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

Mao-Yuan Su1,6†, Yu-Sen Huang1, Emi Niisato2†, Kelvin Chow3, Jyh-Ming Jimmy Juang4, Cho-Kai Wu4, Hsi-Yu Yu5, Lian-Yu Lin4, Shun-Chung Yang1 and Yeun-Chung Chang1*

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 (Hctsyn) 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 Hctsyn were compared for each method, and the reference ECV (ECV0) was defined using the Hct0. The error between synthetic (ECVsyn) and ECV0 was analyzed for the two ECV methods.

Results: ECV measured using Hct1 and Hctsyn 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 Hctsyn (ECVsyn; 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 ECVsyn (28.5 ± 6.7% vs. 28.4 ± 6.0, p = 0.974) using inline method. ECVsyn 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. ECVsyn 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
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#) can be estimated from the native blood T1 values [14–16]. Treibel [17] and Fent [18] further demonstrated that synthetic ECVs (ECV#) derived from synthetically calculated Hcts (Hct#) demonstrated a strong correlation with ECVs derived from venous Hcts. However, several recent studies have suggested that using ECV# can result in the miscategorization of individual patients [19] and lead to clinical errors using T1 CMR [20]. Therefore, whether ECV# measurements using Hct# 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 mapping 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 (Hct0) and the other measured on a different day (Hct1). Subjects with Hct0 only were defined as the derivation group. The linear equation between blood R1(1/T1) and Hct0 was derived in the derivation group and used to estimate Hct# 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 T1 125–150 ms; T1 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 (Hct0, Hct1) and Hct#. 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]:

\[
\lambda = \frac{\frac{1}{T1_{\text{postcontrast mycardium}}} - \frac{1}{T1_{\text{native mycardium}}}}{\frac{1}{T1_{\text{postcontrast blood}}}} - \frac{1}{T1_{\text{native blood}}}
\]

The ECV values were then obtained by multiplying λ by 1-Hct. For inline ECV mapping, the native and post-contrast 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; interquartile 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
intraclass 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-β 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%).

**Local derivation model for synthetic hematocrit**

The regression between Hct$_1$ and native T$_{1blood}$ was linear ($R^2 = 0.51$, *p* < 0.001), and the regression equation was Hct$_{syn} = [971.6*(1/T_{1blood})] + 0.1818$ (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 ± 6.6% vs. 28.3 ± 6.1%, *p* = 0.789, β = 0.211) and
Using the inline method, ECVs measured with Hct$_1$ and Hct$_{syn}$ were also significantly correlated with ECV$_0$ (Fig. 4b). The coefficient of determination ($r^2$) between ECV$_0$ and ECV$_1$ measured with the inline ECV method was 0.957 ($p<0.001$); the $r^2$ between ECV$_0$ 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 ECV$_0$ and ECV$_1$, and a 0.1% bias (3.58 to 3.85%, Fig. 4f) between ECV$_0$ and ECV$_{syn}$. The ICC coefficient between ECV$_0$ and ECV$_1$ was 0.988 with a 95% CI 0.992–0.982, and between ECV$_0$ 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 ECV$_0$ and ECV$_1$ (28.5 ± 6.7% vs. 28.5 ± 6.2, $p=0.801$, $\beta=0.199$) and ECV$_0$ and ECV$_{syn}$ (28.5 ± 6.7% vs. 28.4 ± 6.0, $p=0.974$, $\beta=0.026$) (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%, $p=0.620$, $\beta=0.378$).

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 Hct$_1$ and Hct$_0$ (Fig. 5a), resulting in no significant difference between these two variables (42.3 ± 4.7% vs. 42.4 ± 4.7%, $p=0.996$, $\beta=0.004$; 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 Hct$_0$ using the conventional ECV method (42.8 ± 3.1% vs. 42.4 ± 4.7%, $p=0.472$, $\beta=0.410$) (Fig. 5d) and using the inline ECV method (42.5 ± 2.8% vs. 42.4 ± 4.7%, $p=0.923$, $\beta=0.072$; 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

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**Table 1 Patient characteristics**

| Characteristic | 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       |
| Tetrology 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

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**Fig. 3**

(a) Linear regression between native blood 1/T1 (R1) and Hct measured on the same day as that of CMR (Hct$_0$).

(b) Correlation graph comparing synthetic ECV error (synECVerror) obtained from the conventional ECV method (red line) and the inline ECV method (black line). Both errors are positively associated with the Hct levels.
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, β = 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 ± 3.5% (n = 81) [26] and 25.4 ± 2.5% (n = 62) [23], respectively. Therefore, a ±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 α = 0.05 for the equivalence study. The two-sided 95% CI was calculated as followed:

\[
\text{m}_1 - \text{m}_2 \pm 1.96 \sqrt{\frac{\sigma_1^2 + \sigma_2^2}{n}}
\]

where m1 and m2 were means; σ1 and σ2 were SDs in the tested ECV and ECV0, respectively, and 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 Hctsyn for each method.

Synthetic extracellular volume error is associated with hematocrit levels

The error associated with ECVsyn measurements obtained from the two methods is shown in Fig. 6. Both errors were positively associated with Hct0, levels, which suggest that ECVsyn could be underestimated at lower Hcts and overestimated at higher Hcts. Based on a sub-analysis of current data, the cut-off value for Hctsyn was determined on the error of ECVsyn was less than 2%. The cut-off range for Hctsyn 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 (ECV1) was significantly correlated with reference ECV (ECV0) 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 ECVsyn and ECV0 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 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. Hcts 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.

Hctsyn can be derived from the native blood T1 values and used to calculate ECVsyn without needing blood sampling. Treibel et al. reported that ECVsyn measured from Hctsyn provide a validated, noninvasive quantification of the myocardial extracellular space without the need for a blood sample [17]. Fent et al. further demonstrated
that ECV\textsubscript{syn} values strongly correlated with conventionally measured ECV at both 1.5T and 3T [18]. In contrast, Raucci et al. proposed that using ECV\textsubscript{syn} might result in a clinically significant miscategorization of pediatric and young adult patients [19]. In addition, Shang et al. further demonstrated that ECV\textsubscript{syn} could lead to clinical errors using 3T CMR, suggesting that the use of ECV\textsubscript{syn} could incorrectly categorize 6–25% of patients [20]. Consistent with some studies, our results showed that the ECV\textsubscript{syn} was strongly correlated with the ECV\textsubscript{0} and revealed no significant difference with ECV\textsubscript{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\textsubscript{syn} error was significantly correlated with Hct, and the relatively large ECV\textsubscript{syn} errors occurred when Hct were lower compared with when they were higher. These findings suggest that the derived coefficients for Hct\textsubscript{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\textsubscript{syn} and ECV\textsubscript{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\textsubscript{syn} based on the ECV\textsubscript{syn} error of <2%. This range is similar with normal range of Hct: 41–50% for men and 36–48% for women. Although ECV\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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
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. ECVsyn 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; ECVsyn: Synthetic ECV; eGFR: Estimated glomerular filtration rate; Hct: Hematocrit; Hct0: Reference hematocrit; Hctsyn: 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.

Author details
1 Department of Medical Imaging, National Taiwan University Hospital, No.7, Chung-Shan South Road, Taipei 100, Taiwan. 2 Siemens Healthcare Limited, vascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. 3 Siemens Medical Solutions USA Inc., Chicago, IL, USA. 4 Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. 5 Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan. 6 Department of Medical Imaging and Radiological Technology, Yuenpei University of Medical Technology, Hsinchu, Taiwan.

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