Comparison of cardiovascular magnetic resonance characteristics and clinical consequences in children and adolescents with isolated left ventricular non-compaction with and without late gadolinium enhancement

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Abstract

Background: Although cardiovascular magnetic resonance (CMR) is showing increasingly diagnostic potential in left ventricular non-compaction (LVNC), relatively little research relevant to CMR is conducted in children with LVNC. This study was performed to characterize and compare CMR features and clinical outcomes in children with LVNC with and without late gadolinium enhancement (LGE).

Methods: A cohort of 40 consecutive children (age, 13.7 ± 3.3 years; 29 boys and 11 girls) with isolated LVNC underwent a baseline CMR scan with subsequent clinical follow-up. Short-axis cine images were used to calculate left ventricular (LV) ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), myocardial mass, ratio of non-compacted-to-compacted myocardial thickness (NC/C ratio), and number of non-compacted segments. The LGE images were analyzed to assess visually presence and patterns of LGE. The primary end point was a composite of cardiac death and heart transplantation.

Results: The LGE was present in 10 (25 %) children, and 46 (27 %) segments were involved, including 23 non-compacted segments and 23 normal segments. Compared with LGE- cohort, LGE+ cohort had significantly lower LVEF (23.8 ± 10.7 % vs. 42.9 ± 16.7 %, p < 0.001) and greater LVEDV (169.2 ± 65.1 vs. 118.2 ± 48.9 mL/m², p = 0.010), LVESV (131.3 ± 55.5 vs. 73.3 ± 46.7 mL/m², p = 0.002), and sphericity indices (0.75 ± 0.19 vs. 0.60 ± 0.20, p = 0.045). There were no differences in terms of number and distribution of non-compacted segments, NC/C ratio, and myocardial mass index between LGE+ and LGE- cohort. In the LGE+ cohort, adverse events occurred in 6 patients compared to 2 events in the LGE- cohort. Kaplan-Meier analysis showed a significant difference in outcome between LGE+ and LGE- cohort for cardiac death and heart transplantation (p = 0.011).

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Background

Left ventricular non-compaction (LVNC) is a genetically and clinically heterogeneous cardiomyopathy characterized by numerous prominent trabeculations, progressive myocardial dysfunction, malignant ventricular arrhythmias, and early mortality [1, 2]. Left ventricular non-compaction can present in isolation or in combination with other congenital heart diseases or genetic neuromuscular conditions [3–5]. Previous work has shown that LVNC accounts for about 9% of cardiomyopathy in childhood [6]. The incidence of isolated LVNC diagnosed at children echocardiograms was estimated to be approximately 0.2% [7].

Cardiovascular magnetic resonance (CMR) may outperform echocardiography in assessing the whole left ventricular (LV) myocardium and also provide precise identification of prominent trabeculations owing to its higher spatial resolution and field of view [8–10]. Furthermore, CMR with late gadolinium enhancement (LGE) is a reliable technique for detecting myocardial fibrosis in vivo, which is related to clinical severity grading and prognosis in adult patients with LVNC [11–15]. Although CMR is showing increasingly diagnostic potential in LVNC, works on the application of CMR in children with LVNC are restricted to several case reports and small case series [16–19]. Therefore, we have assembled a relatively large cohort of children with LVNC, defined by eligibility for CMR, to characterize and compare CMR features and clinical outcomes in children with LVNC with and without LGE.

Methods

Study patients

We prospectively recruited a cohort of consecutive children with isolated LVNC who were referred to the Fuwai Hospital for CMR between June 2006 and December 2013. The diagnosis of LVNC was made on the basis of previously defined CMR and clinical criteria: [9] (a) appearance of 2 distinct myocardial layers; (b) prominent myocardial trabeculations and deep intertrabecular recesses communicating with the LV cavity; (c) end-diastolic ratio of non-compacted-to-compacted (NC/C) myocardium >2.3:1, and (d) absence of other known co-existing cardiac abnormalities. The study complied with the Declaration of Helsinki and was approved by the Fuwai Hospital ethics committee, and informed consent was obtained from the parents of each child with LVNC.

CMR image acquisition and analysis

All CMR exams were performed using a 1.5-T scanner (Siemens Avanto). Retrospective electrocardiographic gated cine images were performed using true fast imaging with steady-state free precession sequence (image parameters: repetition time/echo time [TR/TE] = 40.0/1.1 ms; matrix = 256 × 192 mm; flip angle = 62°) in three long-axis (horizontal and vertical long-axis and LV outflow tract) and continuous short-axis views covering the entire LV from base to apex. Fifteen ± 5 min after the injection of 0.2 mmol/kg of gadolinium-DTPA (Magnevist; Schering, Berlin, Germany), the LGE images were obtained using an inversion recovery sequence (image parameters: TR/TE = 8.7/3.4 ms, matrix = 256 × 256 mm, flip angle = 15°) in three long-axis and standard short-axis views covering the whole LV.

All images were analyzed using a workstation with commercially available software (Siemens Argus). For children with multiple CMR studies, the initial baseline study was used for the primary analysis. Results for LV ejection fraction, ventricular volumes, and myocardial mass were derived from short-axis slices. As previously demonstrated, the papillary muscles were excluded from compacted myocardium because it is difficult to differentiate papillary muscles from dense trabeculations [20]. Left ventricular volumes and compacted mass were indexed to body surface area. The LV sphericity index was calculated as: end-diastolic volume (EDV)/([end-diastolic long-axis diameter]3 × π/6) [21]. The presence or absence of non-compaction and LGE was qualitatively assessed using the AHA 17 segment model [22]. For each segment with non-compaction, the end-diastole NC/C ratio was quantitatively calculated in the short-axis views, and the maximum ratio was then used for analysis. As previously demonstrated, the assessment of NC/C ratio of the apex (segment 17) was excluded [9]. LGE was deemed present only if myocardial enhancement was confirmed on both short-axis and matching long-axis areas using a signal intensity threshold of ≥6 standard deviations (SD) above a remote reference region (Fig. 1). The myocardial layer distributions of LGE were assessed using the following scale: 1 = subepicardial, 2 = mid-wall, 3 = subendocardial, and 4 = transmural (≥75% LV wall thickness). The LGE score was finally summed. The evaluations of non-compaction and LGE were performed by 2 independent expert readers (ML and HC) who were blinded to the clinical data. Discordant findings were resolved by consensus.
Follow-up
All children were followed up via clinic visits or telephone interview after initial CMR examination. The endpoint of the study was cardiovascular death and heart transplantation. The duration of follow-up was determined from the first CMR evaluation date to the occurrence of an endpoint. Complete follow-up was available for all children.

Statistical analysis
Normality was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± SD and assessed using unpaired t tests or Wilcoxon’s rank-sum tests. Categorical variables were expressed as frequencies (percentages) and assessed using the χ² or Fisher exact tests. Correlation analyses were performed using the Spearman’s rank correlation test. Survival curve was generated by the Kaplan-Meier method and compared by the log rank test. The statistical analysis was performed using SPSS for Windows 16.0 (Chicago, IL, USA). A two tailed p value of < 0.05 was considered statistically significant.

Results
Baseline characteristics
A cohort of 40 children was diagnosed with isolated LVNC. An additional 8 children with prominent trabeculations who met CMR diagnostic criteria were associated with either congenital heart diseases and thus excluded from the study, such as atrial septal defect (n = 4), Ebstein’s anomaly (n = 1), aorto-left ventricular tunnel (n = 1), membranous subaortic stenosis (n = 1), bicuspid aortic valve (n = 1). Twenty-nine children (72 %) were male and 11 (28 %) were female. The mean age at the time of initial CMR scan was 13.7 ± 3.3 years (range, 1.5-17 years). Three children (8 %) had a family history of LVNC. Twenty-one children (53 %) presented primarily with signs and symptoms of congestive heart failure. Seven children (18 %) presented with documented ventricular arrhythmias and 1 patient (3 %) presented with aborted sudden death. Five children (13 %) were referred for evaluation of unexplained syncope. Two children (5 %) presented with a primary complaint of chest pain. No children had signs of systemic emboli. Clinical and demographic characteristics of the study population are summarized in Table 1.

CMR findings
The detailed CMR characteristics of children with LVNC are listed in Table 2. The mean LV ejection fraction (EF) and EDV index were 38.1 ± 17.4 % and 131.0 ± 55.8 mL/m², respectively. No thrombus was detected in LV cavity on CMR. Non-compaction was present in 372 LV segments. The mean number of non-compacted segments per patient was 9.3 ± 2.5. The mean NC/C ratio was 3.64 ± 0.94.

A total of 10 (25 %) children with LVNC showed LV LGE. The LGE was observed in 46 segments, including 23 non-compacted segments and 23 normal segments. Of these, LGE- children, LGE+ children had significantly lower LVEF (23.8 ± 10.7 % vs. 42.9 ± 16.7 %, p < 0.001) and greater LVEDV (169.2 ± 65.1 vs. 118.2 ± 48.9 mL/m², p = 0.010), LV end-systolic volume (131.3 ± 55.5 vs. 73.3 ± 46.7 mL/m², p = 0.002), and sphericity indices (0.75 ± 0.19 vs. 0.60 ± 0.20, p = 0.045). There were no differences in terms of number of non-compacted segments, NC/C ratio, and
There was a similar distribution of non-compaction between LGE+ and LGE- children, which was more frequently observed on the apical segment than on the mid-cavity and basal segments (Fig. 2).

### Table 1 Baseline characteristics

| Variable                  | All Children (n = 40) | Presence of LGE (n = 10) | No (n = 30) | p Value |
|---------------------------|-----------------------|--------------------------|-------------|---------|
| Age (years)               | 13.7 ± 3.3            | 14.0 ± 2.1               | 13.6 ± 3.6  | 0.753   |
| Male, n (%)               | 29 (73)               | 9 (90)                   | 20 (67)     | 0.233   |
| Family history of LVNC, n (%) | 3 (8)               | 1 (10)                   | 2 (7)       | 1.000   |
| Dyspnoea, n (%)           | 21 (53)               | 9 (90)                   | 12 (40)     | 0.004   |
| Chest pain, n (%)         | 2 (5)                 | 0                        | 2 (7)       | 1.000   |
| Syncope/pre-syncope, n (%)| 7 (18)                | 1 (10)                   | 6 (20)      | 0.651   |
| NYHA functional class     | 2.4 ± 1.0             | 3.0 ± 0.9                | 2.1 ± 0.9   | 0.016   |
| I, n (%)                  | 10 (25)               | 1 (9)                    | 9 (30)      |         |
| II, n (%)                 | 11 (28)               | 1 (9)                    | 10 (33)     |         |
| III, n (%)                | 14 (35)               | 5 (55)                   | 9 (30)      |         |
| IV, n (%)                 | 5 (12)                | 3 (27)                   | 2 (7)       |         |
| Abnormal ECG, n (%)       | 36 (90)               | 10 (100)                 | 26 (87)     | 0.559   |
| VT/VF, n (%)              | 7 (18)                | 3 (30)                   | 4 (13)      | 0.361   |

### Table 2 Cardiovascular magnetic resonance characteristics

| Variable                  | All Children (n = 40) | Presence of LGE (n = 10) | No (n = 30) | p Value |
|---------------------------|-----------------------|--------------------------|-------------|---------|
| Heart rate (beats/min)    | 86.5 ± 22.8           | 92.3 ± 24.8              | 84.6 ± 22.2 | 0.360   |
| Body surface area (m²)    | 1.6 ± 0.3             | 1.5 ± 0.2                | 1.6 ± 0.4   | 0.861   |
| LV long-axis diameter (mm)| 84.1 ± 12.0           | 86.1 ± 9.3               | 83.4 ± 12.8 | 0.534   |
| LV Sphericity index       | 0.64 ± 0.21           | 0.75 ± 0.19              | 0.60 ± 0.20 | 0.045   |
| LVEF (%)                  | 38.1 ± 17.4           | 23.8 ± 10.7              | 42.9 ± 16.7 | <0.001  |
| LVEDV index (mL/m²)       | 131.0 ± 55.8          | 169.2 ± 65.1             | 118.2 ± 48.9| 0.010   |
| LVESV index (mL/m²)       | 87.8 ± 54.6           | 131.3 ± 55.5             | 73.3 ± 46.7 | 0.002   |
| Stroke volume index (mL/m²)| 43.2 ± 13.4         | 37.9 ± 17.0              | 44.9 ± 11.8 | 0.152   |
| Myocardial mass index (mL/m²)| 56.1 ± 19.0       | 64.6 ± 17.2              | 53.3 ± 19.0 | 0.107   |
| Maximum NC/C ratio        | 3.64 ± 0.94           | 3.76 ± 1.24              | 3.60 ± 0.84 | 0.645   |
| Number of non-compacted segments | 9.3 ± 2.5         | 9.9 ± 2.8                | 9.1 ± 2.4   | 0.384   |
| Duration of follow-up, years | 3.0 ± 2.2          | 2.6 ± 2.3                | 3.2 ± 2.3   | 0.494   |

Values are mean ± SD or n (%)

### Follow-up

The average length of follow-up was 3.0 ± 2.2 years. During follow-up period, 6 children (15 %) died and 2 (5 %) underwent heart transplantation (Fig. 3), thereby resulting in a 20 % incidence of death and transplantation in the myocardial mass index between LGE+ and LGE- cohort.
total cohort. There was no statistically significant difference in the length of follow-up between LGE+ and LGE- children (2.6 ± 2.3 versus 3.2 ± 2.3 years; p = 0.494). In LGE+ cohort, adverse events occurred in 6 children, including orthotropic heart transplantation in 2 children and death in 4 children. In LGE- cohort, adverse event was identified in 2 children. Kaplan-Meier analysis showed a significant difference in outcome between LGE+ and LGE- cohorts for cardiac death and heart transplantation (Fig. 4).

Discussions

In the relatively large cohort study of children with isolated LVNC diagnosed by CMR, we investigated and compared CMR features and clinical outcomes between LGE+ and LGE- children. The overall occurrence of LGE (25 %) was lower to that found in previous adult studies [14, 15]. The LGE+ cohort exhibited a more maladaptive LV remodeling and higher incidence of cardiovascular death and heart transplantation.

CMR is showing increasing diagnostic potential in LVNC owing to a comprehensive identification and quantification of the extent of non-compacted myocardium [10, 20, 23]. The utility of CMR with LGE for detecting myocardial fibrosis is well established, which has also been confirmed in our previous report of the adult patient with LVNC [24]. Several studies have described a high prevalence of LGE in patients with LVNC, and LGE has been shown to be associated with ventricular arrhythmias as well as ventricular dysfunction [12–14]. Our previous study have shown that LGE was present in 19 (40 %) of the 47 patients and was more common in patients with ventricular arrhythmias by 24-h Holter electrocardiography recordings [12]. Dodd et al. [25] showed that the amount of trabecular LGE was correlated significantly with LVEF and an independent predictor of LVEF. Nucifora et al. [14] reported LGE was found in 55 % of patients and correlated with clinical severity and ventricular dysfunction. In keeping with their reports, our study showed LGE+ children had more severe LV dysfunction and NYHA functional class.

Similar to previous studies [12, 13], the distribution of LGE was strikingly heterogeneous and involved not only non-compacted segments but also normal segments in
presence of LGE has been shown to be a strong discriminator of adverse outcomes in dilated and hypertrophic cardiomyopathies [30, 31], a very limited amount of data has been available on the prognostic value of LGE in children with LVNC. Our study showed a significantly higher rate of cardiac death and heart transplantation in LGE+ children. We propose that the presence of LGE could therefore potentially play an important role in stratification of treatment in children with LVNC. However, this finding should be interpreted with caution owing to the small sample size and lower occurrence of end-point events in the cohort. The pathophysiology and meaning of LGE in children with LVNC need to be elucidated in the future studies.

Limitations
The present study has several limitations. First, the number of the cohort was still small owing to the relatively rare pediatric entity and a single-center nature. Second, there were potential selection and referral biases in our cohort, given most children clinically referred for CMR investigation had dramatic symptoms that may not be universally applicable to all populations. Third, LGE+ children had more adverse LV remodeling at baseline, which leads to indefinite relationship between the presence of LGE and adverse events. In order to conclusively ascertain incremental prognostic value of LGE in children with LVNC, larger studies with longer follow-up are required.

Conclusions
In children with LVNC, the LGE is present in up to one-fourth of children with LVNC, and LGE+ children exhibited a more maladaptive LV remodeling and higher incidence of cardiovascular death and heart transplantation. The potential clinical utility of LGE in children with LVNC needs to be investigated by larger sample size studies with longer follow-up.

Abbreviations
LVNC: Left ventricular non-compaction; CMR: Cardiovascular magnetic resonance; LV: Left ventricular; LGE: Late gadolinium enhancement; NC/C: Non-compacted-to-compacted; EDV: End-diastolic volume; ESV: End-systolic volume; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; VT: Ventricular tachycardia; VF: Ventricular fibrillation; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Competing interests
The authors declare that they have no competing interests.

Authors’ contribution
JP and SZ were responsible for the conception and the design of the study. HC drafted the manuscript. WC, WX, CC and GY interpreted and analysed the data. CH, JC and JW were involved in clinical acquisition of data. ML and HC performed the consensus read of CMR results. JC and S2 helped draft the manuscript. LL helped to acquire and interpret pathologic image. SKP gave critical revision of the manuscript. All authors have seen and approved the final version of the manuscript.
Author’s information

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