Synthetic extracellular volume fraction—state of play

Thomas A. Treibel · James C. Moon

Received: 5 October 2017 / Accepted: 12 October 2017 / Published online: 7 November 2017
 © Springer-Verlag GmbH Austria 2017

Comment on: Kammerlander et al. Extracellular volume quantification by cardiac magnetic resonance imaging without hematocrit sampling—ready for prime time? *Wien Klin Wochenschr.* 2017 Oct 4; <https://doi.org/10.1007/s00508-017-1267-y>.

Cardiac function is determined by an interplay between myocardial cellular and interstitial components. Remodelling of the extracellular matrix (ECM) is a continuous, dynamic process occurring in health and disease, including adaptive and adverse remodelling. The advent of cardiovascular magnetic resonance (CMR) offered first accurate quantification of ventricular geometry and function, later myocardial tissue characterization for focal fibrosis (with late gadolinium imaging) and now quantification of diffuse ECM expansion (diffuse fibrosis or infiltration) by T1 mapping via the extracellular volume fraction (ECV) technique [1]. The ECV technique is a promising imaging biomarker [2], and has clear benefits in infiltration, particularly amyloidosis, but also for diffuse fibrosis with early data suggesting that ECV is a prognostic indicator with a power equivalent to, but independent of that delivered by another common biomarker, the left ventricular ejection fraction (LVEF) [3]. T1 mapping measures the longitudinal relaxation time, which is altered by myocardial fibrosis, edema, iron overload and infiltrative diseases, such as amyloidosis [1]. After administration of a gadolinium-

based extracellular contrast agent, T1 is shortened. The ECV is derived from the ratio of changes in signal in myocardium and blood precontrast and postcontrast. Because the contrast partitions the extracellular space (between myocytes and between red cells, respectively), the ratio of signal change in blood and myocardium is the ratio of the extracellular water in the two compartments. ECV can be simply calculated, integrating blood extracellular water into the equation (=1 minus hematocrit). This step adds value, but slows clinical adoption, because a blood test and post-processing is required.

Recently, we developed a new approach that quantifies ECV without the hematocrit (Hct) [4]. It has long been established that blood T1 is higher in anemia (technically, R1, the inverse of T1 is proportional to blood Hct) [5]; therefore, a synthetic Hct and synthetic ECV can be derived. This we found was highly correlated to conventional ECV, the histologic gold standard collagen volume fraction and predicted outcome. Because pre-T1 maps and post-T1 maps can be co-registered, and blood is detectable (blood goes from longest T1 to shortest T1 before to after contrast), we could implement an inline tool on a clinical CMR scanner creating an immediate ECV map [4]. The synthetic technique has been reproduced by Fent et al. on different CMR vendor platforms at 1.5 and 3.0 T [6], but Raucci et al. raised concerns over the potential miscategorization of individual patients with this approach [7].

In this current work Kammerlander et al. validated the synthetic ECV methodology from an experienced center in Vienna where they have a T1 mapping registry of 513 consecutive patients. Their methodology was sound: venous Hct was measured just before the CMR scan. They used a slightly different T1 mapping sequence (sampling scheme in heartbeats rather than seconds). They used a derivation cohort of 200

T. A. Treibel, PhD · J. C. Moon, MD (✉)
 Barts Heart Centre, St Bartholomew's Hospital, 2nd Floor,
 King George V Block, London, EC1A 7BE, UK
james.moon@bartshealth.nhs.uk

T. A. Treibel, PhD · J. C. Moon, MD
 Institute of Cardiovascular Science, University College
 London, London, UK

to derive a local blood R1 to hematocrit equation. As found previously, synthetic Hct was moderately correlated with actual Hct ($R = 0.55$), but synthetic ECV highly correlated ($R = 0.96$) with actual ECV. On Bland-Altman analysis, the mean difference was 0.007% with limits of agreement between -4.32 and 4.33% for ECV and -0.216% with limits of agreement between -8.34 and 7.91 for Hct. The authors therefore concluded that the synthetic ECV methodology is translatable to other centers, but as highlighted in the original work, it requires a local derivation of the R1:Hct relationship as it is unlikely that the T1 mapping sequence, CMR scanner, and Hct machine are identical. The correlation was weaker ($r^2 = 0.35$) than in the original paper ($r^2 = 0.51$) and by Fent et al. ($r^2 = 0.50$), which may be due to a narrower range of Hct (median 40%, interquartile range IQR 37.1–43.0%) underrepresenting extreme values. Furthermore, no reproducibility data for synthetic or laboratory Hct were available. This is important as prior work suggested that Hct measurement contributes significant variability and potentially more than the differences contested between T1 mapping approaches.

At another level, the ECV approach is an example of anchoring an indirect non-invasive cardiac measurement with a more direct peripheral body measurement, rather like measuring the brachial blood pressure, doing aortic valve velocity measurement and deriving intracavity pressures (the valvuloarterial impedance). Here, the peripheral venous blood sample is a surrogate for an intraventricular cavity sample (i.e. substituting the blood pool). This assumption may not be robust: indeed, the $R1_{\text{blood}}$ measured in the ventricular cavity may be both more accurate and precise than the peripheral venous sampling, explaining why the synthetic ECV performance appears better than it should given the moderate correlation of R1 and peripheral Hct [3]. There are, however, other sources that affect the relaxation rate of blood, such as flow, oxygen content, body temperature and contributions from other biological variables, and these need further investigation (e.g. red cell shape and size, other macromolecules, and even added substances, e.g. intravenous iron or other paramagnetic substances) [4]. Blood iron has been reported as having a strong influence on blood T1 in health [8], and should confound, although Hct and serum are frequently correlated which may mitigate.

Rauci et al. raised concerns that the use of synthetic Hct for the calculation of ECV may result in miscategorization of individual patients [7]. They found in 114 children and young adults undergoing CMR at 1.5 T using a 5(3)3 modified look-locker inversion recovery (MOLLI) precontrast and a 4(1)3(1)2 MOLLI postcontrast that a local derivation is crucial, but even with a local derivation there was only a weak correlation between $R1_{\text{blood}}$ and Hct ($r^2 = 0.16$, $p < 0.001$), resulting in worse correlation between measured and synthetic ECV with worse limits of agreement (be-

tween -10% and 8%). They showed that using a cut-off for abnormal ECV of 28.5% (evaluating for accuracy compared to the measured ECV) identified 23% miscategorizations with a locally derived model (37% when applying the published model, although this would not be recommended anyway). They therefore concluded that synthetic Hct and ECV may have some utility in large retrospective research cohorts where measured Hct data are not available; however, caution should be taken if looking at individual patient data in such research cohorts, and validation with measured Hct should be made when available. Concerns regarding miscategorization therefore need to be addressed in future studies.

The T1 mapping field is rapidly advancing to the point of widespread clinical utility [1]. New guidelines are in press [9], ECV maps are now routine in some centers, but ECV standardization is on-going. Quality control systems, commercial sequences, mega-registries (e.g. Global CMR Registry, HCM Registry, UK Biobank) are in progress, and will provide high volumes of new insights in what is now the most active CMR research area. Inline synthetic ECV, automatically generated during scanning, ready for immediate analysis is an attractive further incremental development. The work of Kammerlander et al. should be applauded, and the technique appears now close to being ready for widespread adoption.

Funding TAT and JCM are directly and indirectly supported by the University College London Hospitals NIHR Biomedical Research Centre and Biomedical Research Unit at Barts Hospital, respectively.

Conflict of interest T.A. Treibel and J.C. Moon declare that they have no competing interests.

References

1. Moon JC, et al. Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson*. 2013;15:92.
2. Schelbert EB, et al. Therapeutic targets in heart failure: refocusing on the myocardial interstitium. *J Am Coll Cardiol*. 2014;63(21):2188–98.
3. Wong TC, et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. *Eur Heart J*. 2014;35(10):657–64.
4. Treibel TA, et al. Automatic measurement of the myocardial interstitium: synthetic extracellular volume quantification without hematocrit sampling. *JACC Cardiovasc Imaging*. 2016;9(1):54–63.
5. Fullerton GD, Potter JL, Dornbluth NC. NMR relaxation of protons in tissues and other macromolecular water solutions. *Magn Reson Imaging*. 1982;1(4):209–26.
6. Fent GJ, et al. Synthetic myocardial extracellular volume fraction. *JACC Cardiovasc Imaging*. 2017; <https://doi.org/10.1016/j.jcmg.2016.12.007>.

7. Raucci FJ Jr., 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(1):58.
8. Rosmini S, et al. Hematocrit, iron and HDL-cholesterol explain 90% of variation in native blood T1. *J Cardiovasc Magn Reson.* 2016;18(1):O86.
9. Messroghli DRM, Moon JC, Ferreira V, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert E, Taylor AJ. Clinical recommendations for cardiac mapping of T1, extracellular volume, T2, and T2*: 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; <https://doi.org/10.1186/s12968-017-0389-8>.