Quantification of Myocardial Iron Deficiency in Nonischemic Heart Failure by Cardiac T2* Magnetic Resonance Imaging

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The aim of this study was to use T2* cardiac magnetic resonance (CMR) imaging to quantify myocardial iron content in patients with heart failure (HF) and to investigate the relation between iron content, cardiac function, and the cause of HF. CMR data were analyzed from 167 patients with nonischemic and 31 with ischemic HF and 50 patients with normal ventricular function. Short-axis T2* imaging was accomplished using 3-T scanner and multiecho gradient-echo sequence. Myocardial T2* value (M-T2*) was calculated by fitting the signal intensity data for the mid−left ventricular (LV) septum to a decay curve. Patients with nonischemic HF were categorized into patients with LV ejection fraction (LVEF) <35% or ≥35%. The relation between nonischemic HF with LVEF <35% and the risk for major adverse cardiac events was analyzed by multivariate logistic regression analysis using M-T2* and HF biomarkers. M-T2* was significantly greater for patients with nonischemic HF (LVEF <35%: 29 ± 7 ms, LVEF ≥35%: 26 ± 5 ms) than for patients with normal LV function (22 ± 3 ms, p <0.0001) or ischemic HF (22 ± 4 ms, p <0.001). The odds ratio was 1.21 for M-T2* (p <0.0001) and 1.0015 for brain natriuretic peptide (p <0.0001) in relation to nonischemic HF with LVEF <35%. Furthermore, this value was 0.96 for systolic blood pressure (p = 0.012) and 1.02 for M-T2* (p = 0.03) in relation to the risk for major adverse cardiac events in patients with nonischemic HF. In conclusion, T2* CMR demonstrated the robust relation between myocardial iron deficiency and nonischemic HF. M-T2* is a biomarker that can predict adverse cardiac function in patients with nonischemic HF. **(Am J Cardiol 2014;113:1024−1030)**

T2* cardiac magnetic resonance (CMR) has been used for the assessment of myocardial iron overload in patients with thalassemia,[1−3] whereas the assessment of myocardial iron deficiency using T2* CMR has not been examined. Although we hypothesize that myocardial iron deficiency itself mediates the development of cardiac dysfunction and morphological aberration, the role of myocardial iron deficiency in the pathophysiology of heart failure (HF) according to the specific cause of HF remains poorly understood. Therefore, the aim of this study was to quantify myocardial iron content in patients with nonischemic and ischemic HF using T2* CMR and to examine the role of myocardial iron deficiency in HF according to the specific cause of HF.

Methods

Two hundred twenty-eight consecutive patients who had been admitted to our hospital from June 2010 to March 2013 with symptomatic congestive HF and echocardiographic left ventricular ejection fraction (LVEF) <50% were prospectively enrolled in this study. Congestive HF was diagnosed by the following clinical symptoms and signs according to the Framingham criteria: typical symptoms, neck vein distension, peripheral edema, lung rales, S3 gallop, and tachycardia together with representative chest radiography findings. The diagnosis and cause of HF were established at admission or thereafter using a 12-lead electrocardiogram, transthoracic echocardiography, and, when necessary, stress perfusion imaging, coronary angiography, or myocardial biopsy. We excluded patients with end-stage renal failure requiring dialysis therapy; patients with previously implanted pacemaker or cardioverter-defibrillator, other implanted devices or metal objects contraindicated for a magnetic resonance scanner; patients with claustrophobia; patients with significant arrhythmia; patients with congenital heart disease; patients with leukemia; and patients undergoing treatment for anemia. After stabilization of clinical conditions, patients underwent CMR and standard blood tests, including measurements of brain natriuretic peptide (BNP). Informed consent for registration in our database and for use of patient data within this clinical study was obtained in accordance with the guidelines of the ethics committee of

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See page 1029 for disclosure information.

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Table 1
Characteristics of all patients

Clinical Characteristic	Nonischemic Heart Failure		Ischemic Heart Failure (n = 31)	Normal (n = 50)
	LVEF <35% (n = 73)	LVEF ≥35% (n = 94)		
Men	48 (66)	47 (50)	22 (71)	27 (54)
Age (yrs)	51 ± 16	56 ± 14	62 ± 12	59 ± 14
Diabetes mellitus	3 (4)	9 (10)	6 (19)	3 (6)
Hypertension	6 (8)	4 (4)	9 (29)	5 (10)
Systolic blood pressure (mm Hg)	114 ± 24	118 ± 21	123 ± 21	123 ± 27
Diastolic blood pressure (mm Hg)	70 ± 19	67 ± 14	70 ± 14	72 ± 16
Heart rate (beats/min)	82 ± 19	76 ± 28	74 ± 13	76 ± 18
Hemoglobin (g/dl)	13.9 ± 2.1	13.3 ± 1.6	12.8 ± 2.1	13.1 ± 1.6
Estimated glomerular filtration rate (ml/min/1.73 m^2)	75 ± 30	70 ± 25	59 ± 26	73 ± 12
BNP (pg/ml)	626 ± 1,180	221 ± 300	354 ± 688	39 ± 30
Cardiac MR measurement				
LV end-diastolic volume (ml)	247 ± 97	139 ± 45	164 ± 60	109 ± 27
LV end-systolic volume (ml)	192 ± 86	72 ± 30	104 ± 51	43 ± 13
LVEF (%)	23 ± 8	49 ± 10	40 ± 12	61 ± 5
No. of patients who underwent LGE	70	88	25	50
LGE positive	41 (59)	49 (56)	25 (100)	0

Data are presented as mean ± SD, n (%), or n.
MR = magnetic resonance.

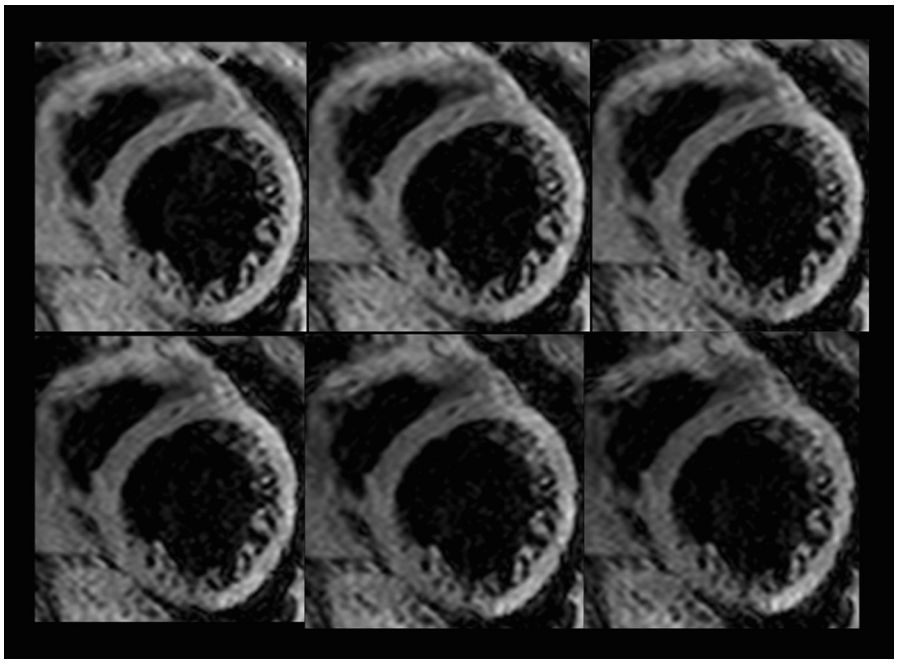

Figure 1. T2* images for a 58-year-old man with nonischemic heart failure. Echo times correspond to 2.9, 4.4, and 5.8 ms from the left of the top and 7.3, 8.8, and 10.3 ms from the left of the bottom.

our hospital. Thirty patients with secondary cardiomyopathy, valvular disease, and metabolic diseases were excluded from final analysis. Therefore, the data presented here were derived from the remaining 198 patients, including 31 (16%) with ischemic HF and 167 (84%) with nonischemic HF cause. In addition, patients with nonischemic HF were divided into patients with LVEF <35% and ≥35% on cine CMR. Patient backgrounds are summarized in Table 1.

In the entry period of this study, patients with suspected cardiomyopathy underwent the same examinations as the HF group for diagnosis. Fifty of the patients who satisfied the following 3 criteria were enrolled in this study as normal ventricular function group: (1) LVEF ≥55% on cine CMR; (2) negative for late gadolinium enhancement (LGE) on CMR; and (3) BNP <100 pg/ml.

After receiving optimal medical treatment and being discharged from the hospital, 167 patients with nonischemic HF were examined by cardiologists at the outpatient clinic of our hospital at least every 3 months for a mean follow-up period of 20 months. Physicians determined the necessity for blood tests, electrocardiography, chest radiography, echocardiography, and other examinations. The primary end

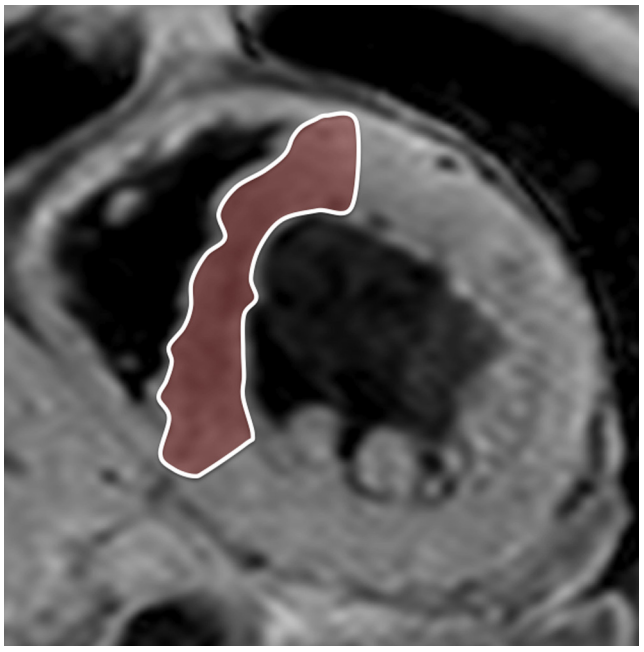

Figure 2. One large region of interest (ROI) was placed in the mid-LV septum, and the mean myocardial intensity for the ROI was measured for each T2* image with 6 different echo times.

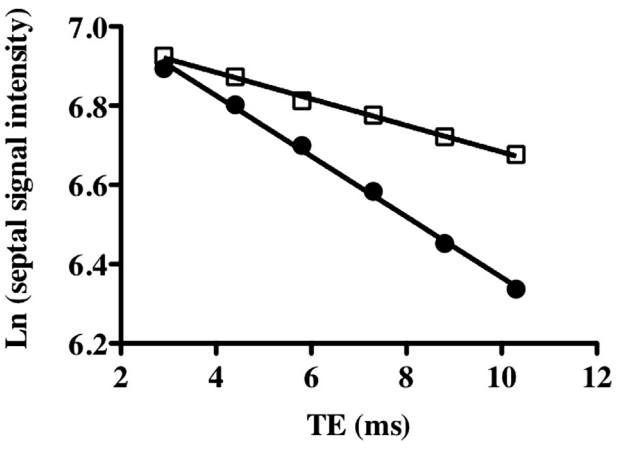

Figure 3. Graph shows methods of calculating myocardial T2* value. Abscissa represents 6 different echo times and ordinate represents natural logarithm (Ln) of the mean signal intensity for the ROI. Minus reciprocal number of the slope of linear regression equation corresponds to T2* value. The 58-year-old man with nonischemic heart failure (□ $y = -0.034x + 7.02$, $r^2 = 1.00$, T2* = 30 ms) is the same subject as in Figure 1. Data from a 38-year-old man with ischemic heart failure (●; $y = -0.076x + 7.13$, $r^2 = 1.00$, T2* = 13 ms) is also included. TE = echo time.

point was major adverse cardiac events (MACEs) consisting of cardiac death or HF hospitalization or a left ventricular (LV) assist device before heart transplantation because of pump failure that was refractory to medical treatment.

All patients underwent 3-T magnetic resonance imaging (Achieva 3.0T Quasar Dual; Philips Healthcare, Best, the Netherlands) equipped with dual-source parallel radiofrequency transmission, 32-element cardiac phased-array coils for radiofrequency reception, and a 4-lead vector cardiogram used for cardiac gating. Cine balanced turbo field echo sequences in 2-, 3- and 4-chamber views and a stack of short-axis images acquired in parallel to the atrioventricular groove from the base to apex were performed. Cine images were analyzed with the use of dedicated software (Extended Workspace, Philips Healthcare). Initially, short-axis images were previewed from the base to the apex in a cinematic mode, then endocardial and epicardial contours for end-diastole and end-systole were manually traced. Delineated contours were used for the quantification of LV volumes and LVEF.

A midventricular short-axis slice was obtained for T2* measurements. The black blood T2* acquisition used a breath-hold multiecho gradient-echo sequence (flip angle 30°, matrix size 200 × 123, sample bandwidth 2,275 Hz/pixel, slice thickness 8 mm, and field of view 320 mm). The short-axis images were acquired within a single breath-hold at 6 echo times from 2.9 to 10.3 ms at approximately 1.5-ms increments. A double inversion recovery pulse was applied on the R wave, and the inversion time extended into diastole, generating a set of 6 similar images at increasing echo times[4,5] (Figure 1). One large full-thickness region of interest was placed in the mid-LV septum, distant from the lungs and cardiac veins, which are otherwise known to cause susceptibility artifacts[6] (Figure 2). The signal intensity of these regions of interest was plotted against the echo time used for each image. The resulting points form an assumed exponential decay curve, as the image signal decreases with increasing echo time. An exponential function was fitted to the data, using the following equation:

Table 2
Pearson correlation coefficient of T2* value in all patients

Parameter	Pearson r	p Value
Age	0.21	0.0006
Systolic blood pressure	−0.012	0.85
Hemoglobin	−0.1	0.1
Mean corpuscular hemoglobin concentration	−0.067	0.28
Mean corpuscular volume	−0.021	0.73
Estimated glomerular filtration rate	−0.062	0.32
BNP	−0.18	0.0049
Septal wall thickness	−0.044	0.48
LV end-diastolic volume index	0.34	<0.0001
LV end-systolic volume index	0.35	<0.0001
Stroke volume	−0.054	0.39
LVEF	−0.34	<0.0001

Table 3
T2* value for septum with and without late gadolinium enhancement (LGE)

	LGE (+)		LGE (−)	
	T2* (ms)	No. of Patients	T2* (ms)	No. of Patients
Nonischemic heart failure				
LVEF				
<35%	29.7 ± 7.1	32	28.8 ± 6.6	38
≥35%	26.1 ± 5.2	35	25.4 ± 4.9	53
Ischemic heart failure	22.0 ± 4.7	14	22.1 ± 2.0	11

Data are presented as mean ± SD.

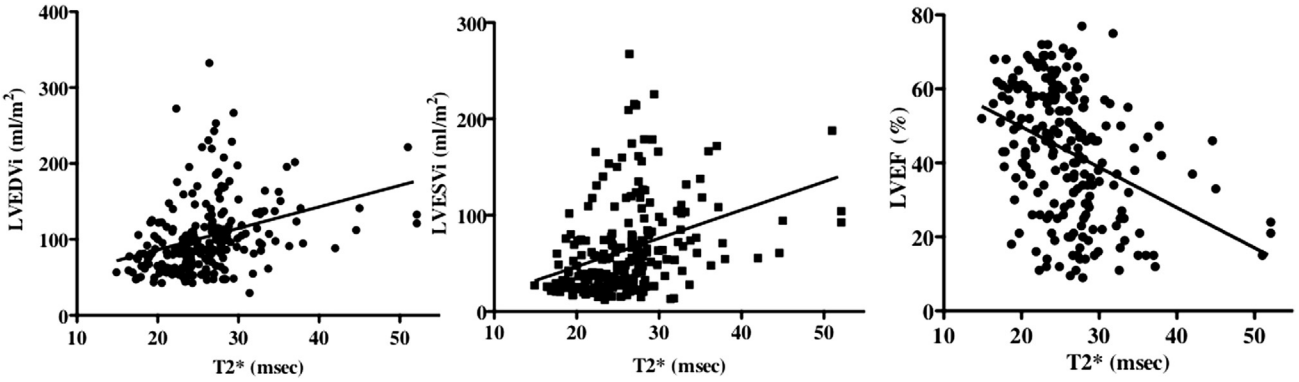

Figure 4. Scatter plot of T2* and LV functional parameters LVEDVi *(left panel)*, LVESVi *(middle panel)*, and LVEF *(right panel)* for 167 patients with nonischemic HF and 50 patients with normal LV function. T2* had significant correlations with LV functional parameters. Best-fit line is shown (LVEDVi: Pearson r = 0.34, p <0.0001; LVESVi: Pearson r = 0.37, p <0.0001; and LVEF: Pearson r = −0.38, p <0.0001). LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index.

Table 4
Multivariate stepwise regression analysis for T2* in nonischemic heart failure and normal (n = 217)

Parameter	Regression Coefficient, β	F Value	p Value
LV end-diastolic volume index	0.039	1.17	0.28
LV end-systolic volume index	−0.029	0.36	0.55
LVEF	−0.12	5.04	<0.05

$$y = Ke^{-TE/T2*},$$

where K represents a constant, TE represents the echo time, and y represents the image signal intensity (Figure 3). In 30 randomly selected patients, T2* measurement was repeated at least 1 month later by the same primary reader and by an additional investigator who was blinded to the results from the initial study to determine the reproducibility of T2* measurements. The reproducibility of T2* measurements was evaluated by calculating inter- and intraobserver variability, defined as the absolute difference between the corresponding repeated measurements and expressed in percentage of their mean.

Subsequently, 0.1 mmol/kg of gadolinium contrast (Magnevist; Bayer HealthCare, Osaka, Japan) was administered by way of the antecubital vein. LGE images were obtained with an inversion-recovery 3-dimensional T1 turbo field echo sequence (fast gradient-echo pulse sequence) performed 10 minutes after contrast injection. The inversion time was adjusted to a completely null normal myocardium. LGE was not performed in 9 patients with nonischemic HF and in 6 patients with ischemic HF because of renal dysfunction. The short-axis LGE image was assessed using the American Heart Association/American College of Cardiology classification of 17 standardized LV short-axis imaging. LGE was considered positive if the hyperenhanced area involved >50% of the wall thickness.

Continuous data are expressed as means ± SD. For comparison of parameters among 4 patient groups, Tukey's multiple comparison test was used. The correlation between T2* value and the other parameters was analyzed using Pearson's correlation coefficient and multivariate stepwise regression analysis. Receiver operating characteristic analysis was performed to determine the optimal cutoff of T2* value for the relation to nonischemic HF with LVEF <35% or the prediction of risk for MACE. After univariate logistic regression analysis, multivariate logistic regression analysis was performed using the statistically appropriate number of significant variables identified by univariate analysis to determine their relation to nonischemic HF with LVEF <35% or to the risk of MACE. All statistical tests were 2-sided. A p value of <0.05 was considered to indicate statistical significance. These analyses were performed using the JMP statistical program package (version 9.0; JMP, Inc., Cary, North Carolina).

Results

T2* value had significant correlations with LV functional parameters (LV end-diastolic volume index, LV end-systolic volume index, and LVEF), which were observed in all patients. There were weak correlations between the T2* value and age and between T2* value and BNP. No correlation between T2* value and any other factor was observed (Table 2). No difference in T2* value between with and without LGE was observed in each patient group (Table 3). T2* value was significantly greater for patients with nonischemic HF (LVEF <35%: 29 ± 7 ms and LVEF ≥35%: 26 ± 5 ms) than for normal patients (22 ± 3 ms, p <0.0001) and patients with ischemic HF (22 ± 4 ms, p <0.001). In patients with nonischemic HF, T2* value was significantly greater for patients with LVEF <35% than those with LVEF ≥35% (p <0.0001). There was no difference in T2* value when comparing normal patients and those with ischemic HF. In nonischemic HF and normal, the univariate correlation analysis showed moderate correlations between T2* value and LV functional parameters (Figure 4). The multivariate stepwise regression analysis showed a significant correlation only between T2* value and LVEF (Table 4). Inter- and intraobserver variability of T2* measurements in a subset of 30 randomly selected patients were 4.0 ± 3.5% and 4.3 ± 3.3%, respectively.

In relation to nonischemic HF with LVEF <35%, multivariate logistic regression analysis showed that chi-

Table 5
Relevance to nonischemic heart failure with left ventricular ejection fraction <35% in all patients (n = 248)

Parameter	Univariate Logistic Analysis			Multivariate Logistic Analysis			
	Chi-Square	Odds Ratio	p Value	Chi-Square	Odds Ratio	95% CI	p Value
Age	10.04	0.97	0.0015	1.68	0.99	0.96−1.01	0.19
Gender	2.55	0.63	0.11				
Systolic blood pressure	2.99	0.99	0.084				
Hemoglobin	7.27	1.24	0.007	8.18	1.32	1.09−1.62	0.004
Estimated glomerular filtration rate	2.75	1.01	0.097				
BNP	13.88	1	0.0002	18.13	1	1.00−1.002	<0.0001
T2*	31.81	1.22	<0.0001	34.93	1.21	1.13−1.31	<0.0001

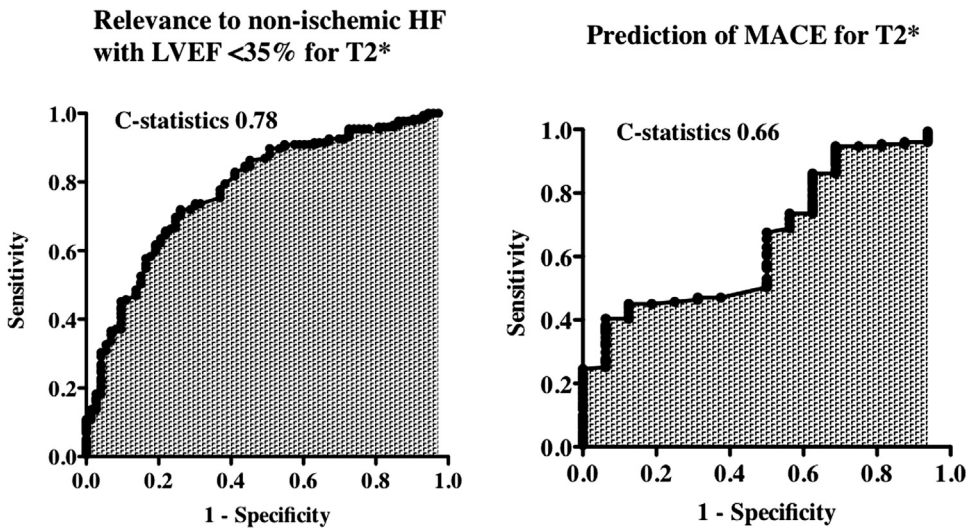

Figure 5. Receiver operating characteristic analysis (ROC) for relevance to nonischemic HF with LVEF <35% for T2* in all patients *(left)* and for prediction of MACE in patients with nonischemic HF *(right)*. ROC analysis revealed that optimal T2* threshold was 26.3 ms for identifying patients with nonischemic HF with LVEF <35%, with a sensitivity of 74% and a specificity of 72%. The optimal T2* threshold was 25.1 ms for predicting MACE with a sensitivity of 94% and a specificity of 40%.

Table 6
Risk for major adverse cardiac event in patients with nonischemic heart failure (n = 167)

Parameter	Univariate Logistic Analysis			Multivariate Logistic Analysis			
	Chi-Square	Odds Ratio	p Value	Chi-Square	Odds Ratio	95% CI	p Value
Age	0.04	0.99	0.85				
Gender	1.05	0.57	0.43				
LVEF	7.05	0.95	0.01	2.58	0.97	0.93−1.01	0.11
Systolic blood pressure	5.99	0.96	0.014	6.31	0.96	0.93−0.99	0.012
Hemoglobin	0.04	1.03	0.83				
Estimated glomerular filtration rate	0.41	0.99	0.52				
BNP	0.44	1.0001	0.51				
T2*	5.83	1.09	0.016	4.7	1.1	1.01−1.21	0.03
LGE	1.98	0.44	0.27				

square and the odds ratio were 30.87 and 1.21 for T2* value, 18.13 and 1.002 for BNP, and 8.18 and 1.32 for hemoglobin, respectively (Table 5). Receiver operating characteristic analysis revealed an optimal T2* threshold of 26.3 ms for identifying patients with nonischemic HF with LVEF <35%, with a C-statistics of 0.78, a sensitivity of 74%, and a specificity of 72% (Figure 5).

During follow-up of 167 patients with nonischemic HF, HF hospitalization was performed in 12 patients (7.2%), and LV assist device was used in 4 patients (2.4%) because of refractory pump failure. One patient died after LV assist device utilization. In relation to the risk for MACE, multivariate logistic regression analysis showed that chi-square and odds ratio were 6.31 and 0.96 for systolic blood

pressure, 4.70 and 1.02 for T2*, and 2.58 and 0.97 for LVEF, respectively. According to univariate logistic regression analysis, no other factors were able to predict the risk for MACE (Table 6). Receiver operating characteristic analysis revealed an optimal T2* threshold of 25.1 ms for predicting MACE, with a C-statistics of 0.66, a sensitivity of 94%, and a specificity of 40% (Figure 5).

Discussion

The present study quantified myocardial iron content in patients with moderate to advanced HF and normal ventricular function using T2* CMR. T2* value was correlated with LV functional parameters and was significantly greater in patients with nonischemic HF than ischemic HF or patients with normal function. Furthermore, among patients with nonischemic HF, multivariate regression analysis showed a significant correlation between T2* value and LVEF. These results suggest that myocardial iron deficiency (as expressed by a high T2* value) is associated with nonischemic HF and impaired LV function. This is the first report to demonstrate that myocardial iron content is reduced in patients with nonischemic HF when compared with patients with ischemic HF or normal function. In addition, multivariate logistic analysis demonstrated that T2* is comparable with BNP in terms of detecting nonischemic HF with LVEF <35%, and that a high T2* value is a candidate to predict the risk for MACE in patients with nonischemic HF.

Iron plays a key intracellular role in many cell types. In cardiac myocytes, this includes an important role within mitochondria and in myoglobin.[7] Dietary iron deficiency in rats results in induced dilated cardiomyopathy characterized by aberrant mitochondrial and irregular sarcomere organization and an increase in reactive nitrogen species and RhoA expression. Morphologic examination showed that the major/minor ventricular diameters and ventricular volume were significantly enhanced in iron-deficient rats.[8] In our study, most patients with nonischemic HF with LV dysfunction had dilated cardiomyopathy or were in the dilated phase of hypertrophic cardiomyopathy, which is similar to the morphologic characteristics seen in hearts from iron-deficient rats.

T2* value is dependent on a variety of factors, including macroscopic variables, structural variations at the microscopic level (such as capillary density, fibrosis, or inhomogeneous iron deposition),[9] the presence of deoxygenated hemoglobin, and relative myocardial perfusion. In ischemic HF, deoxygenated hemoglobin is often present after the hemorrhagic infarct, fibrosis, and calcium deposition in the infarcted tissue, which may result in a low T2* value. In the present study, there was no difference in T2* value between with and without midseptal LGE in each patient group (Table 3). Accordingly, a low T2* value may not directly reflect myocardial fibrosis, expressed as the presence of LGE. From our data, it is not possible to determine whether patients had absolute iron deficiency (reduced iron stores) or relative iron deficiency (decreased systemic iron availability despite overall normal total/body iron). In the present study, serum iron and ferritin were measured in 49 (20%) and 23 (9%) of 248 patients. Pearson correlation coefficient of T2* showed $r = 0.05$ for serum iron and $r = -0.38$ for ferritin, respectively. T2* might be reduced iron stores, expressed as the decrease of ferritin. Furthermore, T2* and the factors of anemia such as hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume did not have relevance (Table 2).

A 3-T scanner equipped with dual-source parallel radiofrequency transmission enables the reduction of the inhomogeneity artifact.[10] A multiecho gradient-echo with black blood T2* sequence avoids magnetic susceptibility artifact and measurement error, which may otherwise confound measurements of myocardial T2* in vivo.[11] This study is the first report to describe the clinical utility of high T2* value, as assessed using 3-T CMR. The calibration analysis of magnetic resonance relaxometry against the absolute iron concentration in the human heart demonstrated that myocardial T2* provided a robust ($r^2 = 0.910$) correlation with chemically assayed cardiac iron. Furthermore, there are difficulties with T2* measurement in heavily iron-loaded tissue in which signal decay is rapid, requiring very short echo times.[1] Conversely, high T2* values accurately reflect low iron concentrations in the myocardium. T2* value for patients with normal function was 22 ± 3 ms, which is almost 1/2half value to the normal range (52 ± 16 ms) reported in previous studies using 1.5 T scanner.[2]

We acknowledge that the present study is limited by T2* measurement using 1 magnetic resonance imaging system in a single center. The transferability of T2* technique is important to increase the utility of CMR T2* measurements and would help to assure that results from different magnetic resonance imaging scanners at different centers would be comparable. One important factor for T2* value is the selection of range of echo times. In all cases, the relation between echo times and myocardial signal intensity transformed into natural logarithms became linear (the mean correlation coefficient 0.99). These data support the echo times used in this analysis as reasonable for the accurate calculation of T2*.

Disclosures

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