T1 or ECV? Depends on the methods

Vanessa M. Ferreira, SB MD DPhil[1], Stefan K. Piechnik, MScEE, PhD, DSc[1]

[1]Oxford Centre for Clinical Magnetic Resonance Research, Radcliffe Department of Medicine, University of Oxford

Brief title: T1 or ECV?

Address: Level 0 – OCMR, John Radcliffe Hospital,
Headley Way, Oxford,
United Kingdom,
OX39DU

Telephone: +44 1865 221172

Fax: +44 1865 740449

Email: vanessa.ferreira@cardiov.ox.ac.uk

Disclosure: Drs. Ferreira and Piechnik acknowledge support from the National Institute of Health Research (NIHR) Biomedical Research Centre, Oxford, and the British Heart Foundation Centre of Research Excellence, Oxford. Dr. Ferreira is funded by the British Heart Foundation. Dr. Piechnik has patent authorship rights for U.S. patent 9285446 B2 (systems and methods for Shortened Look Locker Inversion Recovery [Sh-MOLLI] cardiac gated mapping of T1), granted March 15, 2016; all rights transferred to Siemens Medical.

In patients with heart failure due to non-ischemic cardiomyopathies, the value of cardiovascular magnetic resonance (CMR) imaging in predicting adverse clinical outcomes is well-established (1, 2). In addition to accurate assessment of cardiac structure and function, CMR offers superior non-invasive myocardial tissue characterization compared to other cardiac imaging modalities. Late gadolinium enhancement (LGE) imaging helps to distinguish between ischemic and non-ischemic heart disease via distinctive patterns of focal fibrosis. However, LGE analysis relies on an area of presumed normal myocardium for nulling, in order to provide image contrast against areas of abnormality, which renders LGE suboptimal for detecting diffuse myocardial fibrosis (DMF).

CMR T1- relaxometry offers a non-invasive, directly quantitative method to characterize diffuse pathology, without the need for any presumed areas of normal tissue. The extracellular volume (ECV) may be quantified by measuring T1 before and after the administration of an extracellular gadolinium-based contrast agent, adjusting to the individual's blood hematocrit. An expanded ECV may act as a surrogate marker of interstitial fibrosis, after excluding potential confounders, such as cardiac amyloidosis, edema or ischemia (which can increase the coronary vascular space). DMF is of major interest in the characterization of patients with heart failure, as it confers prognostic information, and may be a novel therapeutic target (3).

The prognostic value of CMR T1 and ECV

In patients with dilated cardiomyopathy (DCM), the presence of LGE has prognostic power, associated with increased cardiovascular mortality, ventricular arrhythmic events and rehospitalization for heart failure (1). CMR myocardial T1 and ECV have also demonstrated

prognostic value in both ischemic and non-ischemic heart disease (4), including patients with cardiomyopathies and heart failure (5-9). Potential pathophysiologic mechanisms that increase myocardial T1 and ECV in DCM include replacement fibrosis, diffuse interstitial myocardial fibrosis (3) and myocardial inflammation or chronic myocarditis.

In this issue of the *Journal*, Vita et al. studied patients with dilated cardiomyopathy (most with coronary disease/ischemia ruled out by a combination of invasive angiography, non-invasive stress testing, or a combination of clinical criteria with cardiac investigations), using CMR native T1-mapping, ECV, LGE and partition coefficient lambda (gad). The T1-mapping used the cine Look-Locker approach (10), with image analysis performed on 3 short-axis left ventricular slices, divided into 6 segments. Signal intensity time curves for each of the 18 segments were used for fitting into an analytical expression for the inversion recovery to obtain the effective relaxation coefficient T1*, subsequently converted into an estimate of tissue T1. LGE images were semi-quantified by using signal intensity (SI) threshold cut-offs of 2-SD, 3-SD, 4-SD and 6-SD above the mean SI of remote myocardium on the same slice. CMR-derived biomarkers were associated with MACE after a median of 3.8 years. The investigators found that mean ECV, as well as extent of ECV, predicted heart failure outcomes better than native T1 or LGE. For every 10% increase, mean ECV portended a 2.8-fold adjusted increase risk to MACE.

The strengths of this study and discussion

In terms of CMR tissue characterization, the presence of non-ischemic LGE in DCM has already been established to predict worse clinical outcomes in heart failure patients (1). Vita et al. make an important contribution to building the evidence base for the prognostic value of CMR T1-mapping, showing that ECV predicts heart failure outcomes in DCM, and, in their

material, better than native T1 and LGE. Interestingly, Puntmann et al. had also examined the prognostic value of T1, ECV and LGE in a multicentre study of DCM patients, and found that native T1 was the sole independent predictor of all-cause and HF composite endpoints in multivariable analyses. They used a Modified Look-Locker Inversion recovery (MOLLI) variant (8).

This point on T1 method differences between two studies with seemingly opposite findings deserves further discussion. Although there may be differences in patient selection between the two studies, the use of different T1-mapping methods may be an important factor that can produce differing results. The T1-mapping method used by Vita et al. was a cine Look-Locker technique with inversion preparation. It may be argued that, due to relatively narrower range of inversion times, it is less optimal for the quantification of native T1 values, with about twice as much noise when compared to the more recent MOLLI T1-mapping sequences (11, 12). The results of the study are reassuring in that the traditional Look-Locker method remains robust in ECV quantification, and that ECV has added value, with clear correlation and prediction of important clinical outcomes that were not entirely driven by LGE; however, the use of the cine Look-Locker method may have disadvantaged the performance of native T1 in this study. With the availability of modern pixel-wise T1-mapping methods optimised to measure both native and post-contrast T1 ranges for ECV quantification with equal precision, further studies may shed more light on how much the achieved results depend on the choice of methods.

Another strength of the study by Vita et al. was that it utilized spatial information from the Look-Locker T1 and ECV quantification, rather than only using average T1 or ECV values for the whole myocardium or just septum typically seen in most published reports. The

investigators attempted to glean spatial information by dividing the myocardium into 6 segments, showing that ECV in the anteroseptal location had the strongest association with MACE, and that the number of segments with high ECV also showed a linear increase in annual MACE rates. The approach of extracting spatial information, extent and patterns of myocardial abnormalities should also be applied to contemporary pixel-wise T1-mapping, which can not only provide additional information beyond conventional LGE tissue characterization, but may begin to help distinguish different disease entities or severity within a single disease (13, 14).

Summary and future directions

CMR T1- and ECV-mapping continue to demonstrate clinical utility in advanced myocardial tissue characterization and predicting important outcomes in common cardiac conditions. To be truly useful in daily clinical practice, we need methods that are optimized for detecting subtle myocardial changes beyond those currently afforded by conventional tools, and advanced image analysis that are not cumbersome or time-consuming, preferably implemented inline to provide immediate visual diagnostics for busy clinicians. More importantly, CMR mapping needs to demonstrate added value that either impacts on clinical decision-making, saves costs and/or lives. This is a growing field of research still rapidly accumulating evidence, and this study by Vita et al. represents another achievement for CMR parametric mapping as a new technology that is expected to change clinical practice.

References

1. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The Prognostic Value of Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging in Nonischemic Dilated Cardiomyopathy: A Review and Meta-Analysis. JACC Cardiovasc Imaging. 2018;11(9):1274-84.

2. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The Role of Cardiovascular Magnetic Resonance Imaging in Heart Failure. J Am Coll Cardiol. 2009;54(15):1407-24.

3. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol. 2011;57.

4. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: 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;19(1):75.

5. Wong TC, Piehler K, Meier CG, Testa SM, Klock AM, Aneizi AA, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation. 2012;126.

6. Wong TC, Piehler KM, Kang IA, Kadakkal A, Kellman P, Schwartzman DS, 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.

7. Duca F, Zotter-Tufaro C, Kammerlander AA, Panzenbock A, Aschauer S, Dalos D, et al. Cardiac extracellular matrix is associated with adverse outcome in patients with chronic heart failure. Eur J Heart Fail. 2017;19(4):502-11.

8. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S, et al. T1-Mapping and Outcome in Nonischemic Cardiomyopathy: All-Cause Mortality and Heart Failure. JACC Cardiovasc Imaging. 2016;9(1):40-50.

9. Schelbert EB, Piehler KM, Zareba KM, Moon JC, Ugander M, Messroghli DR, et al. Myocardial Fibrosis Quantified by Extracellular Volume Is Associated With Subsequent Hospitalization for Heart Failure, Death, or Both Across the Spectrum of Ejection Fraction and Heart Failure Stage. J Am Heart Assoc. 2015;4(12).

10. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. Circulation Cardiovascular imaging. 2010;3(6):727-34.

11. Nacif MS, Turkbey EB, Gai N, Nazarian S, van der Geest RJ, Noureldin RA, et al. Myocardial T1 mapping with MRI: comparison of look-locker and MOLLI sequences. J Magn Reson Imaging. 2011;34(6):1367-73.

12. Piechnik SK, Jerosch-Herold M. Myocardial T1 mapping and extracellular volume quantification: an overview of technical and biological confounders. 2018;34(1):3-14.

13. Ferreira V, Piechnik S, Dall'Armellina E, Karamitsos T, Francis J, Ntusi N, et al. Native T1-mapping detects the location, extent and patterns of acute myocarditis without the need for gadolinium contrast agents. J Cardiovasc Magn Reson. 2014;16(1):36.

14. Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NA, et al. Pheochromocytoma Is Characterized by Catecholamine-Mediated Myocarditis, Focal and Diffuse Myocardial Fibrosis, and Myocardial Dysfunction. J Am Coll Cardiol. 2016;67(20):2364-74.