

Utilization of Synthetic Hematocrit Derived from Cardiac MRI for Estimating Extracellular Volume

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ABSTRACT

Objective: For a correct estimation of extracellular volume, patients' blood samples must be taken at least within 24 hours after cardiac magnetic resonance imaging, which may cause problems in immediate or retrospective evaluation. The aim of this study is to demonstrate the applicability of synthetic hematocrit for the calculation of extracellular volume.

Materials and Methods: Cardiac magnetic resonance images including T1 mapping were retrospectively reviewed. Medical records of each patient were also collected and patients who had blood samples including hematocrit values within 24 hours of cardiac magnetic resonance imaging were included in the study. Simple linear regression along with intraclass correlation coefficient were used to calculate the coefficient of determination and agreement between the two measurements of hematocrit and extracellular volume values. The compatibility of the synthetic extracellular volume with the native extracellular volume was analysed using "Kappa Analysis".

Results: Synthetic and native hematocrit values showed significant correlation ($p < 0.001$). Synthetic hematocrit had a high intraclass correlation coefficient (0.833). Kappa analysis for each region (Apex $\kappa = 0.88$, Mid $\kappa = 0.75$, Basal $\kappa = 0.87$) showed significant interobserver reliability ($p < 0.001$).

Conclusion: Synthetic hematocrit formulas for each vendor may help improve synthetic extracellular volume values without contrast administration.

Keywords: Cardiovascular diagnostic techniques (D003935), cardiac imaging techniques (D057791), magnetic resonance imaging (D008279), computer-assisted image processing (D007091).

INTRODUCTION

Cardiac Magnetic Resonance Imaging (CMR), in addition to assessing cardiac anatomy and myocardial motion, is a part of the main work-up to study myocardial pathology due to its superior tissue characterization and enhancement properties. Normal myocardium improves homogeneously and is lately washed out. However, myocardial scar tissue, fibrosis, or edema show late gadolinium enhancement due to retention of contrast in the extracellular space, which has an increased volume

in these pathologies [1]. Extracellular volume (ECV) indirectly indicates cardiac remodelling and is a quantitative parameter for prognosis of myocardial pathologies [2].

T1 mapping techniques grant quantification of fibrosis, but also allow the diagnosis of myocardial disease [3-5]. T1 mapping allows the estimation of the longitudinal relaxation time (known as the T1 value), i.e., the rate at which protons to regain their longitudinal magnetization after a radiofrequency

pulse. T1 mapping can be obtained via balanced steady-state free precession (SSFP) based shortened or non-shortened modified lock-locker inversion recovery (MOLLI) [5].

The evaluation of T1 values enables the ECV estimation. To calculate the ECV, the T1 values and the hematocrit value must be known, as shown in the formula [3]:

$$ECV = \left\{ \frac{1/T1_{myopost} - 1/T1_{myopre}}{1/T1_{bloodpost} - 1/T1_{bloodpre}} \right\} \times (100 - \text{hematocrit})$$

For correct estimation of ECV, patients blood samples must be taken at least within 24 hours of CMR [3], which may cause problems with immediate or retrospective evaluation of the patient. Therefore, synthetic hematocrit estimation using longitudinal relaxation rate of blood without blood sampling

was proved to be feasible [6]. The longitudinal relaxation rate (R1) is the frequency function of the T1 value (R1=1/T1) and the R1 value of blood has a linear relationship with the hematocrit [7, 8]. Hematocrit which is derived from precontrast T1 blood value is called synthetic hematocrit [6]:

$$\begin{aligned} \text{Synthetic Hematocrit}_{MOLLI} &= 866/T1_{bloodpre} - 0.1232 \\ \text{Synthetic Hematocrit}_{shMOLLI} &= 727.1/T1_{bloodpre} - 0.0675 \end{aligned}$$

This study was designed to test the applicability of synthetic hematocrit measurement in our own patient population by different observers.

ROI was drawn at the blood pool avoiding the papillary muscles to obtain native and postcontrast T1 values of the blood.

MATERIALS and METHODS

Approval for the study was obtained from Institutional Ethics Board. Informed consent was not obtained as this was a retrospective study.

Synthetic hematocrit values were estimated using the above formula. Both native and synthetic ECV values were also estimated using the native and synthetic hematocrit values, respectively.

Between November 2017 - July 2018, CMR including T1 mapping were retrospectively reviewed. Medical records of each patient were also collected and patients who had blood samples including hematocrit values within 24 hours of CMR imaging were included in the study.

Statistical analysis was performed using IBM SPSS Statistics 23 software. Simple linear regression was used to calculate the coefficient of determination and "Intraclass Correlation Coefficient" was used to evaluate the agreement between both measurements of hematocrit and ECV values. The compatibility of the synthetic ECV with the native ECV was analysed using "Kappa Analysis" after classifying both measurements with a cut-off value of 28%.

CMR was performed on a 1.5T scanner (Aera 1.5T, Siemens Healthcare, Germany). T1 mapping sequences were acquired using balanced SSFP-based MOLLI for basal, middle, and apical short-axis slices of the left ventricle. Imaging parameters for each patient were: 358x420 mm field of view, 1.0 number of excitation, 8.0 mm slice thickness, 276 msn time of repetition, 1.1 msn time of echo, 100 msn inversion time, and 35 degree flip angle.

Image analysis was performed using Syngo.via software (Siemens Healthcare, Germany). Region of interest (ROI) was manually drawn by a radiologist in basal, middle, and apical slices of the left ventricle to obtain both native and postcontrast T1 values of the myocardium. Epicardial fat and blood pool were avoided in ROI placement (Figure 1). Another

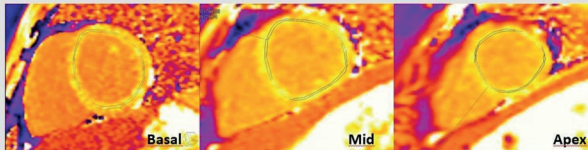
$$\text{Synthetic Hematocrit} = \frac{866}{T1_{bloodpre}} - 0,1232$$


Figure 1. For synthetic hematocrit estimation, the equation for MOLLI based T1 mapping is used. ROIs were manually drawn circumferential without coinciding with the subendocardial section. For each region, both pre- and postcontrast T1 values of blood and myocardium are collected as shown. Native and synthetic hematocrit and ECV values are compared for each region.

RESULTS

Sixty-one patients; 33 male and 28 female, fulfilled the aforementioned criteria and were included in the study. Indications for CMR imaging were non-ischemic cardiomyopathy (n=48), myocardial infarction (n=7), myocarditis (n=5) and constrictive pericarditis (n=1). The mean age was 52 years (range 11-80 years), and 7 patients were under 18 years of age.

Mean native hematocrit was 40.4%, while hemoglobin levels ranged from 12.1 gr/dl - 15.8 gr/dl. The mean synthetic hematocrit value was 40.1%. Also, the mean synthetic ECV values for each segment were 29.2% for basal segment, 28.1% for mid segment and 27.7% for apex segment while native values were 29.1%, 28.3% and 28.1% respectively (Table 1).

Synthetic and native hematocrit values showed significant correlation (p 0.001). Synthetic hematocrit had a high intraclass correlation coefficient (0.833).

Table 1. Mean native and synthetic Hematocrit and ECV values

Native	Mean Value	Synthetic	Mean Value
Hematocrit	40.4%	Hematocrit	40.1%
Basal ECV	29.2%	Basal ECV	29.1%
Mid ECV	28.1%	Mid ECV	28.3%
Apex ECV	27.7%	Apex ECV	28.1%

The synthetic ECV values had a high correlation. The intraclass correlation coefficient was 0.977 for the basal, 0.964 for the middle, and 0.981 for the apical region. No significant difference was found between basal, mid and apical ECV values (Table 2, Figure 2).

Synthetic ECV values were false-positive (over 28%) in four of the measurements, which were from apical (n=1), middle (n=2), and basal (n=1) layers. Synthetic ECV values were false-negative (below 28%) in 12 of the measurements derived from apical (n=3), middle (n=6), and basal (n=3) layers.

Table 2. Applicability of Synthetic Formula and Correlation Coefficient

	Synthetic Basal ECV	Synthetic Mid ECV	Synthetic Apex ECV	Synthetic Hematocrit
Intraclass Correlation Coefficient	0.977	0.964	0.981	0.833

Kappa analysis for each region showed significant interobserver reliability between synthetic and native ECV values (Apex $\kappa=0.88$, Mid $\kappa=0.75$, Basal $\kappa=0.87$; p 0.001) (Table 3).

DISCUSSION

Our results showed that synthetic ECV values estimated from three different regions of the myocardium showed excellent correlation with native ECV.

ECV represents the extracellular matrix and it is known to increase in various pathologies such as edema and fibrosis. The ECV value has an impact on both diagnosis and prognosis, which is why its evaluation has become a routine part of CMR examination.

Similar to our study, a couple of studies using both 1.5T and 3T magnets found a significant correlation between native and synthetic hematocrit and ECV values [9, 10]. Kammerlander et al. proposed their own synthetic hematocrit formula for their vendor, which had a stronger correlation compared to the previously published one [6].

On the other hand, two studies found moderate [11, 12] and one study found poor [13] However, the ECV values in these studies showed excellent correlation, which was explained by the formula, since only significant changes in the hematocrit value can have an effect on the ECV, while the other parameters remain constant. Although we found an excellent correlation between native and synthetic hematocrit, the correlation was stronger for ECV, which may be the result of this calculation.

Robison et al also estimated a ROC curve for synthetic ECV and compared it to native ECV and found only moderate diagnostic performance with a sensitivity of 71% and a specificity of 98%. Raucci et al. showed that 37% of patients were miscategorized when synthetic ECV was used. Shang et al. also found significant miscategorization

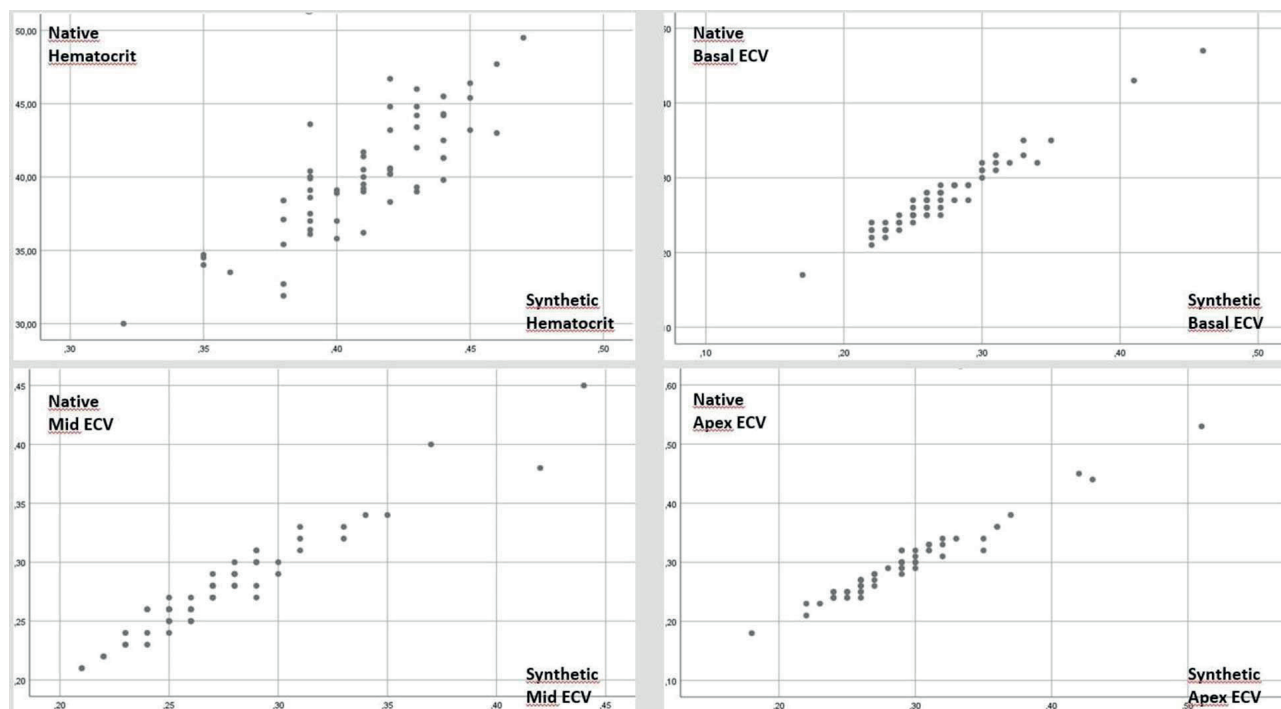


Figure 2. The graphs, acquired via simple regression analysis. The proximity of each dots shows the high validity. Note that the validity for synthetic estimation is higher on ECV calculation.

Table 3. Compatibility of ECV and Hematocrit

	Constant	Unstandardized Coefficient	p	R ²	κ
Synthetic Basal ECV	-0.005	1.033	<0.001	0.953	0.87
Synthetic Mid ECV	0.013	0.966	<0.001	0.930	0.75
Synthetic Apex ECV	-0.955	1.048	<0.001	0.962	0.88
Synthetic Hematocrit	-5.427	1.112	<0.001	0.695	

(8-18%) of patients with synthetic ECV. In our study, miscategorization was present in 6.5-13.1% of subjects, 6.5% for the apical and basal regions, 13.1% for the middle region; and overall, false negatives were higher than false positives, and both were higher in measurements from the middle region compared to the rest. Raucci et al. also had measurements from the middle of the left ventricle, which could be the result of a high proportion of false categorizations. This could lead us to consider whether ROI placement in the myocardium could affect the accuracy of synthetic hematocrit and ECV calculations.

The small sample size and heterogeneous group including patients under 18 years of age are the main limitations of our study. In addition, only one MRI machine with 1.5 Tesla was used in this study. Larger estimation studies with formulas for

the vendor used in the study are needed to obtain accurate results for synthetic ECV calculation [11, 13]. Further studies involving different regions of the myocardium may also suggest localization for accurate measurements of synthetic ECV.

Synthetic ECV values have a significant correlation with native values, but large-scale studies with measurements from different regions of the myocardium need to be performed to find more accurate results. Specific hematocrit formulas for each manufacturer could also help to improve synthetic ECV values.

CONFLICT of INTEREST STATEMENT

The authors have no conflict of interest.

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