (1100, 1143)	NA
ECV					
All	All	All	95	NA	25.9 (25.6, 26.2)
All	1.5	All	55	NA	25.9 (25.5, 26.3)
Siemens	1.5	MOLLI	33	NA	25.8 (25.3, 26.3)
Siemens	1.5	ShMOLLI	7	NA	26.9 (25.9, 27.6)
Philips	1.5	MOLLI	15	NA	25.6 (24.7, 26.6)
All	3.0	All	40	NA	25.9 (25.4, 26.5)
Siemens	3.0	MOLLI	17	NA	26.4 (25.6, 27.2)
Philips	3.0	MOLLI	21	NA	25.4 (24.9, 26.0)

Note.—Data in parentheses are 95% confidence intervals. ECV = extracellular volume, MOLLI = modified Look-Locker inversion recovery, NA = not applicable, ShMOLLI = shortened modified Look-Locker inversion recovery.

Study Characteristics

Study characteristics are shown in Tables E1 and E2 (online).

The 120 articles on native T1 included 5541 healthy participants. Ten articles presented multiple study groups for a total of 138 study groups. One-hundred-sixteen of 138 study groups (84.1%) in the native T1 meta-analysis

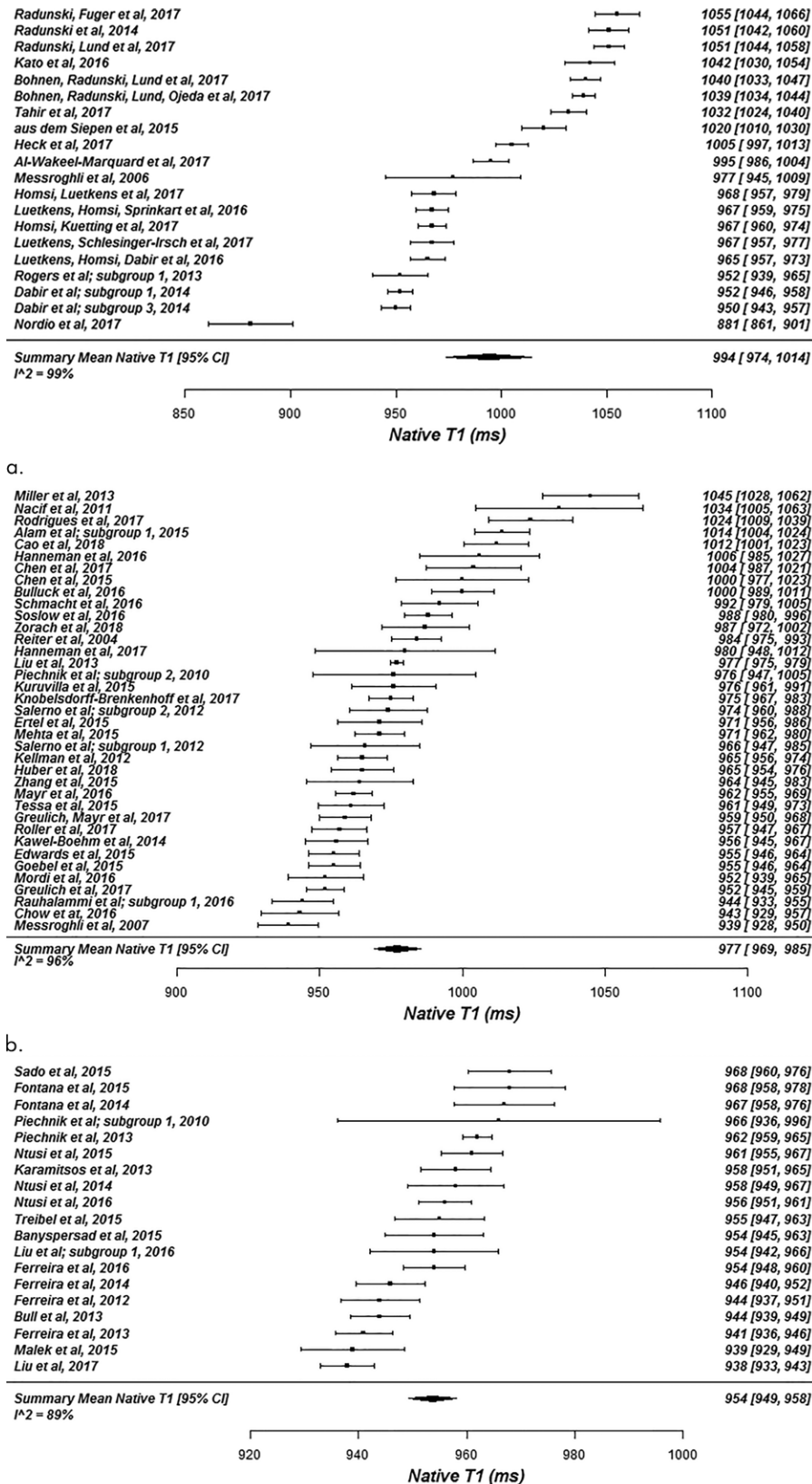


Figure 2: Forest plots of native T1 studies at 1.5-T cardiac MRI in healthy participants. Studies are grouped by vendor and pulse sequence scheme. **(a)** Native T1 studies from Philips modified Look-Locker inversion recovery (MOLLI) subgroup, **(b)** native T1 studies from Siemens MOLLI subgroup, and **(c)** native T1 studies from Siemens MOLLI subgroup. Studies with multiple subgroups are noted by author last name and year of publication.

included less than 50 participants and only three study groups (2.2%) included more than 100 participants. Mean age of participants was 50 years and 51.0% (2826 of 5541) were men.

The 81 ECV articles included a total of 3872 healthy participants. Seven articles presented multiple study groups for a total of 95 study groups. Similarly, 81 of 95 study groups (85%) in the ECV meta-analysis included less than 50 participants and only two studies (2%) included more than 100 participants. In these studies, the mean age of the study participants was 52 years and 50.0% (1936 of 3872) were men. The largest study was conducted by Liu et al (24) and included 1231 participants; this study was included in both native T1 and ECV meta-analyses.

Pooled Analysis of Native T1

The summary mean of all native T1 study groups studied at 1.5 T was 976 msec (95% CI: 969, 983) and at 3.0 T it was 1159 msec (95% CI: 1143, 1175) (Table 1). There was substantial heterogeneity in both pools; I^2 was 99% in both the 1.5-T and 3.0-T pools. The forest plots of native T1 study groups at 1.5 T and 3.0 T are shown in Figures 2 and 3, respectively. Table 1 shows the overall mean native T1 by field strength and the mean native T1 subgrouped by field strength, vendor, and pulse sequence. Table 2, A and B show significant differences in the pooled mean native T1 by field strength, vendor, and pulse sequence. The Siemens shortened MOLLI pulse sequences showed on average a 23 msec shorter T1 time at 1.5 T, and a 22 msec shorter T1 time at 3.0 T than the Siemens MOLLI pulse sequences. Philips MOLLI yielded T1 values that were 17 msec longer at 1.5 T, and 70 msec shorter at 3.0 T compared with Siemens MOLLI.

There was no evidence of a small study or publication bias in the 1.5-T or 3.0-T pools as assessed by the funnel plot and Egger test.

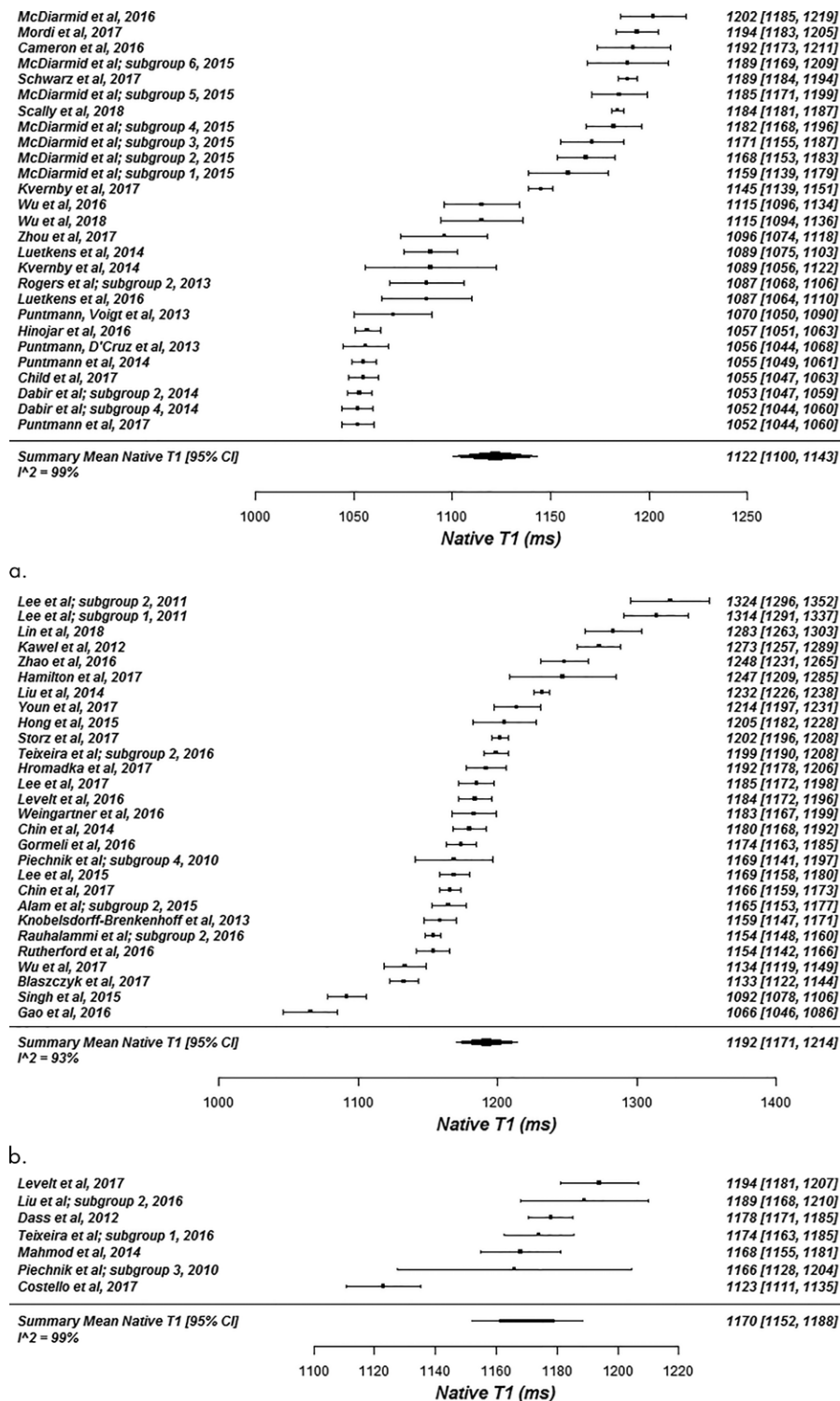


Figure 3: Forest plots of native T1 studies at 3.0-T cardiac MRI in healthy participants. Studies are grouped by vendor and pulse sequence scheme. **(a)** Native T1 studies from Philips modified Look-Locker inversion recovery (MOLLI) subgroup, **(b)** native T1 studies from Siemens MOLLI subgroup, and **(c)** native T1 studies from Siemens shortened MOLLI subgroup. Studies with multiple subgroups are noted by author last name and year of publication.

Pooled Analysis of ECV

The summary mean of all ECV study groups was 25.9% (95% CI: 25.6%, 26.2%; Table 1). The summary mean of all ECV study groups at 1.5 T was 25.9% (95% CI: 25.5%, 26.3%).

This was equal to the summary mean of all study groups at 3.0 T (25.9%; 95% CI: 25.4%, 26.5%). Again, there was substantial heterogeneity found in the pools of study groups separated by field strength (I^2 was 94% and 90% at 1.5 T and 3.0 T, respectively) and in the pool of all ECV study groups (I^2 was 93%). The forest plots of ECV studies are shown in Figures 4 and 5. Subgroup analysis was performed to determine the magnitude and statistical significance of the difference between subgroups of studies on the basis of field strength, vendor, and pulse sequence scheme, as shown in Table 2, C. The difference in pooled mean ECV between subgroups ranged from 0.2% to 1.5%, with the largest difference found between the 1.5 T-Siemens shortened MOLLI subgroup and the 3.0-T Philips MOLLI subgroup. The subgroups with the most similar pooled mean ECV were 1.5-T Siemens MOLLI (pooled mean, 25.8%), 1.5-T Philips MOLLI (pooled mean, 25.6%), and 3.0-T Philips MOLLI (pooled mean, 25.4%).

There was no evidence of a small study or publication bias in the pool of ECV studies, assessed by the funnel plot and Egger test.

Metaregression Analysis of Native T1 and ECV

The metaregression analysis of the pool of native T1 studies conducted at 1.5 T identified vendor ($\beta = -25.02$ [Philips as the reference vendor]; $P < .01$) and pulse sequence scheme ($\beta = -29.25$ [MOLLI as the reference pulse sequence scheme]; $P < .01$) as covariates that have statistically significant associations with native T1. Metaregression of the pool of native T1 studies conducted at 3.0 T identified vendor ($\beta = 67.31$ [Philips as reference vendor]; $P < .01$), flip angle ($\beta = -4.98$; $P \leq .01$), and interpulse delay ($\beta = 22.19$; $P = .03$) as covariates that have a statistically significant association with native T1. Metaregression

did not identify any statistically significant association with age ($P = .51$ and $P = .81$ at 1.5 T and 3 T, respectively), percentage of male participants ($P = .16$ and $P = .41$ at 1.5 T and 3 T, respectively), and native T1 time at either field strength.

Table 2: Analyses According to Subgroup

A: Comparison of Native T1 Time by Subgroup at 1.5 T

Parameter	Pulse Sequence	Myocardial Native T1 at 1.5 T		
		Siemens		Philips
		MOLLI (msec)	ShMOLLI (msec)	MOLLI (msec)
Siemens	MOLLI	977 (969, 985)*	-23 (<.01)	17 (.11)
Siemens	ShMOLLI		954 (949, 958)*	40 (<.01)
Philips	MOLLI			994 (974, 1014)*

B: Comparison of Native T1 Time by Subgroup at 3.0 T

Parameter	Pulse Sequence	Myocardial Native T1 at 3.0 T		
		Siemens		Philips
		MOLLI (msec)	ShMOLLI (msec)	MOLLI (msec)
Siemens	MOLLI	1192 (1171, 1214)*	-22 (.12)	-70 (<.01)
Siemens	ShMOLLI		1170 (1152, 1188)*	-48 (<.01)
Philips	MOLLI			1122 (1100, 1143)*

C: Comparison ECV by Subgroup

Parameter	Pulse Sequence	Myocardial ECV				
		Siemens 1.5 T		Philips 1.5 T	Siemens 3.0 T	Philips 3.0 T
		MOLLI	ShMOLLI	MOLLI	MOLLI	MOLLI
Siemens 1.5 T	MOLLI	25.8 (25.3, 26.3)*	1.1 (.02)	0.2 (.63)	0.6 (.22)	-0.4 (.30)
Siemens 1.5 T	ShMOLLI		26.9 (25.9, 27.6)*	-1.3 (.01)	-0.5 (.38)	-1.5 (<.01)
Philips 1.5 T	MOLLI			25.6 (24.7, 26.6)*	0.8 (.12)	-0.2 (.63)
Siemens 3.0 T	MOLLI				26.4 (25.6, 27.2)*	-1.0 (.04)
Philips 3.0 T	MOLLI					25.4 (24.9, 26.0)*

Note.—Unless otherwise indicated, data are the difference between the subgroup in the row and the subgroup in the column; the associated *P* value is in parentheses. ECV = extracellular volume, MOLLI = modified Look-Locker inversion recovery, ShMOLLI = shortened modified Look-Locker inversion recovery.

* Data are pooled mean of each subgroup; data in parentheses are 95% confidence intervals.

The meta-regression of all ECV study groups identified pulse sequence scheme ($\beta = 1.17$ [MOLLI as the reference pulse sequence scheme]; $P = .02$), percentage of male participants ($\beta = -2.43$; $P = < .01$), and contrast agent (Gadovist, $\beta = -1.36$ [$P < .01$]; Magnevist, $\beta = -1.28$ [$P < .01$]; and Multihance, $\beta = -1.89$ [$P < .01$]; gadoterate meglumine was the reference contrast agent) as covariates that affect measured ECV values.

Coefficient of Variance of Native T1 and ECV and Sensitivity Analyses

The coefficients of variance of the pools of native T1 and ECV studies are shown in Table E3, A and B (online). The pooled coefficient of variance of all ECV studies was 0.12, which was higher than both the pooled coefficient of variance of native T1 at 1.5 T (coefficient of variance, 0.04) and at 3.0 T (coefficient of variance, 0.03).

Discussion

Our study comprehensively analyzed studies in the literature that measured native T1 and ECV in healthy adult participants. The mean native T1 was 976 msec (95% CI: 969, 983) at 1.5

T, and 1159 msec (95% CI: 1143, 1175) at 3.0 T. The difference in native T1 between 1.5 T and 3.0 T field strengths was expected because of the known dependence of T1 on magnetic field strength. For ECV, we found equal values at 1.5 T and 3.0 T (25.9% and 25.9%, respectively) with a mean value of 25.9% (95% CI: 25.6%, 26.2%). Given that ECV is proportional to the ratio of the gadolinium concentration in the myocardium to that of the blood-pool, which as a given field strength is proportional to the $1/T1$ after contrast administration - $1/T1$ before contrast administration of the myocardium and blood pools, respectively. These results suggest that pooled ECV values determined from current clinically available pulse sequences should be comparable between examinations performed at 1.5 T and 3.0 T.

We also determined the uncertainty in native T1 and ECV within the individual studies, as defined by the coefficient of variance. We found that the mean coefficient of variance of native T1 of studies performed at 1.5 T was 0.04 and the mean coefficient of variance of native T1 at 3.0 T was 0.03. For ECV, the coefficient of variance was similar at both field strengths with an average coefficient of variance of 0.12. Because the cohorts were composed of healthy participants,

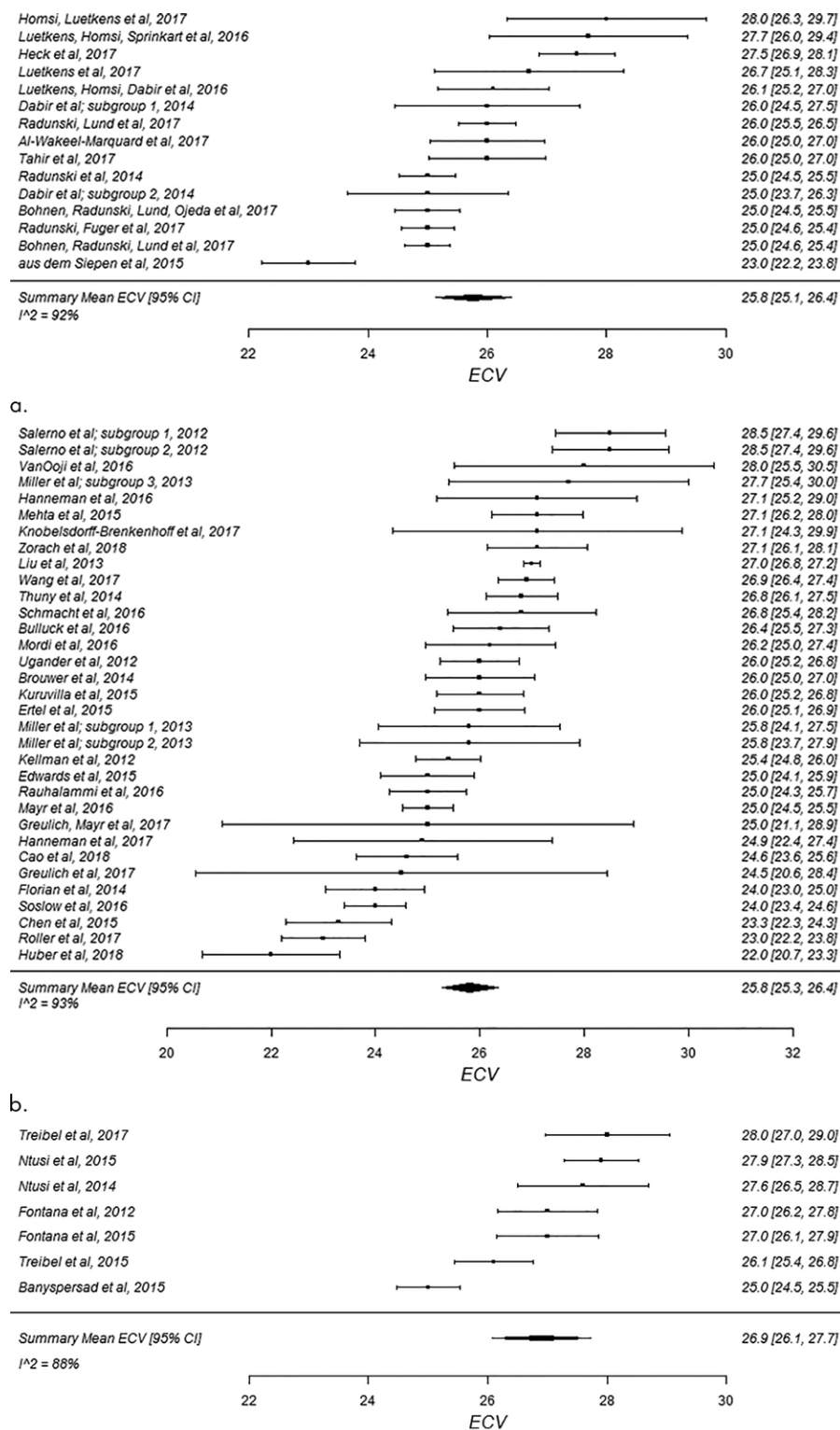


Figure 4: Forest plots of extracellular volume (ECV) studies at 1.5-T cardiac MRI in healthy participants. Studies are grouped by vendor and pulse sequence scheme. **(a)** ECV studies from Philips modified Look-Locker inversion recovery (MOLLI) subgroup, **(b)** ECV studies from Siemens MOLLI subgroup, and **(c)** ECV studies from Siemens shortened MOLLI subgroup. Studies with multiple subgroups are noted by author last name and year of publication.

this finding is consistent with a higher precision for measuring native T1 compared with measuring ECV. The higher coefficient of variance of the ECV measurement results from

propagation of the uncertainties of at least four T1 measurements and the hematocrit, which are used to calculate this parameter. The direct implication is that the greater coefficient of variance of ECV may require a larger relative change in ECV to detect differences between healthy participants and those with cardiac pathologic results.

There are a number of factors which likely contributed to the heterogeneity of T1 parameters between studies. One factor of particular interest was flip angle; a flip angle of 50° was associated with a lower native T1 value compared with a flip angle of 35°. The etiologic cause of this effect is due to differences in the effective T1 during steady-state free precession readouts, as well as potentially magnetization transfer effects that result in underestimation of native T1 at a higher flip angle (28). At 3.0 T, issues related to both B₀ and B₁ inhomogeneity could also be confounding factors. Further, the timing between inversion pulses, which affects the amount of signal recovery, and the assumption of full recovery between inversions can cause biases in T1 values, particularly at a higher heart rate where there may not be complete recovery between inversion pulses (28,29). There are also a number of patient-level covariates such as sex, age, and hematocrit that can affect the T1 measurements in individual participants.

Sex differences in native T1, particularly in women before menopause also need to be considered because, prior to menopause, women tend to have higher T1 values (24,30). MOLLI-based sequences are sensitive to a number of confounding factors which have been well described in the literature resulting in an underestimate of so-called true T1 as measured by standard techniques in phantoms (31). Whereas pulse sequences such as saturation recovery single-shot acquisition or saturation pulse prepared heart rate independent inversion

recovery result in more accurate estimates of native T1, the relatively lower precision and lack of widespread implementation limited the prevalence of these techniques in the literature

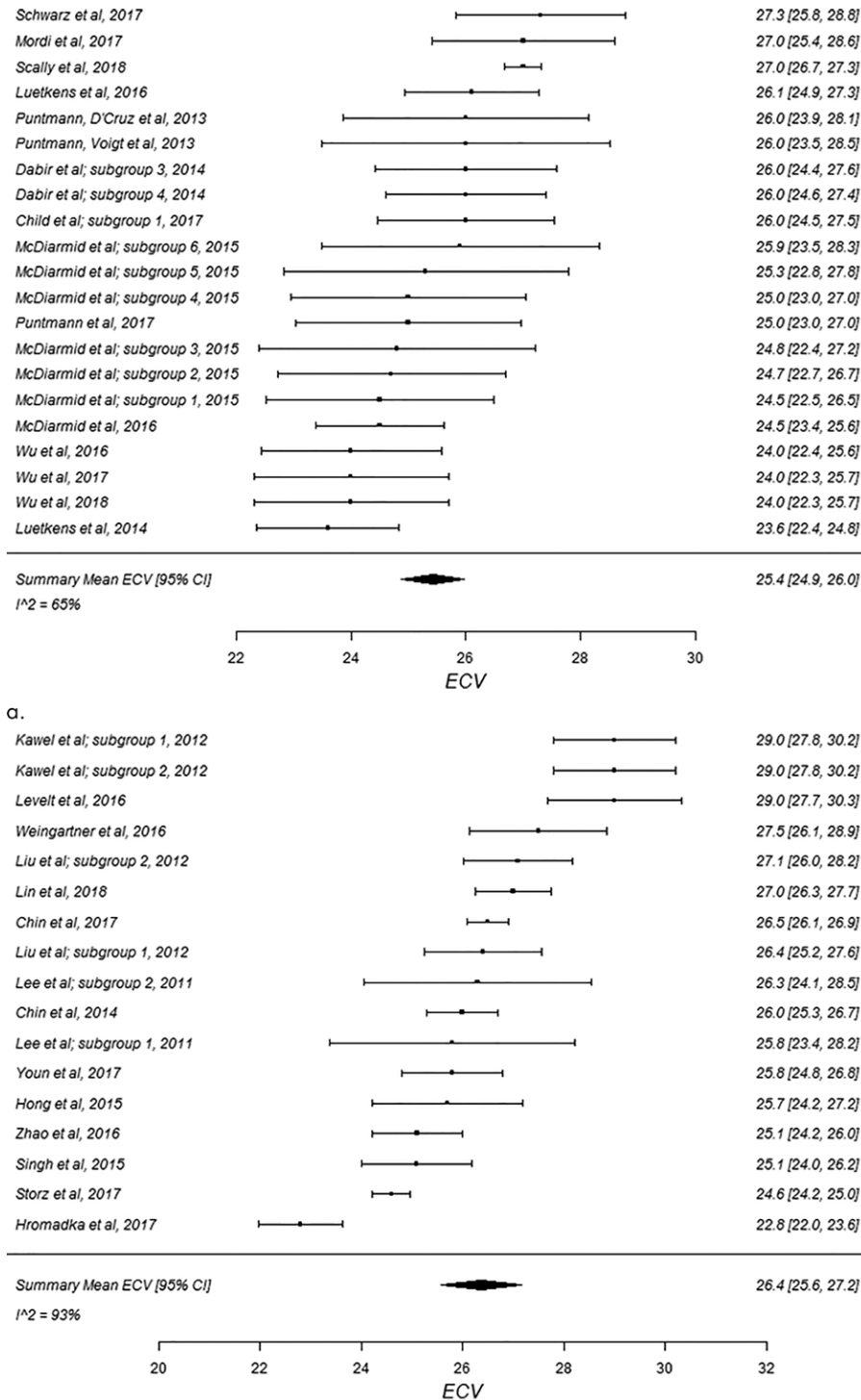


Figure 5: Forest plots of extracellular volume (ECV) studies at 3.0-T cardiac MRI in healthy participants. Studies are grouped by vendor and pulse sequence scheme. **(a)** ECV studies from Philips modified Look-Locker inversion recovery (MOLLISubgroup and **(b)** ECV studies from Siemens MOLLISubgroup. Studies with multiple subgroups are noted by author last name and year of publication.

(32,33). Free breathing approaches could potentially overcome some of the precision issues enabling the use of these more accurate techniques, which are less sensitive to systematic variations (34).

In an effort to limit intra- and interpatient variability, it is important that individual institutions establish optimized

protocols and sequence parameters for T1 mapping and minimize changes to these parameters over time; this is emphasized in the 2017 Society for Cardiovascular Magnetic Resonance parametric mapping guidelines (23). Regarding ECV, although this measurement is robust across field strengths, it is important that institutions use a consistent contrast agent, dosage, and postcontrast measurement time. Further, rather than accept ranges provided by vendors, local institutional control groups should be used to derive institution-specific reference ranges for native T1 and ECV values, which is also recommended in the Society for Cardiovascular Magnetic Resonance guidelines (23). Finally, phantom validation should be used to ensure the longitudinal stability of native T1 and ECV measurements, and to understand and quantify potential biases in multicenter trials (4,7).

As a result of the existing heterogeneity in native T1 and ECV measurements across imaging centers, a universal normal range cannot be determined. Despite this statistical heterogeneity, however, the relatively small absolute variations in T1 measurements and ECV should be considered when making clinical decisions. With further standardization of sequence parameters among sites and vendors, broader or at least sequence-vendor specific normal ranges could potentially be established.

There were several limitations to our study, a number of which are common to most meta-analyses and some that are unique to our study. There was nonuniform reporting of participant recruitment methods and data, and, likewise, details of all pulse sequence parameters and how they may have varied between scans were not available for analysis. There was only sufficient data to investigate for vendor-specific differences between Philips and Siemens scanners and, similarly, we chose to only include studies that used MOLLISubgroup and shortened MOLLISubgroup as the pulse sequence scheme because of the dearth of other schemes in the literature. It is possible that by excluding other vendors and pulse sequences we have artificially decreased the measured heterogeneity of the data. However, the vast majority of the studies reported in the

literature used a MOLLI-based pulse sequence, and thus this meta-analysis provided an assessment of the variability by using these clinically available pulse sequences. Data from other pulse sequences and vendors is included in the supplemental information for completeness (Table E4 [online]). Because of nonuniform reporting, we could not specifically analyze covariates, such as heart rate, which may be of interest because some pulse sequences have potential heart rate dependence for acquisition of native T1 (29). Further, T1 values could not be assessed on a per-subject basis because only study-level covariates were available for analysis. These covariates all likely contribute to the residual heterogeneity that was present despite subgroup analyses and metaregression analysis.

It is important to recognize that I^2 simply indicates that observed heterogeneity is real; it should not be used to determine whether or not the observed heterogeneity is clinically relevant (31,35). Whether or not the differences appreciated between studies represents a clinically significant difference is yet to be determined. Nonetheless, the observed degree of heterogeneity in this study precludes the derivation of a universal normal range for native T1 and ECV from the current data in the literature. An important caveat is that a study-level meta-analysis provides an estimate and 95% CI of the pooled mean, but cannot define the “normal range” for native T1 and ECV, which would require patient-level data (35). Notably, a significant majority of studies had small sample sizes, most less than 50 participants and almost all fewer than 100 participants. It is unclear how relevant traditional measures of publication bias, which are geared at identifying a relationship between effect size and likelihood of publication, are to meta-analysis of healthy participants. In this study, which was systematic review of control groups, it seems unlikely that individual studies would be more or less likely to be published on the basis of the mean native T1 or ECV value of the control group.

We determined the mean native T1 and ECV at 1.5 T and 3.0 T by using data abstracted from over 100 articles in a comprehensive analysis of the current T1 mapping literature. Our analysis revealed a small coefficient of variance and relatively small range of differences in native T1 and ECV across studies. Whereas there was heterogeneity in the measured native T1 and ECV, a portion of this heterogeneity was explained by population demographics and cardiac MRI covariates including field strength, vendor, pulse sequence, and flip angle. Of note, there was no relationship between date of publication and native T1 or ECV. Our analysis highlights the importance of fixed T1 mapping protocols and pulse sequence parameters in the minimization of intra- and interpatient variability and strongly supports the derivation of local reference ranges of native T1 and ECV at individual institutions to guide clinical decision making. The implications of this meta-analysis strongly align with the current Society for Cardiovascular Magnetic Resonance guidelines for parametric mapping (23). Finally, our analysis highlights the paramount importance of standardizing cardiac MRI protocols across imaging centers to reduce heterogeneity and facilitate the development of standardized

normal ranges, which will broaden the clinical effect of T1 and ECV measurements.

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