

The relationship between clinical stage, prognosis and myocardial damage in patients with Duchenne-type muscular dystrophy: five-year follow-up study

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The evaluation of myocardial damage by [^{123}I] 15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP) imaging, which represents free fatty acid metabolism, has not been reported in patients with Duchenne-type muscular dystrophy (DMD). To date, the relationship between clinical stage, prognosis and myocardial damage has not been evaluated by radionuclear cardiac imaging. The main goal of this study was to elucidate the relationship of quantitative indices of myocardial damage obtained by radionuclear cardiac imaging ([^{201}Tl] and [^{123}I] BMIPP) to clinical stage and incidence of severe cardiac events in patients with Duchenne-type muscular dystrophy (DMD). **Methods:** The study population consisted of 28 male patients with DMD. The average age at the beginning of observation was 19.1 ± 7.4 yrs. Nuclear tomographic imaging was performed using [^{201}Tl] and [^{123}I] BMIPP. The mid-ventricular short axial slices were classified into four anatomical regions, and the normalized count data in these areas (TL, BM) were obtained. The endpoint was the occurrence of heart failure during the follow up period. **Results:** Thirteen cases of heart failure occurred during the 5-year follow-up period, including three cases with cardiac death due to congestive heart failure. Clinical staging correlated directly with TL ($p = 0.0118$) and BM ($p = 0.0401$) in the whole left ventricle. In regional TL analysis, an association was observed only in the septum ($p = 0.0151$), and in the anterior ($p = 0.0361$) region. The only discrepancy between the tracer parameters (TL – BM) in the septum was observed with the radionuclear cardiac values, which exhibited a relationship with cardiac events ($p = 0.0124$). This discordance, TL < BM, was contrary to that usually observed in patients with ischemic heart disease. **Conclusion:** The septum is the critical area of significance for cardiac events and outcome in patients with DMD. The uptake of [^{201}Tl] in this area was representative of the clinical stage, and TL-BM correlated well with the prognosis.

Key words: cardiac event, thallium-201, iodine-123-BMIPP, radionuclide imaging, SPECT

INTRODUCTION

DUCHENNE MUSCULAR DYSTROPHY (DMD) is a heritable,

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recessive, X-linked myopathy, which causes death in early adulthood.^{1–6} Congestive heart failure (CHF) is the most important cause of death.⁷ The onset of CHF is variable, which influences the prognosis in individual cases. Although myocardial fibrosis has been evaluated by [^{201}Tl] myocardial imaging in patients with DMD,^{9–11} there have been few studies evaluating disturbances of free fatty acid metabolism using [^{123}I]-15-(*p*-iodophenyl)-3-(*R,S*)-methylpentadecanoic acid (BMIPP).¹² The objective of this study was to elucidate the relationship

Table 1 Degree of skeletal muscular dysfunction

Degree	Activity	Numbers of patients
1	Going up and down stairs without handrails	0
2	Going up and down steps with handrails	0
3	Standing up from sitting position	0
4	Walking	3
5	Crawl on hands and knees	5
6	Crawl with difficulties	7
7	Sitting only	9
8	Unable to sit	2

between quantitative indices of myocardial damage, obtained by nuclear cardiac imaging ($[^{201}\text{Tl}]$ and $[^{123}\text{I}]$ BMIPP), and the degree of skeletal muscular dysfunction and cardiac events (heart failure and death), in patients with Duchenne-type muscular dystrophy.

METHODS

Study subjects

The patient population consisted of 28 males with DMD. Two cases were excluded due to a lack of echocardiographic data, and the remaining 26 cases were suitable for assessment.

The average age at the first imaging study was 19.1 ± 7.4 yrs, and the degree of skeletal muscular dysfunction (Table 1) ranged from 4 to 8. The diagnosis of DMD was based on typical clinical features, muscle biopsy, serum enzyme activity, electromyography, family history, and gene analysis.⁷

Radionuclide imaging acquisition and reconstruction of images

$[^{201}\text{Tl}]$ and $[^{123}\text{I}]$ BMIPP imaging were performed on different days with a 1-week interval. A dose of 111 MBq of radionuclide tracer was administered intravenously for both studies. A starCam 4000 (General Electric, Milwaukee, USA) equipped with a general purpose collimator was used for data acquisition and data analysis. The image acquisitions were performed 30 minutes after tracer injection. Energy peaks were generated as $72 \text{ keV} \pm 20\%$ for $[^{201}\text{Tl}]$ and $159 \text{ keV} \pm 20\%$ for $[^{123}\text{I}]$ BMIPP. Thirty-two planar images were acquired for 30 seconds each, over a 180-degree arc extending from the 45-degree right anterior oblique to the 45-degree left posterior oblique projection. Using a filtered back projection, trans-axial slices (6 mm thick) and the short axis of the left ventricle were constructed.

Quantitative analysis of radionuclide myocardial imaging

The count data from 2 slices of the mid-portion of the left ventricle, the most reliable data of all slices, were aver-

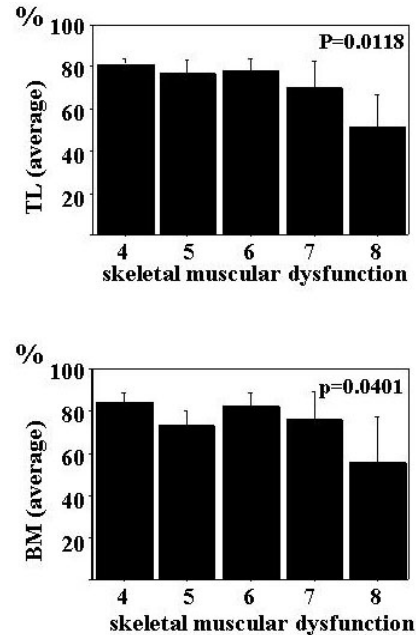


Fig. 1 The degree of skeletal muscular dysfunction and normalized tracer uptake (average of 4 anatomical regions). The degree of the skeletal muscular dysfunction correlated both with TL ($p = 0.0118$) and BM ($p = 0.0401$). TL: Normalized average of regional $[^{201}\text{Tl}]$ uptake (%), BM: Normalized average of regional $[^{123}\text{I}]$ BMIPP uptake (%), Skeletal muscular dysfunction: The degree of skeletal muscular dysfunction.

aged. The left ventricular short axis slice was divided into 4 regions: anterior, septal, inferior, and lateral. The highest count in the whole left ventricle was defined as 100%, and the normalized average of regional tracer uptake (TL and BM) was measured in these 4 regions (90°) and in the whole left ventricle (360°).

Echocardiography

Echocardiography was performed with a Toshiba PowerVision 6000 ultrasound diagnostic system (Toshiba Corp., Tokyo, Japan). Parasternal short-axial views, on expiration in the left semirecumbent position, were recorded on videotape. The left ventricular diastolic dimension (LVDd) was evaluated at the mid-portion of the left ventricle in the short axial slice. When LVDd was found to be increased by greater than 5 mm during the follow up period, echocardiographic worsening was diagnosed.

Follow-up procedures

The five-year follow up study was begun after the first radionuclear study was performed. Patients were evaluated for chest X-ray and 2-dimensional echocardiography, annually, and at the time of dyspnea due to congestive heart failure up to 5 years. CHF (event) was assumed to be positive when the following two conditions were satisfied;

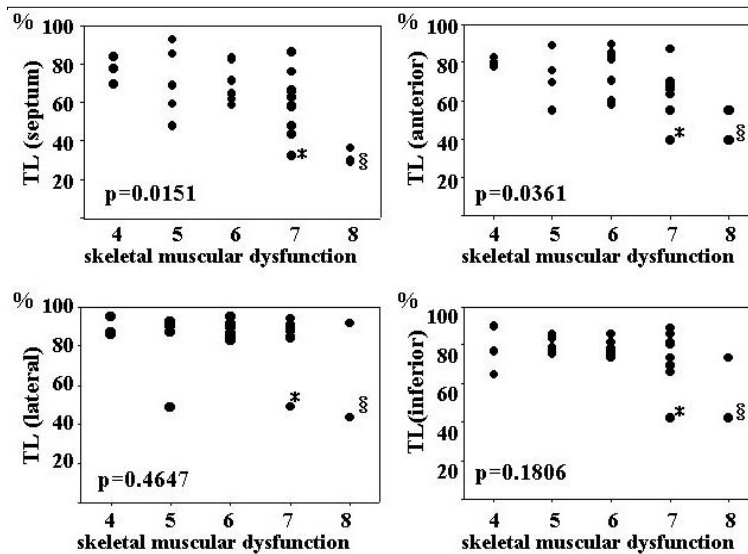


Fig. 2 The degree of skeletal muscular dysfunction and normalized tracer uptake (regional). Significant differences in TL were observed according to the degree of the skeletal muscular dysfunction in septal and anterior regions. TL: Normalized average of regional [^{201}Tl] uptake (%), Skeletal muscular dysfunction: The degree of skeletal muscular dysfunction.

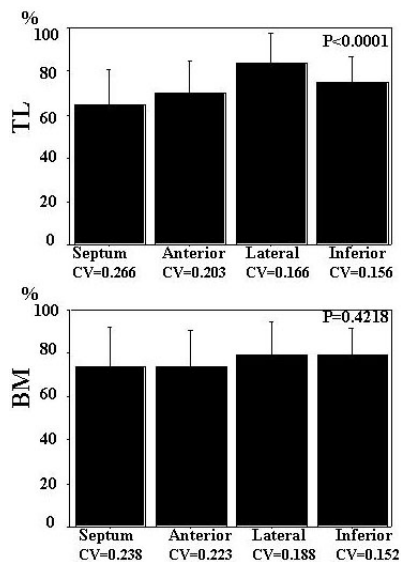


Fig. 3 Comparison of TL by 4 anatomical regions. Septal and anterior regions exhibited more variance of TL than the other 2 regions, although BM was relatively homogeneous among the 4 regions. TL was lower in the septum and anterior regions than in the other 2 regions. TL: Normalized average of regional [^{201}Tl] uptake (%), BM: Normalized average of regional [^{123}I] BMIPP uptake (%), CV: Coefficient of variance (%).

1. Clinical symptoms such as edema, dyspnea due to CHF.
2. Pulmonary edema in chest X-ray and/or worsening of left ventricular diastolic dimension in echocardiography.

Statistics

The relationship of myocardial involvement in the radionuclear study and the degree of skeletal muscular dysfunction, and the difference in the mean counts of the tracers by region was tested by ANOVA. Radionuclide parameters and prognosis were compared with unpaired t test. Statistical significance was defined as $p < 0.05$.

RESULTS

Thirteen cases, including three deceased cases due to congestive heart failure, exhibited a cardiac event throughout the follow up period.

Myocardial damage in the radionuclear study and degree of skeletal muscular dysfunction

The degree of the skeletal muscular dysfunction correlated both with TL ($p = 0.0118$) and BM ($p = 0.0401$) (Fig. 1). As the TL data demonstrated a lower p-value than the BM data, TL was compared with the degree of skeletal muscular dysfunction in each of the 4 anatomical regions. Significant differences in TL were observed according to the degree of the skeletal muscular dysfunction in septal and anterior regions (Fig. 2). These 2 anatomical regions exhibited more variance of TL than the other 2 regions, although BM was relatively homogeneous among the 4 regions (Fig. 3).

Relationship between cardiac events and radionuclide parameters

The study patients were classified into two groups on the basis of the presence or absence of cardiac events (heart

Table 2 Relationship between cardiac hard event and radionuclide parameters

parameter	anatomical region	p-value
TL	average	0.4868 (n.s.)
TL	septum	0.0768 (n.s.)
TL	anterior	0.4369 (n.s.)
TL	lateral	0.4846 (n.s.)
TL	inferior	0.9482 (n.s.)
BM	average	0.8491 (n.s.)
BM	septum	0.9397 (n.s.)
BM	anterior	0.4033 (n.s.)
BM	lateral	0.9391 (n.s.)
BM	inferior	0.6908 (n.s.)
TL – BM	average	0.4155 (n.s.)
TL – BM	septum	0.0124
TL – BM	anterior	0.8005 (n.s.)
TL – BM	lateral	0.4698 (n.s.)
TL – BM	inferior	0.3525 (n.s.)

The only parameter which demonstrated a difference between two groups was TL – BM in septum. TL: Normalized average of regional [²⁰¹Tl] uptake (%), BM: Normalized average of regional [¹²³I] BMIPP uptake (%), TL – BM: Difference in the normalized average of regional tracer uptake.

failure and/or death). TL, BM and the difference between the two tracers (TL – BM) were compared between the groups for each of the 4 anatomical regions (Table 2). The only parameter which exhibited a significant difference between the two groups, was TL-BM in the septum (Fig. 4). When the negative value of TL-BM was assumed to be indicative of the cardiac event, sensitivity, specificity and accuracy were 100%, 30.8% and 65.4%, respectively.

Case presentation

A representative case is presented in Figure 5. The patient was 17 years of age at the time of the radionuclear studies, and he subsequently died five years later of congestive heart failure. The radionuclear studies demonstrated a discrepancy in the accumulation of the two tracers in the septum (TL = 71.2, BM = 87.1, TL – BM = –15.9).

DISCUSSION

Duchenne-type muscular dystrophy (DMD) is an inherited (X-linked, recessive) myopathy, caused by mutations in the dystrophin gene, which has a poor prognosis.¹⁻⁷ Death occurs in early adulthood due to respiratory failure or congestive heart failure.⁷ When the onset is assumed to be at birth, the time to the occurrence of the cardiac event (i.e., heart failure and/or death), is variable for each case; which often affecting the prognosis. Furthermore, in the present study there were several cases, which exhibited a cardiac event at about twenty years of age, although some cases survived to the age of thirty years, without any event. Although cardiac involvement did not correlate with skeletal muscle weakness in a previous investiga-

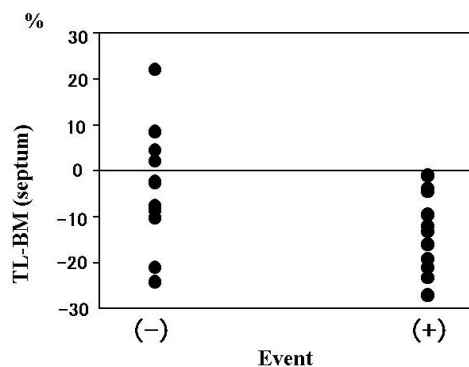


Fig. 4 Relationship between TL – BM in septum and hard cardiac events. TL – BM was the only parameter which demonstrated a difference between two groups. TL – BM: Difference of the normalized average of regional tracer uptake.

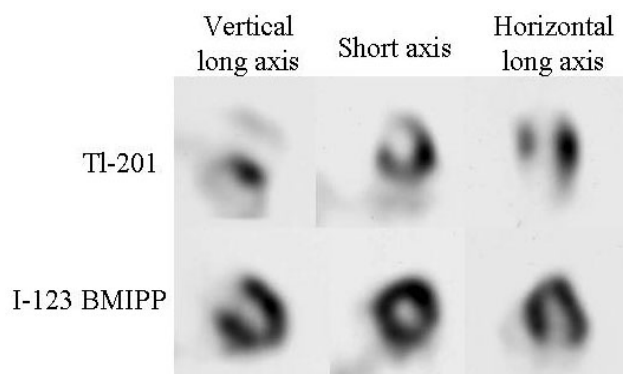


Fig. 5 Representative case of event (+) group. The patient was 19 years of age at the time of the first radionuclear studies, and he died of congestive heart failure during the follow up period. The radionuclear studies demonstrated the discrepancy of the accumulation of the two tracers in the septum (TL = 71.2, BM = 87.1, TL – BM = –15.9).

tion,¹³ a relationship was demonstrable when the cardiac evaluation was confined to scintigraphy in our investigation.

[²⁰¹Tl] Cardiac imaging,⁹⁻¹¹ echocardiography,¹⁴⁻²⁰ magnetic resonance imaging,²¹ spectroscopy²² and ¹⁸F-FDG positron CT²³ have previously been reported as clinical approaches for the evaluation of myocardial involvement in patients with DMD. The uptake of [²⁰¹Tl] tracer was considered to represent viable myocardium, free of fibrosis, and myocardial damage was reported to begin from the posterior wall.^{9,23}

The results of the present investigation indicate that viable myocardium in the inferior and lateral wall was preserved in most cases, although a variable degree of myocardial damage was demonstrated in the septum and anterior wall. In these anatomical regions, the amount of viable myocardium correlated with the degree of skeletal muscular dysfunction. However, low counts of tracer uptake did not necessarily guarantee a poor prognosis, as

shown in Figure 2. For example, two surviving cases demonstrated very low counts in all regions (* , §), and moreover, one case was included in the no-cardiac event (-) group (§). Furthermore, even the deceased cases demonstrated high counts of tracer uptake.

The only parameter that correlated well with prognosis was TL - BM in the septum. Interestingly, all the cases in which TL - BM in the septum were found to be a positive value (i.e., defects of [¹²³I] BMIPP were more severe than those of [²⁰¹Tl]) experienced no cardiac event, without exception. Fatty acid metabolism was considered to be damaged, although viable myocardium was preserved in these cases. Furthermore, congestive heart failure may not occur until myocardial fibrosis has advanced in the septum. Corrado et al., reported that left ventricular systolic dysfunction was a powerful predictor of prognosis in patients with DMD,²⁴ which was consistent with our results when it was considered that the systolic dysfunction was caused by myocardial fibrosis.

On the other hand, all cases which experienced a cardiac event demonstrated a negative value of TL - BM in the septum. This difference (TL - BM) was considered to be the necessary condition for predicting a positive cardiac event. This was the most significant outcome demonstrated in the present study, although the overall accuracy was not absolute. The worsening of LVDd may have been underestimated, due to the deformity of the chest. Consequently, this may have also increased the incidence of false-negative cases, and might have decreased the specificity of the findings. In the myocardium, the negative value of TL - BM, the tracer uptake of BMIPP in the damaged/predisposed myocardium may be greater than that in the normal myocardium, as fatty acid metabolism would not occur in fibrotic tissue. The major component of myocardial uptake of BMIPP consisted of the triglyceride (TG) pool.²⁵ The total amount of the TG pool was unchanged,²⁶ and back-diffusion of non-metabolized BMIPP into the blood was increased in ischemic heart disease.²⁷ Although there have been no reports in DMD, an increase in the TG pool or decrease in back-diffusion may partially explain the results in the present study. One possible additional mechanism may be delayed metabolism of free fatty acids in the cardiac myocytes. It is not clear whether such changes in the TG pool or BMIPP uptake correlated with cardiac events.

A clear predictor of the prognosis of DMD, especially subsequent congestive heart failure and death, has not been established to date. However, cardiac events in DMD are likely to be multi-factorial, and in the present study the radionuclide parameter was demonstrated to be one of the more powerful predictors. The septum is considered to be one specific region, for which the radionuclear parameters correlated well with the degree of skeletal muscular dysfunction and prognosis. Previous reports have described that the damage in DMD began to occur from the posterior wall. The myocardium has been

considered to be functionally and histologically homogeneous. Since the radionuclear findings at the specific region were related to cardiac events, heterogeneous and unknown factors (e.g. gene expression), may exist, and may be associated with prognosis.

Study limitation

Although the damage in DMD began to occur from the posterior wall, this region was not evaluated in this study, as the analysis was limited to the mid-portion of the left ventricle.

The quantitative analysis of nuclear cardiac imaging was performed on the premise that the intact myocardium existed as the control. However, defective radionuclear accumulation can be underestimated when diffuse myocardial damage is present.

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