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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^0 velocity) was obtained by tissue Doppler imaging and the E/e^0 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.

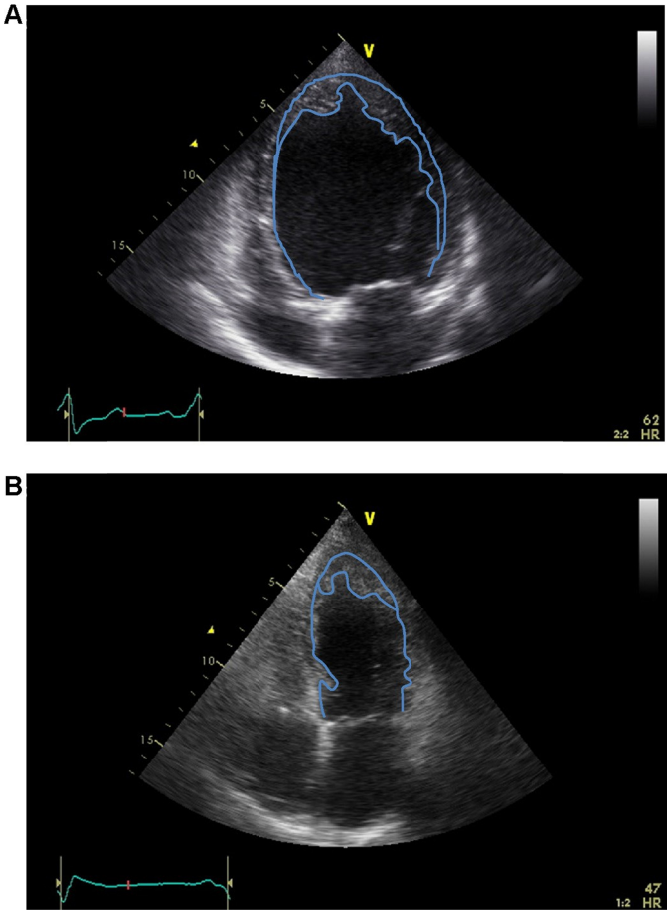

Fig. 1. Representative example of echocardiographic measurement of left ventricular hypertrabeculation area in apical four-chamber view (A) at baseline and (B) at 6 months' follow-up. (LV Hypertrabeculation Area) = (The Outer Edge of LVHT) – (The Inner Edge of LVHT). LVHT, left ventricular hypertrabeculation.

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Statistical analyses

Continuous variables were summarized as mean ± standard deviation if normally distributed, and as median and interquartile range otherwise. Normality was evaluated by the Shapiro–Wilk W test. Comparisons of baseline characteristics between patients with and without LVRR were assessed using Student's t-test and the Mann–Whitney U test for normally and non-normally distributed data, respectively. To elucidate the prolonged influence of LVRR on clinical outcome, Kaplan–Meier curves were calculated from 6 months (the start-point) to the time of cardiac events (cardiac death, mechanical circulatory support, and hospitalization for heart failure) and compared using the log-rank test. A mixed-model repeated-measures analysis of variance was used to compare the two groups from baseline until 24 months. Associations between the regression of LVHT, as estimated by changes in LVHT area, and the changes in LV systolic function were tested using Pearson or Spearman correlation. The optimal receiver-operating characteristic (ROC) curve cut-off value for predicting cardiac events was chosen as the value maximizing sensitivity and specificity. A value of $p < 0.05$ was considered to indicate statistical significance. All analyses were performed using commercially available software (SPSS, version 21.0; SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics and conventional echocardiography at baseline

No patients are dropped out and all patients completed the follow-up. The clinical characteristics are listed in Table 1. LVRR, defined as an absolute increase in LVEF of more than 10% at 6 months' follow-up, was observed in 9 patients (39%). Age, hemoglobin level, past history of heart failure hospitalization, and duration of heart failure in patients without LVRR at baseline were significantly higher compared to those in patients with LVRR. As to drug therapies at baseline, the use of angiotensin-converting enzyme inhibitors and/or angiotensin type 1 receptor blockers, beta-blockers, and aldosterone antagonists in patients without LVRR was significantly more frequent compared to those in patients with LVRR. At 6 months' follow-up, the use of cardiac resynchronization therapy and aldosterone antagonists in patients without LVRR was significantly more frequent compared to those in patients with LVRR. Conventional 2D echocardiographic features are listed in Table 2. Baseline echocardiographic parameters, such as LVEF, LV GLS, LVHT area, LV area, and the percentage of LVHT area divided by LV area at end-systole in the three apical views did not differ between the two groups at baseline. Furthermore, there was no difference in the location of LVHT, which was most frequently the apex, followed by the lateral wall, between the two groups.

Clinical changes during the follow-up period

Fig. 1 shows the representative example of the regression of LVHT in apical four-chamber view. Fig. 2A shows the changes in the maximum ratio of NC/C in the LV myocardium from baseline to 24 months' follow-up. There was a significant interaction between the two groups ($p < 0.001$ for interaction). The maximum NC/C ratio decreased significantly in patients with LVRR compared to baseline values, and this improvement was maintained throughout the remainder of the 24-month term of this study. In patients with LVRR, LVEF at 6 and 12 months' follow-up showed significant improvement compared to baseline values, whereas the improvement at 24 months was not significantly different to that observed at 6 months ($p = 0.071$). In patients without LVRR, LVEF did not differ significantly during the entire follow-up period (Fig. 2B).

Table 3 summarizes the serial changes in blood pressure, LV morphology, and plasma BNP levels. There were significant interactions between the two groups with regard to LV GLS, LVHT area, LV area, and the percentage of LVHT area ($p = 0.002$, $p = 0.002$, $p < 0.001$, and $p < 0.001$ for interaction, respectively). LV GLS, LVHT area, LV area, and the percentage of LVHT area showed significant improvement at 6, 12, and 24 months in patients with LVRR compared to baseline values. In patients without LVRR, LV GLS and LVHT area did not differ significantly during follow-up. Plasma BNP levels were significantly improved at 6, 12, and 24 months in patients with LVRR compared to baseline values, whereas patients without LVRR showed no significant difference in plasma BNP levels during follow-up. The mean follow-up period

Table 1
Baseline characteristics.

	LVRR present at 6 months ($n = 9$)	LVRR absent at 6 months ($n = 14$)	p-Value
Age, years	47 ± 14	60 ± 6	0.028
Male/Female	7/2	9/5	0.16
Heart rate (beats/min)	76 ± 12	71 ± 15	0.14
Systolic pressure (mmHg)	119 ± 23	102 ± 17	0.21
Diastolic pressure (mmHg)	74 ± 12	65 ± 9	0.11
Body mass index (kg/m^2)	22.1 ± 3.9	21.8 ± 3.3	0.89
NYHA class (I/II/III/IV)	0/3/6/0	0/1/10/3	0.059
Hemoglobin (g/dL)	14.3 ± 1.9	12.6 ± 1.7	0.031
Albumin (g/dL)	4.2 ± 0.4	3.8 ± 0.3	0.057
Creatinine (mg/Dl)	1.2 ± 0.9	1.3 ± 0.4	0.64
BNP (pg/mL)	846 [306, 1017]	617 [231, 1074]	0.86
Atrial fibrillation	4 (44)	6 (43)	0.41
Left bundle branch block	2 (22)	3 (21)	0.56
Past history of heart failure hospitalization	7 (78)	13 (93)	0.046
Duration of heart failure (months)	6 [5, 60]	36 [17, 90]	0.036
Past history of stroke	0	2 (16%)	0.26
Medication, baseline/at 6 months			
ACE-I/ARB	3 (33)/8 (88)	14 (100)/14 (100)	0.001/0.32
Beta blocker	3 (33)/9 (100)	118 (79)/14 (100)	0.030/1.00
Aldosterone antagonist	0 (0)/3 (33)	10 (77)/13 (93)	0.001/0.01
Warfarin	1 (11)/2 (22)	7 (50)/8 (62)	0.04/0.05
CRT-P (D), baseline/at 6 months	0 (0)/4 (44)	2 (14)/10 (71)	0.24/0.025

Data are shown as mean values ± standard deviation, median [25th, 75th percentiles], or n (percentage).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; BNP, brain-type natriuretic peptide; CRT-P(D), cardiac resynchronization therapy pacemaker (defibrillator); LVRR, left ventricular reverse remodeling; NYHA, New York Heart Association.

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Table 2
Baseline echocardiographic characteristics and Doppler flow data.

	LVRR present at 6 months (n = 9)	LVRR absent at 6 months (n = 14)	p-Value
Left atrial diameter (mm)	43.5±7.3	51.5±9.3	0.14
LV end-diastolic diameter (mm)	75.2±9.9	71.7±10.8	0.48
LV end-systolic diameter (mm)	67.2±8.8	63.0±11.2	0.40
Transmitral flow			
Peak E velocity (m/s)	0.94±0.33	0.95±0.35	0.52
Peak A velocity (m/s)	0.60±0.27	0.59±0.24	0.92
E/A	1.56±1.24	1.61±1.45	0.60
Deceleration time (ms)	145.8±68.6	157.7±63.2	0.59
Pulmonary venous flow			
Peak S-velocity (m/s)	0.28±0.16	0.36±0.18	0.07
Peak D-velocity (m/s)	0.55±0.19	0.57±0.21	0.51
Peak A-velocity (m/s)	0.25±0.09	0.22±0.09	0.35
Mitral annulus TDI			
E/e^0 (septum)	17.7±1.2	19.1±8.8	0.53
E/e^0 (lateral)	13.1±3.5	14.0±7.6	0.58
LV end-diastolic volume (mL)	278±84	247±92	0.43
LV end-systolic volume (mL)	205±67	180±74	0.42
LV ejection fraction (%)	26.2±8.1	28.1±8.7	0.26
LV global longitudinal strain (%)	-7.1±2.5	-6.9±2.3	0.85
Mean values of LV hypertrabeculation area in apical three-chamber view (cm^2)	11.6±3.0	9.6±1.9	0.33
Mean values of LV area in apical three-chamber view (cm^2)	50.8±10.4	47.6±12.5	0.53
(LV hypertrabeculation area) ×100/LV area (%)	22.9±2.7	20.6±3.4	0.11
LVHT location			
Apex	9 (100)	13 (93)	0.44
Anterior wall	1 (11)	3 (21)	0.55
Lateral wall	7 (78)	14 (100)	0.67
Inferior wall	5 (56)	7 (50)	0.81
Septal wall	1 (11)	3 (21)	0.55

Data are shown as mean values±standard deviation, median [25th, 75th percentiles], or n (percentage).
e^0, peak early diastolic velocity of the mitral annulus; LV, left ventricle/left ventricular; LVRR, left ventricular reverse remodeling; TDI, tissue Doppler imaging.

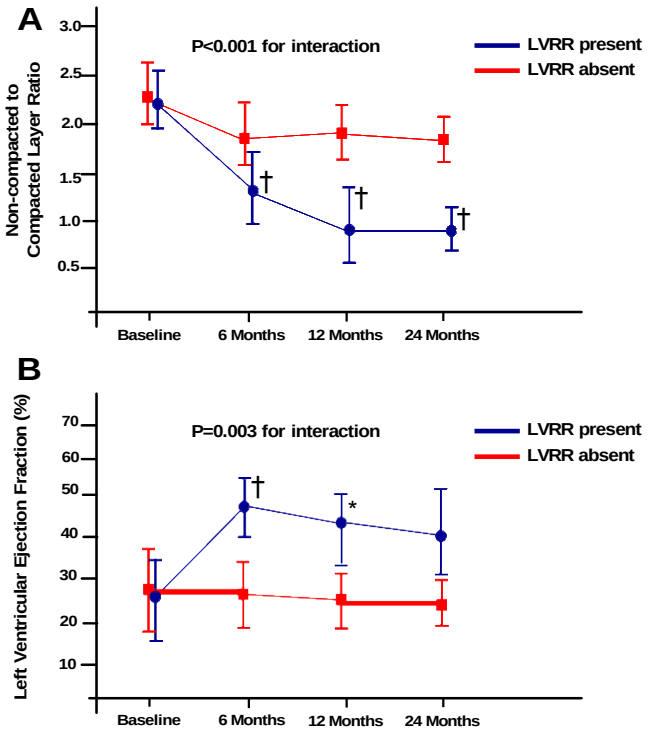

Fig. 2. Changes in (A) the maximum ratio of the non-compacted to the compacted layer in the left ventricular myocardium and (B) left ventricular ejection fraction at baseline, and 6, 12, and 24 months after optimal therapy. *p < 0.05 versus baseline. †p < 0.01 versus baseline. LVRR, left ventricular reverse remodeling.

was 49.3 months (range 9.6–79.5) in patients without LVRR and 78.8 months (range 42.8–105.3) in patients with LVRR. Patients with LVRR were tracked for longer than patients without LVRR (p = 0.004).

Fig. 3 shows the linear correlation between the changes in LVEF/LV GLS and the changes in the mean values of LVHT area calculated from the three apical views from baseline to 6 months' follow-up. Changes in the mean values of LVHT area showed a significant negative and positive correlation with changes in LVEF and LV GLS (r = -0.78 and r = 0.61, p < 0.001 and p = 0.002, respectively). During follow-up, cardiac death occurred in 7 patients (50%) without LVRR, whereas no patients with LVRR died (log-rank, p = 0.003) (Fig. 4A). Mechanical circulatory support was used in 3 patients without LVRR, but was not used in patients with LVRR (log-rank, p = 0.001) (Fig. 4B). Hospitalization for heart failure occurred in 10 patients (71%) without LVRR, whereas there was 1 patient with LVRR (log-rank, P < 0.001) (Fig. 4C). In the Kaplan–Meier curves for cardiac events on the basis of the changes in the degree of LVHT, the patients with the maximum ratio of NC/C in the LV myocardium of smaller than double at 6 months' follow-up (incompatible with Jenni's echocardiographic criteria, n = 13) showed significantly better prognoses than did those compatible with the above criteria at the same period (n = 10) (Fig. 4D–F).

Predictor of cardiac events

On the basis of the changes in LVHT from baseline to 6 months' follow-up, ROC curves for predicting cardiac events are shown in Fig. 5. As determined by ROC curve analysis for predicting cardiac death, the regression in the ratio of the NC/C >0.41 (sensitivity 75.0%, specificity 80.0%) and the regression in the LVHT area >2.2 cm^2 (sensitivity 87.5%, specificity 74.3%) at 6 months' follow-up predicted the event free from cardiac death.

Reproducibility

The intraobserver coefficient of variation for LV GLS was 7.3% and the interobserver coefficient was 6.3%. The bias and limits of agreement of intra- and interobserver variabilities were 0.4±2.4% and 0.5±2.0%, respectively.

Discussion

To the best of our knowledge, this is the first study to demonstrate the relationship between the regression of LVHT and prognosis. The main findings can be summarized as follows: (1) we described several cases of regression of LVHT in adult patients during the follow-up period, indicating that LVHT might be reversible in some patients; (2) the regression of LVHT, as estimated by a change in LVHT area, showed a significant correlation with the change in LV systolic function, as expressed by LVEF and LV GLS; (3) LVRR in adult patients with the diagnosis of LVNC was observed in 39% (9 cases of 23 patients) and was associated with a better prognosis compared to that in patients without LVRR; and (4) long-term echocardiographic follow-up of cardiac function demonstrated that LVEF and LV GLS in patients with LVRR had improved significantly at 6 months, and this improvement was maintained throughout the remainder of the 24-month term of this study, whereas no such change was seen in patients without LVRR.

Previous reports indicated that LV systolic dysfunction that fulfills the echocardiographic criteria for LVNC sometimes showed

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Table 3
Clinical parameters at baseline, 6, 12, and 24 months (M) after optimal therapy.

	LVRR present at 6 months ($n = 9$)					LVRR absent at 6 months ($n = 14$)					Mixed model ANOVA		
	Baseline	6 M	12 M	24 M		Baseline	6 M	12 M	24 M		Time* Group	Time	Group
LVNC appearance (No/No. at risk)	9/9	1/9	1/9	0/7		14/14	9/14	6/11	5/9				
SBP (mmHg)	119 23	119 35	117 31	109 26		102 17	99 20	103 16	99 16		0.71	0.88	0.072
DBP (mmHg)	74 12	69 19	71 16	65 13		65 9	65 11	61 11	64 10		0.56	0.68	0.15
LVEDV (mL)	278 84	158 52[y]	163 57[y]	153 51[y]		247 92	262 104	225 85	243 114		<0.001	<0.001	0.102
LVESV (mL)	205 67	87 36[y]	96 50[y]	98 45[y]		180 74	194 93	175 72	195 99		<0.001	<0.001	0.035
LV GLS (%)	−7.1 2.5	−10.7 1.8[*]	−10.3 2.0[*]	−10.7 2.9[*]		−6.9 2.3	−7.2 2.7	−7.1 2.7	−5.8 1.9		0.002	0.003	0.005
LVHT area (cm^2)	11.6 3.0	5.3 2.4[y]	3.3 1.4[y]	3.2 0.7[y]		9.6 1.9	9.8 2.3	8.1 3.2	9.2 3.5		0.002	0.003	0.005
LV area (cm^2)	50.8 10.4	34.6 9.2[y]	32.7 9.4[y]	31.6 8.2[y]		47.6 12.5	46.9 12.2	45.6 12.2	47.8 14.6		<0.001	<0.001	0.055
(LVHT area/LV area (%)	22.9 2.7	15.4 5.5[y]	9.7 2.2[y]	10.6 2.7[y]		20.6 3.4	21.4 3.4	17.5 4.1	19.2 3.4		<0.001	<0.001	<0.001
BNP (pg/mL)	846 [306, 1017]	22 [10, 42][y]	40 [17, 146][y]	33 [15, 68][y]		617 [231, 1074]	424 [246, 655]	301 [203, 687]	368 [171, 552]		0.079	<0.001	0.027

Data are shown as mean values ± standard deviation, or median [25th, 75th percentiles].
BNP, brain-type natriuretic peptide; DBP, diastolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; LVHT, mean values of left ventricular hypertrabeculation; LVNC appearance, left ventricular non-compaction cardiomyopathy appearance, i.e. appearance defined as a ratio of non-compacted layer to compacted layer in the left ventricular myocardium of more than double, measured at end-systole in a parasternal short-axis view; LVRR, left ventricular reverse remodeling; SBP, systolic blood pressure.
[*] $p < 0.05$ versus baseline.
[y] $p < 0.01$ versus baseline.

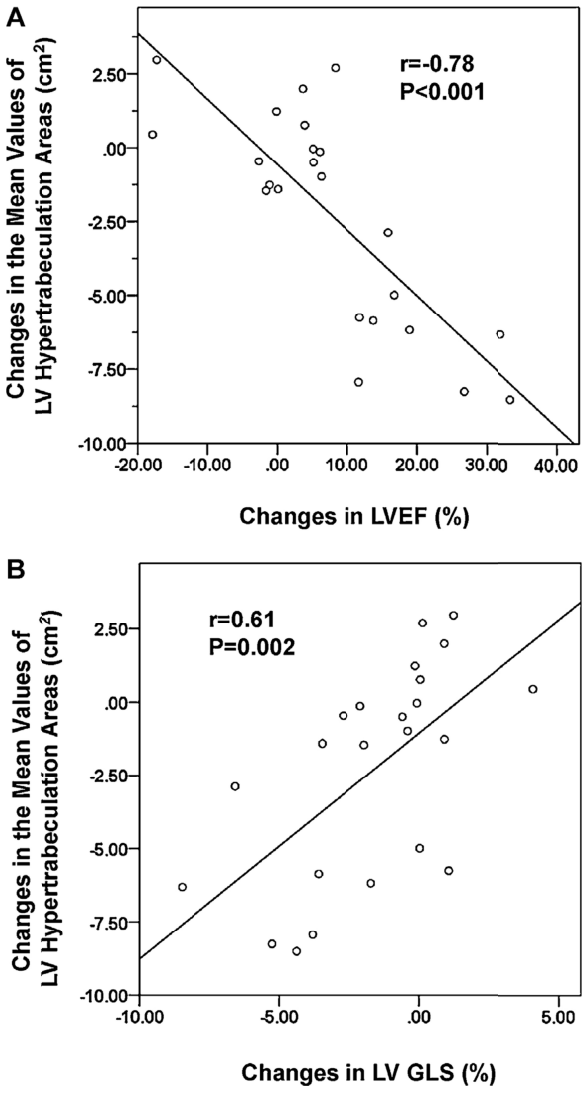

Fig. 3. (A) Linear correlation between changes in left ventricular hypertrabeculation area and changes in left ventricular ejection fraction from baseline to 6 months' follow-up. (B) Linear correlation between changes in left ventricular hypertrabeculation area and changes in left ventricular global longitudinal strain from baseline to 6 months follow-up. LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain.

regression of LVHT after optimal therapy [6–9]. Stö llberger et al. reported the disappearance of LVHT after biventricular pacing in a patient with polyneuropathy. In this report, LVHT was assumed to represent a compensatory mechanism of the failing myocardium as an attempt to increase the inner myocardial surface and hence the stroke volume. Therefore, improvement in LV systolic function and a decrease in LV size were accompanied by the disappearance of LVHT [7]. This study might indicate that regression of LVHT is associated with an improvement in LV systolic function, as shown in our study. In a study by Gati et al., 102 pregnant women with a morphologically normal LV myocardium at baseline were evaluated longitudinally with echocardiography and 26 (25%) of them developed de novo LVHT during pregnancy. During the postpartum follow-up period of 24 months, 19 (73%) women demonstrated complete resolution of LVHT and 5 showed regression. In some women, de novo LVHT appeared in response to increased LV loading conditions during pregnancy; this phenomenon showed a reversible change after delivery, following normalization of blood volume [21]. The reversible de novo LVHT in this report might partially explain why LVHT is reversible in

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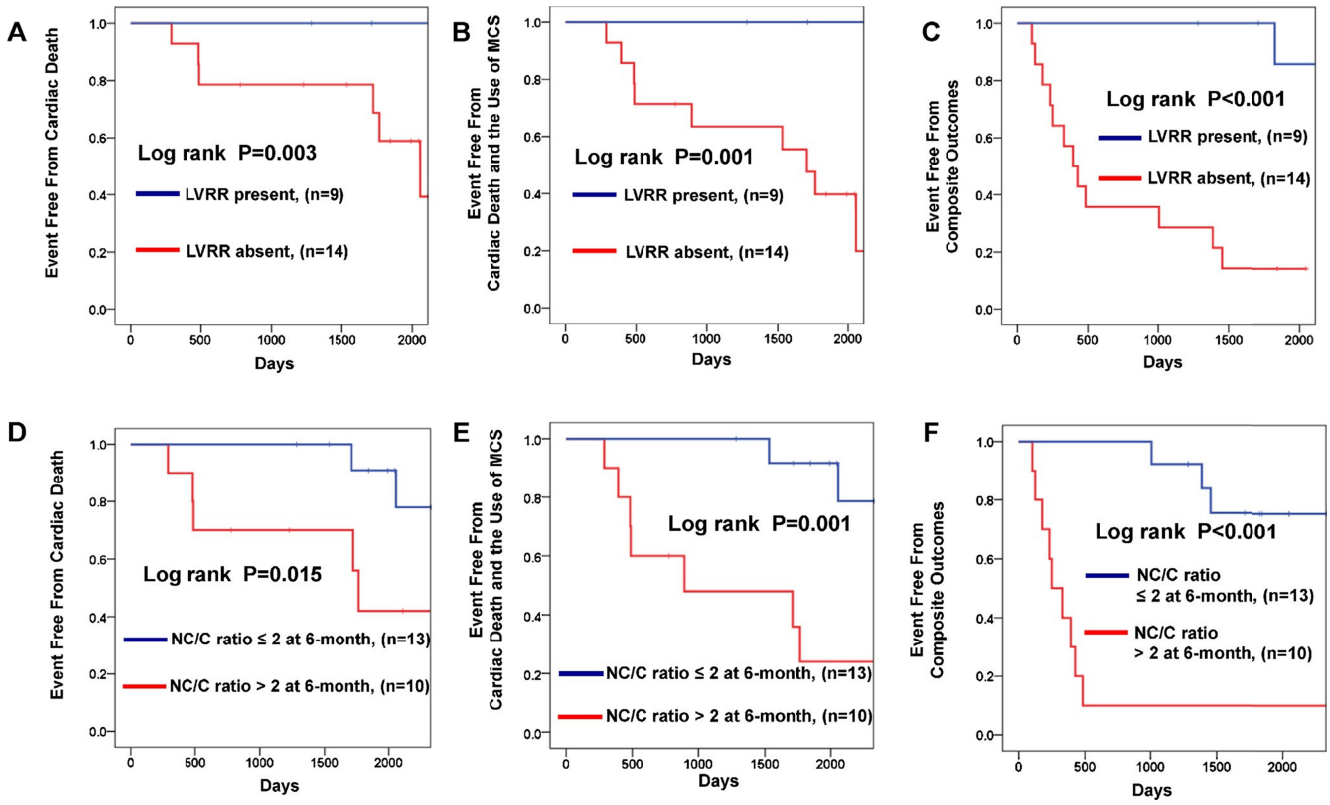

Fig. 4. Kaplan–Meier curves for (A) cardiac death, (B) cardiac death and the use of MCS, and (C) composite outcomes according to the presence of LVRR. Kaplan–Meier curves for (D) cardiac death, (E) cardiac death and the use of MCS, and (F) composite outcomes according to the maximum ratio of the non-compacted to the compacted layer in the left ventricular myocardium. Composite outcomes were cardiac death, the use of mechanical circulatory support, and hospitalization of heart failure. LVRR, left ventricular reverse remodeling; MCS, mechanical circulatory support; NC/C, the non-compacted to the compacted layer.

some patients with heart failure who have been subjected to an increased cardiac preload, as described in our study.

The major complications of LVNC are heart failure, arrhythmia, thromboembolic events, and sudden cardiac death [22,23]. However, little is known about the etiology, diagnostic criteria, incidence, or clinical outcomes associated with LVNC in adults [2]. In our study of adult patients with LVNC appearance, cardiac death occurred in 7 patients (30%) during a follow-up period of 61 months. Oechslin et al. reported the characteristics and outcomes in 34 adults with LVNC, among whom there were 12 deaths (35%) during a follow-up period of 44 months [5]. This was similar to our results.

Previous studies of patients with LV systolic dysfunction found that LVRR in those patients is associated with a favorable prognosis [24–27]. Merlo et al. reported that LVRR in idiopathic dilated cardiomyopathy patients was found in 89 of 242 patients (37%) and patients with LVRR showed a better prognosis compared to those without LVRR during 110 months [24]. However, there are no data regarding the relationship between LVRR and prognosis in patients with LVHT. In our study, patients with LVRR showed a better prognosis compared to those without LVRR, and this phenomenon is similar to those in patients with dilated cardiomyopathy. A recent report about the prognostic impact of LVHT in patients with dilated cardiomyopathy demonstrated that the cardiovascular events did not appear to be influenced by the degree of LVHT at baseline [28]. In our study, there was no difference in the degree of LVHT between the patients with LVRR and without at baseline. Therefore, it is difficult to elucidate the prognosis for cardiovascular events only in terms of the baseline LVHT degree. We firstly demonstrated that the regression of the LVHT, assessed by changes in NC/C ratio and LVHT area, during the follow-up period had a clinical impact on cardiovascular events in patients with LVHT.

Jenni's echocardiographic criterion, namely a NC/C ratio of >2 obtained at end-systole in a parasternal short-axis view, is the most commonly used criterion for the detection of LVNC [10,29–31]. It has previously been validated against dilated cardiomyopathy, hypertensive heart disease, and valvular heart disease and showed good sensitivity and specificity [32,33]. For this reason, we used Jenni's echocardiographic criteria for the selection of the patients in our study.

Our findings demonstrated that some patients showed regression of LVHT, suggesting that LVHT could be reversible. However, it is difficult to reconcile this with the view of LVNC as a primary and genetic cardiomyopathy. Kohli et al. reported that 30 patients (15%) fulfilled Jenni's echocardiographic criteria for LVNC out of 199 patients with LV systolic dysfunction in a single center [4]. This study demonstrated current echocardiographic diagnostic criteria are too sensitive and result in over-diagnosis of LVNC in patients with LV systolic dysfunction as shown in our study. Therefore, we should consider that we might sometimes misclassify a transient cardiomyopathy as LVNC with the use of current morphological criteria alone [7].

Clinical implications

Our study demonstrated that patients without LVRR had a worse prognosis. Patients without LVRR were older and the use of cardiac resynchronization therapy and aldosterone antagonists at 6 months' follow-up was significantly more common than in patients with LVRR. Differences in the patients' characteristics might have been influenced by diagnoses in different phases of the

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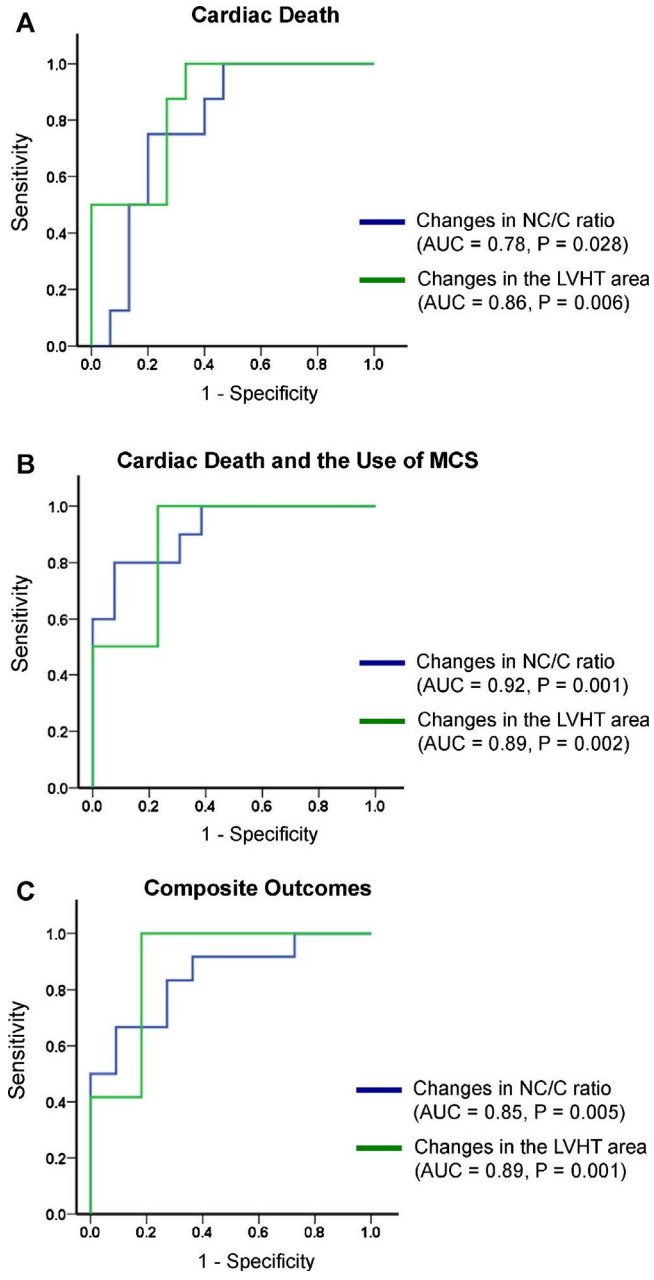

Fig. 5. Receiver-operating characteristic (ROC) curves for predicting (A) cardiac death, (B) cardiac death and the use of MCS, and (C) composite outcomes according to the changes in the maximum ratio of the NC/C in the left ventricular myocardium and the changes in LVHT area from baseline to 6 months' follow-up. Composite outcomes were cardiac death, the use of mechanical circulatory support, and hospitalization of heart failure. LVHT area, left ventricular hypertrabeculation area; MCS, mechanical circulatory support; NC/C, the non-compacted to the compacted layer.

disease (lead-time bias) and have influenced the clinical course in our study. Therefore, the high adverse outcome rate in patients without LVRR necessitates early recognition and appropriate therapeutic intervention, such as the optimal timing of cardiac transplantation referral in patients without LVRR.

Study limitations

The major limitation of our study was being an observational single center study with a small number of subjects; thus our results should be interpreted cautiously until verified in large-scale multicenter studies. We could not perform propensity matched survival analysis and multivariate regression analysis adjusting for confounding factors, including age, and treatment agents because the small number of patients in each group would not be favorable for the above statistical approach. Therefore, it is hard to justify that improved functional and clinical outcomes are related to LVRR in our study. Second, no other cardiac imaging modalities for the quantification of LVHT or myocardial fibrosis, such as cardiac magnetic resonance imaging, were used. We could not perform cardiac magnetic resonance imaging because some patients with LVHT already had cardiac resynchronization therapy devices implanted. Third, our study did not allow speculation about the pathophysiology of the regression of LVHT and the prediction of LVRR. Indeed, we did not analyze the changes in LV mass and regional LV systolic function using 2D echocardiography. It was difficult to elucidate the changes in LV mass because there was no appropriate measurement of LV myocardium mostly in the non-compacted layer. Fourth, endomyocardial biopsy from the right ventricle was performed in 20 patients mostly one time. We might be unable to exclude completely inflammatory cardiac diseases during the follow-up period. Despite these limitations, our findings provide new insight into the relationship between the regression of LVHT, improvement in cardiac systolic function, and prognosis in patients with LVHT, which may be compatible with the diagnosis of LVNC. It remains unclear whether the presence of LVHT is sufficient to explain the influence of clinical outcomes in adult patients with LVHT compared to those in patients without LVHT. Further large-scale multicenter studies are needed to confirm the prognostic significance of regression of LVHT in patients with LV systolic dysfunction and to also perform multivariate analysis to identify factors that predict patient prognosis.

Conclusions

Regression of LVHT is associated with improvement in LV systolic function, and might be associated with a favorable prognosis in patients with LVHT who fulfill the echocardiographic criteria for LVNC.

Conflicts of interest

No conflicts of interest in this study.

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