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Original article

# Combining passive leg-lifting with transmural myocardial strain profile for enhanced predictive capability for subclinical left ventricular dysfunction in Duchenne muscular dystrophy

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ABSTRACT

*Background:* We previously reported that the transmural myocardial strain profile (TMSP) was an effective predictor for subclinical left ventricular (LV) dysfunction in patients with Duchenne muscular dystrophy (DMD) with preserved LV ejection fraction (LVEF), but its predictive power when used alone proved to be limited.

*Methods:* A total of 95 DMD patients with LVEF of 59 ± 5% (all ≥55%) and age 11.3 ± 3.0 years were analyzed retrospectively. Echocardiography was performed at baseline and 1-year follow-up, and all baseline measurements were repeated during a passive leg-lifting maneuver with legs elevated to approximately 45° from the horizontal position. TMSP of the posterior wall was evaluated from the mid-LV short-axis view. On the basis of our previous findings, TMSP with a notch was adopted as a predictor for evaluation of subclinical LV dysfunction in DMD patients whose LVEF remains preserved.

*Results:* At baseline, normal TMSP comprised 35 patients (37%), and the remaining 60 (63%) were classified as TMSP with a notch. Twenty-nine patients (48%) had developed LV wall motion abnormality at the 1-year follow-up, but this was observed only in the group of patients with TMSP with a notch at rest and also during passive leg-lifting. Furthermore, this group showed significantly more frequent development of LV wall motion abnormality at 1-year follow-up, with better sensitivity, specificity, and positive and negative predictive values for prediction of this abnormality than for other sub-groups.

*Conclusions:* Most DMD patients suffer from progressive skeletal muscle weakness, so that combining TMSP with passive leg-lifting may make TMSP even more effective as a simple and non-invasive predictor of LV subclinical dysfunction.



## Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease affecting approximately 1 in 3500 live-born male children worldwide [1]. DMD is caused by mutations in the dystrophin gene that result in marked reduction or absence of the sarcolemmal protein dystrophin. Death is usually due to cardiac or respiratory failure [2,3], and distinctive pathologic findings have been noted [4]. The incidence of cardiac complications in DMD patients increases with age, affecting 30% of patients by the age of 14 years, 50% by the age of 18 years, and all older patients [5]. Since subclinical left ventricular (LV) myocardial dysfunction may develop and progress early in life, early detection of these changes in DMD patients, so that medical treatment can be administered earlier, is vital for prevention of the development of LV myocardial fibrosis. Previous investigators have reported that myocardial

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strain imaging is effective for the detection of subclinical LV myocardial dysfunction in DMD patients with preserved LV function [6–11]. In addition, we previously reported that the transmural myocardial strain profile (TMSP) was effective for predicting LV dysfunction in such patients [11]. However, these echocardiographic parameters alone proved to have limited predictive power for subclinical LV dysfunction. Although exercise or dobutamine stress echocardiography are well-established methods for the detection of subclinical LV myocardial dysfunction in patients with known or suspected cardiomyopathy whose LV function is normal compared to baseline echocardiographic assessment [12,13], it is difficult for DMD patients to undergo such stress tests due to progressive skeletal muscle weakness with loss of ambulatory ability. On the other hand, the passive leg-lifting maneuver is a non-invasive and cost-effective method to increase preload through a transient increase in venous return. The advantage of this simple maneuver over other stress tests for DMD patients is that it can be easily performed for such patients even when they are in poor physical condition with help from an attendant parent.

Accordingly, the objective of this study was to test the hypothesis that combining passive leg-lifting with assessment of TMSP enhances the capability of the latter to predict subclinical LV dysfunction for DMD patients with preserved LV ejection fraction (EF).

## Materials and methods

### *Study population*

Data for a total of 168 consecutive DMD patients who were treated at the Division of Pediatrics of Kobe University Hospital between August 2007 and December 2013 were analyzed retrospectively. The diagnosis of DMD was confirmed by genetic analysis. Mutation of the dystrophin gene, which forces the abnormal generation of dystrophin messenger RNA by the premature stop codon, was detected in all patients. We excluded DMD patients with (1) atrial fibrillation; (2) left-sided heart failure; and (3) more than mild aortic and/or mitral valvular heart disease. This study was approved by the local ethics committee of our institution, and written informed consent was obtained from all patients.

### *Echocardiographic examination*

All echocardiographic studies were obtained with a commercially available system (Aplio XG; Toshiba Medical Systems, Tochigi, Japan) at baseline and 1-year follow-up. All baseline measurements were repeated during a passive leg-lifting maneuver, in which the legs are elevated to approximately 45° from the horizontal position with the assistance of attendant parents and kept at this position for about 1–2 min while continuously recording echocardiographic data. Digital routine cine loops were obtained from the standard parasternal and apical views from three consecutive beats at the end of expiratory apnea. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Standard LV measurements were obtained from the parasternal long-axis view, and LV volumes and EF were calculated using the Teichholz rule [14]. The pulsed-wave Doppler-derived early diastolic (*E*) and atrial transmitral flow velocity (*A*), the *E*/*A* ratio, and the E-wave deceleration time were obtained from the apical four-chamber view and used for the assessment of LV diastolic function [15]. Digital data were transferred to dedicated offline software (EchoEgent; Toshiba Medical Systems), for subsequent offline strain analysis.

### *Assessment of TMSP*

Tissue Doppler radial strain in the posterior wall was assessed from the mid-LV short-axis view to obtain TMSP as previously described in detail [11,16,17]. Briefly, Doppler angle correction was performed toward the contraction center to obtain radial strain distribution in the posterior wall. Radial strain distribution throughout the myocardium in the form of M-mode color-coded images, as well as the profile of distribution at end-systole, was also obtained (Fig. 1). Moreover, the location of the peak strain was identified, which was determined as the percentage of the distance between the endocardium and the epicardium accounted for by the wall thickness (Fig. 1). Two TMSP patterns were observed at baseline in DMD patients [11] (Fig. 2). One featured a one-peak strain and was located in the endocardium (normal TMSP), and the other featured a two-peak strain with a notch and was located in the subendocardium (TMSP with a notch). Care must be taken to

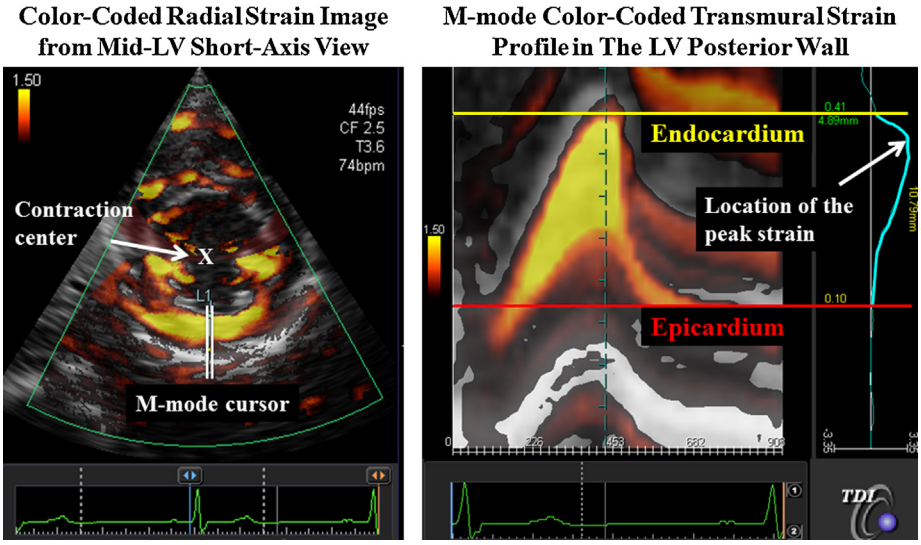


**Fig. 1.** An example of color-coded tissue Doppler radial strain display from the mid-left ventricular (LV) short-axis view at end-systole (left), and corresponding M-mode color-coded transmural myocardial strain profile of the LV posterior wall (right). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)