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Contraction Function of the Left Ventricle in Patients with Dilated Cardiomyopathy: Comparison of Delayed Enhanced MR imaging and indine -123- metaiodobenzylguanidine (123I-MIBG) scintigram

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Objective: The purpose of this study was to compare delayed enhancement (DE) cardiac magnetic resonance (MR) imaging with the indine-123-metaiodobenzylguanidine (123I-MIBG) scintigram for measurement of left ventricular (LV) contraction function in patients with dilated cardiomyopathy (DCM).

Materials and methods: DCM patients (n=29: mean age,51.9years; seven women) were evaluated by both DE cardiac MR imaging and 123I-MIBG scintigram. In all patients biopsy specimen showed disarray of the myocardium that was consistent with DCM. DE cardiac MR images were acquired using a two-dimensional segmented inversion-recovery prepared gradient-echo sequence (TI=250msec) 15minutes after intravenous administration of 0.1 mmol/kg gadolinium.

The average CNR per slice (aCNR) for the LV myocardium was calculated.

123I-MIBG scintigram was acquired at 15minutes and 3 hours (delayed imaging) after intravenous administration of 123I-MIBG (111MBq). The heart-to-mediastinum radioactivity ratio (H/M ratio) and washout rate (WR) was calculated. We evaluated the relationships between aCNR, WR, delayed H/M ratio, and the contraction function of the LV.

Results: In MR imaging, mean aCNR was significantly higher in the low LV ejection fraction (LVEF<25%) group (n=11, 6.6±3.6) than in the high LVEF (≥25%) group (n=18, 2.4±2.9). However, with the 123I-MIBG scintigram, delayed H/M and WR were not significantly different between high (delayed H/M ratio ; 1.7±0.3, WR; 37.6±14.5) and low (delayed H/M ratio; 1.7±0.2, WR; 38.2±14.2) LVEF groups.

Conclusions: DE MR imaging reflects the contraction function of the LV in patients with DCM, which may be related with myocardial fibrosis. DE MR imaging may be more useful to evaluate the contraction function of LV than 123I-MIBG scintigram.

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Keywords: MR imaging; 123I-MIBG scintigram; Myocardial fibrosis; Dilated cardiomyopathy

Introduction

Nonischemic DCM is a primary cardiac disease characterized by decreased 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 with increased collagen content,[1-10] leading to diastolic dysfunction.[11] However, it has been very difficult to noninvasively evaluate the severity of this disease.

In recent years, myocardial viability imaging with delayed contrast enhancement has become widely accepted for the detection and characterization of myocardial infarction and myocardial fibrosis. Scars and fibrosis are depicted as areas of high signal intensity on DE MR images. DE MR imaging is becoming a diagnostic standard for evaluation of myocardial damage with high spatial resolution in various myocardial diseases. This technique has also been used for patients with DCM. According to previous reports, myocardial fibrosis and disarray can show enhancement on DE MR images.[1,12,13]

In patients with DCM, 123I-MIBG scintigram images show abnormalities such as a reduced delayed H/M ratio, heterogeneous distribution of MIBG within the myocardium, and increased MIBG washout from the heart. 123I-MIBG scintigrams have been re-

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ported to be useful for evaluation of LV function in patients with heart failure.[14-19]

We have compared DE cardiac MR imaging with 123I-MIBG scintigrams for measurement of LV contraction function. We also compared these modalities in regard to performance status of patients based on New York Heart Association (NYHA) classification. The purpose of this study was to investigate whether quantification by DE cardiac MR imaging or myocardial 123I-MIBG scintigraphy was useful for noninvasively evaluating myocardial contraction function in patients with DCM.

Materials and methods

patients

Twenty-nine patients with DCM (mean age =51.9, seven women) were enrolled in this study. The diagnosis of nonischemic DCM was made according to the World Health Organization/International Society and Federation of Cardiology criteria.[18,19] None of the patients had clinical symptoms or signs of ongoing myocarditis. Patients with significant coronary artery disease (>50% diameter luminal stenosis in any coronary artery) or LVEF >56% were excluded from this study. Other exclusion criteria were the presence of any contraindications of cardiac MR (CMR), significant valvular disease, hypertrophic cardiomyopathy, any evidence of infiltrative heart disease, or treatment with beta-blockers before the imaging study. In all of the patients, specimens obtained by myocardial biopsy showed disarray, varying degrees of interstitial fibrosis, and/-or myocyte hypertrophy of the myocardium, which were consistent with DCM. Five patients had been treated with angiotensin-converting enzyme inhibitors, four with diuretics, three with digitalis, and two with angiotensin receptor blockades. All patients gave written informed consent, and the protocol was approved by the medical ethics committee.

DE MRI 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 and DE imaging. All images were acquired with ECG gating and breath-holding. DE images were obtained in 8 to 14 matching short axes (8-mm thickness with 0-mm spacing). DE images were acquired by 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, 1.3x1.16 x8 mm^3) 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-DTPA (Schering, Berlin, Germany).

Cardiac 123I-MIBG scintigraphy

In all patients, 123I-MIBG scintigrams were acquired at 15minutes and 3 hours after intravenous administration of 123I-MIBG (111MBq). Anterior planar and single photon emission computed tomography (SPECT) images were obtained by triple-head gamma camera (Prism 3000; Picker-International) with a low-energy high-resolution collimator. The gamma camera was rotated over a 120 °arc with an acquisition time of 40s per image at 5 °intervals for each view. Energy discrimination was provided by a 20% window centered at 159 keV. 64×64 pixel matrix.

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 LVEF group (<25%) and a high LVEF group (≥25%).[2]

For quantification of DE images, we evaluated the signal inten sity (SI) of the myocardium of the LV and skeletal muscles near the heart using a workstation (Advantage Windows 4.2; GE Healthcare).

For the LV myocardium, we manually traced epicardial and endocardial borders including the papillary muscles, and ROIs were placed in each slice. We traced and used the entire LV myocardium (total ROI in myocardium; 151. 3 - 301.2 cm^2) as an 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; 361.0-816.97 cm^2) (Figure 1). If the del-

Figure 1. For measuring signed intensity of the myocardium of the LV (H) and the skeletal muscles (M), we manually traced regions of interest (ROI) in each slice.

toid 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 average signal-to-noise ratio (aSNR) and aCNR per slice in each patient.

Background noise was evaluated as follows: three ROIs (each ROI; approximately 20cm^2, 19.3-21.4cm^2) were placed on the anterior extracorporeal background (one at the top, one in the middle, and one at the bottom of the field of view), and the mean SI ± standard deviation of noise was measured in all three regions.

First, the 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 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 average SI (aSI), aSNR, and 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 evaluate myocardial MIBG uptake, the whole H/M ratio was determined from the delayed anterior planar 123I-MIBG image. The H/M ratio was calculated by drawing ROIs around the LV myocardium and in the upper mediastinum and measuring the average counts per pixel in each ROI.

The global WR was calculated using the following formula: {([H]-[M])early - ([H]-[M])delayed} / ([H]-[M])early x 100(%), where [H] = mean count per pixel in the LV and [M] = mean count per pixel in the upper mediastinum.

Statical analysis

All values are expressed as the mean ±SD. Statistical analysis was performed on clinical and morphological variables with Mann-Whitney's U-test for continuous variables. 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.[18] In all tests, $P < 0.05$ was considered significant.

All statistical analyses were performed using a commercially available software (SPSS, release 11.5; SPSS, Chicago,III).

Results

Table 1 shows the mean LVEF, number of slices of the myocardium, aSI of the myocardium, aSNR, aCNR(Figure 2 and Figure 3), delayed H/M ratio, and WR(Figure 4) in both low and high EF groups. Mean aSI of the myocardium, aSNR, delayed H/M ratio, and WR were not significantly different between the two groups; however, the mean aCNR was significantly higher in the low EF group than in the high EF group.

In DE MR imaging, the aCNR was significantly related to the LVEF (r =0.49, P =0.0073) (Figure 5). On the other hand, the delayed H/M ratio and WR were not significantly related to LVEF (delayed H/M ratio; r=0.01, P=0.952, WR; r=0.06, P=0.756) (Figures 6 and 7).

Table 1. Mean LVEF, number of slices, aSNR, aCNR, early H/M ratio, delayed H/M ratio, and WR in the high LVEF group and low LVEF group.

	High LVEF group (EF≧25%, n=18)	Low LVEF group (EF<25%,n=11)	*P* Value
Mean LVEF	39.2±10.3	17.3±5.9	<0.0001
MR imaging			
Mean number of slices	7.6±1.2	7.4±1.0	0.9462
aSNR	8.4±3.8	12.2±6.4	0.1106
aCNR	2.5±3.0	6.6±3.6	0.003
123I-MIGB scintigram			
Early H/M ratio	1.7±0.2	1.7±0.1	0.9105
Delayed H/M ratio	1.7±0.3	1.7±0.2	>0.999
WR	2.5±3.0	2.5±3.0	0.9284

Note: LVEF = left ventricular ejection fraction
aSNR = average signal-to-noise ratio per one slice
aCNR = average contrast-to-noise ratio per one slice
MIBG = metaiodobenzylguanidine
H/M = heart/mediastinum

Figure 2. A 51-year-old man with nonischemic dilated cardiomyopathy (DCM) and high ejection fraction (45%). 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. The average contrast-to-noise ratio (aCNR) of LV myocardium is 1.5

Table 2 shows the mean aSI of the myocardium, aSNR, aCNR, delayed H/M ratio, and WR in NYHA I-II and NYHA III-IV groups. Mean aSI of the myocardium, aSNR, aCNR, and delayed H/M ratio were not significantly different between the two groups; however, the mean WR was significantly higher in the NYHA III-IV (41.7±12.1) groups than in the NYHA I-II groups (27.7± 14.7).

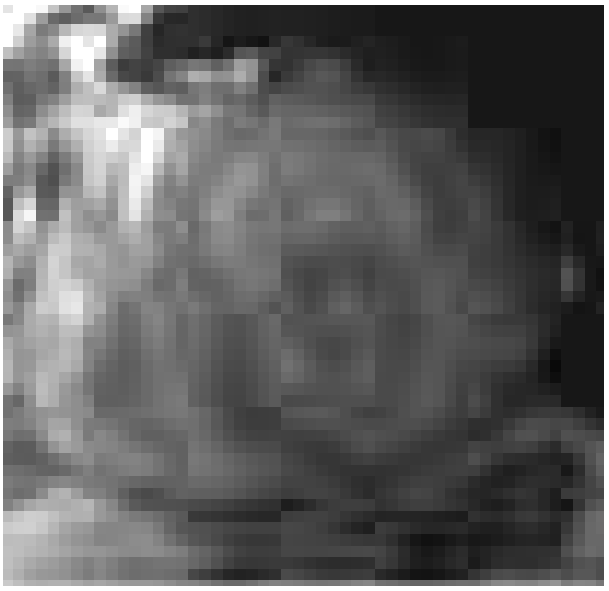

Figure 3. A 38-year-old man with nonischemic dilated cardiomyopathy and low ejection fraction (24%). MR delayed-enhanced image (repetition time msec/echo time msec/inversion time msec, 9.8/4.4/250; Flip angle, 25 degrees) shows diffuse delayed-enhanced areas in the left ventricular myocardium. The aCNR is 13.6

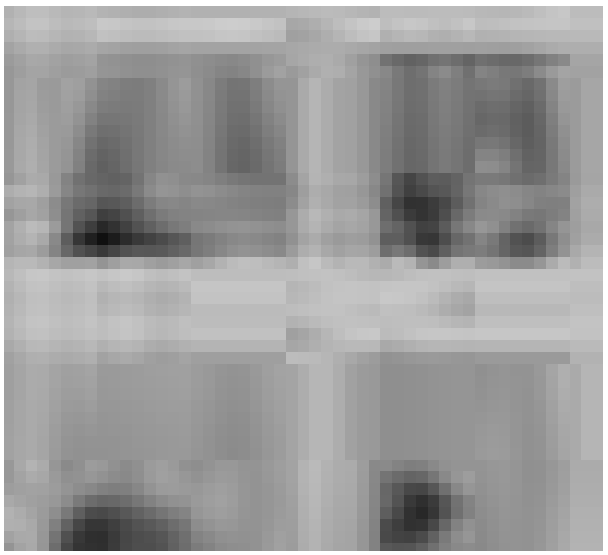

Figure 4. A 50-year-old woman with nonischemic dilated cardiomyopathy and low ejection fraction (19%). Increased lung uptake and severely reduced myocardial uptake are observed on the delayed 123I-MIBG planar image. The delayed H/M ratio is 1.34. The WR is 60%.

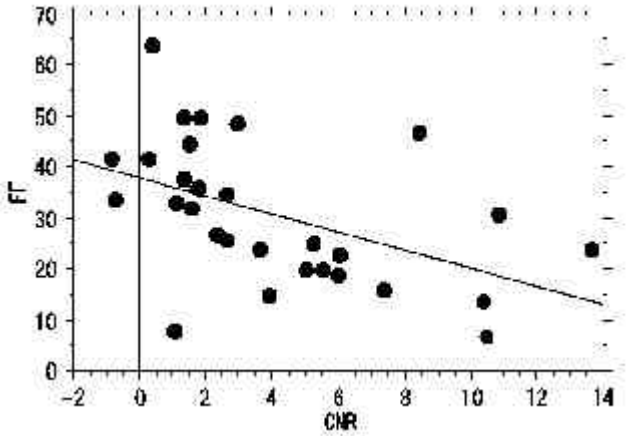

Figure 5. Scatter plots show correlations between LVEF and aCNR. The aCNR was significantly related to LVEF (r =0.49, P = .0073)

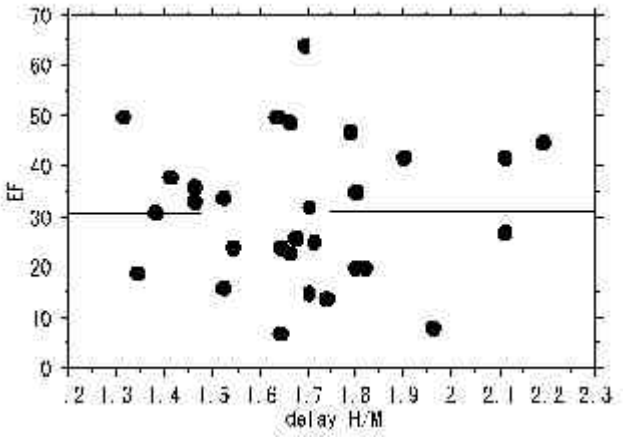

Figure 6. Scatter plots show correlations between LVEF and H/M ratio. The H/M ratio was not significantly related to LVEF (r =0.01, P = .952)

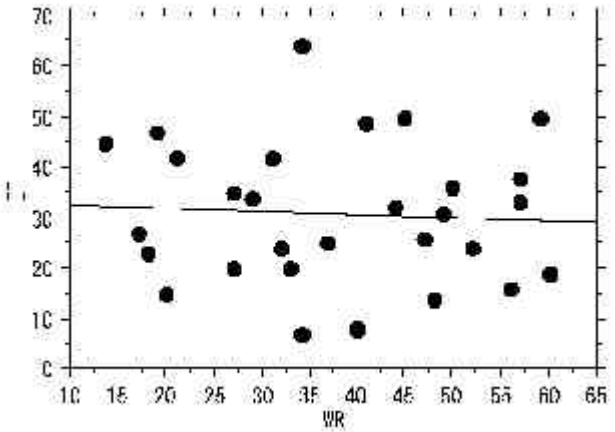

Figure 7. Scatter plots show correlations between LVEF and WR. The WR was not significantly related to LVEF (r =0.01, P = .756)

Table 2. Mean LVEF, number of slices, aSNR, aCNR, delayed H/M ratio, and WR in the NYHA class I-II group and III-IV group.

	NYHA I-II group (n=8)	NYHA III-IV group (n=21)	*P* Value
Mean LVEF	34.8±11.2	29.4±14.8	0.3172
MR imaging			
Mean number of slices	7.5±0.98	7.5±1.5	0.6963
aSNR	4.6±2.6	9.9±5.9	0.3932
aCNR	3.4±3.0	4.31±4.1	0.80721
123MIGB scintigram			
Early H/M ratio	1.7±0.2	1.7±0.2	0.8453
Delayed H/M ratio	1.8±0.3	1.7±0.2	0.3291
WR	27.7±14.7	41.7±12.1	0.0147

Note: LVEF=left ventricular ejection fraction
aSNR=average signal-to-noise ratio per one slice
aCNR=average contrast-to-noise ratio per one slice
MIBG=metaiodobenzylguanidine
H/M=heart / mediastinum

Discussion

Recently, DE MR imaging is rapidly becoming the standard of reference for evaluatory myocardial damage with high spatial resolution in various myocardial diseases.[13] 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.[12] According to a previous report, myocardial fibrosis and disarray can show enhancement on DE images, but DE related to disarray is usually faint.[12] Hence, in DCM patients, delayed enhancement is considered to mainly reflect myocardial fibrosis, which may be caused by inflammation as well as microvascular ischemia.[21,22] However, in previous studies, DE of the myocardium was subjectively evaluated based on the presence or absence of focal DE alone. So far, there are few reports quantitative DE MR imaging. It is not clear how DE cardiac MR imaging would be useful for noninvasive evaluation of myocardial contraction function and clinical severity in patients with DCM.

On the other hand, 123I-MIBG scintigrams are useful for evaluation of LV function in patients with heart failure caused by various heart diseases including DCM.[14-19] In this study, we compared DE cardiac MR imaging with 123I-MIBG scintigrams for measurement of LV function. We also compared these imaging modalities between groups divided according to NYHA classification.

Quantification of DE MR imaging

For DE MR imaging, it is important to determine the inversion time for obtaining optimal image contrast between normal and abnormal myocardium. The optimum TI should be adjusted for each patient to null the signal of normal myocardium.[13] However, use of variable TI makes quantitive assessment of myocardial enhancement difficult. Moreover, diffuse enhancement of the myocardium cannot be evaluated with this technique.

In this study, we used fixed TI for DE MR imaging, and the CNR for LV myocardium was calculated using the SI of the deltoid or trapezius muscle to evaluate diffuse enhancement of the myocardium objectively. The skeletal muscles have a similar histological composition, which may be suitable to be used as a reference ROI. However, further studies are needed to verify which organ or area is most suitable as a reference ROI.

Usually, ischemic myocardial damage shows segmental distribution while in DCM, myocardial fibrosis shows diffuse distribution.[1,2] Therefore, in DCM patients, it is difficult or impossible to measure CNR separately in normal and abnormal territories of the myocardium. Therefore, in the present study we used the whole LV myocardium as the ROI for CNR measurement on DE MR images.

123IMIBG imaging

MIBG is an analog of guanethidine that is taken up by uptake-1 as well as norepinephrine followed by storage in adrenalin-related sympathetic nerve ending. Increased MIBG washuout and reduced uptake in delayed scan were closely related to cardiac events or prognosis. It has also been suggested that myocardial MIBG imaging has a great impact on therapeutic management of the failing heart.[14-19]

It has been reported that reduced myocardial 123I-MIBG accumulation is correlated with diminished LV function in patients with heart failure.[24,25]

DE MR imaging versus 123IMIBG imaging

In this study, the mean aCNR was significantly higher in the low LVEF group than in the high LVEF group. However, there was no significant difference between the two groups in 123I-MIBG scintigrams. In addition, aCNR was significantly related to LVEF ($r=0.49$, $P=0.0073$). On the other hand, delayed H/M ratio and WR were not significantly related to LVEF. These results suggest that DE MR imaging may be more useful for evaluating contraction function than 123I-MIBG scintigrams.

Our study included patients with severe DCM, and it is well known that early uptake of cardiac MIBG tends to decrease in patients with severe DCM; this could be a reason why the delayed H/M ratio and WR were not significantly related to LVEF in our study.

Our study shows that the mean WR was significantly higher in NYHA class III-IV groups than NYHA I-II groups. On the other hand, DE MR imaging was not significantly different between these two groups. Hence, in patients with DCM, 123I-MIBG findings may more precisely reflect the severity of clinical symptoms than MR imaging. This result suggests that clinical symptoms are related not only to contraction function but also to abnormalities of the myocardial adrenergic nervous system. However, further studies are required to clarify this issue.

Clinical implications

This study shows that aCNR was significantly related to LVEF, which may reflect myocardial fibrosis. In previous reports, LVEF was a powerful and independent predictor of prognosis in patients with DCM. The severity of left ventricular dysfunction can be correlated with patients' outcome. Therefore, DE MR imaging is useful for evaluation of myocardial damage and prediction of prognosis.

Our results also show that the mean WR was significantly higher in NYHA functional class III-IV than NYHA I-II groups. Previous studies showed that NYHA functional classes below IV are predictors of prognosis.[2,26-31] For, patients who received beta-blocker treatment , NYHA functional class and WR are improved .That is why 123I-MIBG scintigraphy is a very useful tool for evaluating the myocardial adrenergic nervous system, which is improved in patients medication.[15-18]

Study limitations

This study includes several limitations. First, the small number of patients included in this study was a limitation.

As a second limitation, we evaluated the uptake of MIBG only in the anterior and inferior areas of the heart, and the MIBG count was obtained from an average of these two ROIs in each patient. Therefore our data may not represent overall MIBG uptake. However, even in normal subjects, the myocardial uptake of MIBG can be inhomogeneous and reduced in the inferoposterior segment of the heart. With use of a single, large ROI encompassing an overall heart, MIBG uptake may be overestimated because the MIBG count around the heart is included.[16]

As a third limitation, there may be a problem in quantifying the cardiac MIBG images. In the present study, 13 patients had an exceedingly low H/M (<1.7) on the early images. This may introduce underestimation when drawing ROIs manually on cardiac MIBG images of patients with heart failure.

Conclusion

DE MR imaging reflects the contraction function of the LV in patients with DCM, which may reflect myocardial fibrosis. DE MR imaging may be more useful for evaluation of contraction function of the LV than 123I-MIBG scintigram images. Analysis of DE MR imaging, especially aCNR, is expected to provide a potential technique for evaluating LV function and myocardial fibrosis in patients with DCM.

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