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Adenosine Stress and Rest T1 Mapping Can Differentiate Between Ischemic, Infarcted, Remote, and Normal Myocardium Without the Need for Gadolinium Contrast Agents

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the potential of T1 mapping at rest and during adenosine stress as a novel method for ischemia detection without the use of gadolinium contrast.

BACKGROUND In chronic coronary artery disease (CAD), accurate detection of ischemia is important because targeted revascularization improves clinical outcomes. Myocardial blood volume (MBV) may be a more comprehensive marker of ischemia than myocardial blood flow. T1 mapping using cardiac magnetic resonance (CMR) is highly sensitive to changes in myocardial water content, including MBV. We propose that T1 mapping at rest and during adenosine vasodilatory stress can detect MBV changes in normal and diseased myocardium in CAD.

METHODS Twenty normal controls (10 at 1.5-T; 10 at 3.0-T) and 10 CAD patients (1.5-T) underwent conventional CMR to assess for left ventricular function (cine), infarction (late gadolinium enhancement [LGE]) and ischemia (myocardial perfusion reserve index [MPRI] on first-pass perfusion imaging during adenosine stress). These were compared to novel pre-contrast stress/rest T1 mapping using the Shortened Modified Look-Locker Inversion recovery technique, which is heart rate independent. T1 values were derived for normal myocardium in controls and for infarcted, ischemic, and remote myocardium in CAD patients.

RESULTS Normal myocardium in controls (normal wall motion, MPRI, no LGE) showed normal resting T1 (954 $\pm$ 19 ms at 1.5-T; 1,189 $\pm$ 34 ms at 3.0-T) and significant positive T1 reactivity during adenosine stress compared to baseline (6.2 $\pm$ 0.5% at 1.5-T; 6.3 $\pm$ 1.1% at 3.0-T; all $p < 0.0001$). Infarcted myocardium showed the highest resting T1 of all tissue classes (1,442 $\pm$ 84 ms), without significant T1 reactivity (0.2 $\pm$ 1.5%). Ischemic myocardium showed elevated resting T1 compared to normal (987 $\pm$ 17 ms; $p < 0.001$) without significant T1 reactivity (0.2 $\pm$ 0.8%). Remote myocardium, although having comparable resting T1 to normal (955 $\pm$ 17 ms; $p = 0.92$), showed blunted T1 reactivity (3.9 $\pm$ 0.6%; $p < 0.001$).

CONCLUSIONS T1 mapping at rest and during adenosine stress can differentiate between normal, infarcted, ischemic, and remote myocardium with distinctive T1 profiles. Stress/rest T1 mapping holds promise for ischemia detection without the need for gadolinium contrast. (J Am Coll Cardiol Img 2016;9:27–36) © 2016 The Authors. Published by Elsevier. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom. This study was supported by the National Institute for Health Research Oxford Biomedical Research Centre based at The Oxford University Hospitals Trust, University of Oxford, United Kingdom. Dr. Liu has received research grant support from a British Heart Foundation Clinical Research Training Fellowship (FS/15/11/31233). Drs. Wijesurendra, Neubauer, and Ferreira acknowledge support from the British Heart Foundation Centre of Research Excellence, Oxford, United Kingdom. Dr. Robson is funded by the Medical Research Council. Drs. Robson and Piechnik have patent authorship rights for: 1) U.S. patent pending 61/387,591. SYSTEMS AND METHODS FOR SHORTENED LOOK LOCKER INVERSION RECOVERY (ShMOLLI) CARDIAC GATED MAPPING OF T1. September 29, 2010. All rights transferred to Siemens Medical; and 2) U.S. patent pending 61/689,067: COLOR MAP DESIGN METHOD FOR IMMEDIATE ASSESSMENT OF THE DEVIATION FROM ESTABLISHED NORMAL POPULATION STATISTICS AND ITS APPLICATION TO CARDIOVASCULAR T1 MAPPING IMAGES. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CAD = chronic coronary artery disease

CMR = cardiac magnetic resonance

LGE = late gadolinium enhancement

LV = left ventricular

MBF = myocardial blood flow

MBV = myocardial blood volume

ROI = region of interest

ShMOLLI = Shortened Modified Look-Locker Inversion recovery

In chronic coronary artery disease (CAD), accurate detection of functional ischemia is important because targeted revascularization improves clinical outcomes (1–3). First-pass myocardial perfusion cardiac magnetic resonance (CMR) during vasodilatory stress directly assesses reductions in microvascular blood flow (MBF), and has demonstrated high diagnostic accuracy for detecting significant coronary stenosis (1–3). However, assessment of MBF alone may not reflect all aspects of ischemia (4–7). Myocardial blood volume (MBV), on the other hand, may be a more comprehensive global marker of ischemia, as it represents the total volume of capacitance vessels in both the microcirculations and macrocirculations (4–6,8,9). Significant coronary artery stenosis induces capillary recruitment with an increase in resting MBV (9). Myocardial blood volume measurements derived from first-pass contrast-based CMR closely reflect the level of microvascular autoregulation (4,5,9). As a surrogate for epicardial CAD, recent animal studies showed that disturbances in MBV can effectively detect anatomically significant coronary stenoses (4,10), and distinguish their functional relevance (11). Moderate and severe coronary stenoses may be better differentiated using the index of myocardial blood volume reserve than by myocardial perfusion imaging (4). Furthermore, MBV may relate better to cardiomyocyte metabolism by reflecting changes in myocardial oxygen consumption, which is a more reliable marker of cellular ischemia (4,6,11,12). Therefore, MBV determination during vasodilatation and at rest may constitute a more complete assessment of ischemia than MBF (via perfusion imaging) alone.

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Native (pre-contrast) T1 mapping is a novel CMR technique that can potentially improve ischemia detection by detecting MBV and myocardial water content. In MRI, hydrogen-proton spin-lattice relaxation time (T1) is a magnetic property of tissue that is prolonged by increased water content (13,14) and, importantly, depends on blood T1 through its partial volume (14). Each tissue type, such as myocardium, has a specific range of normal T1 values, deviation from which is indicative of disease (13,15–20). By measuring and displaying T1 relaxation times pixel by pixel, native T1 mapping provides a quantitative biomarker of intracellular and extracellular environments of the myocardium without the need for intravenous contrast agents (13). T1 mapping is highly reproducible with tight normal ranges (13,14), capable of diagnosing a variety of cardiac diseases (13,15,16,18–22). Increased myocardial T1 values act as a surrogate for increased myocardial water (13); hence coronary vasodilatation, which increases MBV (4–6), is expected to prolong T1 and allow detection of microvascular and myocardial blood volume changes during ischemia (9). We have recently demonstrated the ability of stress/rest T1 mapping to detect increases in MBV from coronary vasodilatation in patients with severe aortic stenosis and nonobstructive coronary arteries, with complete reversal and normalization after aortic valve replacement (23). In summary, stress/rest T1 mapping is a highly promising technique for the detection of ischemia and is particularly attractive for applications in patients with CAD.

In this proof-of-principle study, we demonstrate the ability of T1 mapping, during adenosine vasodilatory stress and rest, to distinguish 4 myocardial tissue classes: normal, infarcted, ischemic, and remote myocardium, as a novel gadolinium-free method for ischemia detection. We performed CMR scans in normal controls and patients with known CAD assessing left ventricular (LV) function (cine), viability (late gadolinium enhancement [LGE]), and ischemia (adenosine stress gadolinium first-pass perfusion), and compared them with novel T1 mapping to establish characteristic stress and rest T1 profiles of these 4 myocardial tissues.

METHODS

Ethical approval was granted for all study procedures and all subjects gave written informed consent.

NORMAL CONTROLS. Twenty normal controls without history of cardiovascular disease, not on cardiovascular medications, and with normal electrocardiograms were recruited. Ten volunteers (7 males, 33 ± 10 years of age) underwent CMR scans at 1.5-T (Avanto, Siemens Healthcare, Erlangen, Germany) and 10 volunteers (7 males, 36 ± 11 years of age) were scanned at 3.0-T (TimTrio, Siemens Medical Solutions), all with identical CMR protocols. All subjects avoided potential adenosine antagonizers (e.g., caffeine) for ≥24 h before CMR scans.

Cine images were obtained as previously described (23). T1 mapping was performed using the Shortened Modified Look-Locker Inversion recovery (ShMOLLI) sequence, which has been shown to be heart rate independent over a wide range of T1 values (13), as previously described (13,14,18,19,21). In brief, T1 maps were acquired at rest and during peak adenosine stress (140 μg/kg/min, intravenously for ≥3 to 6 min) in 3 short-axis (basal, midventricular, apical) slices