Relationship between myocardial involvement in the sub-epicardial legion of the left ventricular posterior wall, and autonomic dysfunction in patients with Duchenne muscular dystrophy

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Abstract

Background: Myocardial fibrosis occurs in the sub-epicardial myocardium of the left ventricular posterior wall in patients with Duchenne Muscular Dystrophy (DMD). In DMD patients, parasympathetic nervous function decreases from the early juvenile phase. The aim of this study was to clarify the relationship between myocardial involvement in the sub-epicardial region of the posterior wall and autonomic dysfunction.
Methods: Twenty-six DMD patients with a normal fractional shortening (FS) of the left ventricle were enrolled in this study. The subjects were divided into a high echoic group (HE) which had a high echoic region in the sub-epicardial side of the posterior wall in the B-mode echocardiography, and a normal echoic group (N) in whom this high echoic region was not seen. Using two-dimensional speckle tracking echocardiography, the peak strain was separately measured in the endocardial side and epicardial side of the posterior wall. Using 24-hr ambulatory electrocardiograms, indices of autonomic function were calculated from analyses of the heart rate variability.
Results: The radial peak strain of the epicardial side of the posterior wall was smaller in the HE groups than in the N groups. The percentage of adjacent normal R-R intervals more than 50 ms different was smaller in the HE groups than in the N groups.
Conclusions: In DMD patients with a decrease of parasympathetic nervous function, the segmental strain of the epicardial side of the posterior wall was decreased. In the epicardial side of the left ventricle, parasympathetic distribution was less than in the endocardial side. A decrease in parasympathetic nervous function might be associated with myocardial involvement in the epicardial side of the posterior wall.

Key words: Duchenne muscular dystrophy, cardiomyopathy, speckle tracking echocardiography, autonomic dysfunction

Introduction

Duchenne type muscular dystrophy (DMD) is a seborrheic recessive inherited disease that causes progressive muscle weakness and muscle atrophy. DMD develops in one of every 3,500 births. The myocardial disorder is present than youth. However, its progression

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is very slow compared to the progress of skeletal muscle weakness. Since patients are often bedridden due to muscle weakness of the whole body until adulthood, they often do not have clinical symptoms even though their heart failure is advanced [1]. Serum cerebral natriuretic peptide (BNP) often does not show an increase even when the left ventricular inner diameter shortening rate (FS) is around 10% [2]. Myocardial injury of DMD takes a pattern of dilated cardiomyopathy, but differs greatly from the typical general dilated cardiomyopathy found by pathology. In general dilated cardiomyopathy, myocardial fibrosis often starts from the endocardium side, which is easily disturbed by ischemia. On the other hand, fibrosis of the left ventricular myocardium of DMD starts lesion from the adventitial side of the left ventricular wall and progresses toward the intima [3]. Analysis by MRI with late gadolinium enhancement has reported that myocardial fibrosis of DMD occurs from the adventitial side of the left ventricular posterior wall from the early years of young [4]. However, the mechanism causing fibrosis to originate from the adventitia side is unknown. We have reported that the local myocardial strain is impaired on the adventitial side of the left ventricular posterior wall [5]. In DMD, the cardiac parasympathetic function is impaired, and as a result, some patients present with sinus tachycardia due to relative sympathetic hypertrophy [6-9]. In this study, we examined the association between myocardial injury early on the left ventricular myocardial adventitia side, and autonomic dysfunction abnormality.

Material and Methods

The subjects were 26 patients with DMD who were hospitalized or hospitalized at the National Hospital Organization Tokushima Hospital from April 2008 to March 2011 and who had a left ventricular inner diameter shortening rate (FS) of 28% or more. Their age was 18.5 ± 8.1 (mean±SD) years old and FS 35.5 ± 7.4%. Diagnosis was based on neurological findings, clinical course, family history, serological creatine kinase value, muscle biopsy, and genetic analysis. According to the Swinyard severity classification [10], all patients had a severity classification of Stage 7 (requiring a wheelchair and requiring assistance to maintain a sitting posture). Patients on a 24-hour ventilator were not included. Patients who could not take a severe and clear heart echo image were excluded from the subject **(Table 1).** This study was approved by the Ethics Committee of the Tokushima National Hospital organization, and informed consent was obtained in writing from all eligible patients.

Cardiac echo diagram and strain analysis

A cardiac echo device, the Hitachi eub6500 with 2-5mhz sector probe, was used. A left ventricular short axis image, the left ventricular expansion period diameter and the left room diameter shortening ratio were measured. In the apex four-cavity cross-section image, we set the sample volume to the mitral tip portion, and measured the pulse Doppler and extended ability index. Using the B-mode image of the left ventricular longitudinal axis image, all patients were classified into two groups: a group with increased luminance on the posterior wall adventitia side (HE group), and a group not showing the increase in brightness (N group). The increase in luminance was visually determined. Patients with a clearly higher brightness compared to the intima side were incorporated into the HE group (Figure 1). In continuous three beats of the left ventricular longitudinal axis image, the radial peak strain of the left ventricular posterior wall was measured by dividing it into the intima side and the adventitia side using the speckle tracking method [11].

Cardiac autonomic nervous function

All patients underwent 24-hour halter ECG using ab SCM-6000 (Fukuda Electronics Co., Ltd., Tokyo). Using the data of the halter ECG, the autonomic nerve index: high frequency (HF), low frequency (LF), LH/HF, the percentage of adjacent RR intervals more than 50 Ms different (% rr50), and the standard

deviation of all normal r-r intervals (SDNN) were calculated.

Statistical analysis

All data represented by the average ± standard deviation (SD). All data were analyzed using the statistical analysis software (Prism 4 version 4.0 c 2005 GraphPad Software, Inc., San Diego, CA), and the probability value of 0.05 was a significant difference. All data was tested using a Wilcoxon Signed-rank test.

Results

The age of the HE group was higher than that of N group (21.6±5.8 vs.14.5±8.0, $p < 0.05$). Heart rate, FS and left ventricular expansion at the end of the period were not different in the two groups. No difference was observed in either of the groups with respect to the extended ability index [Table 1].

In myocardial strain analysis of the heart echocardiogram, the radial peak strain on the adventitial side of the posterior wall of the left ventricle was smaller in the HE group than in the N group (15.1±7.6 vs. 30.2±8.0%, $p<0.01$). Radial peak strain in the inner wall of the posterior wall of the left ventricle was smaller in the HE group than in the N group（24.9±5.9 vs 40.1±11.8%, $p<0.05$）(Figure 2).

In the heart rate variability analysis, the LF/HF, a sympathetic indicator, was not significantly different in the two groups. The parasympathetic nervous index, % RR 50 was smaller in the HE group than in the N group (4.5±4.6 vs. 12.5±10.7%, $p<0.05$)(**Table 2).**

Discussion

In this study, the age distribution of the HE group was significantly higher than that of the N group. Also, the HE group had a higher age and parasympathetic function than the N group. This finding is consistent with the report that the parasympathetic nervous function gradually declines from the early stage of young in DMD, and then progresses [7-9]. We evaluated the increase in brightness using integrated back scatter value and reported a significant IBS value on the outer membrane side of DMD and abnormality of cyclic variation [12]. Sengupta et al. have reported that differences in luminance in the myocardium are evident in the heart muscle, reflecting differences in the arrangement structure of the myocardium in healthy subjects [13]. However, the site of the increase in luminance recognized by DMD is stronger than the pattern in healthy subjects on the epicardial side of the posterior wall of the left ventricular myocardium. It is inferred that the increase in luminance on the adventitia side reflects the degree of myocardial fibrosis. In this study, it was found that local myocardial strain of the site with actual macroscopically high luminance was reduced. From this fact, it seems that the increase in luminance is a finding that can be used to conveniently judge the extent of myocardial injury caused by DMD.

The fact that the parasympathetic nervous index %RR 50 was smaller in the HE group than in the N group indicates that the parasympathetic nervous function was lower in the HE group than in the N group. It has been reported that parasympathetic function decreases with the progress of symptoms [9]. That is consistent with this report that the parasympathetic nervous function declined in the HE group with high age and local myocardial injury. Regarding cardiac autonomic innervation, Kawano and colleagues have reported that the Ach nerve endings of parasympathetic nerves occur more on the inner membrane side of the left ventricular myocardium and there are few on the adventitia side [14]. In DMD, the parasympathetic nervous system depression causes a relative sympathetic hypertrophy state from the early stage as compared with the intima side on the left ventricular adventitia side where there is little parasympathetic innervation. The myocardial injury may occur from the early stage as compared with the intima side. From the above, it was inferred that the localization of autonomic innervation is involved in myocardial fibrosis arising from the adventitia side of DMD.

A limitation of this study is that the MRI delayed contrast imaging of the targeted

DMD patients and the pathological organization could not be evaluated. Another limitation is the influence of internal blocking of β blockers. A beta blocker is used in cases where a decrease in strain is observed in the posterior wall of the left ventricle or in patients who show post-systolic shortening or systolic thinning etc. The N group did not take all patients with β blockers, whereas in the HE group, five cases out of 16 had already started oral administration at the time of the examination. Beta blockers have the effect of suppressing sympathetic nerve function and may have an influence on autonomic nerve heart rate variability analysis results as well.

In conclusion, it was suggested that myocardial damage may occur early on the adventitia side due to parasympathetic dysfunction in DMD.

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Table 1. Conventional echocardiographic parameters in the study groups

		DMD(HE)	DMD(N)	P value
		N=16	N=16	
Age	(y)	21.6±5.8	14.5±8.0	＜0.05
HR	(beats/min)	82±13.8	92±16.2	ns
FS	(%)	34.0±7.3	36.9±7.5	ns
LVEDD	(mm)	39.7±7.5	36.3±5.2	ns
LVESD	(mm)	23.3±5.9	26.7±3.7	ns
E	(cm/s)	23.4±101.0	20.1±83.6	ns
A	(cm/s)	47.8±10.0	46.1±17.8	ns
E/A		2.0±0.4	2.1±0.5	ns

HR: heart rate, FS: fractional shortening of left ventricle, LVEDD: left ventricle end-diastolic dimension, LVESD: left ventricle end-systolic dimension, E: peak mitral early filling velocity, A: peak mitral atrial filling velocity, ns: not significant

Table 2. Heart rate variability data

	DMD (HE)	DMD (N)	P value
	N=16	N=16	
HF (ms^2)	360.5±268.7	590.5±512.0	ns
LF/HF	2.9±1.5	2.9±1.5	ns
% RR50 (%)	4.5±4.6	12.5±10.7	<0.05
SDNN (ms)	83.8±20.9	108.5±44.1	ns

HF: high frequency, LF: low frequency, % RR50: the percentage of adjacent RR intervals more than 50ms different, SDNN: standard deviation of all normal R-R intervals, HE: high echoic group, N: normal echoic group ns: not significant

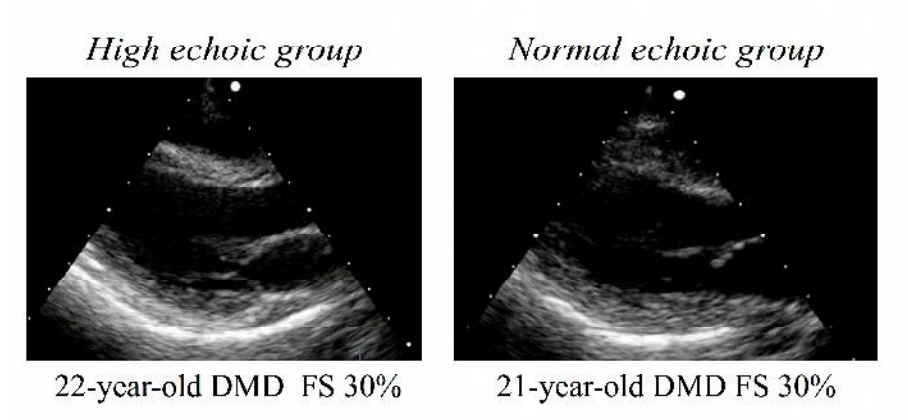

Figure 1. Representative B-mode longitudinal echocardiography recordings for the High Echoic (HE) group and the Normal echoic (N) group
(Left) Representative recording for a high echoic (HE) group of 20 year-old DMD patients. The epicardial side of the left ventricular posterior wall was highly echoic.
(Right) Representative recording for a high normal echoic (N) group of 22 year-old DMD patients. The echo level of the epicardial side of the left ventricular posterior wall was almost the same as that of the endocardial side.

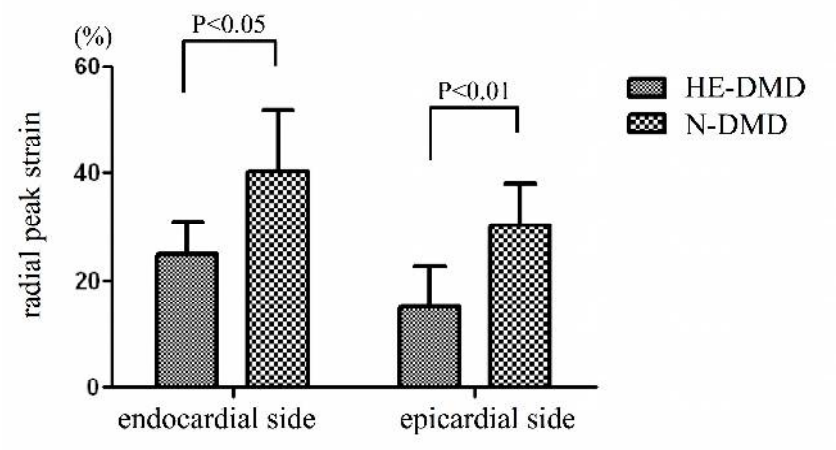

Figure 2. Segmental myocardial strain of left ventricular posterior wall in the study group
Radial peak strain of the endocardial and epicardial sides of the left ventricular posterior wall in the high echoic (HE) DMD group and the normal echoic (N) DMD group study group are shown. Bar and error bars show mean and SD.