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The use of 2-D speckle tracking echocardiography in differentiating healthy adolescent athletes with right ventricular outflow tract dilation from patients with arrhythmogenic cardiomyopathy

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ABSTRACT

Aims: Echocardiographic assessment of adolescent athletes for arrhythmogenic cardiomyopathy (ACM) can be challenging owing to right ventricular (RV) exercise-related remodelling, particularly RV outflow tract (RVOT) dilation. The aim of this study is to evaluate the role of RV 2-D speckle tracking echocardiography (STE) in comparing healthy adolescent athletes with and without RVOT dilation to patients with ACM.

Methods and results: A total of 391 adolescent athletes, mean age 14.5 ± 1.7 years, evaluated at three sports academies between 2014 and 2019 were included, and compared to previously reported ACM patients ($n = 38$ definite and $n = 39$ borderline). Peak systolic RV free wall (RVFW-S_l), global and segmental strain (S_l), and corresponding strain rates (SR_l) were calculated. The participants meeting the major modified Task Force Criteria (mTFC) for RVOT dilation were defined as mTFC+ ($n = 58$, 14.8%), and the rest as mTFC- ($n = 333$, 85.2%). Mean RVFW-S_l was −27.6 ± 3.4% overall, −28.2 ± 4.1% in the mTFC+ group and − 27.5 ± 3.3% in the mTFC- group. mTFC+ athletes had normal RV-FW-S_l when compared to definite (−29% vs −19%, $p < 0.001$) and borderline ACM (−29% vs −21%, $p < 0.001$) cohorts. In addition, all mean global and regional S_l and SR_l values were no worse in the mTFC+ group compared to the mTFC- (p values range < 0.0001 to 0.1, inferiority margin of 2% and 0.1 s^{-1} respectively).

Conclusions: In athletes with RVOT dilation meeting the major mTFC, STE evaluation of the RV can demostrate normal function and differentiate physiological remodelling from pathological changes found in ACM, improving screening in grey-area cases.

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1. Introduction

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiac condition commonly affecting the right ventricle (RV), characterised by fibro-fatty infiltration. [1] Although primarily diagnosed in adulthood, ACM can have important implications in adolescents: 10% of all sudden cardiac deaths (SCD) caused by ACM occur in adolescents, [2] 20% of all SCDs reported in children and adolescents are due to ACM. [3] This is important in adolescent athletes with potentially undiagnosed ACM, where intense exercise can increase the SCD risk, [4] and hasten disease progression. [1]

ACM diagnosis is multimodal, as outlined in the modified Task Force Criteria (mTFC) [5] and the recently proposed Padua criteria. [6] This includes, among other patient characteristics, echocardiographic criteria of right ventricular outflow tract (RVOT)/RV dilation, major structural abnormalities, and global RV systolic dysfunction. These criteria present several limitations when applied in the adolescent athlete: RVOT and RV dilation are common in athletes, [7–12] whereas structural abnormalities, reduced RV fractional area change (FAC) or ejection fraction are rare in children and adolescents with early ACM. [13] Therefore, new tools to help differentiate physiological from pathological remodelling in elite athletes are needed.

In athletes, previous studies have focused mainly on the role of RV speckle tracking echocardiography (STE) in evaluating the impact of exercise induced remodelling on myocardial function, in both adults [14–16] and children [7,17]. There is a gap in knowledge when it comes to the role of RV STE in screening for ACM, with only one previous study showing lower, but within normal limits, RV strain in athletes with RVOT dilation. [18] This is despite evidence that the only functional parameter that differentiated ACM from healthy controls in an adolescent cohort was peak longitudinal RV free wall strain (RVFW-S_l). [13] Likewise, RV strain worsens over time, even in early ACM, while FAC or RVOT diameters remained unchanged. [19]

Our primary aim was to compare RV myocardial global and segmental function of healthy adolescent athletes with RVOT dilation to those without, and to children with definite or borderline ACM. [13] We hypothesized that global and regional RV strain and strain rate will be no worse in athletes who meet the major mTFC for RVOT dilatation (mTFC+) compared to those who do not (mTFC-) but will be better when compared to adolescent ACM patients. Our secondary aim was to investigate the appropriateness of current echocardiographic criteria in adolescent athletes, by describing the prevalence and associated characteristics of RVOT dilation in this group.

2. Methods

2.1. Participant assessment and classification

Male adolescent athletes under 18 years old undergoing cardiac profiling at three sport academies (Manchester United Football Club, United Kingdom, Aspire Academy, Doha, Qatar and Football Club Barcelona, Spain) between 2014 and 2019 were included. We have previously reported on definite and borderline ACM cases, [13] and only the reported descriptive data were utilised here. UK National Research Ethics Service (NRES) and local ethics approval for participating centres (Qatar Anti-Doping Laboratory IRB #E2013000003 and #E20140000012; Hospital Clinic Barcelona HCB/2018/0068) were obtained. Parent/carer and adolescents provided informed consent /assent.

All athletes underwent detailed evaluation, including health questionnaire, anthropometric measurements and 12-lead ECG, as recommended by institutional protocols and approved for sports participation. [20] Practised sport was classified by type (endurance, power, skill and mixed). [21] All athletes were reviewed by the local clinical team if a cardiomyopathy was suspected, underwent the recommended testing (including cardiac magnetic resonance if indicated), and the most recent follow-up information was reviewed.

The athlete study cohort was divided into those who met the major mTFC for RVOT dilation (mTFC+) and those who did not meet these criteria (mTFC-) per current recommendations: [21] PLAX RVOT≥32 mm (19 mm/m^2) or PSAX RVOT≥36 mm (21 mm/m^2). [5] In adolescent athletes the presence of significant RVOT dilation alone might prompt a suspicion of ACM, as reduced RV-FAC or wall motion abnormalities would be very uncommon and highly diagnostic, thus the mTFC+ group reflects the diagnostic grey-area seen in screening.

Two cohorts of adolescents with definite ACM (n = 38) and borderline ACM (n = 39) [13] were included as positive controls, their clinical, demographic, and echocardiographic characteristics being detailed in previously published work. [13]

2.2. Echocardiography

Echocardiography at rest was performed using an Artida or Aplio i900 machine (Canon Medical Systems, Japan) and a 2.0–4.8 MHz transducer. End diastolic RV diameters were measured: RVOT in the parasternal long axis (PLAX) view, proximal RVOT parasternal short axis (PSAX) view, RV inlet (basal, mid segment and apical diameters [13]) and RV length in the RV modified apical four chamber (A4C) view. RV systolic function was quantified using the tricuspid annular plane systolic excursion (TAPSE), RV FAC, peak systolic tricuspid annulus velocity from pulsed wave Tissue Doppler Imaging (PW TDI) (RV S′). In addition, left ventricular ejection fraction (LVEF) by Teichholz or Simpson biplane methods was reported. All measurements were performed at time of clinical evaluation or offline, following the current guidelines. [22–24]

2.3. Speckle tracking echocardiography (STE)

RV apical four chamber (A4C) views were acquired for STE analysis, with up to three cardiac cycles at 50–100 frames per second. The endocardial border was manually traced, and myocardial thickness adjusted. Automated 6 segment tracking was used on one manually selected cardiac cycle. Tracking quality and strain curves were visually inspected, and tracking was adjusted as necessary. When >1 free wall segment did not correctly track the image was discarded (n = 5, 1.3% of analysed RV views).

RV peak systolic longitudinal global strain (RVGL-S_l) and strain rate (RVGL-SR_l), average and segmental RV free wall peak systolic longitudinal systolic strain (RVFW-S_l) and strain rate (RVFW-SR_l) as well as segmental values were analysed offline (Vitrea 7.11.5.29; Canon Medical Systems, Japan). [25] The end systole frame was automatically selected as corresponding to the smallest ventricular volume. All peak systolic strain and strain rate values were extracted from the software output using an in-house script (R version 4.1.0).

To compare mTFC+ athletes with definite and borderline ACM we remeasured strain in mTFC+ athletes using the same equipment (TomTec Arena v4.6,TomTec Imaging Systems, Unterschleißheim, Germany) as in our previous analysis. [13] We excluded 4 mTFC+ athletes due to incompatible file formatting and 1 due to poor tracking. Consequently, 53 of 58 mTFC+ athletes were reanalysed.

2.4. Statistical analyses

Frequencies are given as numbers and percentages, with continuous values as mean ± 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 mTFC+ were explored, with age, BSA, sport group, ethnicity, RV inlet diameters (basal, mid, apical, length), TAPSE, RV-S′, FAC, RVFW-S_l, RVFW-SR_l being considered co-variates in a multivariable regression (adjusted by centre) and reported as odds ratio (OR). A t-test was used to compare mTFC+ athletes to definite and borderline

ACM,(13) utilizing previously reported means and standard deviations [13].

To evaluate whether the strain parameters in mTFC+ subjects were comparable to mTFC- subjects, a non-inferiority statistical approach was chosen, used previously. [26] The "two one-sided t-test" (TOST package) [27] was used, which determines whether the difference between 2 means is between a lower and upper set limit (equivalence limit or delta). This limit was empirically chosen, based on available data, [13,28] to be 2% for S_l and proportionally, 0.1 s^{-1} for SR_l, these values being also <10% of the cohort means and less than one SD. The *p* value for the upper limit test was reported (non-inferiority shown if $p \leq 0.05$), and the test was underpowered if the non-inferiority test p value>0.05 and the *t*-test p value>0.05. This methodology is further detailed in the Supplemental Material (Statistical analyses).

Inter- and intra-observer agreement for mTFC classification were expressed as Cohen's kappa statistic and for STE parameters were expressed as inter-class-coefficient (ICC) on a randomly selected subset of 30 participants, done >6 months apart. A *p*-value ≤0.05 was considered statistically significant. Statistical analyses were conducted using the STATA 16 SE (Stata Corp, Texas, USA).

3. Results

A total of 391 male athletes <18-years old (mean 14.5 ± 1.7, range 9.8–18 years) were analysed from a total of 447 eligible participants. Reasons for exclusion are shown in Supplementary material. Of these, 14.8% ($n = 58$) met major mTFC cut-offs for RVOT dilation (mTFC+ group). Demographic, anthropometric, ECG and practised sport data by mTFC group are shown in Table 1. At the end of the study, no cases of cardiomyopathies were reported in this cohort. The prevalence of abnormal ECG changes and borderline ECG findings [29] were similar in both groups ($p = 0.8$, Table 1).

3.1. Right ventricular size and cardiac function by conventional echocardiography

3.1.1. Right ventricle diameters

All RV chamber quantification measurements are presented in Table S1. Mean RVOT PLAX diameters were 29 ± 4.7 mm and 24.7 ± 3.2 mm for mTFC+ and mTFC-, respectively ($p < 0.0001$; range 16.7–41.7 mm); mean RVOT SAX diameters were 28.2 ± 5.2 mm and 25.2 ± 3.5 mm for mTFC+ and mTFC-, respectively ($p = 0.0001$; range 15–43.3 mm). Indexed RV basal, mid, apical diameters and apex-base length were larger in mTFC+ versus mTFC- subjects.

Table 1
Demographic, anthropometric, ECG and practised sports data.

	mTFC+ $n = 58$	mTFC- n = 333	Total $n = 391$	p value
Age, mean ± SD (y)	14 ± 1.9	14.6 ± 1.7	14.5 ± 1.7	0.03
BSA, mean ± SD (m^2)	1.49 ± 0.35	1.62 ± 0.21	1.6 ± 0.24	0.009
Ethnicity, n (%)*				
Arab	25 (50)	166 (55.7)	191 (54.9)	0.2
Black	9 (18)	70 (23.5)	79 (22.7)	
White	16 (32)	62 (20.8)	78 (22.4)	
Sport type, n (%)**				
Mixed	44 (77.2)	241 (75.3)	285 (75.6)	0.7
Power	5 (8.8)	38 (11.9)	43 (11.4)	
Endurance	6 (10.5)	24 (7.5)	30 (8)	
Skill	2 (3.5)	17 (5.3)	19 (5)	
ECG findings, n (%)***				
Normal	47 (83.9)	253 (80.1)	300 (80.6)	0.8
One borderline finding	8 (14.3)	57 (18)	65 (17.5)	
Abnormal	1 (1.8)	6 (1.9)	7 (1.9)	

BSA, body surface area; ECG, electrocardiogram; mTCF, modified Task Force Criterial; SD, standard deviation.
* n = 33 (missing), $n = 6$ (mixed) and $n = 4$ (south Asian) not included here ** $n = 13$ (referee unclassifiable), n = 1 (missing) not included here ***ECG changes were classified by current criteria. [29] Missing in $n = 19$.
Abnormal ECG:
mTFC+: pathological Q wave (n = 1) mTFC-: T wave inversions ($n = 2$), ST segment depression (n = 2), pathological Q wave (n = 1), >2 premature ventricular complexes on a 10s period (n = 1).

3.1.2. Cardiac systolic function

Conventional RV function parameters and mean LVEF are shown in Table S1. No clinically or statistically significant differences between the mTFC+ and mTFC- groups were found in TAPSE ($p = 0.5$), RV FAC ($p = 0.9$), RV-S′ ($p = 0.6$) or LVEF (p = 0.9) (Table S1). There was a similar prevalence of participants with RV FAC ≤ 33% [5] in both the mTFC+ and mTFC- groups (1.7 vs 2.1%, $p = 0.8$). There were no wall motion abnormalities in either group.

3.2. Right ventricular strain and strain rate

The overall mean RVFW-S_l was −27.6 ± 3.4% (range − 20.6% to −38.2%) and mean RVGL-S_l was −23.2 ± 2.5% (range − 17.6% to −30.9%). An example of STE measurements in athletes with marked RVOT dilation is shown in Fig. 1. Mean global, FW and segmental S_l and SR_l values were numerically similar in both groups, and statistically non-inferior in the mTFC+ compared to the mTFC- group, except for the basal lateral S_l and SR_l, where the comparison was underpowered (Fig. 2 and Table S2).

The mTFC+ athletes strain values were remeasured using the same methodology as previously described, [13] to allow for direct comparison of cohorts. The definite and borderline ACM groups [13] had significantly worse RVFW-S_l compared to mTFC+ athletes (−19% vs −29%, $p < 0.001$ and − 21% vs −29%, $p < 0.001$ respectively) and also RVGL-S_l (−21% vs −25%, $p < 0.001$ and − 23% vs −25%, $p = 0.007$), as shown in Fig. 3. The range of remeasured RVGL-S_l in the mTFC+ group was between −20.2% and − 30.2%, with only $n = 3$ (5%) marginally below the previously proposed cut off for ACM suspicion of −20.4%, which gave optimal accuracy in discerning disease from controls. [13].

3.3. Factors associated with mTFC+ status

In a multivariable model including subject demographic and echocardiographic characteristics, only smaller BSA (OR 21.3/m^2, [1.3;348.1], $p = 0.03$) was associated with a higher probability of meeting mTFC+ echocardiographic RVOT dilation criteria. RV inlet size or systolic function parameters, including RV strain, were not associated with the likelihood of meeting the mTFC. More so, 39 of 58 (67%) mTFC+ participants fulfilled the criteria only after indexing to BSA, and not also by absolute RVOT size.

3.4. Interobserver and intraobserver reliability

Inter-observer agreement for classification into mTFC+/mTFC- groups was 94.9% (Cohen Kappa coefficient = 0.72, random sample $n = 40$), while intra-observer agreement was 100%. Free wall and global RV S_l and SR_l showed very good agreement interobserver and intraobserver agreement (ICC ranging from 0.79 to 0.89). Segmental S_l and SR_l had variable agreement, with ICC ranging from 0.6 to 0.92 (>0.7 in 75% of segmental measurements). All interobserver and intraobserver ICC coefficients for STE RV measurements are detailed in Table S3.

4. Discussion

This study assessed a large cohort of healthy adolescent male athletes with conventional and speckle-tracking echocardiography and found that 14.8% (58 out of 391) met the major mTFC+ cut-off echocardiographic criteria for RVOT size, comparable to the prevalence described in adults. [12,18,30] Nevertheless, there were no significant differences in global, FW or segmental RV-S_l between the athletes with RVOT

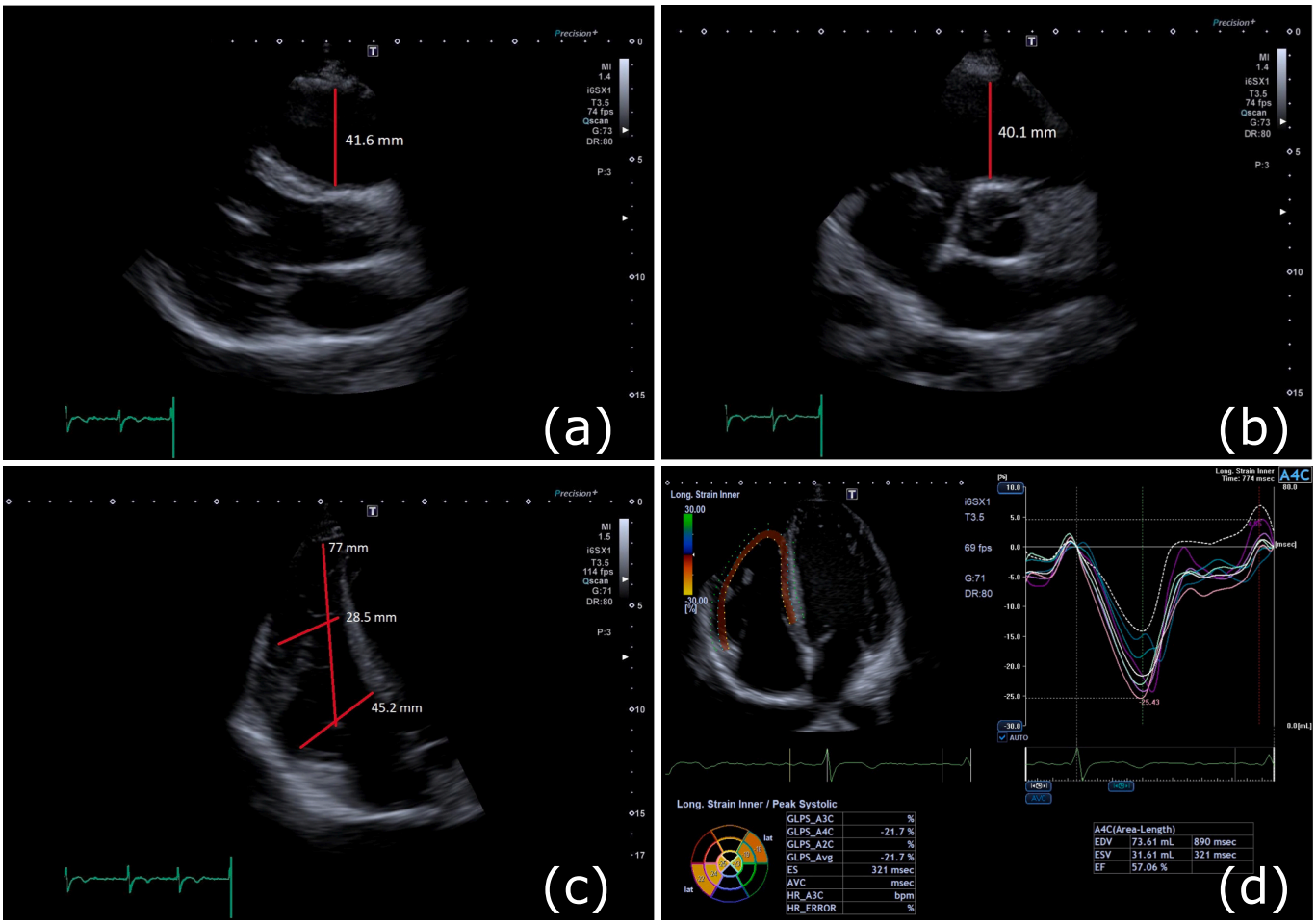

Fig. 1. Echocardiographic images for a 16 year old football player with right ventricular (RV) outflow tract dilation (Panel a - parasternal long axis view, panel b – parasternal short axis view), increased RV inlet diameters (Panel c) and normal longitudinal RV strain values (free wall −23.8%, global −21.5%, Panel d).

dilation and those without. In addition, RV strain was able to differentiate healthy mTFC+ athletes from definite and borderline ACM cases. These results show that current echocardiographic criteria of ACM may not be appropriate for athletes, overestimating the prevalence of an echocardiographic positive criteria, despite normal myocardial function, in all athletes with no other findings that would indicate a diagnosis of ACM (no family or past medical history, normal clinical examination, 12-lead ECG). Therefore, STE could play a role in better differentiating athletes with structural phenotypes on the border between physiological and pathological from ACM cases during screening.

4.1. RV strain as a diagnostic tool for ACM

In ACM patients, even when other clinical or echocardiographic signs are absent, STE can identify subtle changes in myocardial function, global or regional. [13,31,32] This supports using STE as a sensitive assessment tool, especially in diagnostic grey areas, such as athletes with RVOT dilation and suspicion of ACM.

In support of prior work, we found that that RV strain was significantly worse in both the definite and borderline ACM case, compared to mTFC+ athletes. Additionally, only 5% of mTFC+ athletes would meet the previously proposed −20.4% RVGL-S_l cut-off for ACM diagnosis [13], and only by a trivial margin of <0.5% strain, making this a very sensitive threshold even in this population. Thus, RV strain was able to effectively differentiate healthy adolescent athletes with RVOT dilation from age matched definite and borderline ACM cases.

The borderline ACM group, [13] is of interest, as it is very similar, from an echocardiographic perspective to our cohort of healthy athletes meeting the RVOT size mTFC criteria, exhibiting the same pattern of inlet and outlet RV dilation with normal FAC, RV S′ and TAPSE. RV strain was worse in the borderline ACM group, compared to the mTFC+ athletes, showing that in cases where conventional echocardiography parameters fail to differentiate possible disease, STE measurements can be of added value.

4.2. Using STE to characterise RV myocardial function in athletes

Conventional echocardiographic parameters of RV function in athletes are comparable to non-athlete individuals, [8] with the exception of FAC, which was shown to have lower reference values than in the general population. [11] RV strain in athletes has been described as lower, higher or comparable to controls, depending on the various study characteristics. [7,14–16,33] The mean RVFW-S_l (−27.6%) observed in our cohort is only slightly different than the mean reported in a systematic review of normal values in children (−30.1%, range − 20.8% to 34.1%), [34] and similar to that previously described in non-athlete adolescents (−27 ± 4%). [13]

A previous report evaluated a cohort of professional athletes, stratified by mTFC criteria for RVOT dilation, in a similar manner to the current study, and found statistically different RVGL-S_l in the mTFC+ group (−22% versus −23%), and similar global SR_l, segmental S_l and SR_l. The authors concluded that the observed differences were not clinically significant. [18] We used a non-inferiority comparison approach and found that our two study groups had a mean difference of

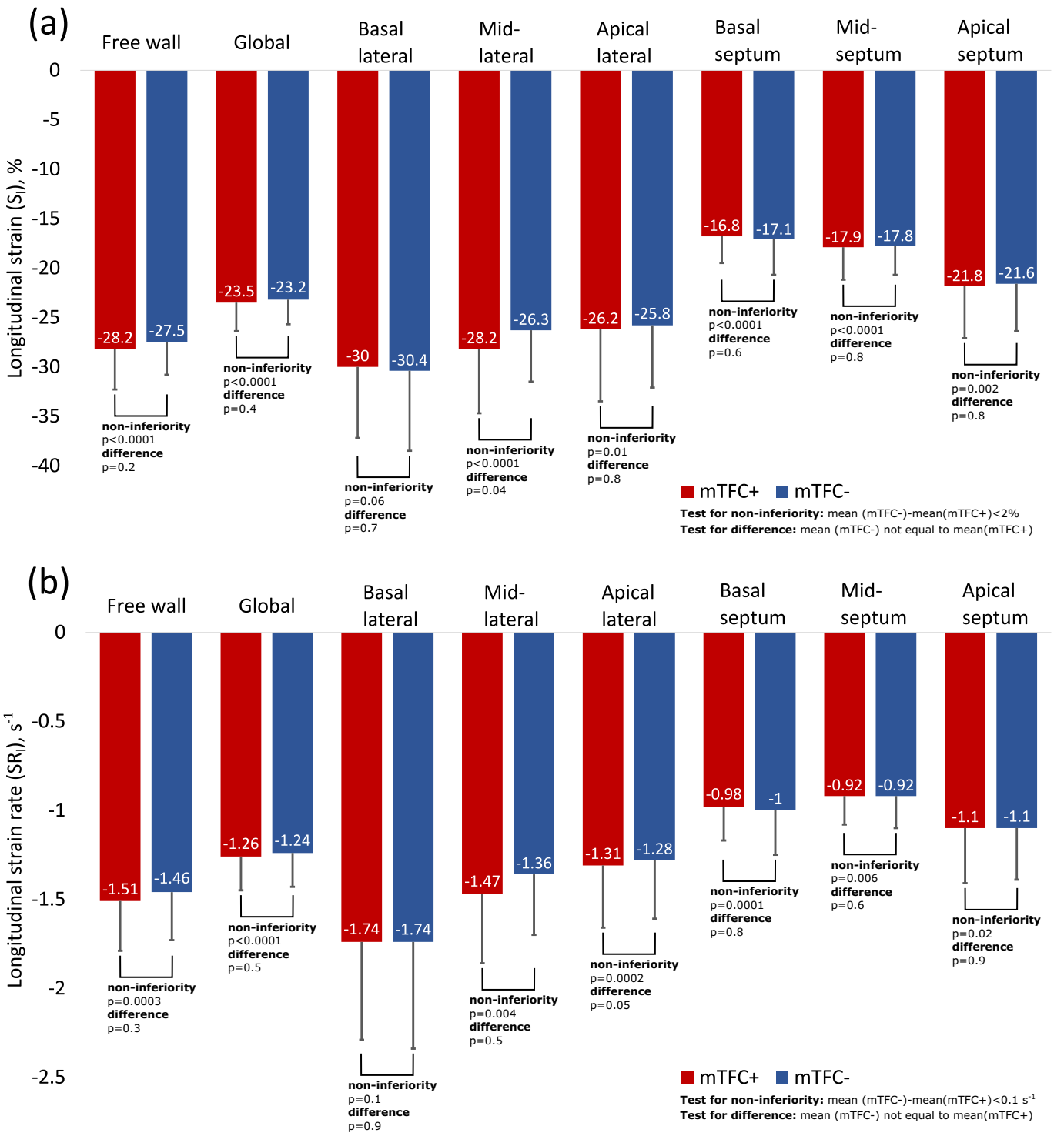

Fig. 2. Global and regional right ventricle longitudinal strain (S_l, Panel a) and longitudinal strain rate (SR_l, Panel b), in mTFC+ and mTFC- groups. All mean S_l and SR_l in the mTFC+ group are numerically comparable to those in the mTFC- group, and with the exception of the basal lateral segment (where the comparison is underpowered), also statistically non-inferior, within the predefined margins.
Values are expressed as means, with confidence interval bars representing standard deviation, detailed in Table S2. For further interpretation of *p* values, see Supplementary Material – Statistical analysis.

<1% in both global and free-wall RV-S_l, differences which are not clinically relevant, and similar segmental S_l and SR_l. Minor changes in RVGL-S_l have been reported in athletes previously, [17] and this could be due some degree of RV inlet dilation resulting in lower deformation for the same stroke volume. [35]

4.3. *Defining normal RVOT size in paediatric athletes*

Major issues affecting the ACM diagnostic criteria is that they are not validated in athletes and do not take into consideration the body size variability of growing children. European recommendations propose that in the athletic population, only major dimensional criteria indexed

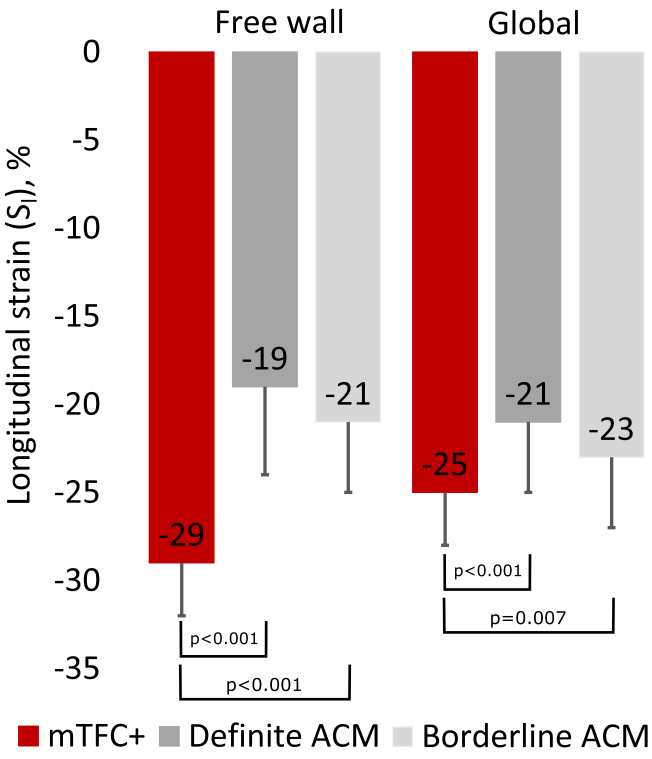

Fig. 3. Right ventricle free wall longitudinal strain (RV-FW S_l) and global longitudinal strain in athletes with right ventricular outflow tract dilation (mTFC+), compared to definite and borderline cases of arrhythmogenic cardiomyopathy (ACM). [13] All measurements done using the same methodology and software.

to BSA should be used to define RV enlargement, [21] but this does not address the issues of different training regimens, volumes and intensities or somatic growth. Our study shows a high prevalence of RVOT dilation by current criteria, with those in the mTFC+ group being younger and smaller compared to mTFC-. In fact, among all individual characteristics, having a smaller BSA was the only factor associated with meeting the major RVOT cut-off values. This means that indexing to BSA does not eliminate the high probability of misclassification, as previously suggested. [21] The new Padua criteria have eliminated RVOT size, and instead propose a diagnosis based on RV volume, but do not determine cut-off values, nor report paediatric or athlete specific data. [6] Our results suggest that a reasonable approach would be to define a RV size nomogram specific to paediatric athletes, with appropriate scaling, and augment the RV size criteria with more sensitive functional parameters, such as those derived from RV STE. Alternatively, RVOT to RV inlet diameter ratio have also been proposed to better describe RV dilation patterns. [9]

4.4. Including RV strain could improve ACM diagnostic criteria

Among adolescent athletes, a dilated RVOT is a common echocardiographic finding when assessing for ACM, usually without personal or family history of heart disease, no clinical or ECG abnormalities, normal FAC, TAPSE and RV S′. This is the case in all 58 participants from our mTFC+ group, where there would be limited evidence to guide which of these athletes should undergo further testing. Data from previous studies, [11,12,17] and our own, showed that RVOT dilation is prevalent in athletes, so a diagnosis of ACM would seem unlikely, given the normal global RV function and lack of wall motion abnormalities. On the other hand, young patients with certain or highly probable ACM can have normal RV systolic function by conventional parameters and an absence of RV structural abnormalities. [13] There is limited research in this age group, and evidence from adult studies might not be readily extrapolated. RV strain, including segmental evaluation, has been shown to predict ACM diagnosis in adolescents, [13] and in our study it could differentiate ACM from grey-area athletes.

5. Limitations

This is a retrospective analysis of data gathered both prospectively and retrospectively and shares the strengths and limitations of both designs. Because the clinical echocardiography reports were issued by more than one clinician, there is an expected degree of variability in conventional parameters, but this does not affect RV strain measurements. We only had access to male sports teams, and thus were not able to evaluate differences between boys and girls, although we did have the advantage of diverse ethnicities. This study did not include a non-athlete negative control group, as athletes without RVOT dilation were considered virtually healthy normal controls. The positive controls of definite and borderline ACM adolescents were not prospectively recruited but were part of an analysis by our group to answer a different research question. [13] We re-analysed the mTFC+ athletes using the same software and methodology to allow for head-to-head comparison with the previously acquired data and minimise bias. The values reported in this work should be extrapolated to general practice taking into consideration vendor specific variations in STE measurement. Nevertheless, we report normal values based on two software, one of which is vendor independent. This analysis focused on the RV specific criteria for ACM and did not evaluate left ventricle function parameters. Detailed training information such as session types, duration and frequency were not systematically collected and were not included

6. Conclusion

A high proportion of healthy adolescent athletes meet the echocardiographic RVOT size criteria for ACM, underlying the limitations of current guidelines when applied to this population, within which these criteria were not validated. STE RV regional and segmental mechanics in athletes meeting major mTFC for RVOT dilation were found to be comparable to those of athletes with non-dilated RVOT. We show for the first time that adolescents with definite or borderline ACM [13] have significantly worse RV strain compared to healthy mTFC+ athletes. Hence, in young healthy athletes with RV remodelling, STE may be useful to exclude ACM during screening.

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Disclosure

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

CRediT authorship contribution statement

Dan M. Dorobantu: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Nathan Riding:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Gavin McClean:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **María-Sanz de la Garza:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Marc Abuli-Lluch:** Investigation, Data curation, Writing – original draft,

Writing – review & editing. **Chetanya Sharma:** Investigation, Writing – original draft, Writing – review & editing. **Nuno Duarte:** Validation, Investigation, Writing – original draft, Writing – review & editing. **Maria Carmen Adamuz:** Investigation, Resources, Writing – review & editing. **Victoria Watt:** Investigation, Resources, Writing – review & editing. **Robert M. Hamilton:** Methodology, Investigation, Resources, Writing – review & editing. **Diane Ryding:** Investigation, Resources, Data curation, Writing – review & editing. **Dave Perry:** Investigation, Resources, Data curation, Writing – review & editing. **Steve McNally:** Investigation, Resources, Data curation, Writing – review & editing. **A. Graham Stuart:** Investigation, Methodology, Validation, Resources, Writing – original draft, Writing – review & editing, Supervision. **Marta Sitges:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision. **David L. Oxborough:** Validation, Resources, Writing – original draft, Writing – review & editing. **Mathew Wilson:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing. **Mark Friedberg:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Craig Williams:** Conceptualization, Methodology, Investigation, Resources, Data curation, Project administration, Funding acquisition, Writing – original draft, Writing – review & editing, Supervision. **Guido E. Pieles:** Conceptualization, Methodology, Investigation, Resources, Data curation, Project administration, Funding acquisition, Writing – original draft, Writing – review & editing, Supervision.

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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.2023.04.001.

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