JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 1, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.11.002

T1 Mapping by CMR Imaging

From Histological Validation to Clinical Implication

Andreas A. Kammerlander, MD,* Beatrice A. Marzluf, MD, MSc,* Caroline Zotter-Tufaro, MSc,* Stefan Aschauer, MD,* Franz Duca, MD,* Alina Bachmann, MD,* Klaus Knechtelsdorfer,* Matthias Wiesinger,* Stefan Pfaffenberger, MD,* Andreas Greiser, PhD,† Irene M. Lang, MD,* Diana Bonderman, MD,* Julia Mascherbauer, MD*

ABSTRACT

OBJECTIVES The purpose of this study was to prospectively investigate the diagnostic and prognostic impact of cardiac magnetic resonance (CMR) T1 mapping and validate it against left ventricular biopsies.

BACKGROUND Extracellular volume (ECV) expansion is a key feature of heart failure. CMR T1 mapping has been developed as a noninvasive technique to estimate ECV; however, the diagnostic and prognostic impacts of this technique have not been well established.

METHODS A total of 473 consecutive patients referred for CMR (49.5% female, age 57.8 ± 17.1 years) without hypertrophic cardiomyopathy, cardiac amyloidosis, or Anderson-Fabry disease were studied. T1 mapping with the modified Look-Locker inversion recovery (MOLLI) sequence was used for ECV calculation (CMR-ECV). For methodological validation, 36 patients also underwent left ventricular biopsy, and ECV was quantified by TissueFAXS analysis (TissueFAXS-ECV). To assess the prognostic value of CMR-ECV, its association with hospitalization for cardiovascular reasons or cardiac death was tested in a multivariable Cox regression model.

RESULTS TissueFAXS-ECV was 26.3 ± 7.2% and was significantly correlated with CMR-ECV ($r = 0.493$, $p = 0.002$). Patients were followed up for 13.3 ± 9.0 months and divided into CMR-ECV tertiles for Kaplan-Meier analysis (tertiles were ≤25.7%, 25.8% to 28.5%, and ≥28.6%). Significantly higher event rates were observed in patients with higher CMR-ECV (log-rank $p = 0.013$). By multivariable Cox regression analysis, CMR-ECV was independently associated with outcome among imaging variables ($p = 0.004$) but not after adjustment for clinical parameters.

CONCLUSIONS CMR T1 mapping allows accurate noninvasive quantification of ECV and is independently associated with event-free survival among imaging parameters. Its prognostic value on top of established clinical risk factors warrants further investigation in long-term studies. (J Am Coll Cardiol Img 2016;9:14–23) © 2016 by the American College of Cardiology Foundation.

Extracellular matrix expansion is a hallmark of heart failure. Data from animal and human studies suggest that increased extracellular volume (ECV) is a key finding in both systolic and diastolic heart failure regardless of the cause of the cardiomyopathy (1–7). Given the important prognostic role of myocardial extracellular matrix expansion, a simple and safe method for its quantification is most desirable. Recently, the ability of cardiac magnetic resonance (CMR) to quantify myocardial tissue characteristics by measuring the longitudinal relaxation (T1) time has been demonstrated (8–15). Several

From the *Division of Cardiology, Medical University of Vienna, Vienna, Austria; and †Siemens Healthcare GmbH, Erlangen, Germany. This study received support from the Austrian Society of Cardiology (Dr. Mascherbauer), the Österreichischer Herzfonds (Dr. Mascherbauer) and the Austrian fellowship grant KLI 245 (to Dr. Mascherbauer) and KLI 246 (Dr. Bonderman). Siemens Healthcare GmbH (Erlangen, Germany) provided the T1-mapping prototype as a work-in-progress package but had no influence on study design, data processing, or statistical analysis. Dr. Greiser is an employee of Siemens Healthcare GmbH. Dr. Lang has received grants and speakers' fees from Actelion Pharmaceuticals, Bayer, United Therapeutics, and AOP Orphan Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 19, 2015; revised manuscript received October 30, 2015, accepted November 3, 2015.

approaches have been studied (16); however, native T1 mapping and the calculation of ECV by use of native and post-contrast T1 maps have been described as the most promising measures of extracellular matrix expansion (11).

Native T1 mapping identifies pathological changes affecting the intracellular or extracellular space, such as myocardial edema in acute myocardial infarction or in myocarditis (17–19), amyloid deposition (20,21), iron overload (22), or glycosphingolipid storage in Anderson-Fabry disease (23). With the use of T1 maps before and after administration of gadolinium-based contrast agents, the ECV can be estimated (8). Elevated ECV as quantified by CMR (CMR-ECV) has been demonstrated in cardiac amyloidosis (24–26), acute myocarditis (27), and hypertrophic cardiomyopathy sarcomere mutation carriers, even in the absence of myocardial hypertrophy (28). Several clinical trials are currently investigating the potential role of T1 mapping in various clinical settings, such as timing of surgery in aortic stenosis (NCT01755936), or are evaluating the cardiotoxic effects of chemotherapy (NCT01719562) (29).

SEE PAGE 24

However, despite a rapidly growing body of evidence indicating the clinical usefulness of this novel technique, its prognostic significance is still not well defined. Furthermore, although inversion recovery methods such as the modified Look-Locker inversion recovery (MOLLI) sequence demonstrate excellent precision and are highly reproducible when tightly controlled protocols are used (30), no final consensus has yet been reached concerning a preferred T1-mapping technique (11). Its reliability is also limited by a lack of validation data against in vivo myocardial biopsies because of heterogeneity of techniques and small patient numbers (**Table 1**) (8,9,13,31–37). Although T1-mapping data appear to have great prognostic potential, only a few studies have reported on the prognostic impact of T1 mapping by CMR (13,38–41).

The present study prospectively evaluates the diagnostic and prognostic significance of CMR T1 mapping for ECV calculation in 473 consecutive patients, of whom 36 underwent left ventricular (LV) biopsy for methodological validation.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CMR = cardiac magnetic resonance

ECV = extracellular volume

LGE = late gadolinium enhancement

LV = left ventricular

MOLLI = modified Look-Locker inversion

NT-proBNP = N-terminal prohormone brain natriuretic peptide

RV = right ventricular

METHODS

STUDY DESIGN. This was a prospective, observational study performed at the Medical University of Vienna, approved by the local ethics committee. Between July 2012 and February 2015, 473 consecutive patients without hypertrophic cardiomyopathy, cardiac amyloidosis, or Anderson-Fabry disease referred for CMR were invited to participate. Those patients who also underwent coronary angiography were invited to undergo myocardial biopsy. Written informed consent was collected before study enrollment from all patients. The Medical University of Vienna represents a university-affiliated tertiary care center with a high-volume multimodality-imaging facility.

CLINICAL DEFINITIONS. At the time of CMR, demographic data (age, sex, body mass index, body surface area) and comorbidities were assessed. These included atrial fibrillation (documented episode during the previous 6 months), arterial hypertension (≥140/90 mm Hg or antihypertensive treatment), hypercholesterolemia (total serum cholesterol 240

TABLE 1 Overview of Studies Validating Various T1-Mapping Methods Against Histological Specimens

First Author (Ref. #)	T1-Mapping Method	Patient Population	r and p Values
Flett et al. (8)	EQ-CMR ECV	18 AS and 8 HCM patients	$r^2 = 0.796$, $p < 0.001$
Fontana et al. (33)	ShMOLLI EQ ECV Multiple breath-hold ECV	18 AS patients	$r^2 = 0.685$, $p < 0.001$ $r^2 = 0.589$, $p < 0.001$
White et al. (37)	ShMOLLI single-bolus ECV ShMOLLI EQ ECV	18 AS patients	$r^2 = 0.69$, $p < 0.001$ $r^2 = 0.71$, $p < 0.001$
Bull et al. (32)	ShMOLLI native T1	19 AS patients	$r = 0.655$, $p = 0.002$
Miller et al. (36)	DynEq-CMR MOLLI ECV	6 Explanted hearts	$r^2 = 0.893$, $p = 0.004$
Iles et al. (34)	Multiple breath-hold post contrast	9 Patients with heart failure after orthotopic heart transplantation	$r = -0.70$, $p = 0.003$
Mascherbauer et al. (13)	Multiple breath-hold post contrast	9 Patients with heart failure and preserved ejection fraction	$r = 0.977$, $p < 0.001$
Iles et al. (35)	Multiple breath-hold post contrast	4 Explanted hearts; 8 patients with myectomy for HCM	$r = -0.78$, $p = 0.003$
Aus dem Siepen et al. (31)	MOLLI ECV	24 Patients with DCM	$r = 0.85$, $p < 0.01$

AS = aortic stenosis; CMR = cardiac magnetic resonance; DCM = dilated cardiomyopathy; DynEq = dynamic equilibrium; ECV = extracellular volume; EQ = equilibrium; HCM = hypertrophic cardiomyopathy; (Sh)MOLLI = (shortened) modified Look-Locker inversion recovery sequence.