Magnetic Resonance Imaging 34 (2016) 1141–1145

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.mrijournal.com

Original contribution

Superiority of the extracellular volume fraction over the myocardial T1 value for the assessment of myocardial fibrosis in patients with non-ischemic cardiomyopathy☆

Keisuke Inui [a], Masaki Tachi [b], Tsunenori Saito [a], Yoshiaki Kubota [a], Koji Murai [a], Koji Kato [a], Hitoshi Takano [a], Yasuo Amano [b], Kuniya Asai [a,*], Wataru Shimizu [a]

[a] Department of Cardiovascular Medicine, Nippon Medical School, Japan
[b] Department of Radiology, Nippon Medical School, Japan

ARTICLE INFO

Article history:
Received 12 March 2016
Accepted 16 May 2016

Keywords:
T1 mapping
Extracellular volume fraction
Non-ischemic cardiomyopathy
Modified Look-Locker inversion recovery

ABSTRACT

Purpose: This study aimed to assess the efficacies of the myocardial T1 value and the extracellular volume fraction (ECV) for determining the severity of myocardial fibrosis in patients with non-ischemic cardiomyopathy.
Materials and methods: Myocardial fibrosis is considered the most important indicator of cardiac damage associated with non-ischemic cardiomyopathy. Recently, modified Look-Locker inversion recovery imaging (MOLLI) has been used for T1 mapping and measurement of the ECV for the assessment of myocardial fibrosis. The present study included 22 patients (mean age, 61.5 ± 12.7; 21 male) with non-ischemic heart failure. Motion corrected myocardial T1 mapping was automatically performed using a MOLLI sequence, and the ECV was estimated from the pre- and post-contrast blood and myocardial T1 values corrected for the hematocrit level. All endomyocardial biopsy specimens were obtained from the inferoposterior left ventricular wall. The percentage of myocardial fibrosis (%F) was determined after Elastica Masson-Goldner staining as follows: (fibrosis area/[fibrosis area + myocardial area]) × 100.
Results: No correlation was noted between the %F and the pre- ($r = 0.290$, $p = 0.191$) or post-contrast T1 values ($r = -0.190$, $p = 0.398$); however, a significant correlation was noted between the %F and ECV ($r = 0.750$, $p < 0.001$).
Conclusions: In this study, the ECV reflected the extent of myocardial fibrosis, but the pre- and post-contrast T1 values did not. The ECV may be used to estimate the severity of myocardial fibrosis in patients with non-ischemic cardiomyopathy.

1. Introduction

Myocardial fibrosis is one of the most common histological features of failing hearts and is both a cause and a consequence of heart failure (HF). Myocardial fibrosis has been reported as a major independent predictor of adverse clinical outcomes in patients with non-ischemic cardiomyopathy [1–3]. Several methods are present for the assessment of myocardial fibrosis, including measurement of biomarkers [4], endomyocardial biopsy (EMB) [5], and cardiac magnetic resonance (CMR) [1,3]. EMB is a commonly used direct assessment method for identifying myocardial fibrosis and the responsible etiology, including myocarditis and dilated cardiomyopathy (DCM) [5–7]. However, EMB is limited by the inherent risks of invasive procedures [8,9]. Additionally, because of the small sample size and the possibility of sampling error, the histological findings acquired with EMB do not necessarily reflect the extent of myocardial fibrosis in the entire heart [10]. CMR has emerged as a non-invasive imaging method that allows for the comprehensive assessment of myocardial anatomy and function [11–13].

Recent technical improvements, namely T1 mapping with a modified Look-Locker inversion recovery (MOLLI) sequence, have facilitated accurate quantitation of diffuse or interstitial fibrosis [14]; with these improvements, CMR possesses tremendous prognostic potential for a wide variety of ischemic and non-ischemic diseases [15–17]. The pre-contrast T1 value may be used to distinguish healthy individuals from patients with acute myocarditis [18], Takotsubo cardiomyopathy [19], amyloidosis [20], Anderson-Fabry disease [21], and hypertrophic cardiomyopathy (HCM) or DCM [22]. However, the pre-contrast T1

☆ Grant Support: None.
* Corresponding author at: Department of Cardiovascular Medicine, Nippon Medical School, 1-1-5 Sendagi Bunkyo-ku, Tokyo, Japan 113-8603. Tel.: +81 3 3822 2131; fax: +81 3 5685 0987.
E-mail address: kasai@nms.ac.jp (K. Asai).

http://dx.doi.org/10.1016/j.mri.2016.05.008
0730-725X/

value is limited by an inability to clearly distinguish interstitial from myocyte signal intensity, and the accuracy is reduced with longer T1 values [23].

Previous studies have reported correlations between the post-contrast T1 value and histological fibrosis [15,24,25]. However, the post-contrast T1 value may be affected by the gadolinium (Gd) dose, clearance rate, time after bolus injection, body composition, and hematocrit level [26]. Recently, the extracellular volume fraction (ECV) has been shown to be a possible CMR biomarker for HF [23,27]. The ECV is calculated from the pre- and post-contrast blood and myocardial T1 values, corrected for the blood hematocrit level, and is less affected by imaging and patient conditions. However, the relationship between the extent of myocardial fibrosis related to non-ischemic HF and the pre- and post-contrast T1 values and ECV of the entire heart has not been investigated thoroughly, especially in reduced ejection fraction patients [28].

The purpose of the present study was to evaluate the correlation between ECV and the extent of myocardial fibrosis, determined using EMB. Subsequently, we aimed to determine whether the pre- or post-contrast myocardial T1 values or the ECV was reflective of the severity of myocardial fibrosis in non-ischemic cardiomyopathy patients with a reduced ejection fraction.

2. Materials and methods

2.1. Study population

This study included 22 consecutive patients with non-ischemic cardiomyopathy with reduced ejection fraction who were admitted to the Nippon Medical School Hospital between March 2012 and February 2014. All patients underwent both CMR and EMB to evaluate the etiology of cardiomyopathy and the extent of fibrosis. Non-ischemic cardiomyopathy was defined as reduced left ventricular function (left ventricular ejection fraction [LVEF] < 30%) without significant coronary artery disease (defined as the presence of >50% luminal stenosis on coronary angiography, or prior myocardial infarction), myocarditis, severe valvular disease, or severe renal failure (estimated glomerular filtration rate 30 mL/min/1.73 m^2). The present study complies with the Declaration of Helsinki, and was approved by the institutional review board of Nippon Medical School. Written informed consent was obtained from all patients.

2.2. CMR imaging

Magnetic resonance imaging (MRI) was performed using a 3.0-T imaging system (Achieva; Philips Healthcare, Best, the Netherlands), with cardiac phased-array coils, electrocardiogram (ECG) gating, and breath holding. Cine imaging was performed using a 2-dimensional (2D) steady-state free precession (SSFP) sequence with the following parameters: repetition time (TR), 4.1 ms; echo time (TE), 2.0 ms; flip angle, 55 degrees; in-plane resolution, 1.6 × 1.7 mm^2; slice thickness, 8 mm with a 2-mm slice gap; and 20–24 phases per cardiac cycle. MOLLI imaging was performed before, and 10 min after, the intravenous injection of 0.15 mmol/kg of extravascular gadolinium-based contrast agents (i.e., Gd-DTPA, Gd-DOTA, Gd-DTPA-BMA), with a 2D inversion-recovery single-shot SSFP sequence; 8 images were acquired using 2 inversion blocks with a pause for 3 heartbeats [29]. The parameters for MOLLI imaging were as follows: TR, 2.1 ms; TE, 0.87 ms; flip angle, 35 degrees; in-plane resolution, 1.9 × 1.9 mm^2; and slice thickness, 10 mm. Thereafter, late gadolinium enhancement (LGE) imaging was performed using a 2D inversion-recovery T1-weighted gradient-echo sequence with the following imaging parameters: TR, 8.1–10.0 ms; TE, 2.9 ms; flip angle, 15 degrees; in-plane resolution, 1.8 × 1.2 mm^2; and slice thickness, 10 mm.

Cine MRI involved the entire heart, and volumetric parameters following CMR were derived semi-automatically using a dedicated workstation (ViewForum; Philips Medical Systems, Best, the Netherlands). The LVEF, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left ventricular myocardial mass were measured and normalized to the body surface area and presented as indices. The presence of LGE was determined by consensus of 2 experienced radiologists, who were blinded to the EMB results. MOLLI images were acquired in basal and mid left ventricle short-axis views [30]. Exponential fitting with a “maximum likelihood” estimator was used to perform T1 mapping; subsequently, the pre- and post-contrast T1 values of the entire left ventricle were determined.

The ECV was determined to assess myocardial fibrosis, as described previously [14,31,32]. ECV = λ (1 − hematocrit), where λ = (1/T1 of the myocardium post-contrast − 1/T1 of the myocardium pre-contrast)/(1/T1 of the blood post-contrast − 1/T1 of the blood pre-contrast).

2.3. Endomyocardial biopsy

All EMB specimens were obtained from the left ventricular inferoposterior wall using a 6-F bioptome (Cordis; Johnson & Johnson Co, New Brunswick, NJ, USA) via a retrograde approach, under radiographic guidance with continuous ECG monitoring. Biopsy specimens were fixed in 20% neutral buffered formalin, embedded in paraffin, and cut into 3 μm sections; visualization was performed with the Elastica Masson-Goldner (EMG) stain [33]. Histopathological findings were evaluated morphometrically. Photomicrographs were obtained in each case, with a NIS-Elements Documentation System (version 3.22; Nikon Instruments, Tokyo, Japan) and a digital microscope camera system (Nikon DS-Ri 1; Nikon Instruments). One experienced cardiovascular pathologist, who was blinded to the clinical results, calculated the parameters using the ImageJ analysis software version 1.43 (National Institutes of Health, Bethesda, MD, USA) and Adobe Photoshop software version CS4 (Adobe Systems Inc., San Jose, CA, USA). After EMG staining, the images were re-colored as follows: fibrosis, green; myocardium, red; areas with edema, blood vessels, and vacuolar degeneration, blue. The percentage of myocardial fibrosis (%F) was calculated using the following formula: %F = (fibrosis area/[fibrosis area + myocardial area]) × 100 (Fig. 1). [34] Adipose tissue, blood vessels, and edematous areas were excluded from the calculations. The calculations were based on average measurements from 5 photomicrographs at ×10 magnification. The observational interval between CMR imaging and EMB was ≤18 days (mean, 6 days).

We evaluated the correlations of the pre- and post-contrast T1 values and ECV with the %F. Moreover, we divided patients into high %F and low %F groups based on the median %F value; the correlations between the ECV and %F were evaluated in the high %F and low %F groups.

2.4. Statistical analysis

All data are expressed as mean ± standard deviation. The median value of %F is also shown. Pearson's correlation coefficients were used to evaluate the correlations of the pre- and post-contrast T1 values and ECV with the %F and the correlation between the ECV and %F in the high %F or low %F groups. All statistical analyses were performed using the SPSS software package version 21 (IBM, Armonk, NY, USA), and a p value of <0.05 was considered statistically significant.

3. Results

Patient characteristics are summarized in Table 1. The mean age of the patients was 61.5 ± 12.7 years, mean hematocrit level was 43.3 ± 5.4%, and mean brain natriuretic peptide level was 401 ± 328 pg/mL. The CMR findings are presented in Table 2. The pre-contrast