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Importance of Sex-Specific Regression Models to Estimate Synthetic Hematocrit and Extracellular Volume Fraction

Quantification of the extracellular volume (ECV) requires hematocrit to be measured from the patients. A linear association between blood pool native T1 and hematocrit has been shown to estimate hematocrit and ECV (termed synthetic hematocrit and ECV, respectively) (1). However, the variabilities in synthetic hematocrit and ECV due to age and sex are not well described. We aimed to compare measured versus synthetic hematocrit and ECV in hypertensive patients and examine the effects of age, sex, and myocardial hypertrophy on the differences observed. We hypothesized sex-specific regression models improve estimation of synthetic hematocrit and ECV because of sex-related differences in blood pool native T1.

In 143 hypertensive patients (91 men; median age 60 years [interquartile range: 51 to 66 years]) from the REMODEL (Response of the Myocardium to Hypertrophic Conditions in the Adult Population) study (NCT02670031), myocardial T1 mapping with the modified Look-Locker inversion recovery sequence was performed at 1.5-T (MAGNETOM Aera, Siemens Healthineers, Erlangen, Germany). Native and 20-min post-contrast myocardial T1 maps were acquired using the acquisition scheme of 5(3)3 and 4(1)3(1)2, respectively. Conventional ECV values of the basal and midventricular short-axis slices were calculated using measured hematocrit on scan day (2). Synthetic hematocrit and ECV of the same slices were assessed automatically with an inline module (Siemens WIP#1041). Left ventricular hypertrophy (LVH) was defined according to age- and sex-specific normal reference ranges (3).

A total of 286 measured and 249 synthetic ECV maps were analyzed. The inline module failed to generate 20 ECV maps and 17 ECV maps were excluded from analysis because of suboptimal motion correction. Synthetic hematocrit overestimated measured hematocrit (0.457 ± 0.026 vs. 0.421 ± 0.037; $p < 0.0001$) by 8.6 ± 7.7%. A greater mean difference was observed in women (12.3 ± 7.7% vs. 6.5 ± 6.9%; $p < 0.0001$) and in older individuals (≥60 years of age vs. <60 years of age: 9.6 ± 8.2% vs. 7.6 ± 7.0%; $p = 0.03$). The magnitude of overestimation in synthetic hematocrit was similar in those without ($n = 106$; 8.8 ± 7.8%) and with ($n = 37$; 8.1 ± 7.3%) LVH ($p = 0.52$). Consequent to the higher synthetic hematocrit estimated, the synthetic ECV was lower compared with measured values (0.248 ± 0.020 vs. 0.264 ± 0.026; $p < 0.0001$) (Figure 1A). Underestimation of synthetic ECV was worse in women (−8.9 ± 8.5% vs. −4.3 ± 6.0%; $p < 0.0001$) and in older individuals (−6.8 ± 7.4% vs. −5.0 ± 7.2%; $p = 0.05$). LVH status had similar magnitude of underestimation in synthetic ECV ($p = 0.29$).

Synthetic hematocrit was estimated using blood pool native T1 values specific to our cohort:

$$\text{All patients: hematocrit} = 574.7 \cdot (1/T1_{\text{blood pool}}) + 0.05369$$

$$\text{Women: hematocrit} = 258.5 \cdot (1/T1_{\text{blood pool}}) + 0.2343$$

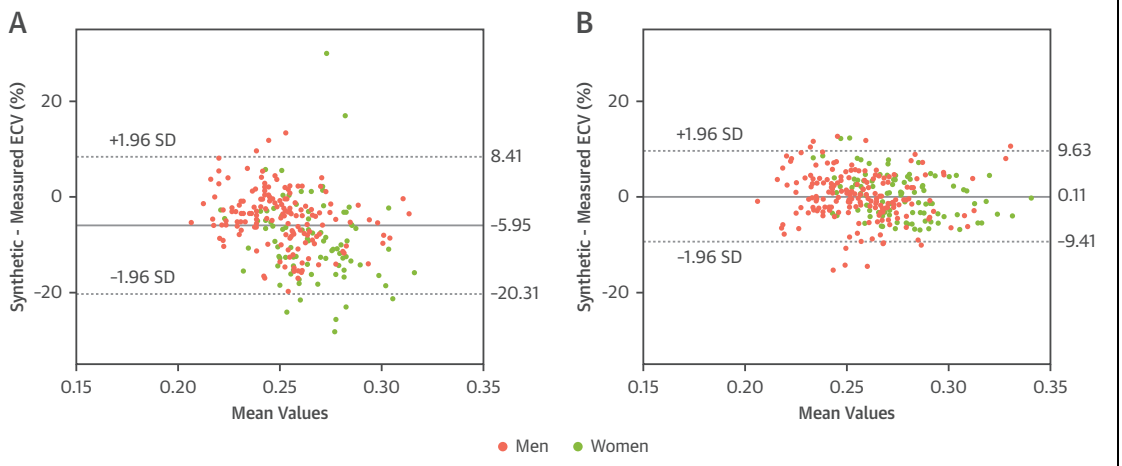
$$\text{Men: hematocrit} = 592.7 \cdot (1/T1_{\text{blood pool}}) + 0.05232$$

Using a single locally derived regression model, synthetic hematocrit (0.421 ± 0.019) and ECV (0.263 ± 0.022) were similar compared with measured values. A small but clear sex-related difference between synthetic and measured ECV remained: synthetic ECV underestimated measured ECV in women (−3.1 ± 4.9%) and overestimated measured values in men (1.9 ± 5.0%; $p < 0.0001$). No clinically important differences in estimation were seen with age ($p = 0.04$) and LVH status ($p = 0.30$).

Women had higher blood pool native T1 compared to men (1,592 ± 76 ms vs. 1,556 ± 77 ms; $p < 0.001$). Using sex-specific regression models, synthetic hematocrit (0.421 ± 0.024) and ECV (0.263 ± 0.024) (Figure 1B) were similar compared with measured values. Sex-specific regression models minimized differences between synthetic and measured values related to sex (women vs. men: 0.1 ± 4.5% vs. 0.1 ± 5.0%), age (≥60 years of age vs. <60 years of age: −0.3 ± 5.5% vs. 0.5 ± 4.1%; $p = 0.15$), and LVH status (without LVH vs. with LVH: −0.1 ± 4.9% vs. 0.6 ± 4.8%; $p = 0.33$).

A single regression model is not ideal in estimating hematocrit and ECV in both sexes. Instead, sex-specific regression models improved accuracy by correcting for sex-related differences in blood pool native T1. A recent study reported misclassification of patients using synthetic ECV and recommended

FIGURE 1 Comparison of Synthetic and Measured ECV Using Different Regression Models



(A) Based on the published model, synthetic extracellular volume (ECV) underestimated measured ECV with wide limits of agreement (mean difference −5.95 ± 7.33%). **(B)** Conversely, the difference was small using sex-specific regression models (mean difference 0.11 ± 4.85%).

measured hematocrit to be used (4). In the absence of measured hematocrit, we suggest sex-specific regression models of synthetic hematocrit unique to the population be established and tested before use. The variabilities in synthetic ECV (±4% to 6% based on our models) should be accounted for if used to monitor disease progression or treatment response. The study has only examined hypertensive patients that might limit generalizability. The relatively low number of women and the range of hematocrit (0.309 to 0.535) studied are other potential study limitations.

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Long-Term Outcome of Patients With Low/Intermediate Risk Myocarditis Is Related to the Presence of Left Ventricular Remodeling in Addition to the MRI Pattern of Delayed Gadolinium Enhancement

Acute myocarditis (AM) refers to a series of heterogeneous clinical manifestations, ranging from asymptomatic course, heart failure, arrhythmia, to cardiogenic shock. Low-risk patients according to conventional criteria remain the most common form, and 80% of patients are discharged from hospital with normalized left ventricular (LV) function (1). Nevertheless, at long-term follow-up, all types of AM may lead to adverse outcomes, including progression to dilated cardiomyopathy.

The presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) has been