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Original article

Regression of left ventricular hypertrabeculation is associated with improvement in systolic function and favorable prognosis in adult patients with non-ischemic cardiomyopathy

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ABSTRACT

Background: We sometimes experience regression of left ventricular hypertrabeculation (LVHT), which is compatible with the diagnosis of LV non-compaction cardiomyopathy (LVNC) in adult patients. However, little is known about the association between LVHT regression and LV systolic function in adult patients.

Methods: We prospectively examined 23 consecutive adult patients who fulfilled the echocardiographic criteria for LVNC. LV reverse remodeling (RR) was defined as an absolute increase in LV ejection fraction of >10% at 6 months follow-up. LVHT area was calculated by subtraction from the outer edge to the inner edge of the LVHT at end-systole.

Results: The mean follow-up period was 61 months. LVRR was observed in 9 patients (39%). The changes in the mean LVHT area showed significant correlation with the changes in LV ejection fraction ($r = -0.78$, $p < 0.0001$). Cardiac death occurred in 7 patients (50%) without LVRR, but no patients with LVRR died (log-rank, $p = 0.003$). Furthermore, composite of cardiac death and hospitalization for heart failure occurred in 10 patients (71%) without LVRR, whereas there was one patient with LVRR (log-rank, $p < 0.001$).

Conclusions: Regression of LVHT is associated with improvement in LV systolic function. LVRR might be associated with a favorable prognosis in patients with LVHT.

Left ventricular (LV) non-compaction cardiomyopathy (LVNC) is a rare, congenital heart disease characterized by LV hypertrabeculation (LVHT), which is thought to be the result of a failure of trabecular regression during normal embryonic development [1–4]. LVNC is usually associated with LV systolic dysfunction, an increased incidence of thromboembolism, and ventricular arrhythmia [4,5].

Previous reports in adults indicated that LV systolic dysfunction that fulfilled the echocardiographic criteria for LVNC sometimes showed regression of LVHT and LV reverse remodeling (LVRR) after optimal therapy [6–9]. However, little is known about the relationship between the regression of LVHT and LVRR in adult patients with LVHT, which may be compatible with the diagnosis of LVNC. The aim of this study was to clarify the relationship between the regression of LVHT and LVRR.

Methods

Study population

This study was a prospective observational study conducted between December 2005 and December 2014 in a single center. We included all consecutive patients who were referred to our department with non-ischemic LV systolic dysfunction and an LV ejection fraction (LVEF) <40%. There were 300 patients with LV systolic dysfunction during the period. All patients had undergone coronary angiography, and had no significant coronary artery disease, defined as >50% diameter narrowing in any of the major

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coronary arteries. Among them, we found 23 consecutive adult patients (7.7%) who fulfilled Jenni's echocardiographic criteria for LVNC in our study [10]. These criteria are based on a double-layered appearance of the LV myocardium on two-dimensional (2D) echocardiography. Patients with LVHT, which may be compatible with the diagnosis of LVNC, are defined as having a ratio of non-compacted layer to compacted layer (NC/C) in the LV myocardium of more than double, measured at end-systole in a parasternal short-axis view. Patients with a history of other congenital, acquired, or significant valvular heart disease, or neuro-muscular disease [11] were excluded from our study. No patients showed inflammatory findings, such as cardiac sarcoidosis and endomyocarditis, on the basis of the endomyocardial biopsy from the right ventricle ($n = 20$), gallium scintigraphy ($n = 3$), and past history from the medical records at baseline. The institutional review board approved the protocol, and written informed consent was obtained from each patient before the ultrasound examination.

Ultrasound examination and measurement

All ultrasound examinations were performed using a commercially available echocardiographic machine with an S3 transducer (Vivid Seven System, GE Healthcare, Horten, Norway). Parasternal and apical projections were obtained according to the recommendations of the American Society of Echocardiography [12,13]. The left atrial diameter was determined from the M-mode recording as the largest distance between the posterior aortic wall and the posterior left atrial wall at end-systole. The thicknesses of the interventricular septum and LV posterior wall and the LV end-diastolic and end-systolic diameters were determined from the M-mode recording at the level of the chordae. The LV end-diastolic volume (EDV), end-systolic volume (ESV), and EF were calculated using biplane Simpson's methods from apical four- and two-chamber views. Pulsed Doppler echocardiographic measurements of the transmitral and pulmonary venous flow velocities were obtained by positioning the sample volume at the level of the mitral tips and 1 cm below the ostium of the right upper pulmonary vein, respectively. The off-line analysis of transmitral flow and pulmonary venous flow was performed with the use of dedicated software (EchoPAC Version 112, GE Healthcare). Three consecutive beats were measured and averaged for each measurement during sinus rhythm. In atrial fibrillation rhythm, an index beat, a beat following two preceding intervals that were nearly the same, was used for each measurement [14,15]. The peak velocities of early (E) and late filling (A) waves, the E/A ratio of peak velocities, and the deceleration time (DT) of the E-wave were measured from transmitral flow velocities, and the peak velocities of systolic (S), diastolic (D), and A waves, together with the S/D ratio of peak velocities, were also measured from the pulmonary venous flow velocities. The early diastolic mitral annular velocity of the septal and lateral mitral annulus (e′ velocity) was obtained by tissue Doppler imaging and the E/e′ ratio was calculated. The location of LVHT was assessed and categorized as apical if it involved the LV apex and as anterior, lateral, or posterior if it involved the anterior, lateral, or posterior in each LV segment from the three apical views [16]. With respect to 2D speckle-tracking echocardiography, the second-harmonic B-mode images were obtained for offline analysis (EchoPAC Version 112). Apical four- and two-chamber, and long-axis views were used for the measurements of LV longitudinal strain. The LV endocardial border of the inner edge of the compacted layer was manually traced on the end-systolic frame, and the software subsequently and automatically traced the borders in the other frames. LV global longitudinal strain (GLS) was calculated as the mean longitudinal peak negative strain from each of three apical views during a cardiac cycle [17].

Clinical and long-term assessment

The study patients were treated with angiotensin-converting enzyme inhibitors and/or angiotensin type 1 receptor blockers and beta-blockers in addition to diuretics according to the guidelines [18]. The indication for cardiac resynchronization therapy was advanced heart failure along with LV diastolic diameter >55 mm, LVEF <35%, QRS interval >120 ms, or mechanical dyssynchrony with narrow QRS [19]. LVHT areas were calculated by subtraction from the outer edge of the LVHT area to the inner edge of the LVHT area at end-systole in the three apical views (Fig. 1). LVRR was defined as an absolute increase in LVEF of more than 10% at 6-month follow-up [20].

Interobserver and intraobserver variability

The inter- and intraobserver variabilities for LV GLS were studied in a group of 20 randomly selected subjects, using measurements by one observer, repeated twice >2 weeks after the first measurements, and by two observers who were unaware of each other's measurements. The bias (mean difference) and limits of agreement (1.96 standard deviation of difference) between the first and second measurements were determined. To assess reproducibility, the coefficient of variation was calculated as the standard deviation of the difference divided by the mean.

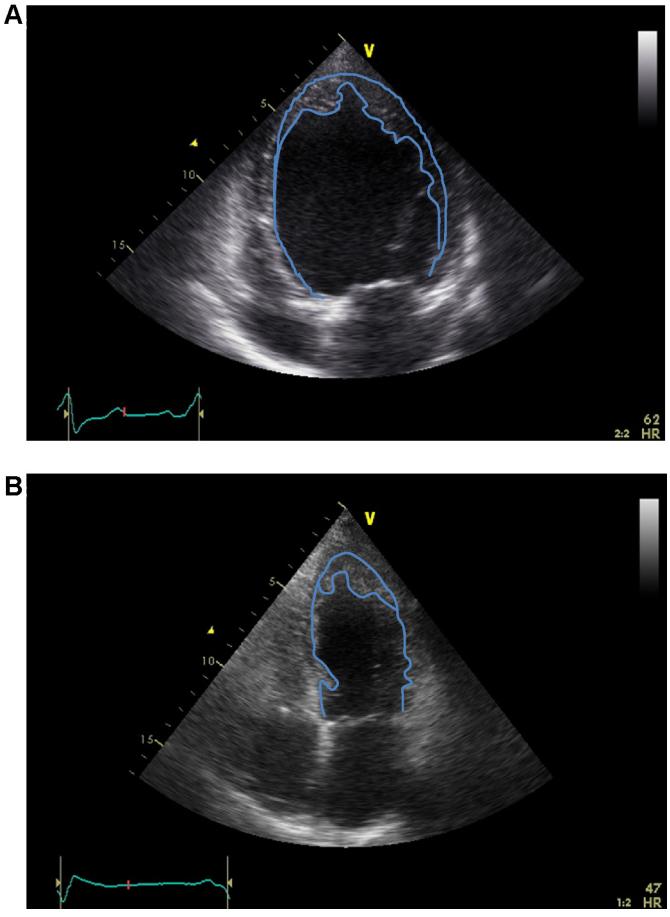

Fig. 1. Representative example of echocardiographic measurement of left ventricular hypertrabeculation area in apical four-chamber view (A) at baseline and (B) at 6 months' follow-up. (LV Hypertrabeculation Area) = (The Outer Edge of LVHT) − (The Inner Edge of LVHT). LVHT, left ventricular hypertrabeculation.

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