New Generation Cardiac Parametric Mapping: the Clinical Role of T1 and T2 Mapping

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Introduction

Cardiovascular magnetic resonance (CMR) is an essential tool in cardiology and excellent for cardiac function and perfusion. However, a key, unique advantage is its ability to directly scrutinize the fundamental material properties of myocardium – 'myocardial tissue characterization'.

Between 2001 and 2011, the key methods for tissue characterization have been sequences 'weighted' to a magnetic property – T1-weighted imaging for scar (LGE) and T2-weighted for edema (area at risk, myocarditis). These, particularly LGE imaging, have changed our understanding and clinical practice in cardiology.

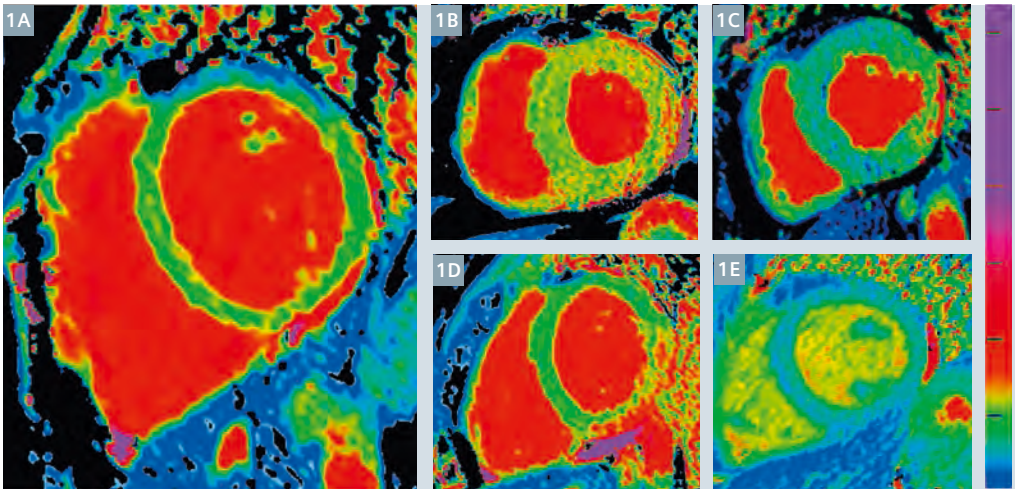
However, there are limitations to these approaches: Both are difficult to quantify – the LGE technique in particular is very robust in infarction, but harder to quantify in non-ischemic cardiomyopathy. A more fundamental difference is that sequences are designed to optimize contrast between 'normal' and abnormal – a dichotomy of health and disease. As a result, global myocardial pathologies such as diffuse infiltration (fibrosis, amyloid, iron, fat, pan-inflammation) are missed.

Recently, rapid technical innovations have generated new 'mapping' techniques. Rather than being 'weighted', these create a pixel map where each pixel value is the T1 or T2 (or T2*), displayed in color. These new sequences are single breath-hold, increasingly robust and now widely available. With T1 mapping, clever contrast agent use also permits the measurement of the extracellular volume (ECV), quantifying the interstitium (odema, fibrosis or amyloid), also as a map. Early results with these methodologies are exciting – potentially representing a new era of CMR.

T1 mapping

Initial T1 measurement methods were multi-breath-hold. These were time consuming and clunky, but were able to measure well diffuse myocardial fibrosis, a fundamental myocardial property with high potential clinical significance [1]. Healthy volunteers and those with disease had different extents of diffuse fibrosis [2], and these were shown to be clinically significant in a number of diseases. T1 mapping methods based on the MOLLI* approach with modifications for shorter breath-holds, better heart rate independence and better image registration for cleaner maps, however, transformed the field – albeit still with a variety of potential sequences in use [3-5]. There are two key ways of using T1 mapping: Without (or

* The product is currently under development; is not for sale in the U.S. and other countries, and its future availability cannot be ensured.



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Native T1 maps of **(1A)** healthy volunteer (author VM): the myocardium appears homogenously green and the blood is red; **(1B)** cardiac amyloid: the myocardium has a higher T1 (red); **(1C)** Anderson Fabry disease: the myocardium has a lower T1 (blue) from lipid – except the inferolateral wall where there is red from fibrosis; **(1D)** myocarditis, the myocardium has a higher T1 (red) from edema, which is regional; **(1E)** iron overload: the myocardium has a lower T1 (blue) from iron.

before) contrast – Native T1 mapping; and with contrast, typically by subtracting the pre and post maps with hematocrit correction to generate the ECV [6].

Native T1

Native T1 mapping (pre-contrast T1) can demonstrate intrinsic myocardial contrast (Fig. 1). T1, measured in milliseconds, is higher where the extracellular compartment is increased. Fibrosis (focal, as in infarction, or diffuse) [7-8], odema [9-10] and amyloid [11], are examples. T1 is lower in lipid (Anderson Fabry disease, AFD) [12], and iron [13] accumulation.

These changes are large in some rare disease. Global myocardial changes are robustly detectable without contrast, even in early disease. In iron, AFD and amyloid, changes appear before any other abnormality – there may be no left ventricular hypertrophy, a normal electrocardiogram, and normal conventional CMR, for example – genuinely new information. In established disease, low T1 values in AFD appear to absolutely distinguish it from other causes of left ventricular hypertrophy [12] whilst in established amyloid T1 elevation tracks known markers of cardiac severity [11].

A note of caution, however. Native T1, although stable between healthy volunteers to 1 part in 30, is dependent on platform (magnet manufacturer, sequence and sequence variant, field strength) [14]. Normal reference ranges for your setup are needed.

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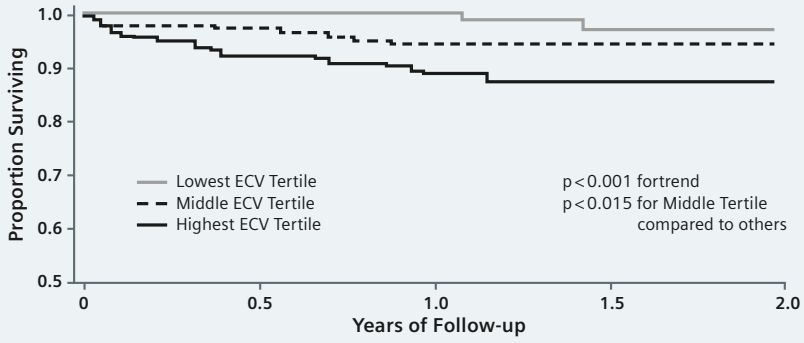
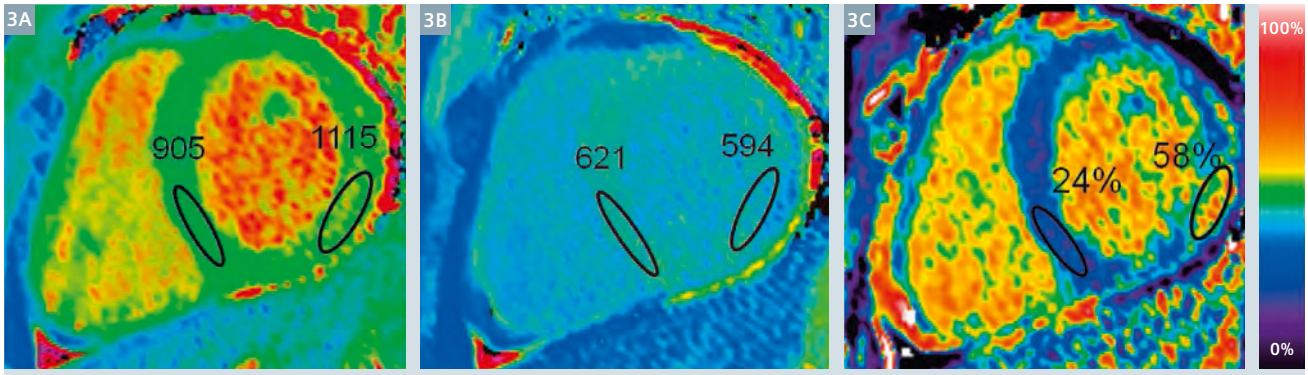


2 ECV in non scar areas (LGE excluded) is associated with all-cause mortality [21].

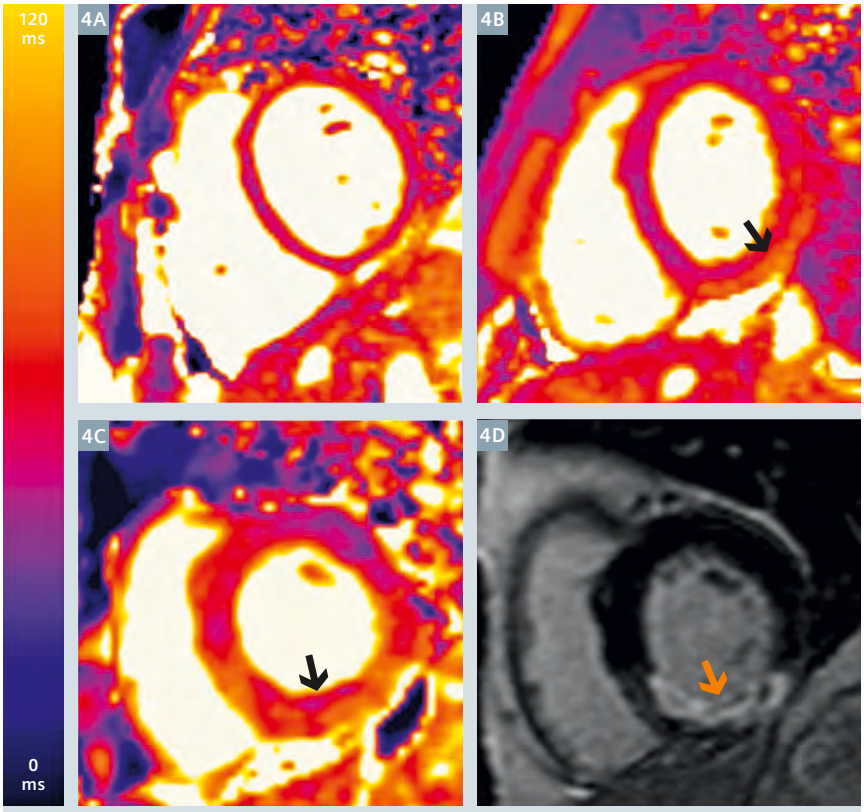
The signal acquired is also a composite signal – generated by both interstitium and myocytes. The use of an extracellular contrast agent adds another dimension to T1 mapping and the ability to characterize the extracellular compartment specifically.

Extracellular volume (ECV)

Initially, post-contrast T1 was measured, but this is confounded by renal clearance, gadolinium dose, body composition, acquisition time post bolus, and hematocrit. Better is measuring the ECV. The ratio of change of T1 between blood and myocardium after contrast, at sufficient equilibrium (e.g. after 15 minutes post-bolus – no infusion generally needed) [15, 16], represents the contrast agent partition coefficient [17], and if corrected for the hematocrit, the myocardial extracellular space – ECV [1]. The ECV is specific for extracellular expansion, and well validated. Clinically this occurs in fibrosis, amyloid and odema. To distinguish, the degree of ECV change and the clinical context is important. A multiparametric approach (e. g. T2 mapping or T2-weighted imaging in addition) may therefore be useful. Amyloid can have far higher ECVs than any other disease [18] whereas ageing has small changes – near the detection limits, but of high potential clinical importance [19, 20]. For low ECV expansion diseases, biases from blood pool partial volume errors need to be meticulously addressed. Nevertheless, even modest ECV changes appear prognostic. In 793 consecutive patients (all-comers but excluding amyloid and HCM, measuring outside LGE areas) followed over 1 year, global ECV predicted short term-mortality (Fig. 2)



3 A patient with myocarditis. On the left side a native T1 map showing the higher T1 value in the inferolateral wall (1115 ms); in the centre, a post-contrast T1 map showing the shortened T1 value after contrast administration (594 ms); on the right side the derived ECV map showing higher value of ECV (58%) compared to remote myocardium.



4 **(4A)** T2 mapping in a normal volunteer (author VM). **(4B)** High T2 value in patient with myocarditis – here epicardial edema. **(4C)** Edema in acute myocardial infarction – here patchy due to microvascular obstruction – see LGE, **(4D)**.

[21]. The same group also found (n ~1000) higher ECVs in diabetics. Those on renin-angiotensin-aldosterone system blockade had lower ECVs. ECV also predicted mortality and/or incident hospitalization for heart failure in diabetics [22].

The use and capability of ECV quantification is growing. T1 mapping is getting better and inline ECV maps are now possible where each pixel carries directly the ECV value (Fig. 3) – a more biologically relevant figure than T1 [6].

T2 mapping

T2-weighted CMR identifies myocardial odema both in inflammatory pathologies and acute ischemia, delineating the area at risk. However, these imaging techniques (e. g. STIR) are fragile in the heart and can be challenging, both to acquire and to interpret. Preliminary advances were made with T2-weighted SSFP sequences, which reduce false negatives and positives [23, 24]. T2 mapping seems a further increment [25] (Fig. 4). As with T1 mapping, global diseases such as pan-myocarditis may now be identified by T2 mapping, and preliminary results are showing this in several rheumatologic diseases (lupus, systemic capillary leak syndrome) and transplant rejection, detecting early rejection missed by other modalities [26, 27].

Conclusion

Mapping – T1, T2, ECV mapping of myocardium is an emerging topic with the potential to be a powerful tool in the identification and quantification of diffuse myocardial processes without biopsy. Early evidence suggests that this technique detects early stage disease missed by other imaging methods and has potential as a prognosticator, as a surrogate endpoint in trials, and to monitor therapy.

Progress is rapid; challenges remain. Delivery across sites and standardization is now beginning with new draft guidelines for T1 mapping in preparation. Watch this space.

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