T1-mapping of the remote myocardium – when normal is not normal

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Cardiovascular magnetic resonance (CMR) is an excellent imaging modality to characterize the heart in coronary artery disease (CAD), particularly using the powerful late gadolinium enhancement (LGE) technique to delineate scar tissue. LGE relies on an area of presumed-normal myocardium for nulling, to highlight areas of abnormality based on relative signal intensities; however, in many cardiac diseases, very little of the myocardium remains normal. T1-mapping is an emerging CMR technology that unmasks underlying abnormalities in otherwise normal-looking myocardium in a directly quantitative fashion, beyond what LGE may inform.

CMR T1-mapping detects abnormalities beyond LGE tissue characterization

The principles of T1-mapping are reviewed elsewhere(1). The basic concept is that each tissue type has a normal range of T1 values, deviation from which may indicate disease or a change in physiology. The native (pre-contrast) myocardial T1 value represents the global signal from both the intra- and extra-cellular spaces, the latter of which is composed of the interstitial and the intravascular compartments. In general, T1 is sensitive to increased free water content. Processes that prolong T1 include myocardial inflammation, edema, and other causes of extracellular volume (ECV) expansion, including infiltration (e.g amyloidosis), interstitial fibrosis, or coronary vasodilatation due to ischemia.

Native T1-mapping has a large body of evidence demonstrating its clinical utility, offering incremental value to LGE tissue characterization(1). For instance, in both hypertrophic and dilated cardiomyopathy, native T1-mapping reveals that even segments with normal wall thickness and no LGE have abnormal T1 values(2,3). T1-mapping can detect subclinical

myocardial involvement in a number of systemic diseases, and may differentiate between various causes of left ventricular hypertrophy(1).

In patients with chronic CAD, Liu et al.(4) demonstrated that, even in remote myocardium with normal wall motion, stress perfusion, and no LGE or upstream coronary stenoses, the resting T1 value is mildly but significantly elevated compared to healthy myocardium. Further, the stress T1 response is blunted compared to normal, demonstrating that abnormal remote myocardium in CAD is discernible by T1-mapping. Possible explanations include microvascular dysfunction or other local autoregulatory processes as part of chronic CAD.

T1-mapping can detect changes in the remote zone early post-ST-elevation myocardial infarction. Native T1 values are increased in remote myocardium, providing independent and incremental prognostic information to traditional outcome markers(5). Remote myocardium also demonstrated persistent expansion of the ECV at 3-months, associated with worsening of contractile function(6) and adverse LV remodelling(7,8). These studies are consistent with literature that acute MI may elicit a pan-cardial response, even in apparently unaffected remote myocardium, that may lead to adverse long-term consequences(9).

Prognostic value of CMR T1-mapping in remote myocardium in chronic CAD

In this issue of *Journal of American College of Cardiology*, Puntmann et al [**Type setters to insert citation****] investigated the prognostic value of native T1 in remote myocardium in a prospective, observational, multicentre longitudinal study of 655 consecutive patients with chronic CAD. They underwent CMR with T1-mapping and LGE, with a median follow-up of 17 months. A single mid-ventricular T1-map per patient was used, with a region of interest

placed in the septum, or another area without LGE in cases of septal infarctions. T1 abnormality was defined as 2 standard deviations above the mean of the method's known normal range. There were 34 deaths (all-cause mortality) and 71 major adverse cardio-cerebrovascular events (MACCE). Native T1 and LGE were both stronger predictors of survival and MACCE compared to LVEF, cardiac volumes and clinical scores ($p<0.001$), which was accentuated in the absence of LGE or LVEF≤35%. Native T1 of remote myocardium was the sole independent predictor of all-cause mortality (Chi^2: 21.7, $p<0.001$), whereas for MACCE, native T1 and LGE extent were joint independent predictors (Chi^2: 25.6 $p<0.001$). Patients with evidence of inducible ischemia were revascularized within 6 weeks of CMR, so ischemia was unlikely the driver of outcomes.

Pathophysiologic mechanisms of increased T1 in remote myocardium

The pathophysiologic mechanisms of elevated native T1 values in remote myocardium in chronic CAD have not been completely elucidated, but potential adaptations in the intracellular, interstitial and intravascular compartments may contribute. In patients with previous acute MIs, the monocytes and macrophages recruited to the remote myocardium as part of the acute response contribute to increased protease activity, including matrix metalloproteinases and cathepsins, which may attack the extracellular matrix(9). This crosstalk between macrophages and resident cells post-MI may influence not only capillary density and the development of fibrosis, but also myocyte apoptosis, contributing to chronic adverse remodelling(9).

The coronary circulation may also contribute to alterations in remote myocardial T1, including changes in myocardial blood flow (MBF), microvascular function and vasodilatory

reserve. In one study of patients with angina who had a chronically-occluded coronary artery with collateral-dependent LV dysfunction but without infarction(10), MBF in the remote myocardium was significantly higher compared to ischemic segments, and also to remote myocardium from patients without LV dysfunction; the glucose uptake was also significantly increased in the remote myocardium, consistent with an increase in regional workload. Increased mechanical load in the remote myocardium may also result in hypercontractile function, compensatory hypertrophy and ultrastructural changes that may influence T1 times(5). Other CMR studies showed that the remote myocardium in patients with chronic CAD demonstrate blunted absolute myocardial perfusion, blood-oxygen-level dependence (BOLD) stress responses, and stress T1 reactivity compared to healthy myocardium, possibly due to coronary microvascular dysfunction(4,11). Microvascular function in remote myocardium also demonstrates changes in coronary resistance control, but the extent to which these microcirculatory alterations impact on the local metabolic and autoregulatory responses in the remote zones(12), and their effects on T1, remain to be fully investigated.

The strengths of this study and future directions

To-date, studies on the prognostic value of native T1-mapping remain sparse. Puntmann et al. [******] significantly added to the current clinical evidence base, providing additional insights into the myocardial characteristics of apparently-normal remote myocardium using native T1-mapping, and highlighting its prognostic value beyond conventional markers. It would be interesting to investigate whether remote myocardium abnormality confers a hidden arrhythmic risk. Being able to characterize the remote myocardium may open new doors for assessing novel therapeutic targets, such as cell therapy, that aim at repairing and enhancing function of the remote, non-infarcted myocardium(13).

For clinical applicability, the avoidance of gadolinium-based contrast agents is an increasingly-recognized benefit, progressing towards minimally-invasive and faster scans. Although this study relied on LGE imaging to identify non-infarcted and remote myocardium, advanced image analysis may eventually allow detection of infarction and ischemia without the help of LGE. The use of T1 thresholds to differentiate normal from abnormal myocardium is method-dependent; thus, method stability is paramount for clinical decision-making, and the use of a common method may facilitate communication between care-providers and wider clinical uptake. Ultimately, CMR parametric mapping is a new technology that allows us to look beyond the façade of apparently-normal myocardium in a wide range of cardiac conditions, and continue to demonstrate their clinical utility with a growing evidence base that promises to change clinical practice.

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