Can a MR Imaging Scanner Accurately Measure Hematocrit to Determine ECV Fraction?*

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Focal fibrosis, most due to myocardial infarction, is readily identified by cardiac magnetic resonance (CMR) using widely validated late gadolinium enhancement methods. However, many common conditions of the heart, ranging from hypertrophic cardiomyopathy to idiopathic dilated cardiomyopathy or myocarditis, are histologically characterized by diffuse, interstitial myocardial fibrosis. In these conditions, “T1 mapping” may be used to determine abnormalities in the T1 relaxivity of the myocardium either before or after administration of a gadolinium-based CMR contrast agent (1).

The term T1 mapping involves measuring the T1 time, or spin-lattice relaxation time, on a pixel-by-pixel basis over the entire image field of view. The T1 relaxation time is the time (in milliseconds) for a tissue to obtain approximately 63% of its longitudinal relaxation (parallel to the main magnetic field). Most current magnetic resonance imaging (MRI) scanners include software that allows routine measurement of T1 time for each pixel in a slice of tissue, thus providing a “map” of myocardial T1 times. For reference, the normal T1 time of the heart is approximately 1,000 ms at 1.5-T (2). For comparison, the T1 time of fat (250 ms) is much shorter than myocardium, whereas the T1 time of blood is approximately 1,400 ms. The T1 time of blood depends on temperature, field strength, hematocrit, and oxygenation level (at 3.0-T and higher field strengths) (3).

The term “native T1 time” has been used in the CMR literature when referring to noncontrast CMR images. When the myocardium is replaced by diffuse fibrosis, the native T1 time increases slightly, for example, by 10% to 20% (e.g., dilated and hypertrophic cardiomyopathy (4), whereas post-gadolinium T1 time decreases also by 10% to 20% or so. However, change in T1 time is not specific for fibrosis. Both the native and post-gadolinium T1 times of the myocardium are also altered by other substrates that might occur in the myocardial interstitial space such as edema, lipid (as in Anderson-Fabry disease (5)), iron, or amyloid (6).

The T1 time is reflective of the composite status of both myocytes and interstitium. Using CMR, the extracellular volume (ECV) of the myocardium may be estimated by measuring pre- and post-contrast T1 time of blood and myocardium and the hematocrit. The concentration of gadolinium is directly related to the difference between pre-contrast and post-contrast reciprocal values of T1 (T1 = 1/R, where R indicates relaxivity), leading to the following equation (7,8):

\[ \text{ECV}_{\text{myocardium}} / \Delta R_1^{\text{myocardium}} = \text{ECV}_{\text{blood}} / \Delta R_1^{\text{blood}} \]

Because the ECV of blood is \((1 - \text{hematocrit})\), ECV of myocardium can be calculated as follows:

\[
\text{ECV}_{\text{myocardium}} = \frac{(1 - \text{hematocrit}) \times \left[ \frac{1}{T_1^{\text{myocardium post-contrast}}} - \frac{1}{T_1^{\text{myocardium pre-contrast}}} \right]}{\left[ \frac{1}{T_1^{\text{blood post-contrast}}} - \frac{1}{T_1^{\text{blood pre-contrast}}} \right]}
\]

where hematocrit is expressed as a fraction between 0 and 1. As a percentage of tissue volume, the normal ECV of the myocardium ranges from about 21% to 31%, with a mean of about 25% to 26% (9). Elevated ECV values have been reported in both primary and systemic cardiac disease, including dilated and hypertrophic cardiomyopathy, aortic stenosis, cardiac AL amyloidosis, and myocardial infarction (10).
ECV is reported to be elevated in hypertrophic cardiomyopathy sarcomere mutation carriers even in the absence of left ventricular hypertrophy (11), indicating its value in early disease detection before clinical manifestation. ECV may also be useful to assess cardiotoxicity from anthracycline-based chemotherapy (12) or to monitor therapy success of fibrosis-modulating therapies such as renin-angiotensin antagonists. ECV has been shown to predict all-cause mortality in certain populations (13). ECV has also been identified as a viable surrogate marker of extracellular matrix expansion in research applications for heart failure (14).

An obstacle in CMR studies in determining myocardial ECV has been determining the hematocrit value (15). The hematocrit can be performed by inexpensive laboratory equipment incorporating optical or electrical methods and typically costs on the order of $10 to $30 per test; point-of-care testing costs are about $1 each test kit. The hematocrit may be obtained along with laboratory tests of renal function before CMR, but not all patients require renal function tests. For stable outpatients, renal function laboratory values are accepted to be representative of renal status for up to 30 days before CMR examination, but hematocrit values may fluctuate markedly during this period.

**In this issue of JACC, Treibel et al. (16) propose that hematocrit values may be derived directly from blood measurements during the CMR examination itself. This would provide great efficiency for ECV determination by CMR. The authors plotted laboratory determined hematocrit versus relativity (R1) of blood determined by 2 different CMR pulse sequences (Modified Look-Locker Inversion recovery and Shortened Modified Look-Locker Inversion recovery) in 213 study subjects. R1 was linearly related to hematocrit with a correlation coefficient of 0.51 (Modified Look-Locker Inversion recovery) and 0.45 (Shortened Modified Look-Locker Inversion recovery). Interestingly, despite these relatively low correlation coefficients, ECV using conventional hematocrit measure was closely related to ECV using a CMR “synthetic” hematocrit derived directly from the images (R² = 0.97). The difference between ECV by CMR versus conventional ECV was within about 10% of the mean ECV in 95% of cases. Thus, for practical purposes, the CMR “synthetic” ECV and the conventionally determined ECV were interchangeable: Treibel et al. (16) demonstrated this by showing nearly identical correlation coefficients between ECV with either method and collagen volume fraction in 18 patients with aortic stenosis. Similarly, both synthetic and conventional ECV were equally well related to risk of hospitalization for heart failure or death in 1,172 subjects.

It seems peculiar that despite low agreement between CMR hematocrit and conventional hematocrit (R² = 0.45 to 0.51), ECV by CMR hematocrit correlated very well with ECV by conventional hematocrit (R² = 0.97). The reasons for this are not readily explained by the provided data. One possibility is that the hematocrit varies over a relatively small range (by a factor of 1.4, from 35% to 48%, Treibel et al. [16] Figure 1), whereas ECV varied by a factor of 4-fold in their patients (about from 20% to 80%, Treibel et al. [16] Figure 2). Thus, terms other than hematocrit in the ECV equation may outweigh small variations in hematocrit. Indeed, very high values of ECV greater than about 0.45 are usually seen in focal myocardial scar—focal scar cases are not typically those situations where ECV is of great value. In this regard, ECV, a complex ratio, simply does not change much in the presence of large amounts of diffuse fibrosis: for example, the data of Treibel et al. (16) show that despite 400% variation in collagen fraction in aortic stenosis patients (from 10% to 40%), the ECV only changes by a factor of about 60% (from 0.25 to 0.4).

CMR researchers and clinicians may wish to instantly switch to the “synthetic” ECV method proposed by Treibel et al. (16) on the basis of these results. Unfortunately, there are several caveats that need further assessment. First, their results apply only to the Siemens pulse sequence software MRB17 using pulse sequence parameters shown in the data supplement provided by the authors. Calibrations for other pulse sequences will need similar validation. Also, the results of Treibel et al. have only been validated at 1.5-T CMR; at 3.0-T MRI, there are significant differences in arterial and venous T1 values by CMR (17). The unexpectedly low correlation of conventional and CMR determined hematocrit needs further explanation. Flow artifacts on CMR in the ventricular cavity could cause unexpected variations. Also, the authors show unexpectedly low test/retest results for conventional hematocrit of 10% for blood samples taken with a median time delay of 4 h. However, in the literature, a high precision for hematocrit measurements is reported. The coefficient of variation of 1.1% for measurements for standard laboratory assays of hematocrit has been reported (18). Significant diurnal, postural, and post-prandial variation of the hematocrit has been demonstrated as well as changes with hydration and exercise (19,20). The median time delay of 4 h in test/retest for hematocrit in the current study might explain
the variation of the measurements of conventional hematocrit.

Ordinarily, we would not think of using an approximately $1.5$ million CMR scanner to replace a several thousand dollar, highly accurate piece of laboratory equipment to measure hematocrit. Treibel et al. (16), however, have convincingly shown that either method works equally well in their hands and can provide excellent efficiencies for CMR assessment of diffuse fibrosis. This study also reinforces that the conventional hematocrit should be obtained in close proximity to the time of the actual CMR scan to provide best accuracy. For research studies where blood tests are already routinely being obtained, it seems prudent to continue to obtain gold standard hematocrit values when feasible in order to reduce error in CMR ECV values. CMR is the only noninvasive technique that has been shown to provide an index of diffuse myocardial fibrosis, so the work of Treibel et al. (16) is likely to greatly enhance CMR research studies of cardiomyopathy. The approach of Treibel et al. (16) may also ultimately provide a means to bridge the results of research studies to clinical applications when determination of extracellular volume fraction is of value for clinical decision making.

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REFERENCES


