International Journal of Cardiology 246 (2017) 68–73

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiac magnetic resonance evaluation of left ventricular functional, morphological, and structural features in children and adolescents vs. young adults with isolated left ventricular non-compaction☆

Gaetano Nucifora [a,b,c,*], Karthigesh Sree Raman [a,b], Daniele Muser [d], Ranjit Shah [a,b], Rebecca Perry [a,b,e], Kama A. Awang Ramli [a], Joseph B. Selvanayagam [a,b,e]

[a] Department of Heart Health, South Australian Health & Medical Research Institute, Adelaide, Australia
[b] School of Medicine, Flinders University, Bedford Park, Adelaide, Australia
[c] Northwest Heart Centre, Wythenshawe Hospital, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK
[d] Division of Cardiology, University Hospital "Santa Maria della Misericordia", Udine, Italy
[e] Department of Cardiovascular Medicine, Flinders Medical Centre, Bedford Park, Adelaide, Australia

ARTICLE INFO

Article history:
Received 15 April 2017
Received in revised form 21 May 2017
Accepted 30 May 2017

Keywords:
Cardiac magnetic resonance
Isolated left ventricular non-compaction
Myocardial fibrosis
Late gadolinium enhancement
Strain
Tissue-tracking

ABSTRACT

Aim: To investigate the left ventricular (LV) functional, morphological, and structural features revealed by cardiac magnetic resonance (CMR) in children/adolescents with isolated LV non-compaction (iLVNC), and to compare them with those observed in young adults with iLVNC and healthy controls.
Methods: 56 subjects were included: 12 children/adolescents (mean age 15 ± 3 years, 75% male) and 20 young adults (mean age 35 ± 7 years, 75% male) with first diagnosis of iLVNC, 12 healthy children/adolescents (mean age 15 ± 3 years, 75% male) and 12 healthy young adults (mean age 34 ± 8 years, 75% male). CMR with late gadolinium enhancement (LGE) imaging was performed to evaluate LV function, extent of LV trabeculation, and presence/extent of LV LGE, a surrogate of myocardial fibrosis. Tissue-tracking analysis was applied to assess LV global longitudinal (GLS), circumferential (GCS) and radial (GRS) strain.
Results: The extent of LVNC and the presence/extent of LV LGE in children/adolescents and young adults with iLVNC were similar. Compared to healthy subjects, young adults with iLVNC had significantly lower LVEF; conversely, no significant difference in this parameter was observed between children/adolescents with iLVNC and healthy subjects. However, compared to healthy subjects, LV strain parameters were lower in both children/adolescents and young adults with iLVNC.
Conclusions: Complete phenotypic expression, subclinical impairment of myocardial deformation properties, and cardiac injury occur early in iLVNC patients, being already noticeable in the pediatric age group. The application of CMR myocardial deformation imaging permits earlier detection of LV functional impairment in children/adolescents with iLVNC, which would otherwise be missed with standard CMR imaging.

1. Introduction

Isolated left ventricular non-compaction (iLVNC) is a rare myocardial disorder phenotypically characterized by prominent trabeculations, deep intertrabecular recesses within the LV wall and a thin compacted layer, probably related to an arrest of the normal embryogenesis of endocardium and myocardium [1]. Clinical manifestations of iLVNC are extremely heterogeneous, ranging from asymptomatic status to heart failure, ventricular arrhythmias, and systemic thromboembolism [2].

Cardiac magnetic resonance (CMR) imaging has significantly improved the evaluation of iLVNC patients, due to its ability to provide accurate and reproducible information regarding the LV function, the extent of LV trabeculation, and the presence and extent of myocardial fibrosis during a single examination [3–5]. However, most studies to date have focused on adults with iLVNC, while fewer data are currently available regarding the information provided by CMR in pediatric patients affected by this rare disorder. Also, it is unknown whether pediatric patients with iLVNC exhibit a complete phenotypic expression of the disease compared to the adult counterpart. Hence, the aim of the present study was to investigate the LV functional (by volumetric and myocardial deformation analysis), morphological, and structural features revealed by CMR in children/adolescents with iLVNC, and to compare them with those observed in young adults with iLVNC.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: School of Medicine, Flinders University, Sturt Rd, Bedford Park, Adelaide SA 5042, Australia.
E-mail addresses: gaetano.nucifora@flinders.edu.au, gnucifora@outlook.com (G. Nucifora).

http://dx.doi.org/10.1016/j.ijcard.2017.05.100
0167-5273/

2. Methods

2.1. Study population

The study population included 56 subjects retrospectively identified by the CMR imaging database: 12 consecutive children/adolescents (mean age 15 ± 3 years, 75% male) with a first diagnosis of iLVNC, 20 consecutive young adults with a first diagnosis of iLVNC (mean age 35 ± 7 years, 75% male), 12 healthy children/adolescents (mean age 15 ± 3 years, 75% male) age- and gender-matched to the children/adolescents with iLVNC and 12 healthy young adults (mean age 34 ± 8 years, 75% male) age- and gender-matched to the young adults with iLVNC.

The diagnosis of iLVNC was based on the presence of established CMR and clinical criteria: 1) visual appearance of two distinct myocardial layers (a compacted epicardial layer and a non-compacted endocardial layer); 2) marked trabeculation and deep intertrabecular recesses within the non-compacted layer; 3) non-compacted to compacted end-diastolic myocardial ratio > 2.3 and/or non-compacted to global end-diastolic LV mass ratio > 0.20 and 4) absence of other associated congenital or acquired heart disease [6,7].

Medical records were reviewed to document the presence of family history of iLVNC or dilated cardiomyopathy (DCM), symptoms (chest pain, dyspnea, syncope/presyncope, and thromboembolic events), and abnormalities on resting ECG or 24-hour Holter monitoring (right or left bundle branch block, repolarization abnormalities, atrial fibrillation, frequent premature ventricular contractions, non-sustained or sustained ventricular tachycardia) prior to the CMR examination.

For each patient, cine and contrast-enhanced CMR images were analyzed to evaluate the conventional parameters of LV systolic function and the LV morphological and structural characteristics. Tissue-tracking analysis was also applied to cine long-axis and short-axis CMR images, to assess global LV longitudinal (GLS), circumferential (GCS) and radial (GRS) strain. For comparison purpose, 20 consecutive patients with a first diagnosis of iLVNC in their early adulthood (mean age 35 ± 7 years, 75% male) and 12 healthy children/adolescents (mean age 15 ± 3 years, 75% male) were also included in the study.

2.2. CMR acquisition protocol

CMR studies were performed using a 1.5-Tesla scanner (Siemens Aera, Erlangen, Germany) with a cardiac phased-array receiver surface coil and ECG gating. The vertical and horizontal long-axis cine slices, the left-ventricular outflow tract cine slice and a stack of contiguous short-axis cine slices from the atrio-ventricular ring to the apex were acquired using a steady-state free-precession pulse sequence (slice thickness = 8 mm, no interslice gap, TR/TE = 3.5/1.2 ms, temporal resolution = 30 frames per RR interval). LGE images were acquired using the same slice coverage as long-axis and short-axis cine images 10 min after intravenous injection of 0.1 mmol/kg injection of gadolinium (Gd-DTPA, Gadovist, Bayer, Germany), using a T1-weighted segmented inversion-recovery gradient-echo pulse sequence, individually adjusting the inversion time to optimize nulling of the apparently normal myocardium.

2.3. Cine-CMR and LGE data analysis

Cine-CMR and LGE images were analyzed offline using CMR[42] (Circle Cardiovascular Imaging, Calgary, Canada). The presence of a non-compacted endocardial layer and a compacted epicardial layer, with marked trabeculation and deep intertrabecular recesses within the non-compacted layer, was visually confirmed by screening the cine CMR images [6]. For this purpose, the 17-segment cardiac model, as defined by the American Heart Association/American College of Cardiology statement for standardized myocardial segmentation, was used [8]. The ratio of non-compacted (if present) to compacted myocardium was therefore measured for each LV myocardial segment at end-diastole using the cine long-axis images (Fig. 1). As recommended, the apex (segment 17) was excluded from the quantitative analysis, because it is normally thin and may lead to artificially high ratios [6]. The LV end-diastolic and end-systolic volume (EDV and ESV), the LV ejection fraction (EF) and the compacted, non-compacted and global LV mass were measured using the standard volumetric technique from the cine short-axis images [7]. Volume and mass measurements were indexed to body surface area. As previously described by Jacquier et al. [7], the compacted and global LV mass were assessed at end-diastole by drawing the endocardial border excluding or including the LV trabeculations, respectively. The non-compacted LV mass was then calculated as the difference between the global LV mass and the compacted LV mass (Fig. 1). The dichotomous presence or absence of LGE (a surrogate of myocardial fibrosis [5]) was qualitatively determined for each LV myocardial segment using the 17-segment cardiac model by reviewing the short- and long-axis contrast-enhanced images; regions of elevated signal intensity had to be confirmed in two spatial orientations. Also, the quantitative extent of LV LGE was determined and expressed as a percentage of the LV mass. For this purpose, the LV myocardium was delimited by endocardial and epicardial contours, which were traced manually and a region of interest (ROI) was selected in the effectively nulled myocardium; the mean signal intensity and standard deviation (SD) of the ROI were then measured. The enhanced myocardium was defined as myocardium with a signal intensity >5SD above the mean of the region of interest.

2.4. Tissue-tracking analysis

The assessment of LV myocardial mechanics was performed using a dedicated CMR tissue-tracking software (Tissue Tracking module, CVI[42], Circle Cardiovascular Imaging, Calgary, Canada). Following uploading of the cine short-axis and long-axis images, the brightness was optimized to ensure optimal endocardial/blood pool discrimination; the mitral valve annular plane and the position of LV apex were manually identified at end-diastole. The LV endocardial and epicardial borders (excluding papillary muscles and trabeculae) were then manually traced on the end-diastolic frame of the cine images; the software automatically propagated the contour and followed its features throughout the remainder of the cardiac cycle. Adjustment of contour tracking was made after visual assessment during cine loop playback to ensure that the LV segments were tracked appropriately. As the LV myocardial architecture consists of longitudinally and circumferentially orientated fibers located predominately in the epicardium/endocardium and mid-wall, respectively, longitudinal, circumferential, and radial strain are reflective of subendocardial, mid-wall, and transmural myocardial functions, respectively [9]. Global peak systolic longitudinal strain (GLS) was derived from the long-axis cine images analysis while global peak systolic circumferential (GCS) and radial (GRS) strains were derived from the short-axis cine images analysis (Fig. 2). An investigator blinded to the clinical and all other CMR data performed the tissue-tracking analysis. After an interval of 6 weeks, both this observer and a second experienced observer blindly repeated the tissue-tracking analysis on the same images of 10 randomly selected patients with iLVNC to assess intra- and inter-observer agreement for measures.

2.5. Statistical analysis

Continuous variables are expressed as mean and SD. Categorical data are presented as absolute numbers and percentages. Differences in continuous variables between two groups were assessed using the Student *t*-test or Mann-Whitney *U* test, where appropriate. Differences in continuous variables between more than two groups were assessed using the one-way ANOVA test or Kruskal–Wallis test, where appropriate; when the result of the analysis was significant, post hoc pairwise comparisons using the Bonferroni's correction were performed. Chi-square or Fisher's exact test, where appropriate, was computed to assess differences in categorical variables. The intra- and inter-observer reproducibility of LV myocardial deformation parameters was assessed using the within subject coefficient of variation (CV). Two-tailed tests were considered statistically significant at the 0.05 level. Statistical analysis was performed using the SPSS 21 (SPSS Inc., Chicago, Illinois) software package.

3. Results

Demographic, clinical and CMR imaging characteristics of the study population are summarized in Table 1. No significant difference in the prevalence of family history of iLVNC or DCM ($n = 2$, 17% vs. $n = 3$, 15%) and in the prevalence of symptoms ($n = 5$, 42% vs. $n = 10$, 50%) was observed between the pediatric and adult patients with iLVNC ($p = 1.0$ and $p = 0.73$, respectively). A trend toward a lower prevalence of resting ECG or 24-hour Holter monitoring abnormalities was conversely observed among the pediatric patients with iLVNC compared to the adult group ($n = 3$, 25% vs. $n = 12$, 60%; $p = 0.055$).

Compared to the healthy children/adolescents and the healthy young adults, the young adults with iLVNC had significantly larger LVEDV index and LVESV index, significantly lower LVEF and significantly greater LV compacted mass index; conversely, no significant difference in these parameters was observed between the children/adolescents with iLVNC and the healthy subjects.

The pediatric and the early adulthood group with iLVNC had a similar extent of LVNC, as expressed by the LV non-compacted mass index (28 ± 13 g/m^2 vs. 30 ± 12 g/m^2; $p = 0.65$), the LV non-compacted/global mass ratio (0.34 ± 0.11 vs. 0.35 ± 0.08; $p = 0.79$), the number of LV non-compacted segments (3.8 ± 2.2 vs. 4.4 ± 1.6; $p = 0.40$) and the maximal non-compacted/compacted myocardium ratio (4.2 ± 1.7 vs. 4.3 ± 1.4; $p = 0.90$). Similarly, these two groups had a similar prevalence ($n = 3$, 25% vs. $n = 5$, 25%; $p = 1.0$) and extent of LV LGE, expressed as either numbers of LV segments with LGE (0.8 ± 1.8 vs. 0.8 ± 1.9; $p = 0.96$) or as percentage of LV mass (6.6 ± 7.3% vs. 6.9 ± 9.1%; $p = 0.97$).

Fig. 3 presents the LV myocardial deformation parameters of the study population. Compared to the healthy children/adolescents and the healthy young adults, both the children/adolescents with iLVNC and the early adulthood group with iLVNC had impaired LV GLS (−21 ± 1% vs. −21 ± 2% vs. −17 ± 4% vs. −15 ± 4%; $p = 0.038$ and $p = 0.041$, and $p < 0.001$ and $p < 0.001$, respectively), GCS (−22 ± 2% vs. −23 ± 2% vs. −18 ± 5% vs. −15 ± 5%; $p = 0.047$ and $p = 0.008$, and $p < 0.001$ and $p < 0.001$, respectively), and GRS (45 ± 7% vs. 49 ± 9% vs. 33 ± 15% vs. 25 ± 11%; $p = 0.067$ and