Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Temporal change of myocardial tissue character is associated with left ventricular reverse remodeling in patients with dilated cardiomyopathy: A cardiovascular magnetic resonance study

Takeru Nabeta (MD, PhD)[a], Takayuki Inomata (MD, PhD, FJCC)[a,*], Teppei Fujita (MD)[a], Yuichiro Iida (MD)[a], Yuki Ikeda (MD, PhD)[a], Takanori Sato (MD)[a], Shunsuke Ishii (MD, PhD)[a], Emi Maekawa (MD, PhD)[a], Tomohiro Mizutani (MD, PhD)[a], Takashi Naruke (MD, PhD)[a], Toshimi Koitabashi (MD, PhD)[a], Yusuke Inoue (MD, PhD)[b], Junya Ako (MD, PhD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan
[b] Department of Diagnostic Radiology, Kitasato University School of Medicine, Sagamihara, Japan

ARTICLE INFO

Article history:
Received 23 June 2016
Received in revised form 5 October 2016
Accepted 28 October 2016
Available online xxx

Keywords:
Magnetic resonance imaging
Dilated cardiomyopathy
Left ventricular reverse remodeling
Myocardial tissue characterization

ABSTRACT

Background: Prognostic significance of temporal change in myocardial tissue characterization by cardiovascular magnetic resonance (CMR) has not been elucidated in patients with non-ischemic dilated cardiomyopathy (DCM).

Methods and results: Sixty-eight patients with newly-diagnosed DCM who underwent CMR including late gadolinium enhancement (LGE) both at baseline and during follow-up period were enrolled. LGE score was defined by a signal intensity of $\geq$5 standard deviations above the remote reference myocardium mean. Left ventricular reverse remodeling (LVRR) defined as a LV ejection fraction increase of $\geq$10% and a decrease in indexed LV end-diastolic diameter of $\geq$10% compared to those at baseline was detected in 38% of the patients. There was no significant difference in LGE score between baseline and follow-up (5.8% vs. 7.3%; $p = 0.38$). The change in LGE area (delta-LGE) was significantly lower in patients with LVRR than those without ($-0.5\% \pm 3.4\%$ vs. $3.0 \pm 7.4\%$; $p = 0.02$). On the other hand, T2 ratio during the follow-up significantly reduced (1.95 ± 0.48 vs. 1.67 ± 0.56; $p < 0.01$); however, there was no significant difference in the change in T2 ratio between patients with LVRR and those without (-0.29 ± 0.73 vs. -0.27 ± 0.66; $p = 0.88$). Multivariate logistic analysis indicated that baseline LGE score [odds ratio; 0.78; 95% confidence interval (CI) 0.66 to 0.90; $p < 0.01$] together with delta-LGE (odds ratio; 0.77; 95% CI 0.61 to 0.92; $p = 0.01$) were independently associated with subsequent LVRR ($p < 0.01$).

Conclusions: The temporal change of LGE-CMR score during the clinical course was significantly correlated with following LVRR.

Introduction

Dilated cardiomyopathy (DCM) is characterized by left or both ventricular dysfunction along with increased volume [1,2]. The prognosis of DCM patients has improved during recent decades due to prompt diagnosis and appropriate guideline-directed medical therapy (GDMT) [3,4]. Simultaneously, more patients with DCM have achieved left ventricular reverse remodeling (LVRR), defined as improvement in LV contraction and decrease in LV volume. Furthermore, LVRR is related to favorable prognosis [5–9]. However, it has been difficult to predict who can achieve LVRR by GDMT. Particularly, it has not been fully elucidated whether the temporal change in cardiac tissue characterization is related to subsequent LVRR. Cardiac magnetic resonance (CMR) including late gadolinium enhancement (LGE) can detect myocardial damage, fibrosis, and edema [10–12]. We previously have shown that LGE-CMR at baseline was an independent predictor for LVRR and cardiac events in patients with newly-diagnosed DCM [13]. Therefore, we investigate here the correlation between LVRR and temporal change in myocardial tissue characterization by CMR.

* Corresponding author at: Department of Cardiovascular Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-Ku, Sagamihara, Kanagawa 252-0374, Japan. Fax: +81 42 778 8441.
E-mail address: inotaka@med.kitasato-u.ac.jp (T. Inomata).

http://dx.doi.org/10.1016/j.jjcc.2016.10.017
0914-5087/

Methods

Study subjects

The inclusion criteria were as follows: newly-diagnosed DCM with LV ejection fraction (LVEF) of <45%, LGE-CMR, endomyocardial biopsy at index admission at the time of diagnosis, and follow-up LGE-CMR and echocardiography after discharge.

Exclusion criteria were the presence of significant coronary artery diseases defined as the presence of >50% luminal stenosis on coronary angiography or prior myocardial infarction, infiltrative or inflammatory heart diseases, severe primary valve diseases, preceding tachyarrhythmia, alcohol abuse and/or chronic renal failure with estimated glomerular filtration rate of <30 ml/min/1.73 m^2. Patients who did not undergo follow-up LGE-CMR due to death, received device implantation, or worsening renal function during study period were also excluded.

Clinical measurement and observation

As clinical evaluations at baseline, 12-lead electrocardiogram (ECG), blood sampling, echocardiography, and LGE-CMR were performed at discharge in a clinically stable condition. Patients were treated according to GDMT including beta-blockers and renin–aldosterone system inhibitors [14]. EcLusys high-sensitive troponin T (Hs-TnT) immunoassay (Roche Diagnostics, Mannheim, Germany) was used to detect troponin T with the cut-off value of ≤0.014 ng/ml representing the lowest concentration at which the coefficient of variance was 10%. "Positive for Hs-TnT" was defined as Hs-TnT level of ≥0.015 ng/ml. Transthoracic echocardiography was performed using an APLIO SSA-770A (TOSHIBA, Tochigi, Japan). M-mode images were obtained in the left parasternal long-axis views to measure each chamber dimension and LVEF was calculated according to a modified Simpson's method using biplane images from apical viewpoints. Follow-up LGE-CMR was performed after discharge together with Hs-TnT measurement and echocardiography.

LVRR was defined as an increase in LVEF from ≥10% to a final value of ≥35% together with a decrease in LV end-diastolic diameter index (LVDDi) ≥10% at follow-up echocardiography [7,8]. Cardiac events after follow-up CMR examinations were defined as cardiac death, sudden death, implantation of ventricular assist device, readmission for heart failure exacerbation and major ventricular arrhythmias.

LGE-CMR protocol and analysis

All LGE-CMRs were performed using a 1.5-T clinical scanner (Signa HDxt 1.5T; GE Healthcare, Milwaukee, WI, USA) with a maximum gradient strength of 33 mT/m and a slew rate of 120 mT/m/s. An eight-channel phased-array coil and vector ECG were used for signal reception and cardiac gating, respectively. T2-weighted dark blood short-axis images were acquired with the following parameters: echo time (TE), 58 ms; repetition time (TR), 2 ms; inversion time (TI), 140 ms; slice thickness, 8 mm; interslice gap, 8 mm; and four slices acquired in the LV short axis over two R–R intervals. ECG-gated two-dimensional LGE images were acquired 10–15 min after the intravenous injection of 0.2 mmol/kg gadolinium using a segmented inversion recovery fast gradient-echo sequence with the following parameters: TE, 4.2 ms; TR, 8.0 ms; views per segment, 24; flip angle, 20°; TI, 150–220 ms; bandwidth, ±25 kHz; number of excitations, 1; in-plane resolution, 1.5 × 1.7 mm^2; field of view, 340 mm × 340 mm; slice thickness, 8 mm; interslice gap, 8 mm; and four slices acquired in the LV short axis over two R–R intervals. We measured the signal intensity in the myocardial wall and in skeletal muscle (erector spinae muscle) with T2 weighted dark blood sequence to quantify myocardial edema ratio (T2 ratio) [15]. Region of interest (ROI) was drawn into the septum, anterior, lateral, and inferior wall of myocardium. In addition, ROI was drawn into the erector spinae muscle in same slice. The global signal intensity of myocardium was defined as average of signal intensity of each myocardium. The size of each region of ROI was standardized 19–22 mm^2. T2 ratio was defined and calculated by the ratio of myocardial signal intensity and muscle signal intensity.

The presence of LGE was determined by the agreement of two experienced and independent observers blinded to the patient outcome. The extent of LGE was expressed as "LGE score," defined as an area showing a signal intensity of ≧5 standard deviations (SDs) above the mean of the remote reference myocardium. LGE area was quantified by semiautomatic planimetry on the short-axis images using Ziostation 2 (Ziosoft, Tokyo, Japan). The amount of change for LGE score, T2 ratio, LVEF from the baseline till the follow-up period was defined as ΔLGE score, ΔT2 ratio, ΔLVEF, respectively.

Statistical analysis

Student's t test was used to compare continuous variables, Wilcoxon–Mann–Whitney test was used to evaluate the non-normally distributed continuous variables, and the Chi-square test or Fisher's exact test for categorical variables between groups. Paired t-tests were used to compare the values between baseline and follow-up point. To investigate the factors that associated with subsequent LVRR from baseline variables, univariate screening of all clinical data was performed; and a stepwise backward conditional algorithm was applied to selected candidates with $p < 0.2$ in the univariate analysis to estimate the factors for inclusion in the multivariable logistic regression analysis. Patients were divided into two groups with or without cardiac events. We compared LGE score at baseline CMR and ΔLGE score between two groups. Correlation between continuous variables was examined as appropriate by Pearson's correlation test. All statistical analyses were performed using JMP 11.1.1 (SAS Institute, Cary, NC, USA). All p-values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients with and without LVRR

Eighty-nine patients met inclusion criteria in this study. Among them, there were 3 deaths (2 from cardiac causes), 4 patients with deteriorated renal function, and 14 patients receiving device implantation during the study period in whom follow-up LGE-CMR was not performed. Finally 68 patients were included in this study. Follow-up LGE-CMR was performed 36 ± 24 months after discharge (Fig. 1).

Baseline characteristics are shown in Table 1. Thirty patients (44%) achieved LVRR during follow-up. There was no significant difference in LVEF (30 ± 8% vs. 33 ± 8%; $p = 0.09$) and LVDDi (38 ± 5 mm/m^2 vs. 36 ± 6 mm/m^2; $p = 0.23$) at baseline between patients with LVRR and those without. Follow-up time of LGE-CMR was also not significantly different between the two groups. In most of the subjects, beta-blockers and renin–angiotensin system inhibitors were prescribed at discharge. LGE negative ($p < 0.01$), lower LGE score ($p < 0.01$), and lower T2 ratio ($p = 0.02$) were observed in more patients with LVRR than those without.

Transition of CMR findings during the follow-up

Visual LGE findings did not change during the follow-up in many patients regardless of their baseline LGE results. However, in

Please cite this article in press as: Nabeta T, et al. Temporal change of myocardial tissue character is associated with left ventricular reverse remodeling in patients with dilated cardiomyopathy: A cardiovascular magnetic resonance study. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.10.017