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Is a timely assessment of the hematocrit necessary for cardiovascular magnetic resonance–derived extracellular volume measurements?

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Abstract

Background: Cardiovascular magnetic resonance (CMR)–derived extracellular volume (ECV) requires a hematocrit (Hct) to correct contrast volume distributions in blood. However, the timely assessment of Hct can be challenging and has limited the routine clinical application of ECV. The goal of the present study was to evaluate whether ECV measurements lead to significant error if a venous Hct was unavailable on the day of CMR.

Methods: 109 patients with CMR T1 mapping and two venous Hcts (Hct₀: a Hct from the day of CMR, and Hct₁: a Hct from a different day) were retrospectively identified. A synthetic Hct (Hct_{syn}) derived from native blood T1 was also assessed. The study used two different ECV methods, (1) a conventional method in which ECV was estimated from native and postcontrast T1 maps using a region-based method, and (2) an inline method in which ECV was directly measured from inline ECV mapping. ECVs measured with Hct₀, Hct₁, and Hct_{syn} were compared for each method, and the reference ECV (ECV₀) was defined using the Hct₀. The error between synthetic (ECV_{syn}) and ECV₀ was analyzed for the two ECV methods.

Results: ECV measured using Hct₁ and Hct_{syn} were significantly correlated with ECV₀ for each method. No significant differences were observed between ECV₀ and ECV measured with Hct₁ (ECV₁; 28.4 ± 6.6% vs. 28.3 ± 6.1%, p = 0.789) and between ECV₀ and ECV calculated with Hct_{syn} (ECV_{syn}; 28.4 ± 6.6% vs. 28.2 ± 6.2%, p = 0.45) using the conventional method. Similarly, ECV₀ was not significantly different from ECV₁ (28.5 ± 6.7% vs. 28.5 ± 6.2%, p = 0.801) and ECV_{syn} (28.5 ± 6.7% vs. 28.4 ± 6.0%, p = 0.974) using inline method. ECV_{syn} values revealed relatively large discrepancies in patients with lower Hcts compared with those with higher Hcts.

Conclusions: Venous Hcts measured on a different day from that of the CMR examination can still be used to measure ECV. ECV_{syn} can provide an alternative method to quantify ECV without needing a blood sample, but significant ECV errors occur in patients with severe anemia.

Keywords: Cardiovascular magnetic resonance, Extracellular volume fraction, Hematocrit, T1 mapping

Introduction

The longitudinal relaxation time (T1) before and after the administration of contrast agents has been used to quantify the fraction of extracellular volume (ECV), which represents the extent of the extracellular space and can be used as a surrogate for quantifying diffuse myocardial

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fibrosis [1–4]. An ECV measurement requires a hematocrit (Hct) measurement to correct for contrast volume distributions in blood. The Society for Cardiovascular Magnetic Resonance (SCMR) Consensus Statement recommends that Hcts should be measured within 24 h of the CMR scan [5]. In many clinical practices, patients must have had a renal function evaluation within 3 months before cardiovascular magnetic resonance (CMR) with gadolinium contrast administration, from which a laboratory blood-derived (venous) Hct can be performed. In patients without laboratory bloodwork, an estimated glomerular filtration rate (eGFR) from blood drawn approximately 3 days before CMR can be alternatively used. To achieve accurate ECV measurements, a repeat venipuncture to acquire a Hct is performed on the day of CMR. Therefore, obtaining a venous Hct on the same day of the CMR is possible, but requires additional effort and increases the complexity of translating ECV quantification into routine clinical practice. As mentioned previously, Hct should be measured within 24 h of CMR as it may change over time. However, Hcts also vary with body posture [6] and diurnal fluctuation [7]. Studies have also demonstrated that Hct exhibits hour-to-hour, day-to-day, and even seasonal within-individual fluctuations [8, 9]. It remains unknown whether these variations lead to significant errors in ECV measurements.

Blood consists of two water-containing compartments, erythrocytes and plasma, and the fraction of water in these two compartments is roughly proportional to their fractional volume and is referred to as the Hct. The longitudinal relaxation rate ($R1 = 1/T1$) in blood has been shown to be linearly correlated with Hct [10–13]. Previous studies have proposed that the “synthetic” Hct (Hct_{syn}) can be estimated from the native blood T1 values [14–16]. Treibel [17] and Fent [18] further demonstrated that synthetic ECVs (ECV_{syn}) derived from synthetically calculated Hcts (Hct_{syn}) demonstrated a strong correlation with ECVs derived from venous Hcts. However, several recent studies have suggested that using ECV_{syn} can result in the miscategorization of individual patients [19] and lead to clinical errors using 3T CMR [20]. Therefore, whether ECV_{syn} measurements using Hct_{syn} are feasible for clinical practice remains controversial and needs to be investigated further.

CMR-derived ECV can be evaluated using the region of interest (ROI)-based method either from native and postcontrast T1 maps or directly from ECV mapping. Whether the ECV value determined from the inline ECV mapping is comparable to the conventional T1 maps approach has yet to be established. Therefore, the goals of the present study were to evaluate: (1) whether significant ECV errors were found when the Hct was unavailable on the day of CMR, and (2) whether ECV values determined

from the inline ECV method is comparable with that of the conventional ECV method.

Methods

Patient populations

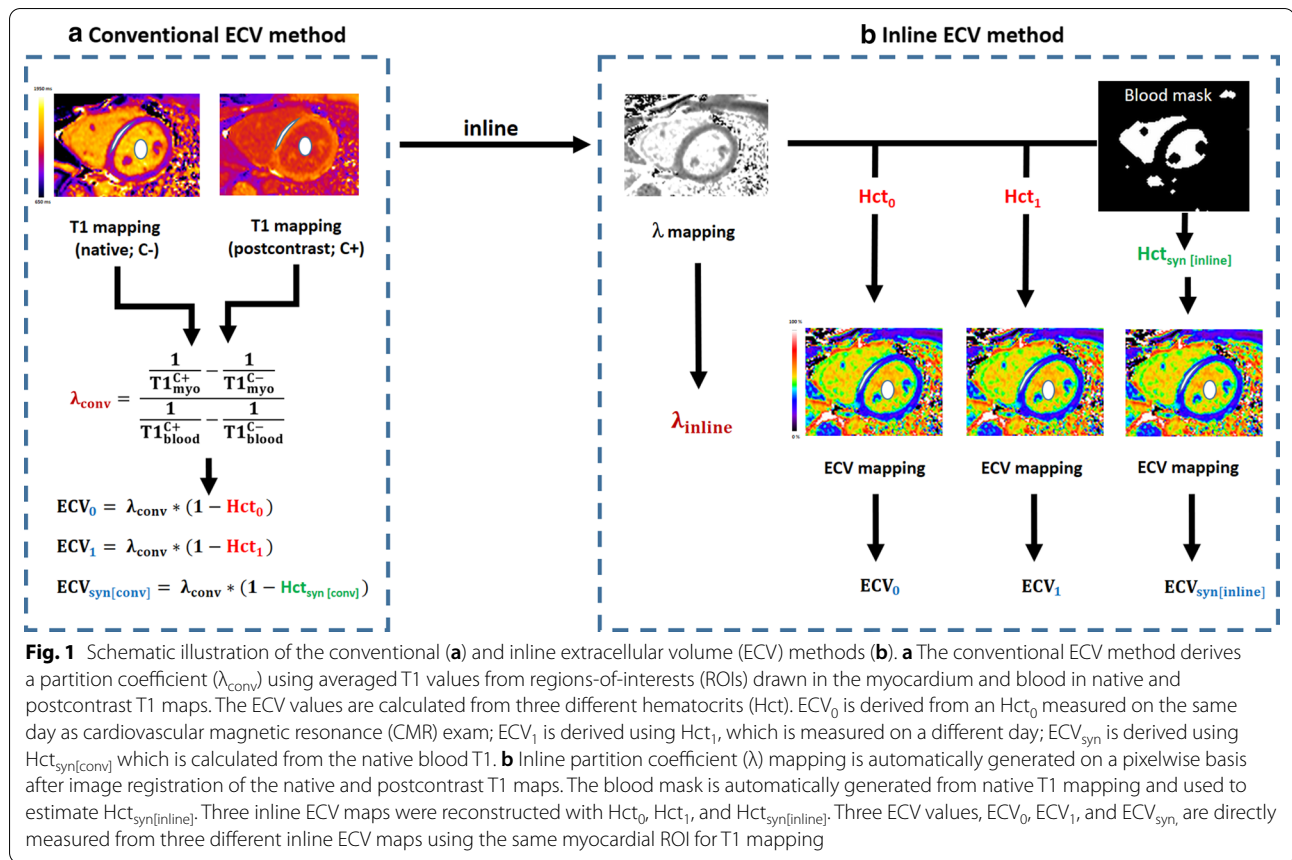
This study was approved by the institutional review board. All the study participants provided written informed consent. Eligible patients underwent CMR and had two venous Hct performed: one measured on the same day of CMR (Hct_0) and the other measured on a different day (Hct_1). Subjects with Hct_0 only were defined as the derivation group. The linear equation between blood $R1(1/T1)$ and Hct_0 was derived in the derivation group and used to estimate Hct_{syn} and calculate a synthetic ECV. Exclusion criteria were uncontrolled arrhythmia, impaired renal function ($eGFR < 30$ ml/min/1.73 m²), or contraindications to CMR (e.g., implanted devices). Clinical and demographic information, including underlying cardiac diagnoses, were collected.

Imaging acquisition

CMR was performed at 1.5T (Magnetom Aera, Siemens Healthineers, Erlangen, Germany) using a 30-channel-body coil and 32-channel spine coil. Myocardial T1 mapping was performed using an electrocardiogram (ECG)-triggered modified Look-Locker inversion recovery (MOLLI) pulse sequence, both before and 10–15 min after a 0.15 mmol/kg intravenous administration of a gadolinium-based contrast agent (Dotarem, Guerbet LLC, Princeton, New Jersey, USA). The MOLLI protocol used a 5(3)3 sampling scheme for native T1 mapping and a 4(1)3(1)2 sampling scheme for postcontrast T1 mapping. Scan parameters were as follows: TE/TR 1.14/2.7 ms; flip angle 35°; bandwidth 977 Hz/Px; minimum TI 125–150 ms; TI increment 80 ms; slice thickness 8 mm; iPAT factor (GRAPPA) 2. Inline ECV mapping was automatically generated from the native and postcontrast T1 maps using an investigational prototype [22, 23]. Three inline ECV maps were reconstructed using venous Hcts (Hct_0 , Hct_1) and Hct_{syn} . Three evenly spaced short-axis slices were sequentially acquired from the left ventricular (LV) base to the apex.

Imaging analysis

Commercial post-processing software (cvi42, Circle Cardiovascular Imaging, Calgary, Canada) was used to analyze ECVs. A flowchart of ECV quantification is illustrated in Fig. 1. ECV, measured from native and postcontrast T1 maps using a region-based method, was defined as the conventional ECV method. The ROIs in the blood and myocardium of the LV were drawn in the central area of the LV cavity and the septal myocardium on the T1-mapping image at the middle slice. The average T1



values of the segmented regions of interest were then computed. After obtaining the native and postcontrast T1 values, a partition coefficient (λ) was calculated by using the following formula [24]:

$$\lambda = \frac{\frac{1}{T1_{myocardium}^{postcontrast}} - \frac{1}{T1_{myocardium}^{native}}}{\frac{1}{T1_{blood}^{postcontrast}} - \frac{1}{T1_{blood}^{native}}}$$

The ECV values were then obtained by multiplying λ by 1-Hct. For inline ECV mapping, the native and postcontrast T1 maps were aligned using non-rigid motion correction and the above formula was applied for each pixel, resulting in a λ map. A 10% tolerance has been included for mismatching resolution/geometry, whereby the larger image was cropped to match the smaller image. The binary blood mask was automatically extracted using pre-defined thresholds and morphological imaging processing operations. The value for blood T1 was calculated as the median of all values of the T1 mapping identified by the blood mask. The native blood T1 was used to estimate Hct_{syn} with the local derivation model. The λ map were scaled by Hct_0 , Hct_1 , and Hct_{syn} to produce their

respective ECV maps. Inline ECV values were measured directly from inline ECV maps using the same myocardial ROIs that were drawn on the T1 mapping in the conventional method (Fig. 1). The ECV measurement using Hct_0 was defined as the reference ECV (ECV_0) for both the conventional and inline ECV methods. ECV_0 was compared with ECV derived from Hct_1 (ECV_1) and the ECV derived from Hct_{syn} (ECV_{syn}) for each method. ECV_{syn} error was defined by differences in ECV using Hct_{syn} and Hct_0 . The partition coefficient estimated from the conventional ECV method (λ_{conv}) was compared with those estimated from the inline ECV method (λ_{inline}). The relative changes in Hcts were assessed by comparing Hct_0 with Hct_1 and Hct_{syn} .

Statistical analysis

Continuous variables were expressed as the means and standard deviations (SDs) or as median (IQR; inter-quartile range) as appropriate, and categorical variables were expressed as percentages. Correlations between the continuous variables were assessed with the use of the Pearson correlation coefficient. Bias and precision were evaluated with Bland–Altman analyses. Agreements between the measurements were assessed via the

intra-class correlation coefficient (ICC) with a two-way random-effects model. Comparisons between values were made using a paired *t*-test for continuous values with normal distributions and a Wilcoxon signed-rank test for continuous values with non-normal distributions. Statistical tests were two-tailed, and a statistical significance was defined as $p < 0.05$. Type II error (β) was calculated and statistical power was estimated by $1 - \beta$ for each comparison. Equivalence analysis was performed to assess whether ECV estimated by Hct_1 and Hct_{syn} were similar with Hct_0 for each method. Sample size calculation for equivalence analysis was evaluated to achieve a 5% two-sided type I error and 90% statistical power [25]. Two-sided 95% confidential interval (CI) for the ECV difference between the two Hcts was used to compare with equivalence margin. Data were analyzed with SPSS (version 26, Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, USA) and GraphPad Prism software (version 5.01, GraphPad Software, Inc., La Jolla, California, USA).

Results

Patient characteristics

812 consecutive patients were available for inclusion between March 2018 and May 2020. We excluded patients with suboptimal image quality ($n = 12$) and no contrast indication ($n = 30$) according to the exclusion criteria. A total of 770 subjects were included in this study. In this cohort, 37 patients without Hct data (5% in total) were excluded. One hundred and ninety-four patients had Hct data and CMR examinations performed on the same day (25.2% in total). Among these patients, 85 patients without a second Hct were used to derive local derivation model for Hct_{syn} and 109 patients who had a second Hct performed were included for further analysis (Fig. 2). The demographics of the study population are summarized in Table 1. The time interval between the date of the second Hct and CMR was 117 days (IQR: 27–274 days). All patients were outpatient referrals. 24 patients (22%) were hospitalized and 16 patients (17%) underwent interventional procedures between the date of the second Hct and CMR. However, there was no significant difference in blood pressure and heart rate between these two time points. Clinical diagnoses consisted of amyloidosis ($n = 3$, 2.8%), Brugada syndrome ($n = 6$, 5.5%), coronary artery disease ($n = 12$, 11%), heart failure ($n = 6$, 5.5%), dilated cardiomyopathy ($n = 3$, 2.8%), Anderson-Fabry disease ($n = 4$, 3.7%), hypertrophic cardiomyopathy ($n = 12$, 11%), myocarditis ($n = 1$, 0.9%), hypertensive cardiomyopathy ($n = 29$, 27%), tetralogy of Fallot ($n = 6$, 5.5%), and suspected cardiovascular disease ($n = 18$, 17%).

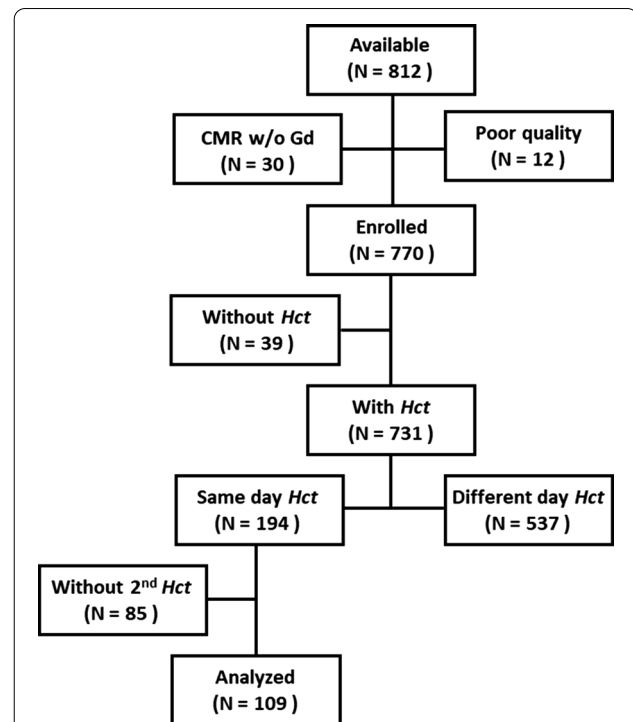


Fig. 2 A flow chart showing the selection process in this study. 812 consecutive patients were available for inclusion in this cohort. A total of 770 subjects were included in this study; 37 patients that did not have hematocrit (Hct) data were excluded. 149 patients had both Hct data and CMR performed on the same day. Among these patients, 109 patients had a second Hct (Hct_1) measure and were included for further analysis

Local derivation model for synthetic hematocrit

The regression between Hct_0 and native $T1_{blood}$ was linear ($R^2 = 0.51$, $p < 0.001$), and the regression equation was $Hct_{syn} = [971.6 * (1/T1_{blood})] + 0.1818$ (Fig. 3a) in the derivation group.

ECV comparisons with differently measured hematocrits and quantification methods

Using the conventional method, ECVs measured with Hct_1 and Hct_{syn} were significantly correlated with ECV_0 (Fig. 4a). The coefficient of determination (r^2) between ECV_0 and ECV_1 was 0.956 ($p < 0.001$); the r^2 between ECV_0 and ECV_{syn} was 0.935 ($p < 0.001$). A Bland–Altman analysis indicated a 0.05% bias (− 2.8 to 2.9%, Fig. 4c) between the ECV_0 and ECV_1 and a 0.2% bias (− 3.2 to 3.6%, Fig. 4e) between the ECV_0 and ECV_{syn} . The ICC coefficient between ECV_0 and ECV_1 was 0.987 with a 95% CI 0.991–0.982, and between ECV_0 and ECV_{syn} was 0.981 with a 95% CI 0.987–0.973. These results showed no significant differences between ECV_0 and ECV_1 ($28.4 \pm 6.6\%$ vs. $28.3 \pm 6.1\%$, $p = 0.789$, $\beta = 0.211$) and

Table 1 Patient characteristics

	N or mean ± SD	% or range
Age (years)	53 ± 19	17–89
Gender		
Male	66	62
Female	43	38
BSA (m ²)	1.73 ± 0.25	1.37–2.24
Heart rate (bpm)	74 ± 15	43–153
LV function		
EDVI (ml/m ²)	60.5 ± 20.3	32.0–156.9
ESVI (ml/m ²)	17.6 ± 15.1	3.3–101.9
EF (%)	73 ± 13	33–93
Diagnosis		
Amyloidosis	3	2.8
Brugada Syndrome	6	5.5
Coronary artery disease	12	11
Heart failure	6	5.5
Dilated cardiomyopathy	3	2.8
Anderson-Fabry disease	4	3.7
Hypertrophic cardiomyopathy	12	11
Hypertensive cardiomyopathy	29	27
Myocarditis	1	0.9
Tetralogy of Fallot	24	5.5
Others CVD	18	17

BSA body surface area, EDVI end-diastolic volume index, ESVI end-systolic volume index, EF ejection fraction, Hct hematocrit, LV left ventricular, CVD cardiovascular disease

ECV₀ and ECV_{syn} (28.4 ± 6.6% vs. 28.2 ± 6.2%, p = 0.450, β = 0.536; Fig. 4g).

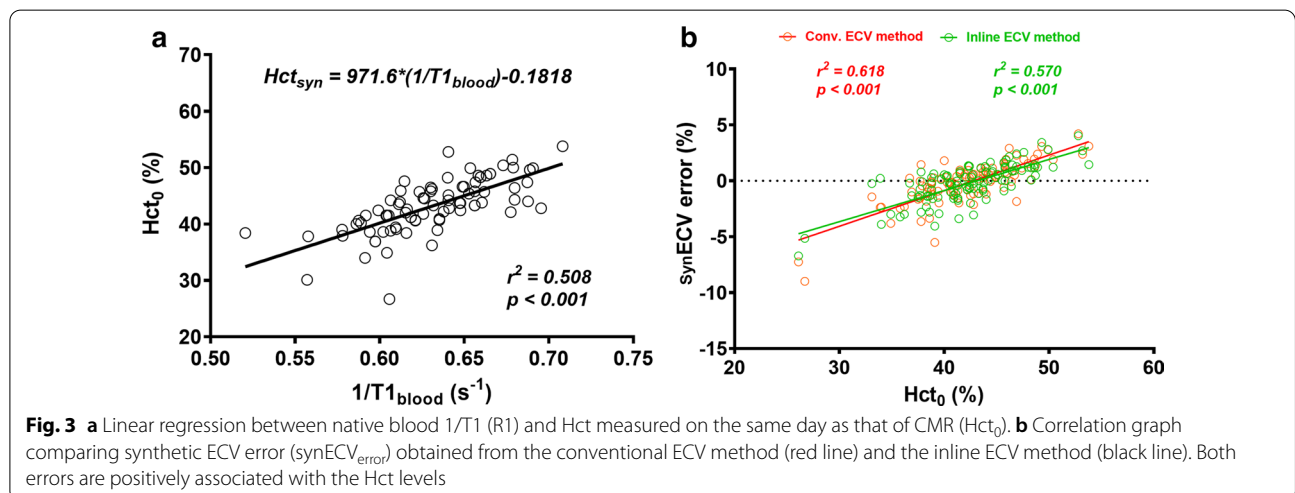
Using the inline method, ECVs measured with Hct₁ and Hct_{syn} were also significantly correlated with ECV₀ (Fig. 4b). The coefficient of determination (r²) between ECV₀ and ECV₁ measured with the inline ECV method

was 0.957 (p < 0.001); the r² between ECV₀ and ECV_{syn} was 0.923 (p < 0.001). Bland–Altman analysis indicated a 0.05% bias (− 2.73 to 2.82%, Fig. 4d) between ECV₀ and ECV₁, and a 0.1% bias (− 3.58 to 3.85%, Fig. 4f) between ECV₀ and ECV_{syn}. The ICC coefficient between ECV₀ and ECV₁ was 0.988 with a 95% CI 0.992–0.982, and between ECV₀ and ECV_{syn} values was 0.977 with a 95% CI 0.984–0.966. These results showed that in using the inline ECV method there was no significant difference between ECV₀ and ECV₁ (28.5 ± 6.7% vs. 28.5 ± 6.2, p = 0.801, β = 0.199) and ECV₀ and ECV_{syn} (28.5 ± 6.7% vs. 28.4 ± 6.0, p = 0.974, β = 0.026) (Fig. 4h).

In addition, the partition coefficient measured from the conventional ECV method was also not different with that measured from the inline ECV method (49.4 ± 11.4% vs. 49.5 ± 11.4%, p = 0.620, β = 0.378).

Hematocrits compared on different sampling days and derived from native blood T1 mapping

Bland–Altman analysis indicated a 0.03% bias (− 5.2 to 5.3%) between Hct₁ and Hct₀ (Fig. 5a), resulting in no significant difference between these two variables (42.3 ± 4.7% vs. 42.4 ± 4.7%, p = 0.996, β = 0.004; Fig. 5b). Regarding Hct_{syn} derived from the two different methods, Bland–Altman analysis indicated a − 0.4% bias (− 7.1 to 6.3%) using the conventional ECV method (Fig. 5c) and a − 0.2% bias (− 7.2 to 6.9%) using the inline ECV method (Fig. 5e). These results showed that Hct_{syn} was not statistically different than Hct₀ using the conventional ECV method (42.8 ± 3.1% vs. 42.4 ± 4.7%, p = 0.472, β = 0.410) (Fig. 5d) and using the inline ECV method (42.5 ± 2.8% vs. 42.4 ± 4.7%, p = 0.923, β = 0.072; Fig. 5f). Since the Hct_{syn} was determined from native blood T1 measurements, we further compared blood T1 measured using these two methods. From Bland–Altman



(See figure on next page.)

Fig. 4 Correlation and comparisons among three extracellular volumes (ECVs) derived from three different hematocrits (Hcts) using the conventional ECV and the inline ECV methods. ECV_1 and ECV_{syn} are both strongly correlated with ECV_0 in the conventional method (a) and the inline ECV method (b). In the conventional method, Bland–Altman plots indicate minimal bias between ECV_1 and ECV_0 (c) and between ECV_{syn} and ECV_0 (e). Similarly, Bland–Altman plots also indicate minimal bias between ECV_1 and ECV_0 (d) and between ECV_{syn} and ECV_0 (f) in inline ECV method. No significant differences among 3 ECVs in the conventional method (g) and the inline ECV method (h) were observed. ECV_0 is derived using an Hct obtained on the day of CMR (CMR; Hct₀), ECV_1 is derived with Hct₁ is measured from a different day than CMR, and ECV_{syn} is derived with Hct_{syn}, which is calculated from native blood T1 mapping

analysis, there was a 1.5 ms bias and confidence limit (–7.2 to 6.9 ms) using the inline method compared with using the conventional method (Fig. 5g), which resulted in no statistical difference between the conventional and inline ECV methods for native blood T1 measurements (1599 ± 84 ms vs. 1598 ± 75 ms, $p=0.648$, $\beta=0.351$; Fig. 5h). Hct comparisons were listed in Table 2.

Equivalence analysis for ECV differences

Normal myocardial ECV in normal subjects has been reported at 1.5T as $25.3 \pm 3.5\%$ ($n=81$) [26] and $25.4 \pm 2.5\%$ ($n=62$) [23], respectively. Therefore, a $\pm 2\%$ defined equivalence margin was considered acceptable in this study. Assuming SD of the ECV difference between the two Hcts was 4%, 207 total samples were needed to achieve a 0.90 power with $\alpha=0.05$ for the equivalence study. The two-sided 95% CI was calculated as followed: $m1 - m2 \pm 1.96 \sqrt{\frac{\sigma_1^2 + \sigma_2^2}{n}}$, where $m1$ and $m2$ were means; σ_1 and σ_2 were SDs in the tested ECV and ECV_0 , respectively, and the n was the sample size ($n=109$). Figure 6 showed the entire CI of ECV differences were within the equivalent margin in both Hct₁ and Hct_{syn} for each method.

Synthetic extracellular volume error is associated with hematocrit levels

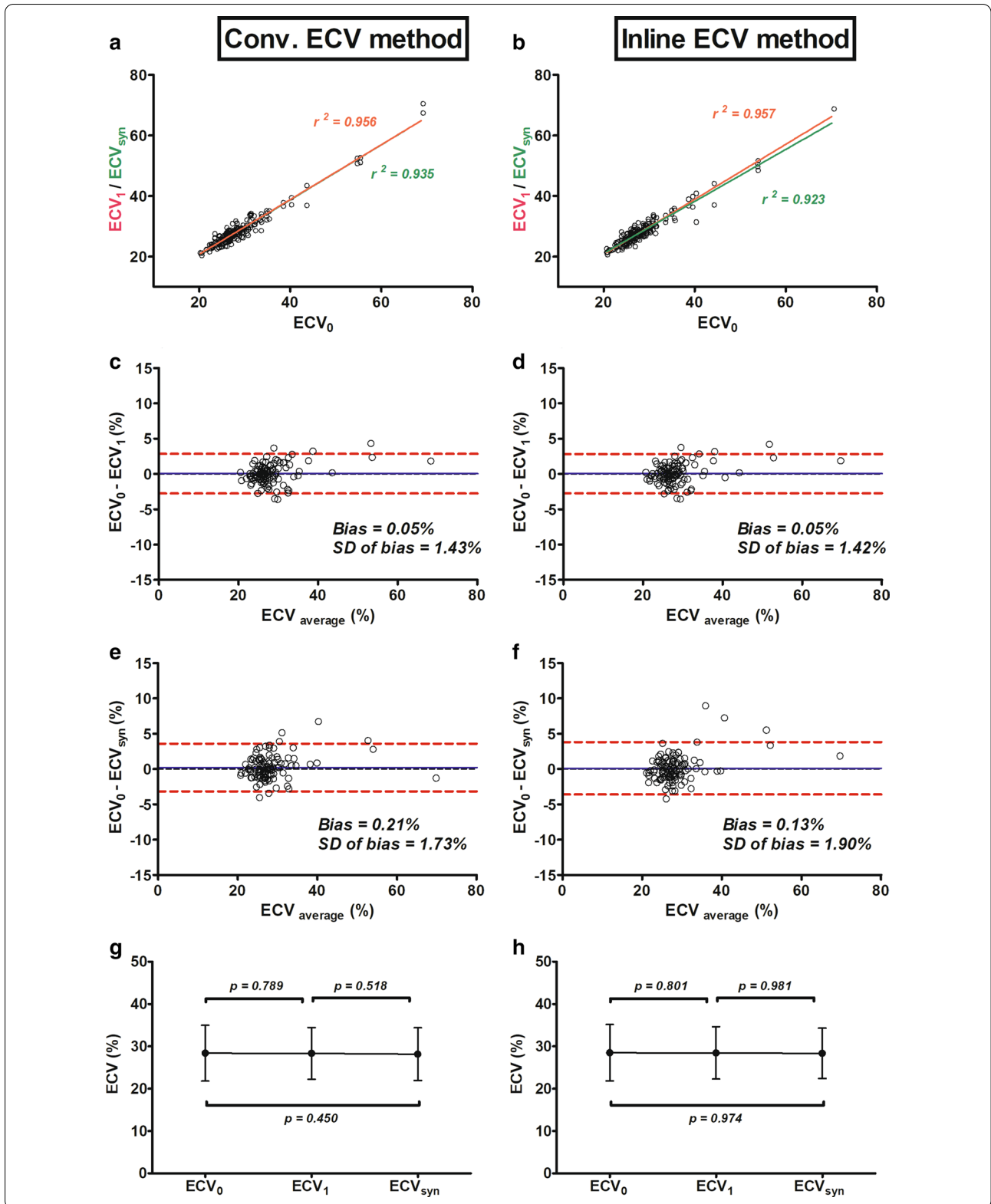
The error associated with ECV_{syn} measurements obtained from the two methods is shown in Fig. 6. Both errors were positively associated with Hct₀ levels, which suggest that ECV_{syn} could be underestimated at lower Hcts and overestimated at higher Hcts. Based on a sub-analysis of current data, the cut-off value for Hct_{syn} was determined on the error of ECV_{syn} was less than 2%. The cut-off range for Hct_{syn} was obtained from 36.5 to 49.0% using the conventional method, and from 36.0 to 50.4% using the inline method, respectively.

Discussion

In this study, we compared ECV measurements with three different Hcts and two ECV methods. ECV measured with venous Hct drawn on a different day from that of CMR (ECV_1) was significantly correlated with reference ECV (ECV_0) using both conventional and inline

ECV methods. Minimal biases and limited discrepancies were also found. These findings demonstrate that for both methods, venous Hcts could be used to estimate ECV, and that it did not matter if the Hct was from the day of CMR or from a different day. In addition, a significant correlation and good agreement between ECV_{syn} and ECV_0 were noted in both methods. These results suggest that ECVs estimated with native blood T1 could be used for an ECV measurement if venous Hct was unavailable. Moreover, the equivalence analysis indicated that 95% CI of ECV differences between the two Hcts lay entirely within the equivalent margin for both methods. These results further strengthen our findings. The partition coefficient determined from the inline ECV method showed no significant difference with that of the conventional ECV method, suggesting that ECV measured using the inline method is reliably compared with ECV measured using the conventional method. Hct are necessary for ECV calculations and have been reportedly shown to be influenced by body posture [6] and diurnal fluctuation [7]. Some studies have also demonstrated that hemoglobin exhibits hour-to-hour, day-to-day, or even seasonal within-individual fluctuations [8, 9]. Thirup et al. [27] performed a meta-analysis to explore the substantial variation of Hcts looking at 12 studies representing 638 healthy adults that had sampling intervals of 1 day to 1–2 months. They reported that both normal within-subject variation and analytical variation were 3%, resulting in an approximately 12% relative change between the two successive Hct measurements. Theoretically, a 1% change in Hct would lead to a 0.67% change in the ECV. Based on this reference, a 12% change in Hct could cause an 8% difference in the ECV. In this study, we demonstrated that there was no significant difference in the measured Hcts and ECVs using Hcts obtained on the same day vs. on a different day from the CMR, which could imply that the day on which an Hct is obtained does not have a significant effect on ECV measurements.

Hct_{syn} can be derived from the native blood T1 values and used to calculate ECV_{syn} without needing blood sampling. Treibel et al. reported that ECV_{syn} measured from Hct_{syn} provide a validated, noninvasive quantification of the myocardial extracellular space without the need for a blood sample [17]. Fent et al. further demonstrated



(See figure on next page.)

Fig. 5 Comparisons among three different hematocrits (Hcts) and between two native blood T1. Bland–Altman plots indicate the minimal bias between Hct_1 and Hct_0 (a), between $Hct_{syn[conv]}$ and Hct_0 (c), and between $Hct_{syn[inline]}$ and Hct_0 (e). There is no statistical difference between Hct_1 and Hct_0 (b), between $Hct_{syn[conv]}$ and Hct_0 (d), and between $Hct_{syn[inline]}$ and Hct_0 (f). Bland–Altman plot indicates a 1.5 ms bias and confidence limit (7.2–6.9 ms) using the inline method compared with using the conventional method (g), which resulted in no statistical difference between the conventional and inline ECV methods for native blood T1 measurements (h). Hct_0 is Hct obtained on the same day as the CMR. Hct_1 is Hct obtained on a different day from the CMR. $Hct_{syn[conv]}$ and $Hct_{syn[inline]}$ are Hcts obtained synthetically from native blood T1 mapping using the conventional and inline ECV methods, respectively

that ECV_{syn} values strongly correlated with conventionally measured ECV at both 1.5T and 3T [18]. In contrast, Raucci et al. proposed that using ECV_{syn} might result in a clinically significant miscategorization of pediatric and young adult patients [19]. In addition, Shang et al. further demonstrated that ECV_{syn} could lead to clinical errors using 3T CMR, suggesting that the use of ECV_{syn} could incorrectly categorize 6–25% of patients [20]. Consistent with some studies, our results showed that the ECV_{syn} was strongly correlated with the ECV_0 and revealed no significant difference with ECV_0 using both methods.

Our results showed that the native blood T1 values measured using the inline ECV method were not significantly different from those measured using the conventional ECV method. This finding suggests that automated blood region segmentation is reliable to estimate the blood T1 compared to conventional ROI method. Despite the blood T1 calculation, several factors that could influence native blood T1 are possible, such as physiologic variation (e.g., hemoglobin oxygenation [28], serum total proteins [29] and temperature), and technical issues (e.g., the efficiency of the inversion pulse, the pulse sequence parameters, the magnetization transfer effects, the magnetic field heterogeneity, and the fitting algorithms) [30–33]. In this study, we demonstrated that for the two ECV methods, ECV_{syn} error was significantly correlated with Hct, and the relatively large ECV_{syn} errors occurred when Hcts were lower compared with when they were higher. These findings suggest that the derived coefficients for Hct_{syn} were only confidently applied to the range in which it was derived and extrapolations that occurred outside of the range resulted in less confident estimates. The patients with very low Hct values could have other blood composition abnormalities that also affect T1 measurements. For these patients, Hct_{syn} and ECV_{syn} should be interpreted with caution, and a venous Hct should be used, if possible. For patients without a timely assessment of Hct, our results demonstrated that the last available Hct is feasible for use in ECV measurements. We defined the cut-off range (36–50%) for Hct_{syn} based on the ECV_{syn} error of <2%. This range is similar with normal range of Hct: 41–50% for men and 36–48% for women. Although ECV_{syn} could lead to ECV error in patients with severe anemia, it also provides an

alternative method to assess ECVs if venous Hcts are unavailable.

The purposes of CMR exams were diverse in this retrospective cohort. Patients with Hct_0 were primarily intended for ECV evaluation. Therefore, only 25.2% of the enrolled CMR patients had Hct data from the same day as CMR, and 5% of patients had no Hct data before CMR. For our institution, two steps were required to obtain Hct_0 in our workflow. First, the laboratory bloodwork was requested with “fractional blood sampling”, with one fraction for estimated eGFR and the other for Hct, so that two laboratory exams were tested simultaneously. Second, patients went to the laboratory department in advance to register for Hct evaluation and brought a blood collection tube to the CMR exam room. Then the blood sample was taken during the peripheral intravenous insertion by a CMR nurse before the exam. Due to number of additional steps required, this resulted in an 80% success rate for Hct_0 collection in our experience. Common points of failure were the physician’s assistant forgetting to remark “fractional blood sampling” on laboratory order sheet, the laboratory technologist omitting the request for two laboratory exams and blood sample not being taken during peripheral intravenous insertion. As Hct_0 collection is not part of our routine workflow, good communications between different departments and keeping patients well-informed were important for ensuring that Hct can be obtained on the same day as the CMR exam.

The conventional ECV method is most often used to quantify diffuse myocardial fibrosis. In these cases, the ROI can be drawn within the myocardium, avoiding the enhanced regions shown on late gadolinium enhancement (LGE) imaging. This method assumes that diffuse fibrosis is distributed homogeneously (uniform ECV) within the non-infarcted regions. However, the spatial variation of diffuse fibrosis is diverse and depends on various cardiomyopathies [34]. Therefore, ECV measurements could be affected by the position of an ROI if any significant regional variation exists in the fibrotic areas. Compared with conventional ECV method, inline ECV mapping not only allowed for ECV measurements at the time of CMR examination, but it also provided an ability to assess the heterogeneity of the myocardial tissue. This

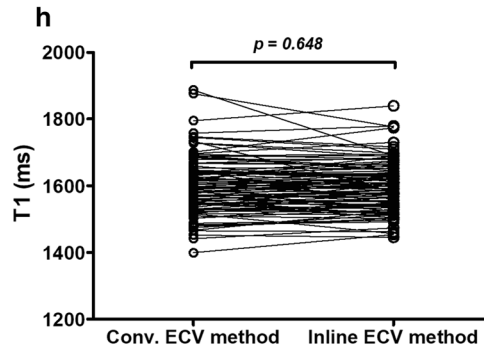
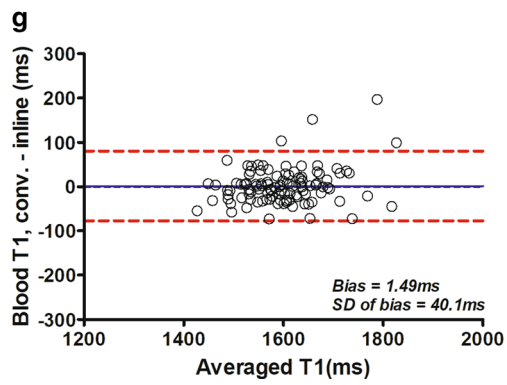
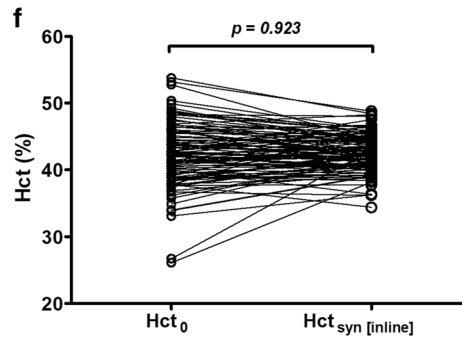
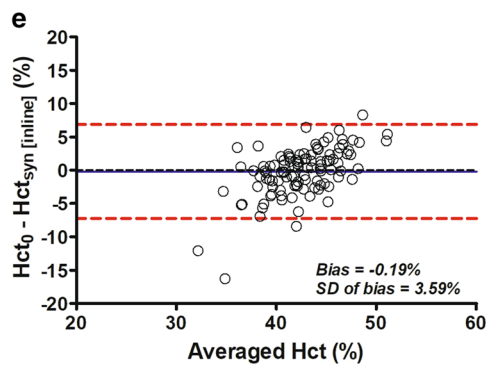
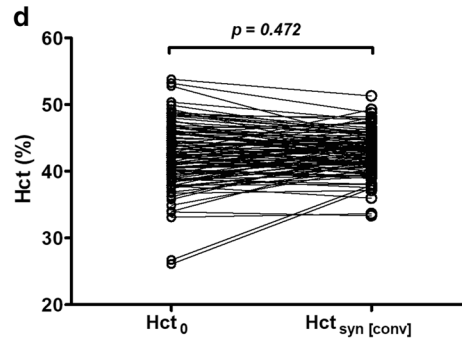
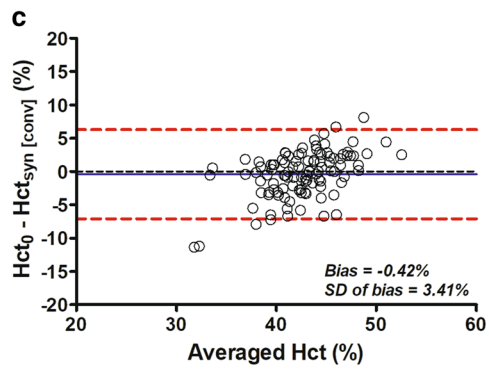
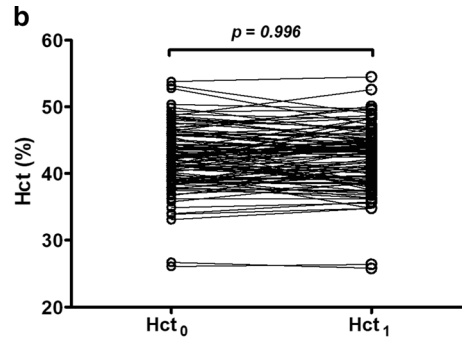
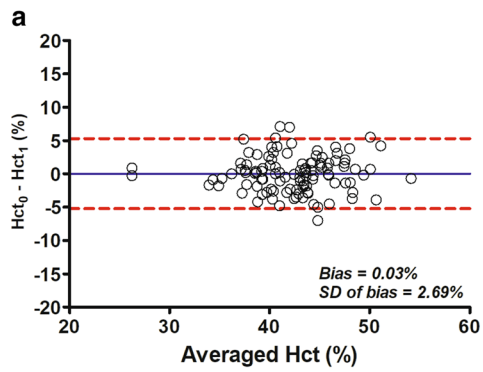


Table 2 Comparison of venous and synthetic hematocrits

	Mean \pm SD	Range
Hct ₀ (%)	42.4 \pm 4.7	(26.1, 53.8)
Hct ₁ (%)	42.3 \pm 4.7	(25.8, 54.5)
Hct _{syn [conv]} (%)	42.8 \pm 3.1	(33.4, 51.3)
Hct _{syn [inline]} (%)	42.5 \pm 2.8	(34.4, 48.8)

Hct₀ is hematocrit (Hct) obtained on the same day as that of CMR. Hct₁ is Hct obtained on a different day from that of CMR. Hct_{syn [conv]} and Hct_{syn [inline]} are Hcts obtained synthetically from native blood T1 mapping using the conventional and inline ECV methods, respectively

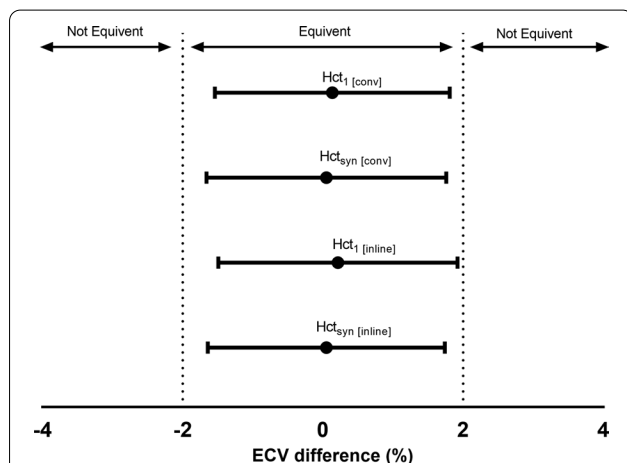


Fig. 6 Interpretation of equivalence of tested hematocrits (Hct₁, Hct_{syn}) to the standard hematocrit (Hct₀) for ECV measurements. The dashed vertical lines indicate the predefined equivalence margins (−2 to 2%) and the horizontal lines represent the 95% confidence interval (CI) of the difference in ECV between compared Hcts.

Equivalence is concluded if the entire CI is within the equivalence margins. Hct_{1 [conv]} and Hct_{1 [inline]} are hematocrits obtained on a different day from that of CMR f using the conventional and inline ECV methods, respectively. Hct_{syn [conv]} and Hct_{syn [inline]} are Hcts obtained synthetically from native blood T1 mapping using the conventional and inline ECV methods, respectively

approach is clinically desirable and could potentially be used to identify subtle differences in myocardial ECVs earlier. In this study we demonstrated that the partition coefficient determined from the inline ECV method was not significantly different with that measured from the conventional ECV method. This result suggests that inline ECV method offers an identical ECV quantification compared to the conventional ECV method.

Study limitations

There are several limitations to our study. First, the ECVs measured using an Hct from a different day from that of CMR were not significantly different from those measured on the same day. This result could be associated

with the lack of a statistical difference in the Hct depending on the time between when the measured Hct and CMR occurred. Although Hct has substantial variation, this variation does not appear to influence ECV measurements. Second, our study was performed with a single T1 pulse sequence (MOLLI), however different sequences of T1 mapping have been reported to yield different absolute ECV values [35]. Third, imaging quality for the ECV mapping was not evaluated in this study. Whether this comparison is identical with different pulse sequences or depends on the quality of ECV mapping is unknown and needs further investigation. Finally, all data were acquired at a single institution using a single CMR vendor. Multi-center studies, including larger numbers of patients, with different vendors should be further performed to validate these results.

Conclusion

Our study demonstrated that venous Hct measured on a different day than that of CMR is still useful for the calculation of ECVs regardless of the quantification method. ECV_{syn} values could provide an alternative method to quantify ECVs without requiring a blood sample but significant error may occur when patients have either extremely low or high Hcts. Inline ECV mapping could provide a method to quickly detect myocardial tissue heterogeneity and measure ECV abnormalities without the timely presence of a Hct.

Abbreviations

CMR: Cardiovascular magnetic resonance; ECG: Electrocardiography; ECV: Extracellular volume fraction; ECV₀: Reference ECV; ECV_{syn}: Synthetic ECV; eGFR: Estimated glomerular filtration rate; Hct: Hematocrit; Hct₀: Reference hematocrit; Hct_{syn}: Synthetic hematocrit; ICC: Intraclass correlation; LGE: Late gadolinium enhancement; LV: Left ventricle/left ventricular; MOLLI: Modified Look-Locker inversion recovery; ROI: Region of interest; SCMR: Society for Cardiovascular Magnetic Resonance; SD: Standard deviation; T1: Longitudinal relaxation time.

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NA

Authors' contributions

MYS and YCC are the guarantors of integrity of the entire study. MYS, EN, KC and YCC conceived the study, analyzed the CMR data and drafted the manuscript. LYL, CKW, HYY and JMJJ recruited the patients. MYS, EN and YSH acquired the CMR data and performed the statistical analyses. YSH, EN and YCC participated in the design and coordination of the study. EN and KC helped to edit the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the IRB of the National Taiwan University Hospital, and all the participants provided written permission to participate in the study.

Consent for publication

Written informed consent was obtained from all the participants for publication of their individual details and images in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

- Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. *Circulation*. 2012;126:1206–16.
- Su MY, Lin LY, Tseng YH, et al. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. *JACC Cardiovasc Imaging*. 2014;7:991–7.
- Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson*. 2016;18:89.
- Rommel KP, von Roeder M, Latuscynski K, et al. Extracellular volume fraction for characterization of patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2016;67:1815–25.
- Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017;19:75.
- Jacob G, Raj SR, Ketch T, et al. Postural pseudoanemia: posture-dependent change in hematocrit. *Mayo Clin Proc*. 2005;80:611–4.
- Sennels HP, Jorgensen HL, Hansen AL, Goetze JP, Fahrenkrug J. Diurnal variation of hematology parameters in healthy young males: the Bispebjerg study of diurnal variations. *Scand J Clin Lab Invest*. 2011;71:532–41.
- Statland BE, Winkel P, Harris SC, Burdsall MJ, Saunders AM. Evaluation of biologic sources of variation of leukocyte counts and other hematologic quantities using very precise automated analyzers. *Am J Clin Pathol*. 1978;69:48–54.
- Maes M, Scharpe S, Cooreman W, et al. Components of biological, including seasonal, variation in hematological measurements and plasma fibrinogen concentrations in normal humans. *Experientia*. 1995;51:141–9.
- Silvennoinen MJ, Kettunen MI, Kauppinen RA. Effects of hematocrit and oxygen saturation level on blood spin-lattice relaxation. *Magn Reson Med*. 2003;49:568–71.
- Lu H, Clingman C, Goyal X, van Zijl PC. Determining the longitudinal relaxation time (T1) of blood at 3.0 Tesla. *Magn Reson Med*. 2004;52:679–82.
- Shimada K, Nagasaka T, Shidahara M, Machida Y, Tamura H. In vivo measurement of longitudinal relaxation time of human blood by inversion-recovery fast gradient-echo MR imaging at 3T. *Magn Reson Med Sci*. 2012;11:265–71.
- Grgac K, van Zijl PC, Qin Q. Hematocrit and oxygenation dependence of blood (1)H(2)O T(1) at 7 Tesla. *Magn Reson Med*. 2013;70:1153–9.
- Braunschweiger PG, Schiffer L, Furmanski P. The measurement of extracellular water volumes in tissues by gadolinium modification of 1H-NMR spin lattice (T1) relaxation. *Magn Reson Imaging*. 1986;4:285–91.
- Martin MA, Tatton WG, Lemaire C, Armstrong RL. Determination of extracellular/intracellular fluid ratios from magnetic resonance images: accuracy, feasibility, and implementation. *Magn Reson Med*. 1990;15:58–69.
- Li W, Grgac K, Huang A, Yadav N, Qin Q, van Zijl PC. Quantitative theory for the longitudinal relaxation time of blood water. *Magn Reson Med*. 2016;76:270–81.
- Treibel TA, Fontana M, Maestrini V, et al. Automatic measurement of the myocardial interstitium: synthetic extracellular volume quantification without hematocrit sampling. *JACC Cardiovasc Imaging*. 2016;9:54–63.
- Fent GJ, Garg P, Foley JR, et al. Synthetic myocardial extracellular volume fraction. *JACC Cardiovasc Imaging*. 2017;10:1402–4.
- Raucci FJ Jr, Parra DA, Christensen JT, et al. Synthetic hematocrit derived from the longitudinal relaxation of blood can lead to clinically significant errors in measurement of extracellular volume fraction in pediatric and young adult patients. *J Cardiovasc Magn Reson*. 2017;19:58.
- Shang Y, Zhang X, Zhou X, Wang J. Extracellular volume fraction measurements derived from the longitudinal relaxation of blood-based synthetic hematocrit may lead to clinical errors in 3 T cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2018;20:56.
- Mewton N, Liu CY, Croisille P, Bluemke D, Lima JAC. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol [Internet]*. 2011a;57:891–903.
- Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. *J Cardiovasc Magn Reson*. 2012;14:63.
- Kellman P, Wilson JR, Xue H, et al. Extracellular volume fraction mapping in the myocardium, part 2: initial clinical experience. *J Cardiovasc Magn Reson*. 2012;14:64.
- Jerosch-Herold M, Sheridan DC, Kushner JD, et al. Cardiac magnetic resonance imaging of myocardial contrast uptake and blood flow in patients affected with idiopathic or familial dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2008;295:H1234-h1242.
- Ahn S, Park SH, Lee KH. How to demonstrate similarity by using noninferiority and equivalence statistical testing in radiology research. *Radiology*. 2013;267:328–38.
- Sado DM, Flett AS, Banyersad SM, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. *Heart*. 2012;98:1436–41.
- Thirup P. Haematocrit: within-subject and seasonal variation. *Sports Med (Auckland, NZ)*. 2003;33:231–43.
- Atalay MK, Reeder SB, Zerhouni EA, Forder JR. Blood oxygenation dependence of T1 and T2 in the isolated, perfused rabbit heart at 4.7T. *Magn Reson Med*. 1995;34:623–7.
- Jiao X, Bryant RG. Noninvasive measurement of protein concentration. *Magn Reson Med*. 1996;35:159–61.
- Kawel N, Nacif M, Zavodni A, et al. T1 mapping of the myocardium: intra-individual assessment of the effect of field strength, cardiac cycle and variation by myocardial region. *J Cardiovasc Magn Reson*. 2012;14:27.
- Kellman P, Arai AE, Xue H. T1 and extracellular volume mapping in the heart: estimation of error maps and the influence of noise on precision. *J Cardiovasc Magn Reson*. 2013;15:56.
- Kellman P, Hansen MS. T1-mapping in the heart: accuracy and precision. *J Cardiovasc Magn Reson*. 2014;16:2.
- Chow K, Flewitt JA, Green JD, Pagano JJ, Friedrich MG, Thompson RB. Saturation recovery single-shot acquisition (SASHA) for myocardial T(1) mapping. *Magn Reson Med*. 2014;71:2082–95.
- Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2011b;57:891–903.
- Roujol S, Weingartner S, Foppa M, et al. Accuracy, precision, and reproducibility of four T1 mapping sequences: a head-to-head comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE. *Radiology*. 2014;272:683–9.

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