The use of 2-D speckle tracking echocardiography in assessing adolescent athletes with left ventricular hypertrabeculation meeting the criteria for left ventricular non-compaction cardiomyopathy

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ABSTRACT

Background: Current echocardiographic criteria cannot accurately differentiate exercise induced left ventricular (LV) hypertrabeculation from LV non-compaction cardiomyopathy (LVNC). This study aims to evaluate the role of speckle tracking echocardiography (STE) in characterising LV myocardial mechanics in healthy adolescent athletes with and without LVNC echocardiographic criteria.

Methods: Adolescent athletes evaluated at three sports academies between 2014 and 2019 were considered for this observational study. Those meeting the Jenni criteria for LVNC (end-systolic non-compacted/compacted myocardium ratio > 2 in any short axis segment) were considered LVNC+ and the rest LVNC-. Peak systolic LV longitudinal strain (S_L), circumferential strain (S_C), rotation (Rot), corresponding strain rates (SR_L/C) and segmental values were calculated and compared using a non-inferiority approach.

Results: A total of 417 participants were included, mean age 14.5 ± 1.7 years, of which 6.5% were LVNC+. Peak systolic LV longitudinal strain (S_L), circumferential strain (S_C), rotation (Rot), corresponding strain rates (SR_L/C) and segmental values were calculated and compared using a non-inferiority approach. None of the athletes showed any additional LVNC clinical criteria. All average S_L, S_C, SR_L, SR_C, and Rot values were not worse in the LVNC+ group compared to LVNC- (p values range 0.0003–0.06), apart from apical SR_C (p = 0.2). All 54 segmental measurements (S_L/S_C, SR_L/SR_C, and Rot) had numerically comparable means in both LVNC+ and LVNC-, of which 69% were also statistically non-inferior.

Conclusions: Among healthy adolescent athletes, 6.5% met the echocardiographic criteria for LVNC, but showed normal LV STE parameters, in contrast to available data on paediatric LVNC describing abnormal myocardial function. STE could better characterise the myocardial mechanics of athletes with LV hypertrabeculation, thus allowing the transition from structural to functional LVNC diagnosis, especially in suspected physiological remodelling.

Keywords:
Left ventricular non-compaction
Paediatric athlete
Apical rotation
Longitudinal strain
Circumferential strain
Hypertrabeculation

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1. Introduction

Left ventricular non-compaction cardiomyopathy (LVNC) is characterised by prominent left ventricle (LV) trabeculae, a thin compacted layer, intertrabecular recesses and the propensity for arrhythmias and cardiac dysfunction [1,2]. The exact causes are not fully understood, being considered to be genetic or embryological [1,2], resulting in abnormal myocardial fibre anatomy and twist mechanics which lead to compensatory hypertrabeculation [3,4]. Clinically, it can present as palpitations or syncope during exertion, ECG changes, heart failure, embolic complications, and as LV dysfunction progresses or arrhythmias occur, sudden cardiac death (SCD) [2,5–7].

Diagnosis of LVNC is based on a combination of personal and family history, clinical and echocardiographic [5–10] or cardiac magnetic resonance imaging (CMR) derived criteria [11]. Their major limitation is that hypertrabeculation can also be the result of physiological adaptation to increased preload associated with athletic training [12], rather than a compensatory mechanism to pathological changes in the myocardium [3]. As many as 8% of adult athletes have hypertrabeculation mimicking LVNC [5,13,14], also seen in healthy controls [12], rather than a compensatory mechanism to pathological changes in logical adaptation to increased preload associated with athletic training [1,2]. The exact causes are not fully understood, characterised by prominent left ventricle (LV) trabeculae, a thin compacted layer, intertrabecular recesses and the propensity for arrhythmias [3,4].

2. Methods

2.1. Participant assessment and classification

Male athletes under 18 years of age evaluated at three sport academies (Manchester United Football Club, United Kingdom, Doha Aspire Academy, Qatar and Barcelona Football Club, Spain) between 2014 and 2019 were considered. Evaluations were done at the beginning of the season (n = 388, 93%), while a small proportion had to be performed either mid-season or after the season end (n = 29, 7%). UK National Research Ethics Service approval was obtained, and local ethics approval for participating centres (Qatar Anti-Doping Laboratory IRB #E2013000003 and #E20140000012; Hospital Clinic Barcelona HCB/2018/0068), and parent/carer and adolescents signed procedure consent forms and/or assent forms, respectively, when not covered by the local institutional consent framework. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

All athletes underwent a detailed evaluation, including health questionnaire, anthropometric measurements and 12-lead ECG, as recommended by the local and institutional protocols and were cleared for sports participation based on the current recommendations [24]. Practiced sport was classified by type (endurance, power, skill or mixed) [25]. All athletes were reviewed by the local clinical team if a cardiomyopathy was suspected, underwent the recommended testing (including CMR if indicated), and the most recent follow-up information was reviewed.

Based on previous literature, the echocardiographic criteria described by Jenni et al. [6] were selected as being the most restrictive in athletes (lowest probability of false positive) [6,13–15]. Those having a ratio of non-compacted (NC) to compacted (C) myocardium of NC/C > 2 during end-systole in any short axis view segment, with prominent trabeculations and deep intratrabecular recesses were considered as LVNC+; and, the rest LVNC− [8]. Individuals where an adequate apical short axis (SAX) view was not available were excluded (Fig. A.1).

2.2. Echocardiography

Echocardiography at rest was performed using either an Artida or an Apio I900 machine (Canon Medical Systems, Japan) and a 2.0–4.8 MHz transducer. LV chamber quantification was performed: LV end diastolic diameter (LVEDD), LV end systolic diameter (LVEDS), interventricular septum thickness (IVS), posterior wall thickness (PW). LV systolic and diastolic function was quantified as follows: LV ejection fraction (LVEF) using the modified Quinones formula (%ΔLVEF = [(1-%ΔLVEF)]/[(1-%ΔLVEF)], %ΔLVEF = LVEDD [2] - LVEDS [2]/LVEDS [2], %ΔL = 15% for normal apical function), peak systolic and left lateral mitral annulus velocity at pulsed wave tissue Doppler Imaging (LV septal and lateral S’), peak mitral E and A wave velocities, peak mitral E’ velocities (mean of lateral and septal values where both are reported), E/A ratio, E/E’ ratio. All measurements were performed by an experienced clinician (G.E.P., A.G. S., D.M.D) either at the time of the clinical evaluation or offline, following current echocardiographic guidelines [26–28].

NC and C myocardium thickness was measured offline in all three short axis views (basal, mid, apical) by DMD and CR, using the Ultra Extend Package v3.2 (Canon Medical Systems, Japan) or Radiant Dicom Viewer 2020 (Medixant, Poland).

2.3. Speckle tracking echocardiography (STE)

Apical 4 chamber (A4C) and short axis (SAX basal, mid and apical) views were acquired for STE analysis (three cardiac cycles at 50–100 frames per second). The endocardial border was traced (automatically in A4C, otherwise manually), myocardial thickness adjusted and automated tracking used on one manually selected best cardiac cycle. Tracking quality and strain curves were visually inspected, and tracking was adjusted if necessary.

Average LV peak systolic longitudinal A4C strain (A4C Sl), average LV basal, mid and apical circumferential peak systolic strain (basal, mid and apical Sc), the corresponding peak systolic strain rates (SR and S’c) as well as peak systolic basal (negative) and apical (positive) rotation (basal and apical Rot) were measured and reported [29]. All STE analyses were performed offline by an experienced clinician (DMD) using the Vitrea 7.11.5.29 (Canon Medical Systems, Japan). The end systole frame was automatically selected as corresponding to the smallest ventricular volume. All peak systolic strain values were extracted from the output using an in-house script (R version 4.1.0).
2.4. Statistical analyses

Frequencies are given as numbers and percentages, continuous values as means±standard deviation (SD). Population characteristics were compared using the t-test with Welch’s approximation (continuous variables) and Fisher’s test (categorical variables). Associations between patient factors and LVNC+ were explored based on descriptive data, with age, BSA, sport group, ethnicity being co-variates in a multivariable logistic regression (adjusted by centre) and reported as odds ratio (OR).

In order to evaluate whether the STE parameters measured in the LVNC+ were comparable to those in the LVNC- group, a non-inferiority statistical approach was used. The “two one-sided t-test” with Welch approximation test (TOST package) [30] was used, which determines whether the difference between two means is between a lower and upper set limit (equivalence limit, or delta). This limit was chosen empirically, based on the limited available data [21], to be 2% for Sl and proportionally 2.5% for Sc, 0.1 for SRl, 0.15 for SRC, and 0.5° for basal/apical rotation. Since only a non-inferiority test was relevant, the p value for the upper limit test was used for the negative values (Sl, SR and basal rotation) and the lower limit test for positive values (apical Rot). This methodology is further detailed in the Supplemental Material (Statistical analyses).

Evaluating differences in average and segmental STE measurements between LVNC+/− groups required 68 statistical tests (same test family), for which a Benjamini-Hochberg (BH) critical value (false discovery rate set at 0.1) was calculated as an adjusted statistical significance level [31], to correct for multiple testing. Thus, an alpha value of \( p \leq 0.05 \) was considered statistically significant unless an adjusted Benjamini-Hochberg critical value is specified.

Inter- and intra-observer agreement were expressed as Cohen’s kappa

![Figure 1](image-url)

Fig. 1. Examples of athletes meeting the left ventricular non-compaction criteria [8]. Each column represents one example (#1-#4) and shows the short axis (SAX) apical and mid views (in end-diastole and end-systole), as well as peak systolic longitudinal apical 4 chamber (A4C) strain (Sl), circumferential strain (Sc), basal rotation (Rot) and apical rotation (Rot). Arrows point to the myocardial segments with hypertrabeculation having an end-systolic non-compacted/compacted (NC/C) ratio ≥2, while asterisks show segments with hypertrabeculation and a NC/C ratio <2.
statistic for LVNC classification (random sample of \( n = 40 \), DMD and CR) and as inter-class-coefficient (ICC) for STE parameters (random sample of \( n = 30 \), DMD and ND). All Statistical analyses were done using the STATA 16 SE (Stata Corp, Texas, USA).

3. Results

A total of 417 healthy male athletes under 18 years of age were included (mean age 14.5 ± 1.7, range 11.6–18 years), from the total of 447 eligible participants (exclusions with reasons in Fig. 1). Of these, 6.5\% (\( n = 27 \)) met the Jenni criteria for LVNC (LVNC+).

Demographic, anthropometric and practiced sport data within the LVNC+/LVNC- groups are shown in Table 1. LVNC+ athletes were older (\( p = 0.03 \)), had higher BSA (\( p = 0.002 \)), and a higher probability of being of Black ethnicity (\( p = 0.005 \)). Due to the risk of selection bias, the associations between LVNC+ and subject characteristics were further evaluated. Only Black ethnicity was found to be associated with LVNC+ status after adjusting for age, weight, height, BSA, practiced sport type and centre (adjusted OR \( = 2.9 \) versus non-Black ethnicity, 95\% CI [1.1;8], \( p = 0.04 \)). At the time of writing, no cases of cardiomyopathies were reported in this cohort as part of usual care at the participating centres. The prevalence of abnormal ECG changes and borderline ECG findings \([32]\) was similar in both groups (Fig. 1). One of the athletes had physical examination, personal or family history suggestive of LVNC.

3.1. Left ventricular structure, size and function by conventional echocardiography

LV size, systolic function or diastolic function parameters measured by conventional echocardiography were normal, and similar between LVNC+ and LVNC- groups (Table A1).

Table 1

| Demographic, anthropometric, ECG and practiced sports data. |
|-----------------|-----------------|-----------------|-----------------|
|                 | LVNC+ \( n = 27 \) | LVNC- \( n = 390 \) | Total \( n = 417 \) | \( p \) value |
| Age, mean ± SD (y) | 15.2 ± 1.5 | 14.5 ± 1.7 | 14.5 ± 1.7 | 0.03 |
| BSA, mean ± SD (m²) | 1.72 ± 0.15 | 1.61 ± 0.26 | 1.62 ± 0.26 | 0.002 |
| Ethnicity, n (%) | | | | |
| Arab | 6 (22.2%) | 188 (48.2%) | 194 (46.5%) | 0.005 |
| Black | 11 (40.8%) | 73 (18.7%) | 84 (20.1%) | |
| White | 7 (25.9%) | 73 (18.7%) | 80 (19.2%) | |
| Other** | 2 (7.4%) | 9 (2.3%) | 11 (2.7%) | |
| Missing | 1 (3.7%) | 47 (12.1%) | 48 (11.5%) | |
| Practiced sport type, n (%) | | | | |
| Mixed | 19 (70.4%) | 285 (73.1%) | 304 (72.9%) | 0.3 |
| Power | 5 (18.5%) | 44 (11.3%) | 49 (11.7%) | |
| Endurance | 1 (3.7%) | 31 (7.9%) | 32 (7.7%) | |
| Skill | 0 | 18 (4.6%) | 18 (4.3%) | |
| Unclassifiable*** | 2 (7.4%) | 12 (3.1%) | 14 (3.4%) | |
| ECG findings, n (%) | | | | |
| Normal | 23 (85.2%) | 294 (78.0%) | 317 (76.5%) | 0.3 |
| One borderline finding | 3 (11.1%) | 68 (18.5%) | 71 (17.1%) | |
| Abnormal | 1 (3.7%) | 5 (1.4%) | 6 (1.4%) | |

BSA, body surface area; SD, standard deviation.

Abnormal ECG:
LVNC+: anterior T wave inversion (\( n = 1 \)), LVNC-: pathological Q wave (\( n = 2 \)), lateral T wave inversion (\( n = 1 \)), ST segment depression (\( n = 1 \)), >2 premature ventricular complexes on a 10s period (\( n = 1 \)).

using the DuBois formula, missing \( n = 2 \)

** \( n = 7 \) (mixed) and \( n = 4 \) (south Asian).

*** \( n = 13 \) (referee), \( n = 1 \) (missing).

**** ECG changes were classified by current criteria \([32]\). Missing in \( n = 23 \).

The distribution of segments with NC/C ratio \( \geq 2 \), \( 0 < \text{NC/C ratio} < 2 \) and no NC layer is shown in Fig. A.2. The LV segments most likely to exhibit a NC/C layer ratio \( \geq 2 \) were: apical lateral (16/27, 59.3\%), apical anterior (6/27, 22.2\%), apical inferior (6/27, 22.2\%), mid anterior (4/26, 15.4\%) and basal anterior (3/27, 11.1\%). Examples of athletes meeting the LVNC+ criteria in our cohort are presented in Fig. 1, along with their corresponding main STE measurement values.

3.2. Left ventricle STE measurements

The overall mean A4C-\( S_l \) was \(-20.7 ± 2% \) (range \(-16.4\% \) to \(-27.6\% \)), mean basal \( S_l \) \(-26.1 ± 3.7\% \) (range \(-16.5\% \) to \(-37.4\% \)), mid \( S_l \) \(-28 ± 3.6\% \) (range \(-17.9\% \) to \(-39.6\% \)) and apical \( S_l \) \(-30.3 ± 4.9\% \) (range \(-19.4\% \) to \(-45.3\% \)). Mean A4C-\( S_l \), A4C-\( SR_l \), basal, mid and apical \( S_l \), basal, mid and apical \( SR_l \) basal and apical rotation were numerically similar in both LVNC+ and LVNC- groups, and also statistically non-inferior in the LVNC+ compared to the LVNC-, with the exception of the apical \( SR_l \) where the comparison was underpowered (Fig. 2 and Table A2).

Segmental measurements were also numerically similar between the two groups, absolute differences ranging from 0.001 to 1.34\% for \( S_l \), 0.002-0.134 s\(^{-1}\) for \( SR/SR_l \) and 0.04-1.1\(^{10}\) for basal/apical Rot. Of all 54 segmental values comparisons done (Fig. 3), 37 (69\%) were statistically non-inferior in the LVNC+ group compared to LVNC-, while in 17 (31\%) the comparison was underpowered, but with mean differences being below the predefined margin (Fig. 3 and Table A3). None of the LVNC+ measurements were found to be significantly worse than those in the LVNC- group.

3.3. Interobserver and intraobserver reliability

Inter-observer agreement for classification into LVNC+/LVNC- groups was 96.7\% (Cohen Kappa coefficient = 0.87), while intra-observer agreement was 100\%. The majority of average and segmental STE measurements showed good or excellent intraobserver and interobserver agreement (ICC range 0.61–0.99, ICC > 0.7 in 95.3\% of measurements), fully detailed in Table A.4.

4. Discussion

In a large group of healthy adolescent athletes from diverse ethnic and sports backgrounds, 6.5\% met the echocardiographic criteria for LVNC, more prevalent in those of Black ethnicity, as seen in adult athlete data \([6,13,14]\). LV regional \( S_l \), \( SR_l \) rotation, as well as strain rate and segmental measurements were no worse in those with hypertrabeculation meeting the LVNC criteria, compared to those without. This contrasts with paediatric cohorts with diagnosed LVNC, where LV strain and rotation were abnormal, even when conventional myocardial function parameters were preserved \([17]\). As such, documenting normal LV function and mechanics, including regional assessment, could differentiate physiological training adaptations from pathological changes seen in LVNC, where abnormal regional function has been shown to be present. This would improve the current diagnostic criteria which still focus on quantifying the degree of hypertrabeculation, rather than the myocardial function, and would offer additional tools during athlete screening and follow-up.

4.1. LV hypertrabeculation in athletes – an issue of over diagnosis

Current imaging criteria for LVNC diagnosis are based on showing hypertrabeculation and ventricular dysfunction \([8-11]\). In athletes, hypertrabeculation is an adaptation to increased preload associated with training, reducing myocardial work for the same cardiac output \([12,33]\), a phenomenon also observed during pregnancy \([16]\). In LVNC this could be to compensate for rigid rotation patterns caused by abnormal myocardial fibre disposition \([3,4]\). Similar structural findings could thus
be secondary to physiological adaptation or pathological development, without any criteria to differentiate the two, outside of when overt LV dysfunction occurs or other non-imaging findings confirm LVNC [3,6]. This issue is common among athletes, especially in those of Black ethnicity, with >18% of adult athletes showing some degree of LV hypertrabeculation, and 1.3%–8.1% fulfilling the Jenni criteria for LVNC [6,13,14]. In our cohort of healthy adolescent athletes, 6.5% met the Jenni criteria, also more prevalent in Black athletes, showing that over-diagnosis of hypertrabeculation is as prevalent in this age group, as in adults. Looking at the affected LV areas, the majority were distributed around the apex, some were mid antero-lateral, and few also had basal involvement, which is uncommon in LVNC [22].

Echocardiographic alternatives to the Jenni criteria, the Chin and St¨ollberger criteria, also have even higher prevalence among athletes [8–10]. Using inaccurate criteria in an athlete is problematic, since even just the suspicion of a cardiomyopathy can significantly affect their eligibility and participation in competitive sports.

4.2. LV strain in the assessment of athletes with LV hypertrabeculation

Current LVNC echocardiographic criteria focus on quantifying the degree of hypertrabeculation, less on evaluating global or regional cardiac function [8–10], despite growing evidence of the role of myocardial mechanics in this pathology. STE has been shown to be useful in the early diagnosis [19] as well as risk stratification of LVNC [20]. Reduced apical $S_c$ [22,23], rigid-body rotation or reduced twist [4,19,21], and a lack of $S_c$ basal-apical gradient [22] were all associated with LVNC, even in those with LVEF>50% [17,19]. These findings support using STE in athletes with hypertrabeculation, to describe the LV function in greater detail, and differentiate physiological from pathological remodelling. There is sufficient data at present to show reduced LV strain parameters, including regional measurements, in non-athlete children with LVNC, or hypertrabeculation [22,23], and in our study we complement this by showing that athletes with similar structural criteria have normal LV function.

Fig. 2. Global and regional left ventricle speckle tracking echocardiography parameters in LVNC+ and LVNC- athletes. Panel a: longitudinal strain (Sl); Panel b: longitudinal strain rate (SR_l); Panel c: circumferential strain (S_c); Panel d: circumferential strain rate (SR_c); Panel e: basal and apical rotation (Rot). All mean $S_l$ and $S_c$ in the LVNC+ group are numerically comparable to those in the LVNC- group and statistically non-inferior, within the predefined margins, except for the apical $S_c$ region (where the comparison is underpowered).

Values are expressed as means, with confidence interval bars representing standard deviation, detailed in Table A.2. Reported are p values (Benjamini-Hochberg critical values) for non-inferiority test and t-test. For statistical tests detailed output and interpretation, see Table A.2 and Supplementary Material – Statistical analysis.
Fig. 3. Left ventricular segmental speckle tracking echocardiography measurements in athletes with left ventricular non-compaction criteria (LVNC+) and without (LVNC-). Panel a: Apical 4 chamber view – peak systolic longitudinal strain (S_l) and longitudinal strain rate (SR_l); Panel b: peak systolic circumferential strain (S_C); Panel c: peak systolic circumferential strain rate (SR_C); Panel d: peak systolic basal and apical rotation (Rot).

Panels a, b, c represent the 16 segments LV model short axis views, and panel d the 6 apical-4-chamber view segments [28]. All values are expressed as means, standard deviations and detailed statistical data in Table A.3. Segments where LVNC+ mean was statistically non-inferior to the LVNC- mean are coloured in green, those with an underpowered comparison in grey.
It was proposed that when suggestive hypertrabeculation is observed in an athlete, as found in our group (Fig. 1), a LVEF<50% could guide the decision for sports participation [6], given that worse outcomes are strongly associated with LV dysfunction [2,5]. Nevertheless, in a small group of 22 athletes with LVNC criteria, half had LVEF<55% or LV dilation, but only two had other abnormalities, and none had sufficient criteria for diagnosis [34]. This leaves the majority of these cases in a “grey area”, with little evidence to inform a decision to clear as normal physiology, or perform further testing. All 27 LVNC+ athletes in our study fall into this category, and yet had comparable LV strain and rotation to those without LVNC echocardiographic criteria. Furthermore, in large general population studies, isolated LV hypertrabeculation was not found to be associated with adverse outcomes [35]. This supports the notion that in athletes, LV hypertrabeculation with normal regional, segmental function and rotation is unlikely to be related to cardiomyopathy, or of clinical consequence, highlighting the role STE could play in their assessment.

4.3. Limitations

This is a retrospective analysis of data gathered both prospectively and retrospectively, and shares both the strengths and limitations of both designs. The echocardiography reports were issued by more than one clinician, with an expected degree of variability, affecting non-primary measurements. Since these are healthy participants, for both designs. The echocardiography reports were issued by more than one clinician, with an expected degree of variability, affecting non-primary measurements. Since these are healthy participants, for

hypertrabeculation and no other signs of cardiomyopathy, as it could allow for fewer additional tests and false positive diagnoses.

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Declaration of Competing Interest

The Author(s) declare(s) that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.09.076.

References


