Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Synthetic Extracellular Volume in Cardiac Magnetic Resonance Without Blood Sampling: a Reliable Tool to Replace Conventional Extracellular Volume

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BACKGROUND: The calculation of extracellular volume (ECV) in cardiac magnetic resonance requires hematocrit, limiting its applicability in clinical practice. Based on the linear relationship between hematocrit and blood T1 relaxivity, a synthetic ECV could be estimated without a blood sample. We aim to develop and test regression models for synthetic ECV without blood sampling in 1.5-T and 3.0-T scanners.

METHODS: A total of 1101 subjects who underwent cardiac magnetic resonance scanning with native and postcontrast T1 mapping and venous hematocrit within 24 hours were retrospectively enrolled. Subjects were randomly split into derivation (n=550) and validation (n=551) subgroups for each scanner. Different regression models were derived controlling for sex, field strength, and left ventricle/right ventricle blood pool and validated in the validation group. We performed additional validation analyses in subgroups of patients with histological validation (n=17), amyloidosis (n=29), anemia (n=185), and reduced ejection fraction (n=322).

RESULTS: In the derivation group, 8 specific models and 2 common estimate models were derived. In the validation group, using specific models, synthetic ECV had high agreement with conventional ECV (R^2, 0.87; $P<0.0001$ and R^2, 0.88, $P<0.0001$; −0.16% and −0.10%, left ventricle and right ventricle model, respectively). Common models also performed well (R^2, 0.88; $P<0.0001$ and R^2, 0.89, $P<0.0001$; −0.21% and −0.18%, left ventricle and right ventricle model, respectively). Histological validation demonstrated equal performance of synthetic and measured ECV. Synthetic ECV as calculated by the common model showed a bias in the anemia cohort significantly reduced by the specific model (−2.45 to −1.28, right ventricle common and specific model, respectively).

CONCLUSIONS: Synthetic ECV provided a promising way to calculate ECV without blood sampling. Specific models could provide the most accurate value, while common models could be more suitable in routine clinical practice because of their simplicity while maintaining adequate accuracy.

Key Words: cardiac magnetic resonance ■ extracellular volume ■ hematocrit ■ synthetic ■ T1 mapping

Cardiac magnetic resonance (CMR) T1 relaxation time mapping is an established technique primarily used to identify diffuse interstitial fibrosis.[1] Disadvantages include strong dependency of the measured values on the local setup, influenced by concomitant, and failure to quantify fibrosis. The inverse of the T1 relaxation time is the R1 relaxation rate, which linearly increases in the presence of paramagnetic contrast agents. By measuring

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CLINICAL PERSPECTIVE

Cardiac magnetic resonance (CMR)-extracellular volume (ECV) mapping is the only noninvasive technique proven to provide a stable indicator of diffuse myocardial fibrosis. It has significant value in the clinical management and prognostic assessment of multiple diseases. However, the promotion of conventional ECV is limited by the need for blood tests at the time of scanning and the high variability of hematocrit. Synthetic ECV obtained using T1 time of the native blood pool omits the process of blood testing, while the results of synthetic hematocrit are in real time, thus avoiding apparent fluctuations in hematocrit due to time, body position, or other reasons. Excitingly, the results of synthetic ECV are almost identical to those of conventional ECV compared with conventional methods, which provides excellent efficiency in the assessment of diffuse CMR fibrosis. In our study, 2 types of models were derived: the specific model can be used in scientific studies or anemic patients because of its highest accuracy; the common model can be used for routine clinical practice due to its high efficiency and practicability. Synthetic ECV increases the potential of ECV in routine clinical CMR and allows for rapid clinical decision-making. Besides, the synthetic ECV provides a means to generate real-time ECV mapping during the scan automatically, an online tool on a CMR scanner to create an instant fully automated ECV map could be implemented on different CMR vendor platforms, which will be an attractive and promising development for each center that could greatly facilitate the broader use of CMR-ECV.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance
ECV	extracellular volume
EF	ejection fraction
LV	left ventricle
RV	right ventricle

T1 relaxation times before and after applying extracellular contrast agents, absolute quantification of the myocardial extracellular volume (ECV) is possible. Previous studies had shown that myocardial fibrosis appears to be reversible both by histologic[2,3] and ECV measures.[4] Furthermore, ECV is strongly associated with risk in a variety of settings.[5–7] The ECV is a reproducible and scanner-independent parameter that accurately measures the proportion of volume occupied by noncardiomyocyte components in myocardial tissue.[8] The images capture whole blood R1 measures, but the plasma concentration is needed since the concentration of Gd contrast in the plasma equilibrates with myocardial interstitial fluid. One needs the hematocrit to convert whole blood R1 to change in plasma R1.[9] Because of the high intraindividual variability of the hematocrit, blood collection is recommended within 24 hours of the CMR scan, limiting the routine clinical use of ECV measurements.[10] Recently, several research groups have proposed a method to determine the ECV by CMR without blood sampling.[11] The iron in hemoglobin exhibits paramagnetic effects, linearly increasing the R1 relaxation time of blood. A "synthetic" hematocrit can be estimated from the native blood T1 relaxation time without blood sampling based on this linear relationship. A good agreement between synthetic and conventional ECV was found in these studies. If confirmed, synthetic hematocrit and ECV could provide a noninvasive quantitative measurement of the myocardial extracellular space when timely hematocrit measurements are not available, facilitating the clinical application of ECV measurements.

However, as a new technology, synthetic ECV remains controversial due to limited experience and the possibility of misclassification in borderline cases.[12] Another issue is the generalization of synthetic hematocrit equations derived in 1 center, as T1 relaxation times highly depend on the local setup. Furthermore, all published models applied ordinary least squares regression to derive model parameters. This leads to underestimating the regression coefficient when the predictor variable is subject to measurement error. Therefore, published models overestimate low and underestimate high hematocrit values. This problem can be overcome using a model II (Deming) regression. We aimed to develop a local synthetic ECV model and validate its accuracy in different samples.

METHODS

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Patient Population

This study retrospectively analyzed 1101 patients who underwent CMR scans between August 2014 and November 2020 at German Heart Center Berlin that had pre- and post-contrast T1 mapping and point of care or laboratory hematocrit measurements from blood samples taken within 24 hours of CMR scanning available. Of these, 652 underwent CMR scans at 3.0T and 449 at 1.5T (Figure 1). Additional clinical information including age, sex, and cardiac diagnoses was collected. Patients on both scanners were randomly split into equally sized derivation (n=550) and validation (n=551) subgroups. This study was approved by the ethics informed committee of the Charite-Universitatsmedizin Berlin (Ethic number: EA2/073/21), and all the subjects in the study gave informed consent.

CMR Protocol

Six hundred fifty-two subjects underwent CMR at a clinical 3T MRI scanner (Ingenia, Philips Healthcare, Best, The

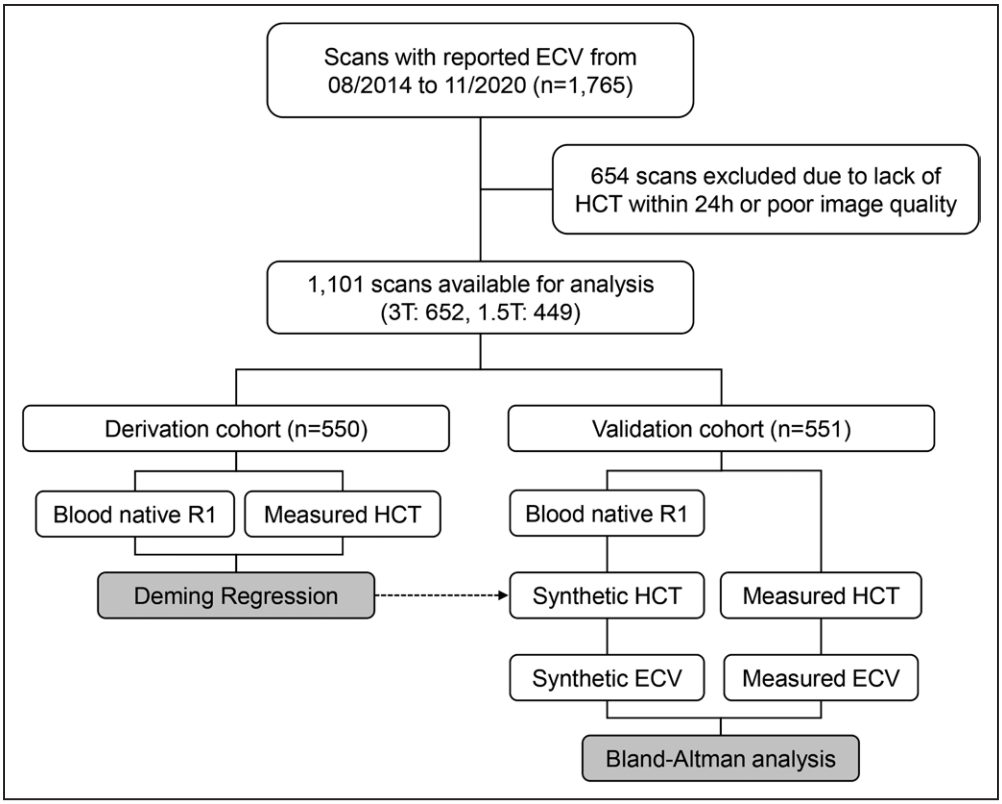

Figure 1. Workflow.
Scans were randomly split into derivation and validation cohorts with equal scanners. Of 654 patients that excluded, 507 cases could not find available hematocrit (HCT) values within 24 h from medical records. One hundred forty-seven cases had poor image quality, which was defined as artifacts in midventricular septum that affect the measurement of T1 mapping. ECV indicates extracellular volume.

Netherlands) MRI with an anterior- and the built-in posterior coil array, where up to 30 coil elements were employed. Four hundred forty-nine subjects were examined at a 1.5T MRI (Achieva, Philips Healthcare, Best, The Netherlands) equipped with a cardiac 5-element phased array coil. Cine images were acquired using retrospectively gated cine-CMR in cardiac short-axis, vertical long-axis, and horizontal long-axis orientations using a balanced steady-state free precession sequence. Native and 15-min post-contrast T1 mapping was performed using a modified Look-Locker (MOLLI) 5s(3s)3s-scheme. Typical imaging parameters were as follows: Acquired voxel size=2.0×2.0×10 mm^3, reconstructed voxel size=0.5×0.5×10 mm^3, balanced steady-state free precession readout, flip angle=35°, parallel imaging (SENSE) factor=2 and effective inversion times between 150 and 3382 ms. Patients received 0.15 mmol/kg of gadolinium-based contrast agent (Gadobutrol 1.0 mmol/mL, Gadovist, BayerAG, Leverkusen, Germany).

CMR Analysis

Image analysis was performed offline using commercially available postprocessing software (Philips Intellispace Portal, Philips Medical Systems Nederland BV, Best, The Netherlands). Left ventricular endocardial contours were drawn manually on short-axis cine images at end-diastole and end-systole for functional parameters, including ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, and cardiac output with indexing for body surface area except for ejection fraction.

Native and postcontrast MOLLI images were corrected for in-plane motion using automatic motion correction. The T1 times were calculated using nonlinear fitting with a maximum likelihood estimator (MLE) by the postprocessing software. In case of extensive artifacts in an imaging sequence, the patient was excluded from the respective analysis at the discretion of the analyzing physician. Regions of interest were drawn conservatively in the ventricular septum[13] and the left- and right-ventricular blood pool on the mid-ventricular short axis and transposed to the corresponding postcontrast image (Figure S1). ECV was calculated from native and postcontrast T1 relaxation times and the hematocrit (Figure 2).

Derivation and Validation

Eight specific regression models for each combination of sex, field strength, and blood pool measurement site (right ventricle [RV] and left ventricle [LV]) were derived. Two common models for LV/RV blood pool with sex and field strength as factors were derived. The models were then used to calculate the synthetic ECV and assess its agreement and correlation with conventionally measured ECV in the validation group. The published model of Fent et al[14] was used for further validation. Subgroup validations were performed in patients with amyloidosis (n=29) and anemia (n=185) from the whole cohort. The diagnosis of amyloidosis was confirmed by pathology as described previously.[15] The diagnosis of anemia was based on laboratory hematocrit: hematocrit <41% in men and <36% in women was defined as anemia.[16]

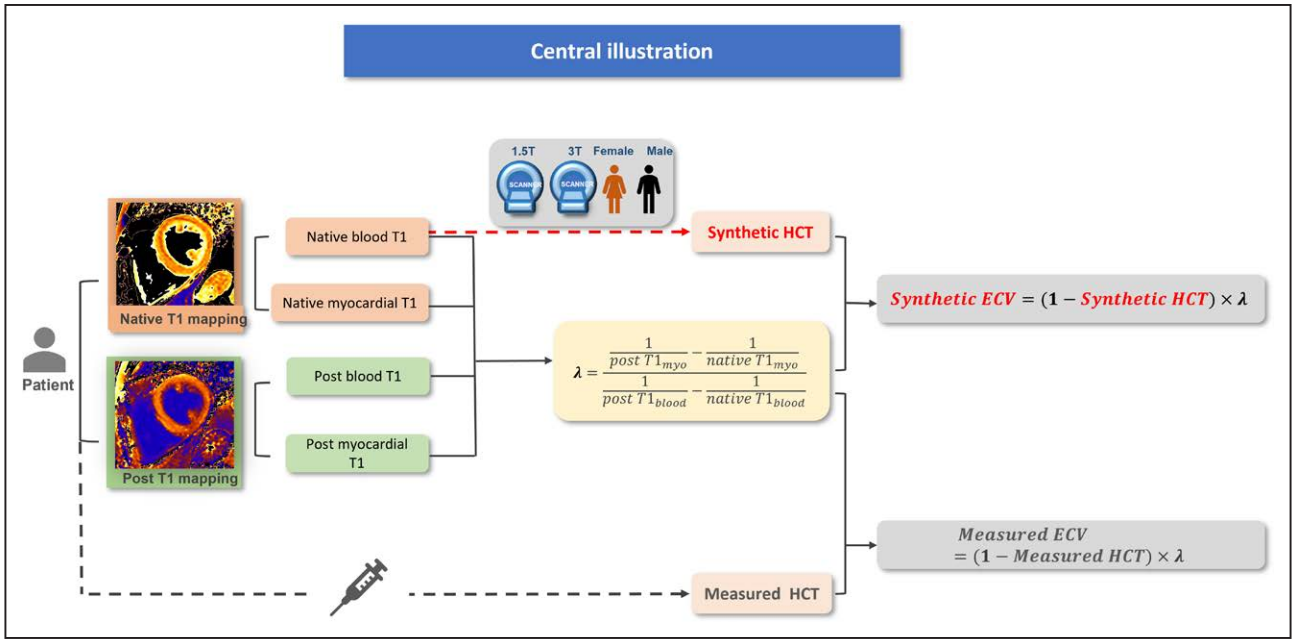

Figure 2. Central illustration for synthetic extracellular volume (ECV) calculation.
The conventionally measured ECV was calculated using standard hematocrit (HCT) measurements, obtained by peripheral venous blood sampling and point-of-care or standard laboratory analysis. Synthetic ECV was calculated using the synthetic HCT estimated from the bloodpool native T1 relaxation time.

Histological Analysis

Histological analysis was performed from myocardial tissue of 17 patients. Analysis of endomyocardial biopsy samples was performed in a specialized laboratory by experienced pathologists.[17] HE and Masson trichrome staining were used for histological examination of myocyte necrosis and interstitial fibrosis. Fibrotic and artifact areas were digitally marked on Masson trichrome-stained endomyocardial biopsy sections and photographed at a magnification of x200 with a Zeiss Axioskop 40 microscope. The area of fibrosis was quantified by using the program Quantuepatho as previously described [17] (Figure 3A and 3B). The histology validation was performed in the best synthetic model after comparison. All samples were analyzed blinded to the CMR findings and ECV values.

Statistical Analysis

Continuous variables were expressed as mean and SD, and categorical variables were expressed as percentages. Comparisons between means were performed using Student *t* test for continuous values with normal distributions and a Wilcoxon signed-rank test for non-normal data. In the derivation cohort, 8 specific models for different groups (male/female, 1.5T/3T, LV/RV blood pool) were derived using Model II (Deming) linear regression analysis, in which R1 was predictor and hematocrit was the response. Two common models for LV/RV blood pool were derived using multiple regression analysis, in which R1, sex, and field strength were predictors and hematocrit was the response. The published model of Fent et al[14] was used for further validation. Synthetic ECVs were calculated using specific and common models. A Bland-Altman analysis was performed for agreement between measured and synthetic ECV in the validation cohort. Correlations between the T1 time, hematocrit, and ECV were assessed using the Pearson or Spearman correlation coefficient. In the subgroup analysis of the amyloidosis cohort, nonamyloidosis patients were matched with amyloidosis patients by sex and scanner. In the ECV misclassification analysis, a new synthetic ECV cut-off value was derived using a receiver operating characteristic curve[18] based on conventionally measured ECV and McNemar test was used in the validation cohort. Statistical tests were 2-tailed, and a $P<0.05$ was considered statistically significant. Data were analyzed with SPSS (version 26, Statistical Package for the Social Sciences, International Business Machines, Inc, Armonk, NY) and GraphPad Prism software (version 9.0.0, GraphPad Software, Inc, La Jolla, CA).

RESULTS

Patients Characteristics

One thousand hundred one subjects (669 male, 60.8%) with a broad spectrum of referral diagnoses were included (Table S1). The average age was 51.8±17.1 years, and the mean conventionally measured ECV was 27.2±6.0%. Patients in both scanners (1.5 and 3T) were randomly split into derivation and validation groups. The patient characteristics are shown in Table 1.

Native T1 Relaxation Time in Different Subgroups

The blood pool native T1 relaxation time at 3T was higher than at 1.5T (1836±101.5 versus 1552±109.6 ms, $P<0.0001$ in LV blood pool; 1784±120.2 versus 1544±116.0 ms, $P<0.0001$ in RV blood pool). Blood

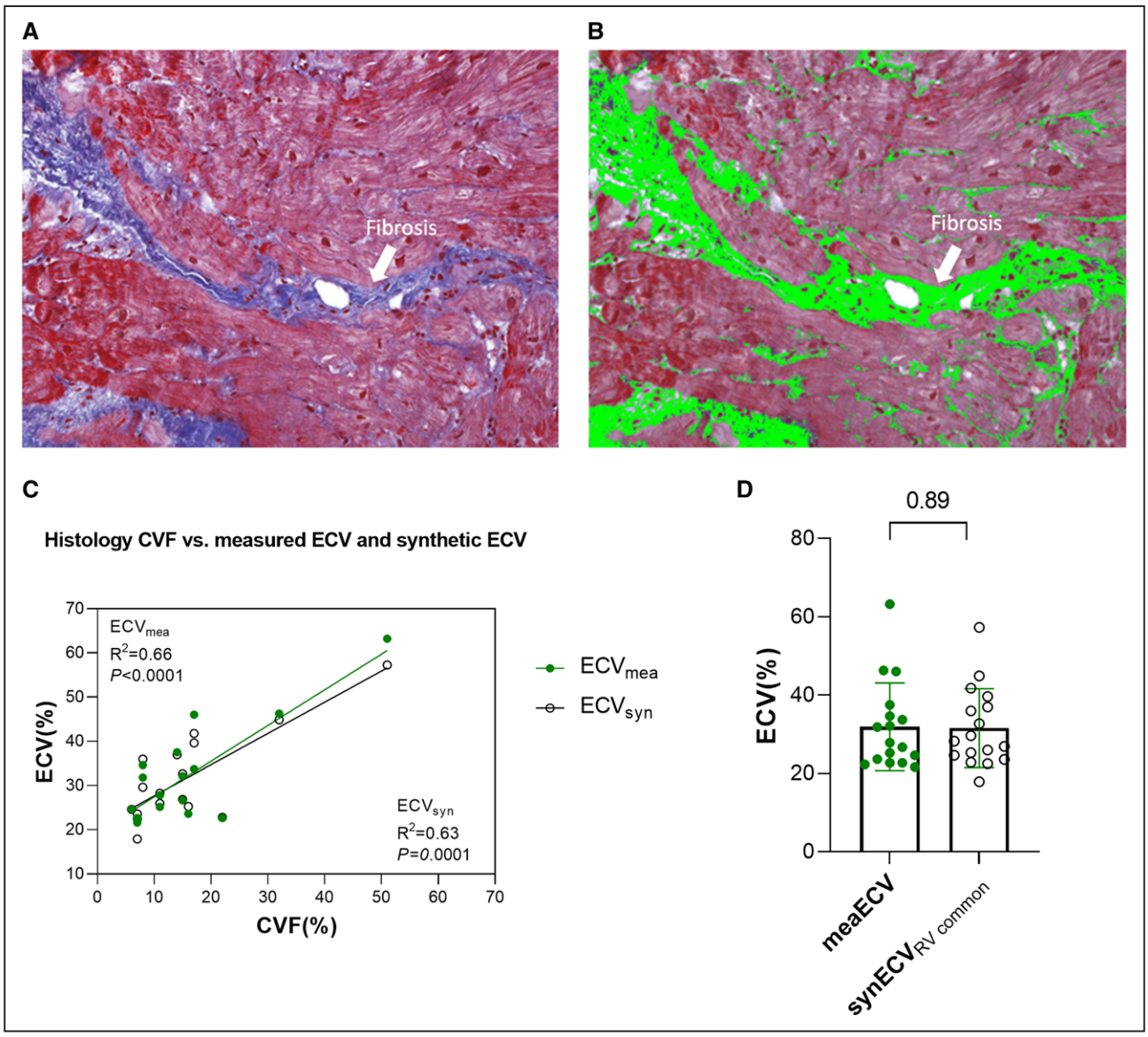

Figure 3. Histology validation.
A and **B**, Quantitative analysis of fibrosis in heart tissue samples. Fibrosis (white arrow, marked green in right figure) in myocardial area. **C**, Using right ventricular common model, synthetic extracellular volume (ECV) and measured ECV correlated well with collagen volume fraction (CVF) (R^2=0.63, *P*=0.0001 for synthetic ECV and R^2=0.66, *P*<0.0001 for measured ECV). **D**, Synthetic ECV had no difference with measured ECV (31.6±10.1% versus 31.9±11.2%, *P*=0.89).

pool native T1 relaxation time was higher in female than in male patients (1878±92 versus 1811±98 ms, *P*<0.0001 in 3T; 1590±101 versus 1525±108 ms, *P*<0.0001 in 1.5T). The LV blood pool T1 relaxation time was higher than that of the RV (1836±101.5 versus 1784±120.2 ms at 3T, 1552±109.6 versus 1544±116.0 ms at 1.5T, *P*<0.0001 and *P*<0.0001, respectively; Figure 4; Table S2)

Derivation

In the derivation cohort, there were 326 subjects (202 male, 62.0%) examined at 3T and 224 (132 male, 58.9%) at 1.5T. The correlation coefficients R^2 of measured hematocrit and native blood R1 ranged from 0.22 to 0.46 (*P* all <0.0001) in the different subgroups (Figure 5). Based on the linear relationship, 8 specific models were derived. To simplify the workflow, common models for LV/RV blood pool were derived (Table 2).

Validation

In the validation cohort, the correlation between synthetic hematocrit and conventionally measured hematocrit was moderate (R^2 range, 0.48–0.55), while the correlation between synthetic ECV and conventionally ECV was strong (R^2 range, 0.87–0.89; Table 3; Tables S3 and S4).

Table 1. Patient Characteristics

Variables	All patients (n=1101)	3.0 T (n=652)		1.5 T (n=449)	
		Derivation (n=326)	Validation (n=326)	Derivation (n=224)	Validation (n=225)
Age, y	51.8±17.1	53.8±17.9	52.1±16.5	48.3±16.4	52.2±17.1
Male, %	669 (60.8%)	202 (62.0%)	202 (62.0%)	132 (58.9%)	133 (59.1%)
BSA, m^2	2.0±0.2	2.0±0.2	2.0±0.3	1.9±0.2	2.0±0.2
LVEF, %	53.7±13.1	54.9±12.4	53.6±13.3	53.6±13.0	52.1±14.0
EDV, mL	168.9±67.2	163.5±62.0	165.9±68.3	174.5±66.3	175.3±73.2
EDVI, mL/m^2	83.4±32.3	81.3±28.5	81.4±30.7	85.4±35.0	87.2±36.3
ESV, mL	83.6±62.5	78.6±55.5	82.5±63.9	86.3±61.0	90.0±70.0
SV, mL	85.2±22.3	84.9±20.0	83.4±22.2	88.3±24.2	85.3±23.4
Native myo T1-time, ms	1174.7±133.1	1273.8±61.8	1271.1±60.8	1031.4±58.1	1034.1±67.0
Native LV blood T1-time, ms	1720.3±174.9	1835.1±96.0	1837.8±106.8	1543.4±93.9	1559.8±123.0
Native RV blood T1-time, ms	1686.3±167.4	1784.2±113.5	1784.7±126.7	1528.4±106.1	1559.2±123.5
meaHCT, %	42.6±5.4	43.4±5.2	42.6±5.3	42.5±5.0	41.7±6.1
meaECV, %	27.2±6.0	26.7±6.2	26.9±5.8	27.6±6.3	27.9±5.5

Data are presented as mean (SD) or n (%). BSA indicates body surface area; EDV, end-diastolic volume; EDVI, end-diastolic volume index; ESV, end-systolic volume; LV, left ventricular; LVEF, left ventricular ejection fraction; meaECV, conventionally measured extracellular volume; meaHCT, conventionally measured hematocrit; RV, right ventricular; and SV, stroke volume.

There was no statistical difference between measured and synthetic hematocrit/ECV (Table S5).

Using specific models, a slight bias and acceptable limits of agreement between measured and synthetic ECVs were observed, and the correlations between ECVs were strong (bias −0.16 and −0.10, R^2=0.87 and R^2=0.88 for LV and RV blood pool derived specific model, respectively; Figure 6A through 6D). Using common models, Bland-Altman analysis also demonstrated slight bias, which was slightly higher than specific models, the

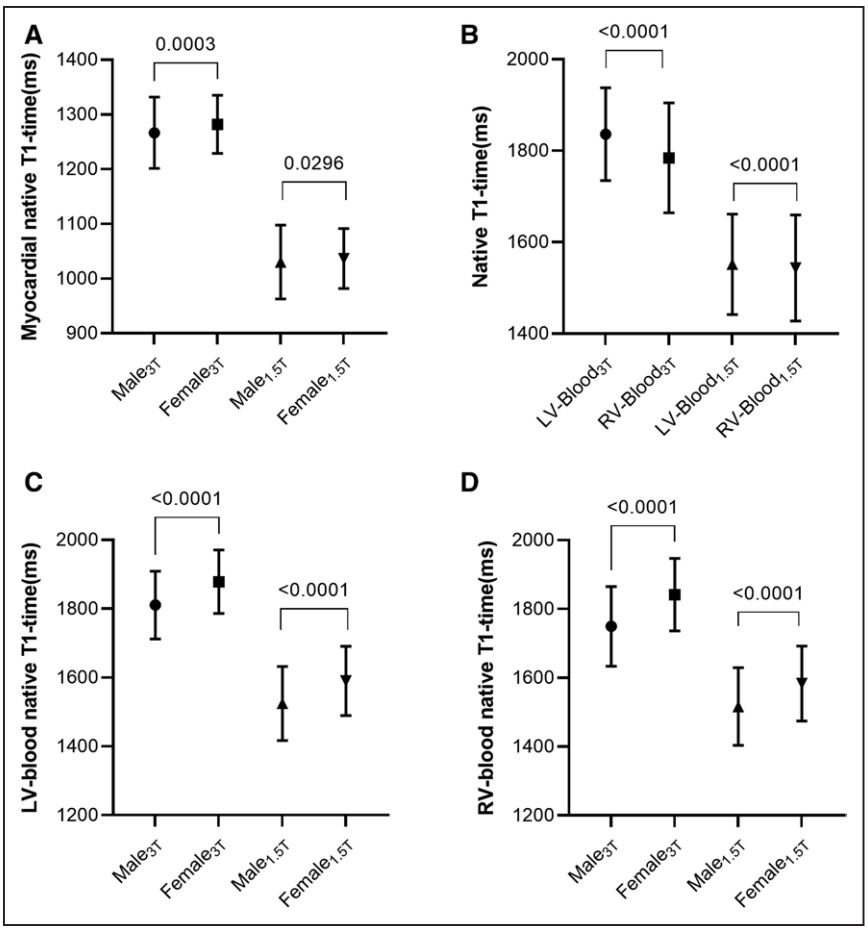

Figure 4. Native T1 relaxation times by sex, field strength, and measurement site.
A, Native myocardial T1 times were different between male and female both in 3T and 1.5T. **B**, Native T1 relaxation times of left ventricle (LV) blood pool were higher than those of right ventricle (RV) blood pool both in 3T and 1.5T (1836±102 versus 1784±120 ms in 3T, 1552±110 versus 1544±116 ms in 1.5T, *P*<0.0001 and *P*<0.0001, respectively.) **C** and **D**, Native blood T1 relaxation times in females were higher than in males in both LV blood pool and RV blood pool, and the value at 3T was higher than at 1.5T.

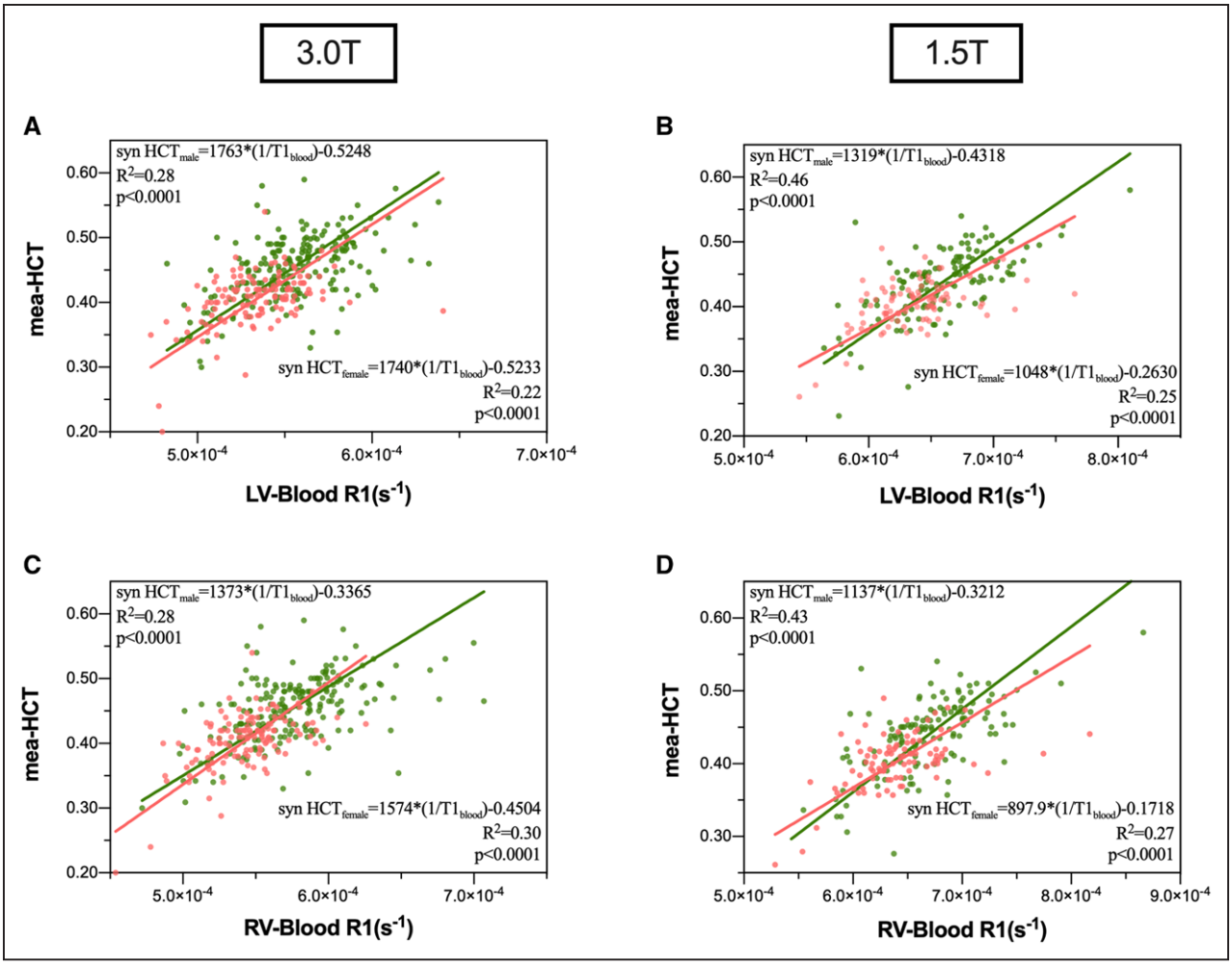

Figure 5. Derivation cohort, regression analysis of measured hematocrit (HCT) vs blood R1 at different sampling sites and field strengths, by sex.

Green for male and orange for female. **A**, HCT versus left ventricle (LV) blood, 3.0T. R^2=0.28 for males, R^2=0.22 for females. **B**, HCT versus LV blood, 1.5T. R^2=0.46 for males and R^2=0.25 for females. **C**, HCT versus right ventricle (RV) blood, 3.0T. R^2=0.28 for males, R^2=0.30 for females. **D**, HCT versus RV blood, 1.5T. R^2=0.43 for males and R^2=0.27 for females. R1=T1 relaxation rate (ms^{-1}). mea HCT indicates measured hematocrit; and syn HCT, synthetic hematocrit.

correlation between measured and synthetic ECVs was strong (bias −0.21 and −0.18, R^2=0.88 and R^2=0.89 for LV and RV blood pool derived model, respectively; Figure 6E through 6H). However, since the limits of agreement of ECV mostly were −4% to 4% for local models, the small bias may be attributable to the under and overestimation. Using published models,[14] the results show a higher bias and lower correlation (Table 3).

Given the good performance of common model derived from the RV blood pool, which showed relatively low bias and high agreement, the RV common model was applied to the following subgroups for validation.

Histology Validation

In the cohort of 17 patients with histological analysis, the average collagen volume fraction (CVF) was 15.5±11.3%, and the average measured ECV was 31.9±11.2%. Synthetic ECVs correlated well with histology CVF, as conventional measured ECV (R^2=0.63, *P*=0.0001, for synthetic ECV; R^2=0.66, *P*<0.0001, for measured ECV). Synthetic ECV showed no statistical difference to measured ECV (31.6±10.1% versus 31.9±11.2%, *P*=0.89; Figure 3C and 3D).

Anemia Cohort Validation

The ECV bias in anemia cohort (n=185) was greater than in the nonanemia cohort (n=916) (−1.21 to −2.45 in the anemia cohort, −0.39 to 0.39 in the nonanemia cohort; Figure 7A). Additional validation using specific models were performed, which showed the specific models could reduce the bias compared with common models (−1.2±2.2% versus −2.4±1.7%, LV specific and common models; −1.3±1.8% versus 2.5±1.5%, RV specific and common models).

Table 2. Equations for Synth ECV Based on Sex and Scanner

Specific models			
Platform	**Sex**	**Blood pool**	**Specific regression equation**
3.0T	Male	LV	syn HCT=1763*(1/$T1_{blood}$)-0.5248
		RV	syn HCT=1373*(1/$T1_{blood}$)-0.3365
	Female	LV	syn HCT=1740*(1/$T1_{blood}$)-0.5233
		RV	syn HCT=1574*(1/$T1_{blood}$)-0.4504
1.5T	Male	LV	syn HCT=1319*(1/$T1_{blood}$)-0.4318
		RV	syn HCT=1137*(1/$T1_{blood}$)-0.3212
	Female	LV	syn HCT=1048*(1/$T1_{blood}$)-0.2630
		RV	syn HCT=897.9*(1/$T1_{blood}$)-0.1718
Common models			
Blood pool	Multiple regression equation		
LV	$synthetic\,HCT = 816.325 \times \frac{1}{LV\ blood\ T1} + 0.024 \times Sex - 0.094 \times Scanner - 0.027$		
RV	$synthetic\,HCT = 694.200 \times \frac{1}{RV\ blood\ T1} + 0.022 \times Sex - 0.075 \times Scanner + 0.03$		

Syn HCT, synthetic hematocrit (0-1). In common models, substitute 1 if the "Sex" was male and "0" for female, substitute "1" if "Scanner" was 1.5T and "0" for 3T. LV indicates left ventricle; and RV, right ventricle.

Amyloidosis Cohort Validation

Further validation was performed in 29 patients with confirmed amyloidosis (Table S6), using 29 matched nonamyloidosis patients randomly drawn from the cohort as the control group. There was no statistical difference between the measured and synthetic ECV in the amyloidosis cohort, as in the control group (51.1±10.3% versus 51.9±10.9% and 27.6±4.7% versus 26.8±4.3%, *P*=0.18 and *P*=0.12, amyloidosis and control group, respectively), the bias of ECVs was only 0.77% in the amyloidosis group (Figure 7B; Figure S2).

Validation in Different LVEF Cohorts

Patients with ejection fraction >50% (n=779) had lower ECV values than those with ejection fraction ≤50% (n=322; 26.2±4.6% versus 29.5±7.9%). There was no statistical difference between the measured ECV and synthetic ECV in both groups (26.2±4.6% versus 26.1±4.3, *P*=0.84 in LVEF>50%, 29.5±7.9% versus 29.5±7.9%, *P*=0.25 in LVEF≤50%), and the bias were small (bias 0.11 and 0.03 in LVEF>50% and ≤50%; Figure S3).

Table 3. Bland-Altman Analysis for Synthetic HCT/ECV and Measured HCT/ECV

Synthetic value, %	Bias	SD of bias	Limit of agreement	R^2	*P* Value
$HCT_{LV\ common}$	0.55	4.03	−7.3 to 8.4	0.49	<0.0001
$HCT_{RV\ common}$	0.46	3.98	−7.3 to 8.3	0.51	<0.0001
$HCT_{LV\ specific}$	0.51	4.54	−8.4 to 9.4	0.48	<0.0001
$HCT_{RV\ specific}$	0.34	4.45	−8.4 to 9.1	0.48	<0.0001
$HCT_{published}$	−0.86	4.45	−9.8 to 7.9	0.38	<0.0001
$ECV_{LV\ common}$	−0.21	1.98	−4.1 to 3.7	0.88	<0.0001
$ECV_{RV\ common}$	−0.18	1.92	−4.0 to 3.6	0.89	<0.0001
$ECV_{LV\ specific}$	−0.16	2.28	−4.6 to 4.3	0.87	<0.0001
$ECV_{RV\ specific}$	−0.10	2.15	−4.3 to 4.1	0.88	<0.0001
$ECV_{published}$	0.46	2.24	−3.9 to 4.8	0.86	<0.0001

ECV indicates extracellular volume; HCT, hematocrit; LV, left ventricle; and RV, right ventricle.

Misclassification Analysis

Based on the conventional ECV cutoff value of 30%, new cutoff value of 29.5% for synthetic ECV was derived in the derivation cohort, misclassification analysis in the validation cohort showed 6% total misclassifications (4% false-negative and 2% false-positive, *P*=0.12; Tables S7 and S8).

DISCUSSION

In this study, we explored the derivation and validation of synthetic ECV models without blood samples. To our knowledge, this is the first study to derive common models for both 1.5T and 3T based on LV and RV blood pool, respectively, and the study with the largest patient sample to date. In addition to validation in entire validate cohort, separate validation analyses in different clinical situations were performed, demonstrating the clinical robustness and reasonable performance of synthetic ECV.

The main findings were the following:

1. Blood pool native T1 relaxation times differ by sex, field strength, and LV/RV blood pool.
2. The accuracy of the common model is similar to that of the specific model, improving clinical utility.

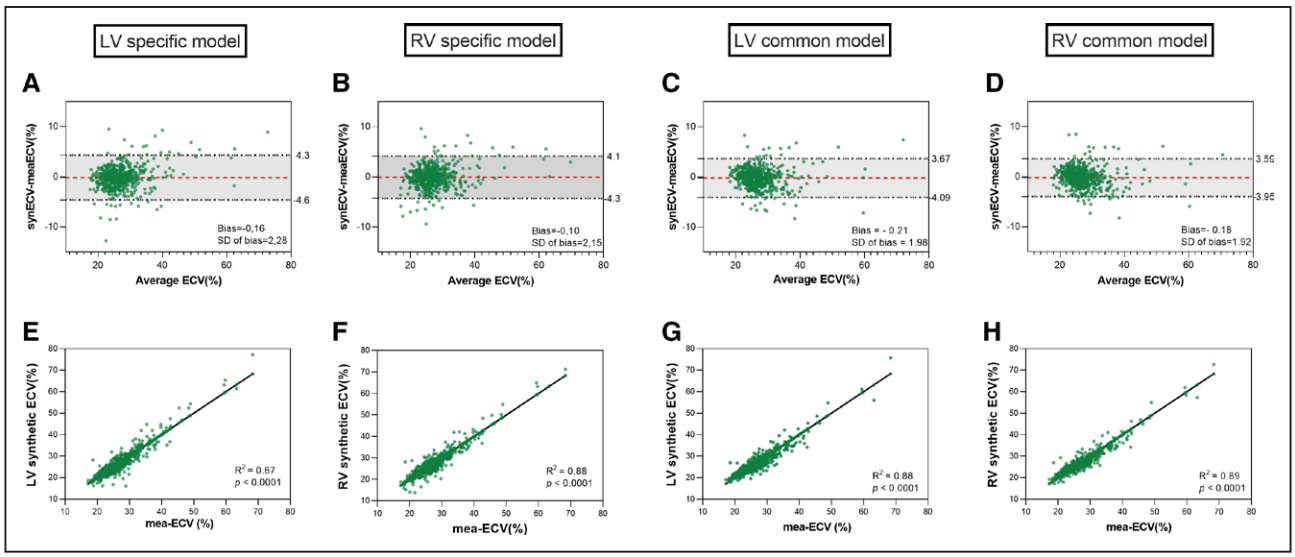

Figure 6. Validation: synthetic and measured extracellular volume (ECV) in specific and common models.
A and **C**, Bias between synthetic ECV estimated with left ventricle (LV) blood pool derived specific model and measured ECV was −0.16% with R^2=0.87. **B** and **D**, Bias between synthetic ECV estimated with right ventricle (RV) blood pool derived specific model and measured ECV was −0.10% with R^2=0.88. **E** and **F**, Bias between synthetic ECV estimated with LV blood pool–derived common model and measured ECV was −0.21% with R^2=0.88. **G** and **H**, Bias between synthetic ECV estimated with RV blood pool–derived common model and measured ECV was −0.18% with R^2=0.89.

3. ECV was underestimated in anemic patients. Our data demonstrated that specific models could minimize the ECV errors in the anemic cohort.

Differences in Native T1 Relaxation Times

In our study, the native blood pool T1 times were 65 to 93 ms higher in females than males, and 184 to 204 ms higher in the 3T scanner than in the 1.5T. The native blood pool T1 relaxation time was higher in the LV than the RV. The reason may be that deoxyhemoglobin is more abundant in venous blood than in arterial blood, which has a paramagnetic effect that lowers the T1 relaxation time. The difference between T1 times of venous blood and arterial blood was also observed before.[19] A potential pitfall arises in patients with unusually low venous or arterial oxygen saturation, which might lower T1 relaxation times irrespective of the hematocrit and lead to false high synthetic hematocrit estimates.

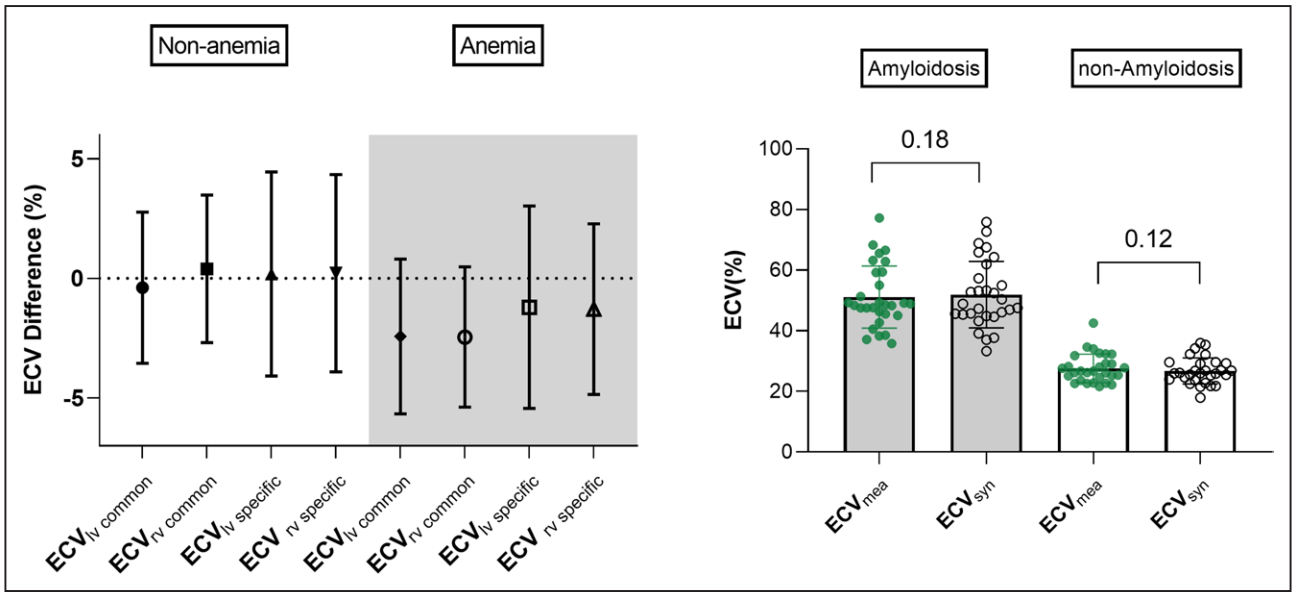

Figure 7. Extracellular volume (ECV) difference in anemia cohort and amyloidosis patients.
A, ECV was underestimated in anemic patients by all models, although less so by the specific models. **B**, There was no statistical difference between the measured ECV and the synthetic ECV in the amyloidosis group and the control group (51.1±10.3% versus 51.9±10.9% and 27.6±4.7% versus 26.8±4.3%, *P*=0.18 and *P*=0.12, respectively.) ECVmea indicates measured extracellular volume; ECVsyn, synthetic extracellular volume; LV, left ventricle; and RV, right ventricle.

Derivation and Validation

Based on the differences of native blood pool T1 values by sex, field strength, and measurement site, 8 specific models and 2 common models were derived. Both the common and specific models performed well in validation analysis. In terms of ECV bias, the specific model had a slight advantage over the common model.

As in previous studies,[11,12,14,20,21] synthetic hematocrit and measured hematocrit were only moderately correlated. Nevertheless, synthetic ECV was highly correlated with measured ECV with only minor bias. In correlation to histological measurements, synthetic ECV performed equally to measured ECV.

Validation in the amyloidosis and anemia cohorts further demonstrated the clinical value of synthetic ECV. The ECV error did not increase significantly with the absolute ECV value in the amyloidosis cohort, suggesting that the synthetic ECV remained highly accurate. The synthetic ECV error was higher in the anemic cohort than in the nonanemic cohort, and the synthetic ECV tended to underestimate the measured ECV. This was consistent with the finding of Su et al.[16] ECV errors were relatively more significant when measured hematocrit was lower. One possible reason is that the measured T1 relaxation time is dependent on more factors than the hematocrit alone, as evidenced by the R^2 below 1. However, the specific model minimized the ECV error in the anemic cohort. The myocardial ECV value in healthy control was 25.3±3.5%[22] and 25.4±2.5%,[23] which was considered an acceptable ECV error of 2.5% to 3.5%. In our study, the ECV errors using all local models, even in the anemia cohort, were within the acceptable ECV error range. However, given the limit of agreement of synthetic ECVs were mostly −4 to 4, we have to acknowledge that small mean differences may be attributable to both under and over-estimation.

The conventional ECV was estimated based on venous blood hematocrit, whereas the ideal hematocrit for ECV calculation should be obtained from the LV blood pool representing arterial blood. As observed, there was a non-negligible difference between T1 values of venous and arterial blood. Therefore, we derived synthetic ECV models depending on RV and LV blood pool separately.

Notably, the validation results of RV models were slightly better than the results of the LV models in our cohort, either with conventional ECV as a reference or with histological results. Possible reasons to consider were that while there is some linear relationship between blood pool T1 time and hematocrit, the hematocrit values used in our conventional measurement of ECV are peripheral venous blood hematocrit, venous T1 time (RV blood pool) seems to be to reflect venous hematocrit better. Second, there was some error between measured hematocrit and RV-synthetic hematocrit, similarly, measured hematocrit and actual LV-synthetic hematocrit. There may be some degree of offset between the differences, instead of bringing the values of RV-synthetic hematocrit and actual hematocrit of the LV blood pool closer together, leading to a higher degree of agreement.

Shang et al[24] showed that synthetic ECV might result in 6% to 25% misclassification. In our study, 7% misclassification was observed. CMR-ECV as a new biological parameter for quantifying diffuse myocardial fibrosis does not have a universal standard cut-off definition to date. Besides, misclassification analysis was not based on the gold standard "tissue biopsy" but on conventional ECV. Therefore, the small proportion of miscategorization cannot offset the excellent overall performance of synthetic ECV.

Clinical Implications

CMR-ECV mapping is the only noninvasive technique proven to provide a stable indicator of diffuse myocardial fibrosis. It has significant value in the clinical management and prognostic assessment of multiple diseases.[25–28] However, the promotion of conventional ECV is limited by the need for blood tests at the time of scanning and the high variability of hematocrit. Synthetic ECV obtained using T1 time of the native blood pool omits the process of blood testing, while the results of synthetic hematocrit are in real time, thus avoiding apparent fluctuations in hematocrit due to time, body position, or other reasons. Excitingly, the results of synthetic ECV are almost identical to those of conventional ECV compared with conventional methods. It increases the potential of ECV in routine clinical CMR and provides a means to generate real time ECV mapping during the scan automatically; an online tool on a CMR scanner to create an instant fully automated ECV map could be implemented at 1.5 and 3T on different CMR vendor platforms. Synthetic ECV is an attractive and promising tool that could greatly facilitate the broader use of CMR-ECV.

Limitations

There are several limitations in our study. Only referral diagnoses were collected, the complete medical history was not analyzed due to time constraints; We used a single T1 sequence (MOLLI); however, different sequences of T1 mapping have been reported to yield different ECV values. Different T1 values for the RV and LV blood pool were found, which may arise from the different oxygen content. However, the exact reason needs further investigation. Also, we found that the values derived from the RV blood pool had lower bias and higher agreement than those derived from the LV blood pool, which requires more explanation. Multicenter studies with different vendors should be further performed to validate these results.

Conclusions

Synthetic ECV provides a reliable tool for clinical promotion of ECV, which avoids unnecessary blood draws and allows real-time assessment of hematocrit and the generation of online automated ECV mapping. Specific models could provide the most accurate value, while common models could be more suitable in routine clinical practice due to their simplicity while maintaining adequate accuracy.

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S3

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