Title: Quantification of Enhancement of Left Ventricular Myocardium in Patients with Dilated Cardiomyopathy Using Delayed Enhanced MR Imaging

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Abstract

The purpose is to evaluate delayed enhancement (DE) of the myocardium in patients with dilated cardiomyopathy (DCM), compared with control subjects. We also evaluated the interrelationships of DE and contractile function.

DCM patients (n=42) and 14 control subjects were evaluated by DE MR imaging, acquired using a two-dimensional segmented inversion-recovery prepared gradient-echo sequence (TI=250msec), 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium.

For the myocardium of LV, we traced epicardial and endocardial borders, and regions of interest (ROIs) were placed in each slice. For analysis of DE images, the signal-to-noise ratio (SNR) and the contrast-to-noise ratio (CNR) of the LV myocardium were calculated. The averaged SNR (aSNR) and averaged CNR (aCNR) per slice of the LV myocardium were calculated. In the DCM group, we also evaluated the interrelationship of DE and the contractile function of the left ventricle (LV).

Mean aSNR was not significantly different between the studied groups; however, mean aCNR was significantly higher in the DCM group (3.5±3.1) than in control subjects

(-4.1±2.1).

In the DCM group, aCNR was moderately related to LV ejection fraction (LVEF) ($r = 0.52$, $P < .0001$). Mean aCNR was significantly higher in the DCM group with low LVEF (<25%) (6.0±2.8) than in the DCM group with high LVEF (≥25%) (2.0±2.3).

In DE MR imaging, the LV myocardium of DCM usually has high aCNR, which may suggest fibrosis. Quantification of aCNR may contribute to the diagnosis of DCM. The level of aCNR seems to correlate with LVEF. Using this technique, quantification of aCNR is objective and very useful for the diagnosis of DCM and contractile function of LV.

Key words: dilated cardiomyopathy, diagnosis, delayed enhancement, magnetic resonance, contractile function

INTRODUCTION

Nonischemic dilated cardiomyopathy (DCM) is a primary cardiac disease characterized by depressed contractility and dilatation of the left and/or right ventricle in the presence of normal coronary arteries [1.2]. In DCM, the interstitium is altered and collagen content is increased [1–10], leading to diastolic dysfunction [11]. The effects of a stiff cardiac interstitium on systolic performance in this patient group, however, remain unclear because reported studies have yielded conflicting results [4,5,7–10]. In particular, the difficulty of performing accurate quantification of fibrosis and contractile function has been a major limitation of these studies [3,4,6,12,13].

In recent years, myocardial viability imaging with delayed contrast enhancement has become widely accepted for the detection and characterization of myocardial infarction. Scar or fibrosis is depicted as an area of high signal intensity on delayed enhancement (DE) MR images. Delayed myocardial enhancement is not specific to myocardial infarction and can be observed in many other cardiac diseases [14-16].

For DE MR imaging, the value of the chosen inversion time (TI) is important, because it determines the contrast between remote (viable) and abnormal myocardium. At the

optimum TI, the signal from a normal myocardium is nulled, while contrast-enhanced tissue is bright, having relaxed past the null point. Generally, operators select optimal TI; however, in this situation, the evaluation of delayed enhancement may not be objective, and it may be very difficult to evaluate diffuse enhancement of the myocardium [14-17].

The purpose of this study was to quantify DE of the myocardium in patients with DCM, comparing with control subjects and to clarify clinical usefulness of this technique. In addition, we evaluate the interrelationships of DE and contractile function in patients with DCM.

MATERIALS AND METHODS

Patient and Control subjects

Patients with DCM (n =42, mean age =52.1± 15.4, nine women) and control subjects (n =14, mean age =48.5± 16.7, three women) underwent MR imaging at our institution between September 2001 and November 2006. There was no difference in age between the two groups (p= 0.435). The diagnosis of nonischemic DCM was made

according to the World Health Organization/International Society and Federation of Cardiology criteria [18,19].

None had clinical symptoms or signs of ongoing myocarditis. Significant coronary artery disease (CAD) (>50% diameter luminal stenosis in any coronary artery) and a normal cardiac MR (CMR) -derived left ventricular ejection fraction (LVEF) (EF>56%) were excluded from this study. Other exclusion criteria were the presence of any contraindications of CMR, significant valvular disease, hypertrophic cardiomyopathy, or any evidence of infiltrative heart disease. In addition, all of the patients with DCM underwent myocardial biopsy. In all, the specimen showed disarray, varying degrees of interstitial fibrosis, and/or myocyte hypertrophy of the myocardium, which were consistent with DCM. Nine patients had been treated with angiotensin-converting enzyme inhibitors, eight with diuretics, five with digitalis, four with angiotensin receptor blockades, and three with beta-blockers before the MR study.

All control subjects (n=14) underwent CMR because of arrhythmia; however, no subjects had abnormalities based on coronary angiography, laboratory testing, echocardiography, and myocardial biopsy, which was performed to rule out various

myocardial diseases. All subjects gave written informed consent, and the protocol was approved by the medical ethics committee.

CMR Imaging

All patients were studied in the supine position using a 1.5-T CMR system (Signa CV/i, GE Healthcare, Milwaukee, Wis) with a 4-element phased-array surface coil. The CMR study consisted of cine steady-state free-precision imaging (repetition time, 3.4 ms; echo time, 1.2 ms; in-plane spatial resolution, 1.6X2 mm) of LV function. All images were acquired with ECG gating and breath-holding. Cine and DE images were obtained in 8 to 14 matching short axes (8-mm thickness with 0-mm spacing). DE images were acquired using a two-dimensional segmented inversion-recovery prepared gradient-echo sequence (repetition time msec/echo time msec/inversion time msec, 9.8/4.4/250; typical voxel size, 1.3 x 1.16 x 8 mm3) 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Schering, Berlin, Germany).

Data Analysis

All MR imaging post processing was performed by a single observer (E.S., with over 10 years of experience in cardiac MR imaging). LVEF was derived from cine images using the MASS software package (MEDIS, Leiden, the Netherlands). On the basis of LVEF results, patients were divided into a low EF group (<25%) and high EF group (≥25%) (2).

For analysis of DE images, we evaluated the signal intensity (SI) of the myocardium of the left ventricle (LV) and skeletal muscles near the heart using workstations (Advantage Windows 4.2; GE Healthcare).

For the LV myocardium, we manually traced epicardial and endocardial borders including the papillary muscles, and regions of interest (ROIs) were placed at each slice. We traded and used all of the myocardium (total ROI in myocardium; 141. 6 – 311.2 cm2) as ROI in all subjects. For the skeletal muscles, we manually traced the borders of the deltoid muscle, and ROIs were placed in the same slice (total ROI in muscle; 359.0–836.87 cm2) (Fig. 1). If the deltoid muscle was too small to trace or was not seen in the slice, we traced the borders of the trapezius muscle

The calculated SI values were divided by background noise (air) to measure the averaged signal-to-noise ratio (aSNR) and averaged contrast-to-noise ratio (aCNR) per

slice in each patient.

Background noise was evaluated as follows:: three ROIs (each ROI; approximately 20cm2, 19.5-21.8cm2)were placed on the anterior extracorporeal background (one at the top, one at the middle, and one at the bottom of the field of view), and the mean SI ± standard deviation of noise was measured in three regions.

First, the signal-to-noise ratio (SNR) of the LV myocardium was calculated using the following equation for each slice: SNR= SImyo/ SDair, where SImyo is SI of the myocardium and SDair is the standard deviation of air.

The contrast-to-noise ratio (CNR) for the LV myocardium was calculated using the following equation for each slice: CNR = (SImyo - SImusc)/SDair, where SImusc is the SI of the muscle.

The total values of SI, SNR, and CNR were then calculated for each patient. The averaged SI (aSI), SNR (aSNR) and CNR (aCNR) per slice for the LV myocardium were calculated using the following equation for each individual: aSI = total value of SI/ total number of slices in each patient. aSNR= total value of SNR/ total number of slices in each patient. aCNR = total value of CNR/ total number of slices in each patient.

To assess the inter- and intraobserver reproducibility of the measurements of aSNR and aCNR, more than 6 months after the first reading, 28 (50%) imaging studies randomly selected from the total sample were separately reexamined by the first reader (E.S.) and a second independent blinded observer (I.S., with over 10 years of experience in cardiac MR imaging).

Statistical Analysis

All values are expressed as the mean ±SD. Statistical analysis was performed on clinical and morphological variables with the paired t test and Mann-Whitney's U-test for continuous variables. The results are expressed as the sensitivity, specificity, and overall accuracy, with 95% confidence intervals (CIs) calculated with the normal approximation method (20). Pearson correlation coefficients were used to examine the correlation of LVEF with aSI, aSNR, and aCNR. Correlation coefficient values of 0.4–1.0 were considered to indicate a correlation (21). In all tests, $P < 0.05$ was considered significant.

We created receiver operating characteristic (ROC) curves and determined the

threshold that led to the optimal values of probabilities in the presence or absence of DCM. This optimal threshold was defined as the intersection of the ROC curve with the bisecting line at which sensitivity equated specificity [22].

Intra- and interobserver agreement for aSNR and aCNR was assessed using linear regression and Bland-Altman analyses. All statistical analyses were performed using commercially available software (SPSS, release 11.5; SPSS, Chicago,Ill).

RESULTS

Table 1 shows the mean LVEF, number of slices of the myocardium, aSI of the myocardium, skeletal muscle, aSNR, and aCNR in both the DCM group and control subjects. Mean aSNR was not significant between the DCM group and control subjects; however, the mean aSI of the myocardium and aCNR were significantly higher in the DCM group than in control subjects. On the other hand, the mean aSI of the muscle was significantly higher in control subjects than in the DCM group.

ROC analyses (Fig 2) demonstrated good discriminatory power for using aCNR to differentiate between the presence and absence of DCM. The best threshold values were

the calculated 0.1 points of aCNR.

When more than 0.1 points of aCNR was used as the threshold for DCM diagnosis, the sensitivity, specificity, and accuracy were 93% (39/41) (95% confidence interval [CI]: 84%, 99%), 86 % (12/15) (95% CI: 58%, 93%), 92 % (61/66) (95% CI: 84%, 97%), respectively.

In the DCM group, In the DCM group, aCNR was moderately related to LV ejection fraction (LVEF) ($r = 0.52$, $P < .0001$). (Figure 3). On the other hand, aSI of the myocardium ($r = 0.26$, $P = 0.105$) and aSNR ($r = 0.23$, $P = 0.215$) was not significantly related to LVEF.

Table 2 shows the mean aCNR in the two groups divided by risk factors such as gender, or by the presence or absence of characteristics of age ≥ 60, ventricular arrhythmias, NYHA functional class below IV, low EF (<25%), chronic renal failure, blood pressure (BP) ≥ 140mmHg at MR study, body mass index, hyperlipidemia, diabetes mellitus, and a family history of cardiomyopathy (parents, siblings, and children). In the DCM group, mean aCNR was significantly higher in the low EF group (<25%) (6.0±2.8) than in the high EF group (≥25%) (2.6±2.3) (Figures 4,5). There was also significant

difference between the group with BP ≥ 140mmHg and the group with BP < 140mmHg; however, there was no significant difference for other factors.

Intraobserver ($r = 0.98$, $P < .0001$) and interobserver ($r = 0.95$, $P < .0001$) measurements of aCNR were also closely correlated.

At Bland-Altman analysis, the mean difference in the measurements of aCNR between the two readers was -0.50± 0.81 (standard deviation). The mean intraobserver difference in the measurements of aCNR was within 0.03 ±0.53 (Fig. 6).

DISCUSSION

Nonischemic DCM is associated with significant morbidity and premature mortality [19]. In patients with ventricular dysfunction, an important mechanism for the occurrence of arrhythmias and failure to respond to treatment is the presence of myocardial fibrosis [15,19,23,24].

Recently, DE MR imaging has become able to depict myocardial damage with high spatial resolution in various myocardial diseases. This technique has also been used for patients with DCM. In a previous study, 59% of patients with DCM did not show

gadolinium enhancement, although 28% demonstrated longitudinal or patchy midwall enhancement [19]. According to previous reports, myocardial fibrosis and disarray can show enhancement on DE images, but DE related to disarray is usually faint. Hence, enhancement mainly means that patients with DCM have myocardial fibrosis, which may be caused by inflammation as well as microvascular ischemia [25, 26]: however, in these studies, DE of the myocardium was subjectively evaluated based on the presence or absence of focal DE alone. To our knowledge, no studies have evaluated the quantification of DE of the myocardium in patients with DCM.

Quantification of delayed enhancement

Ideally, for evaluation of DE of the myocardium, SI of the myocardium should be measured on T1-weighted images without IR; however, it may be difficult to evaluate both focal and diffuse enhancement on T1-weighted images without IR. In addition, artifacts may increase because of the increased signal of contrast media and fat tissue. In this study, we used DE MR imaging with IR, and the CNR for LV myocardium was calculated using the SI of the skeletal muscle. Ideally, CNR of the normal myocardium and the area of abnormal myocardium should be determined; however, it is impossible to

determine the normal myocardium in DCM, because myocardial fibrosis may be diffusely distributed.

Also, it may be problematic to use the SI of the skeletal muscle, since there is great difference between the myocardium and skeletal muscle. However, it seems more problematic to use the SI of the other organs, because the composition of skeletal muscle is more similar to the myocardium than other organs. So far, we think that it may be most suitable to use the SI of the skeletal muscle; however, further studies are needed to verify which organ or area is most suitable.

In DE MR imaging, the optimal inversion time for the myocardium should be selected, and typical values are 175–250 msec [14, 16]. On the other hand, typical values for the inversion time of skeletal muscle are 310-390msec, which is longer than that of the myocardium [27]. In this study, we used a fixed inversion time (250msec), which is the optimal inversion time for the myocardium (Fig. 7) (28). Therefore, SI of the muscle is higher than SI of the normal myocardium, and CNR theoretically tends to be less than 0 points [28]. This study shows that the best threshold values were the calculated 0.1 points of aCNR, the result of which may be adequate for this theory.

DCM group versus control group

This study shows that mean aCNR was significantly higher in the DCM group (3.5±3.1) than in control subjects (-4.1±2.1), indicating that patients with DCM have more myocardial fibrosis than control subjects. When more than 0.1 points of aCNR was used as the threshold for diagnosing DCM, the sensitivity was 93%, specificity was 86 %, and accuracy was 92 % in this study. These results support this theory and suggest that quantification of aCNR is very useful for the diagnosis of DCM; however, this study did not show the diagnostic value between DCM and other myocardial diseases, and further studies are needed.

In this study, aSNR was not significant between the DCM group and control subjects. The reason of this is not completely clear. However, aCNR may be more reliable about myocardial enhancement than aSNR because aCNR has less noise of image than aSNR. On DE MR imaging, myocardial SI may be affected by various factors. Contrast material clearance from the myocardium is determined by several factors: the washout rate of contrast material from the normal myocardium, overall cardiac function, renal function, and possibly the administered dose of contrast material [14]. Therefore, the

inversion time is optimized for each patient just before image acquisition, which may be subjective. In this study, we used a fixed inversion time (250msec) in order to objectively evaluate myocardial SI.

In this study, mean aSI of the myocardium was also significantly higher in the DCM group than in control subjects. Mean aSI of the myocardium may have a diagnostic value, but the results also show that mean aSI of the muscle was significantly higher in control subjects than in the DCM group. These results suggest that aCNR may be more reliable than aSI of the myocardium for the diagnosis of DCM.

According to our results, the mean aSI of the muscle of normal subjects was higher than that of DCM patients, although the reason for this is not clear. Usually, in patients with DCM, abnormal cardiac function limits physical motility, which may cause skeletal muscle atrophy. We hypothesize that the reduction of extracellular fluid volume of the muscle due to atrophy is one reason for this result. In addition, various kinds of cardiomyopathy, such as desmin-related myofibrillar myopathy, can affect both skeletal muscle and myocardium [29]. As a possibility, cardiomyopathy itself caused skeletal myopathy and atrophy in some patients; however, further studies are needed to clarify

this issue.

Delayed enhancement in the DCM group

In previous reports, LVEF was a powerful, independent predictor of prognosis. Whereas the severity of left ventricular dysfunction can be correlated with outcome, the relation between LVEF and survival is weaker in more homogeneous populations, particularly when LVEF falls below 25 % [2,30-33]. This study shows that aCNR was moderate related to LVEF ($r = 0.52$, $P < .0001$) in the DCM group. Mean aCNR was significantly higher in the DCM group with low LVEF (<25%) than in the DCM group with high LVEF (≥25%). In DCM, recent studies showed that the extent of myocardial fibrosis was related to impaired LVEF, but it is sometimes difficult to evaluate the extent of myocardial fibrosis [4,5,7–10]. This study shows that quantification of aCNR on DE MR images is a very useful diagnostic method to noninvasively evaluate the extent of myocardial fibrosis, which can impair LVEF.

Previous studies showed that age, female sex, the presence of ventricular arrhythmias, and NYHA functional class below IV are predictors of prognosis (2, 30-34), although the

predictive reliability of these factors are not high. In this study, aCNR was not significantly related to these factors. On the other hand, aCNR was significantly related to BP. Hypertension is known to be a predictor of prognosis [2, 30-34]; however, the reason why BP was significant in this study is not clear. Further studies are needed to evaluate factors influencing prognosis.

Limitations

As a limitation of this study, we used a gadolinium dose of 0.2 mmol/kg. The optimal dose has not been defined, although doses in the range of 0.1 to 0.2 mmol/kg are suitable, but higher dosing usually requires a longer delay after injection to allow the blood pool signal to fall. Further studies will clarify this issue. Other conditions, such as other myocardial diseases, cause gadolinium uptake in the myocardium, and this must be considered in the interpretation of results in DCM patients.

Second, we used aCNR to assess interstitial fibrosis on DE MR images. In this study, all patients underwent myocardial biopsy for the diagnosis of nonischemic DCM; however, in regard to the severity of myocardial fibrosis, histological comparisons in patients with DCM were lacking. Therefore, further studies on the use of aCNR in DE MR images as a

marker of fibrosis are needed.

three-dimensional images.

Third, the sample size was small because our single hospital followed up so many DCM patients. Multicenter trial studies involving a larger number of patients with a longer follow-up period are needed.

CONCLUSION.

In DE MR imaging, LV myocardium of DCM usually has high aCNR, which may suggest fibrosis. aCNR may be related to the severity of LV dysfunction. Using this technique, quantification of aCNR is objective and very useful for the diagnosis of DCM and contractile function of LV.

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Table

Table 1. Mean LVEF, number of slices, aSI, aSNR, and aCNR in the DCM group and control subjects.

	DCM group (n=42)	Control subjects (n=14)	P Value
Mean LVEF	32.3±13.7	62.8±6.2	<0.0001
Mean number of slices	9.2±1.8	7.5±1.0	0.0012
aSI			
myocardium	13.5±1.5	7.4±2.0	0.0179
skeletal muscle	10.3±0.6	23.2±4.1	<0.0001
aSNR	9.4±4.5	10.35±4.1	0.401

aCNR	3.5±3.1	-4.1±2.1	<0.0001

Note: LVEF = left ventricular ejection fraction

aSI = averaged signal intensity per slice

aSNR = averaged signal-to-noise ratio per slice

aCNR = averaged contrast-to-noise ratio per slice

DCM = dilated cardiomyopathy

Table 2. Patient characteristics for mean aCNR

Patient characteristics	Mean aCNR
Sex	
Male (n=9)	5.1±3.0
Female (n=33)	3.1±3.1
Age	
Age ≥60 (n=15)	3.4±3.8
Age <60 (n=27)	3.6±2.8
Ventricular arrhythmias	
Present (n=20)	3.2±2.6
Absent (n=22)	3.8±3.6
NYHA function class below IV	
Present (n=10)	5.0±3.1

Absent (n=32)	3.1±3.1
LVEF	
LVEF ≥25 (n=16)	2.6±2.3*
LV EF <25 (n=26)	6.0±2.8*
Family history of DCM	
Present (n=10)	3.3±2.0
Absent (n=32)	3.6±3.4
Diabetes mellitus	
Present (n=6)	5.1±3.0
Absent (n=36)	3.2±3.1
Chronic renal failure	
Present (n=2)	1.4±0.4
Absent (n=40)	3.6±3.2
BP at MR imaging	
BP≥140mmHg (n=8)	3.9±3.3*
BP<140mmHg (n=34)	1.8±1.5*

Body mass index	
≥22 (n=7)	3.7±3.4
<22 (n=35)	3.5±2.9
Hyperlipidemia	
Present (n=5)	3.8±3.5
Absent (n=37)	3.7±2.6

Note: aCNR = averaged contrast-to-noise ratio

LVEF = left ventricular ejection fraction

DCM = dilated cardiomyopathy

BP = blood pressure

*significant difference between the groups

Captions for Figures

Figure 1. Epicardial and endocardial borders were manually traced and a region of interest (ROI) was placed in each slice to obtain signal intensity of the LV myocardium (L). Additionally, the borders of the deltoid muscle were manually traced and ROI was placed in each slice to obtain signal intensity of the skeletal muscles (M).

Figure 2. Scatter plots show correlations between LVEF and aCNR. The aCNR was significantly related to LVEF ($r = 0.52$, $P < .0001$). Dotted lines = 95% CIs.

Figure 3.

ROC plots using aCNR to differentiate between the presence and absence of DCM. The best threshold values were the calculated 0.1 points of aCNR (sensitivity, 93%; specificity, 86 %; accuracy, 92 %).

Figure 4. A 41-year-old man in the low EF group (<25%) of nonischemic dilated cardiomyopathy (DCM). MR delayed-enhanced image (repetition time msec/echo time

msec/inversion time msec, 9.8/4.4/250; Flip angle, 25 degrees) shows no focal myocardial DE; however, the averaged contrast-to-noise ratio (aCNR) of LV myocardium is high (10.5).

Figure 5. A 35-year-old man in the low EF group (<25%) of DCM. MR delayed-enhanced image (repetition time msec/echo time msec/inversion time msec, 9.8/4.4/250; flip angle, 25 degrees) shows many focal myocardial DE. The aCNR is also high (12.5).

Figure 6. Bland-Altman plots show satisfactory levels of agreement of (a) the mean difference in measurements of aCNR between the two readers and (b) the mean intraobserver difference in measurements of aCNR. SD = standard deviation.

Figure 7. Plot of SI versus TI for normal myocardium and skeletal muscle for DE inversion-recovery T1-weighted MR imaging. As magnitude data were collected, the recovery curve has the appearance of data points above the x-axis. Image contrast

varies depending on the TI used. Typical values of TI for the myocardium are 175–250 msec (TI1). On the other hand, typical values for the inversion time of skeletal muscle are 310-390msec (TI2), which is longer than that of the myocardium. At TI1, SI of the muscle is higher than SI of the normal myocardium, and CNR tends to be less than 0 points: CNR = (SImyo - SImusc)/SDair, where SImusc is SI of the muscle.