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Right Ventricular Function in Elite Male Athletes Meeting the Structural Echocardiographic Task Force Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Athlete pre-participation screening is focused on detecting pathological conditions like arrhythmogenic right ventricular cardiomyopathy (ARVC). The diagnosis of ARVC is established by applying the revised 2010 ARVC Task Force Criteria (TFC) that assesses RV structure and function. Some athletes may meet structural TFC without having ARVC but we do not know the consequences for RV function. This study compared RV structural and functional indices in male athletes that meet the structural TFC (MTFC) for ARVC and those that do not (NMTFC). We recruited 214 male elite athletes. All participants underwent 2D, Doppler, tissue Doppler and strain (ε) echocardiography with a focused and comprehensive assessment of the right heart. Athletes were grouped on RV structural data: MTFC n=34; NMTFC n=180. Functional data were compared between groups. By selection, MTFC had larger absolute and scaled RV outflow tract (RVOT) diameter compared to NMTFC (P <0.05) but these athletes did not develop a proportional increase in the RV inflow dimensions. There was no difference in global conventional RV systolic function between both groups however, there was significantly lower global RV ε in athletes that MTFC which can be explained, in part, by the RVOT dimension.

Key Words: echocardiography; arrhythmogenic right ventricular cardiomyopathy; Athletes; strain; ARVC
Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) accounts for approximately 14% of sudden cardiac deaths (SCD) in athletes aged between 18 and 35 years (Finocchiaro et al., 2016). Athlete pre-participation screening is focused on detecting and diagnosing conditions like ARVC and this is aided by applying the revised 2010 ARVC Task Force Criteria (TFC) (Marcus et al., 2010; Pelliccia et al., 2017) related to family history, electrocardiographic (ECG) abnormalities, tissue characterisation and RV structural and functional indices (Marcus et al., 2010; McKenna et al., 1994). Both major and minor ARVC TFC can be assessed via echocardiography including the presence of an enlarged RV outflow tract in association with a reduction in RV functional indices such as tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RV FAC).

Chronic exercise training in the athlete causes physiological remodelling of the heart due to frequent exposure to elevated preload (D'Andrea et al., 2013; Oxborough et al., 2012; Pagourelias et al., 2013; Teske et al., 2009a). This adaptation often occurs beyond normal limits, particularly with regards to the RV (Maron & Pelliccia 2006; D'Andrea et al. 2010; Utomi et al. 2013; D’Ascenzi et al., 2017a, 2017b). The size of the RV outflow tract (RVOT) met the structural criteria for ARVC in 6% of endurance athletes (Oxborough et al., 2012) and D’Ascenzi, Pisicchio, et al. (2017) established that 3% of Olympic athletes met the structural RVOT criteria for ARVC (D’Ascenzi et al., 2017a). There is also evidence to suggest that athletes with dilated
RV cavities may have some depression in function (D’Andrea et al., 2015; La Gerche, Macisaac, & Prior, 2012a; Teske et al., 2009a). To further compound diagnostic dilemmas a recent meta-analysis demonstrated that RV functional indices identified in the TFC, such as RV fractional area change (RV FAC), are often normal in patients with ARVC (Qasem et al., 2016).

The assessment of regional measures of RV mechanics using speckle tracking echocardiography (STE) have been reported in athletic heart studies with disparate findings (Mirea, Duchenne, & Voigt, 2016; Utomi et al., 2013). Some studies have demonstrated normal function (D’Andrea et al., 2013; Oxborough et al., 2016; Qasem et al., 2018) whilst others presented regional dysfunction particularly in those athletes with a marked RV phenotype (La Gerche et al., 2012a; Teske et al., 2009a,b). Qasem et al. (2016) identified that RV strain (ε) is likely to be depressed in patients with ARVC with a purported cut-off for global RV ε of -21%. Based on the importance of RV function in diagnosing ARVC, a more detailed functional assessment in those athletes with large RV cavities that meet the structural TFC is required.

In view of this, the aim of this study was to compare conventional RV functional indices and STE measures of RV mechanics in male athletes that meet the structural TFC for ARVC and those that do not meet the structural ARVC TFC. We hypothesize that athletes that meet structural TFC may have lower global and regional RV mechanics.
Methods

Participants

Two hundred and fourteen elite male athletes (mean ± SD age: 23 ± 6 years) who presented for cardiac pre-participation screening were included in the study. Inclusion criteria were; (1) competitive at National level in their specific sporting discipline and (2) no personal or early family history of cardiovascular, respiratory, renal and/or metabolic disease. Athletes were excluded if; (1) they were currently taking prescribed medication and/or (2) had non-training related ECG findings upon screening (Drezner et al., 2017; Sharma et al., 2017). After analysis of RV structure the athletes were split into two groups: 1) those that met the echocardiographic structural TFC (MTFC); indexed RVOT (from the parasternal long axis view; RVOT-PLAX ≥ 19 mm/m²) and indexed RVOT (from the parasternal short axis view; RVOT-PSAX ≥ 21 mm/m²] and 2) those athletes that did not meet echocardiographic structural TFC (NMTFC). Ethics approval was obtained by the Ethics Committee of Liverpool John Moores University and all the athletes provided written informed consent.

Study Design and Procedures

A prospective cross-sectional study design was utilised with the athletes attending for a single testing / screening session. Each session involved the athlete completing a personal health questionnaire, undergoing anthropometric assessment of body mass and height, measurement of brachial artery blood pressure, a 12-lead ECG and a
resting transthoracic echocardiogram. All assessments were overseen by an experienced consultant sports cardiologist. All athletes refrained from alcohol and caffeine consumption for 24 hours prior to testing and did not undertake any exercise training 6 hours prior to assessment. Athletes were excluded if they had a definitive or suggestive diagnosis of cardiovascular disease after full cardiac screening examination and/or any other clinically relevant follow-up test.

Anthropometric Assessment

All athletes’ height and body mass were assessed by using a standard scale and stadiometer (SECA 764, Birmingham, UK). Body surface area (BSA) was calculated using the Mosteller standard formula (Mosteller, 1987). Blood pressure was recorded using an automated sphygmomanometer (DINAMMAP 300, GE Medical System, Milwaukee, Wisconsin, USA).

12-Lead Electrocardiogram

A standard resting 12-lead electrocardiogram (CardioExpress SL6, Spacelabs Healthcare, Washington US) was undertaken in accordance with the American heart Association (Mason, Hancock, & Gettes, 2007). Interpretation was made in agreement with the international criteria for electrocardiographic interpretation in athletes (Drezner et al., 2017; Sharma et al., 2017).

Transthoracic Echocardiography
The echocardiographic examination was performed by one of two experienced echocardiographers (DO / LF) using a Vivid Q ultrasound machine (GE Healthcare, Horten, Norway) with a 2.5-5 MHz transducer. All images were acquired using an echocardiography protocol, in accordance with the American Society of Echocardiography (ASE) (Lang et al., 2015; Rudski et al., 2010), at end expiration over a minimum of 3 cardiac cycles and stored in a raw Digital Imaging and Communications in Medicine format. Images were exported to the offline analysis system (EchoPac V.110.0.2; GE Healthcare, Horten, Norway) and analysis was undertaken by the same sonographers in accordance with ASE guidelines (Lang et al., 2015).

**Conventional 2D and Tissue Doppler:** The RV outflow tract dimension was assessed at 3 specific locations. The proximal aspect was measured from a parasternal long and short axis orientation (RVOT-PLAX and RVOT-SAX respectively) and the distal level from a parasternal short axis view (RVOT2). The RV inflow was assessed using a modified apical four chamber orientation (Rudski et al., 2010), with minor dimensions taken at the basal and mid levels (RVD1 and RVD2 respectively). RV length was measured from apex to the tricuspid annulus (RVD3). To establish relative outflow and inflow dimensions the ratio RVOT-SAX/RVD1 was calculated. RV area was measured in diastole (RVDA) and systole (RVSA) by tracing the RV endocardium using the same modified apical four chamber view and RVFAC was calculated. From a subcostal view, RV wall thickness (RVWT) was measured at mid wall level.
RVOT-PLAX and RVOT-SAX were indexed linearly to BSA in accordance with the TFC but in addition all structural variables were scaled allometrically to BSA according to the law of geometric similarity. Linear dimensions were scaled to BSA\(^{0.5}\) area measurements were scaled directly to BSA (Batterham, George, Whyte, Sharma, & McKenna, 1999).

RV longitudinal function was assessed using pulsed wave tissue Doppler imaging (TDI) and this allowed the derivation of peak myocardial velocities in systole (S’), early diastole (E’) and late diastole (A’). M-mode derived tricuspid annular plane systolic excursion (TAPSE) of the RV lateral wall.

Speckle tracking Echocardiography: Longitudinal RV lateral wall and septal \(\varepsilon\) and strain rate (SR) were assessed from the modified apical four chamber view. Images were optimised to provide an optimal endocardial delineation. To reduce the impact of the beam divergence, the focal point was positioned at mid cavity of the RV. Frame rates were set between 80 and 90 frames per second. Pulmonary valve closure (PVC) was acquired for offline analysis at the RV outflow tract from the pulsed Doppler signal. A narrow region of interest was placed around the RV basal lateral wall through to basal septum. The tracking of the base, mid and apex segments was automatically derived by the software, however, where segments appeared to not track appropriately they were excluded from the subsequent analysis. The 6 myocardial segments provided regional peak and time to peak RV \(\varepsilon\), peak systolic SR (SRS’), peak early diastolic SR (SRE’) and peak late diastolic SR (SRA’). An
average of the 6 segments provided a global value of the same deformation indices.

The difference in ε between the basal and apical segment was calculated at both the
septum and the lateral wall to provide a base to apex ε gradient.

In addition to the peak data, the raw data was exported to an excel spreadsheet
(Excel, Microsoft Corp, Washington, US), where it underwent cubic spline
interpolation to correct for variations in heart rates providing 300 ε and SR points in
systole and 300 points in diastole. This data was then split into 5% increments to
provide a comprehensive temporal assessment of RV ε across the cardiac cycle.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences
(SPSS) (version 23.0, Chicago IL, USA), and the critical α was set a p<0.05. All
parameters were presented as mean ± SD. Normal distribution was tested using a
Kolmogorov-Smirnov test. Analysis between both groups was undertaken using
independent t-tests, where normal distribution was presented, and Mann-Whitney U
tests when the distribution was not normal. Supplementary analysis included
Pearson’s correlation analysis of the association between RV functional indices and
ARVC structural TFC criteria. A multi–linear regression was undertaken to
determine the relative contribution of each independent parameters (i.e. absolute and
scaled RVOT-PLAX) on the dependent variable (i.e. global peak RV ε).
Results

34 athletes met the RV structural TFC (MTFC: mean ± SD; age 25 ± 6 years; body mass 71 ± 12 kg; height 1.8 ± 0.1 m, BSA 1.9 ± 0.2 m²) and 180 athletes did not (NMTFC: mean ± SD; age 23 ± 6 years; body mass 72 ± 8 kg; height 1.8 ± 0.1 m and BSA 1.9 ± 0.1 m²). Group data for systolic and diastolic blood pressure as well as resting heart rate and training history are presented in Table 1. Athletes were from mixed sporting disciplines [Low dynamic sporting disciplines= 15% and 5%, Moderate dynamic sporting disciplines = 6% and 12% and High dynamic sporting disciplines = 80% and 84% for MTFC and NMTFC respectively].

The 12-lead ECG demonstrated similar indicative changes of athletic adaptation in both groups with sinus bradycardia (NMTFC: 83%; MTFC: 85%), ectopic atrial rhythm (NMTFC: 4%), 1st degree AV block (NMTFC: 10%; MTFC: 7%), mobitz type 1 AV block (NMTFC: 1%; MTFC: 4%), partial right bundle branch block (NMTFC: 14%; MTFC: 14%), early repolarisation (NMTFC 76%; MTFC: 75%), sinus arrhythmia (NMTFC: 10%; MTFC: 7%), isolated QRS voltage criteria for left ventricle hypertrophy (NMTFC: 14%; MTFC: 14%) and isolated QRS voltage criteria for right ventricle hypertrophy (NMTFC: 12%; MTFC: 14%). In addition to training related adaptation, T wave inversion in the anterior leads (V1 to V3) was apparent in 4% of the athletes from both NMTFC and MTFC.
RV structural parameters are presented in table 2. As per group allocation, MTFC had larger absolute and scaled RVOT-PLAX compared to NMTFC (P=0.001 and P=0.001, respectively) and RVOT-SAX (P=0.001 and P=0.001, respectively). In addition, MTFC had larger absolute and scaled RVOT^2 (P=0.019 and P=0.009, respectively) as well as RVOT-SAX/RVD1 compared to NMTFC (P=0.001 and P=0.001, respectively). The RV: LV ratio was larger in the NMTFC group (P=0.016).

Standard RV functional indices, tissue Doppler velocities and STE data are presented in Tables 3 and 4. There were no between group differences for TAPSE or RVFAC, however 6% of both groups (n=2 and n=10 in MTFC and NMTFC respectively) had a RVFAC ≤ 33%. Both RVS' and RVA' were lower in MTFC compared to NMTFC (P= 0.021 and P=0.010, respectively). MTFC also had significantly lower global RVε than NMTFC that persisted across the cardiac cycle between 25-85% of systole (Figure 1). There were no differences in global SRS', SRE' and SRA' between groups. MTFC had significantly lower SRE' in the mid lateral wall segment (P=0.026), but with no differences in the base-apex gradient (see table 4). 24% and 6% of MTFC and 7% and 2% of NMTFC had RV ε < 21% and RV S' < 10 cm/s respectively. The 2 athletes that met the full TFC i.e. structural and functional (RVFAC) had RV S' > 10cm/s, RV ε ≥ 21% had a normal ECG.
There was a small but significant correlation between global peak RV ε and both absolute and scaled RVOT-PLAX ($r = 0.21, P = 0.009; r = 0.16, P = 0.044$, respectively). Peak RVS’ correlated with absolute and scaled RVOT-PLAX ($r = -0.17, P = 0.012; r = -0.18, P = 0.008$, respectively). Following multi-linear regression, Absolute and scaled RVOT-PLAX account for 5% ($R^2 = 0.047$) of global peak RV ε and absolute and scaled RVOT-PLAX account for 3% ($R^2 = 0.032$) of RV S’.

**Discussion**

The key findings from this study were (1) athletes that MTFC have larger absolute and scaled RV structural values at inflow and outflow tracts compared to NMTFC, (2) there are no differences between both groups for RV FAC and TAPSE with absolute RV FAC meeting TFC in a small proportion of the athletes, (3) athletes that MTFC have lower global RV ε, SRS’ and SRA’ compared to NMTFC that may, in part, be explained by the larger RVOT dimension.

**Right Ventricular Structure**

ARVC is an inherited genetic disease that is characterized by a fibrofatty replacement of the RV myocardium (Marcus et al., 2010). Due to the variable phenotypical expression and clinical manifestation of the disease, its diagnosis
remains challenging, particularly, in its early stages. The structural changes in ARVC may be absent or subtle and limited to a localized region of the RV called the 'triangle of dysplasia' (Marcus et al., 2010; Rojas & Calkins, 2015), RV inflow tract (sinus), the RV apex, RV outflow tract (Aneq, 2011; Te Riele et al., 2013) or infundibulum (RVOT2) (Basso et al., 1996). Many studies have demonstrated that chronic exercise training leads to RV dilation and acute exercise causes disproportionate wall stress (Douglas & O’Toole, 1990; Heidbuchel, Prior, & La Gerche, 2012; Rojas & Calkins, 2015). Thus, previous athlete heart studies have demonstrated RV enlargement that exceeds the normal cut-off values and fulfill ARVC structural TFC (D’Ascenzi et al., 2017a, 2017b; Oxborough et al., 2012; Zaidi et al., 2013). The current study reports a significant enlargement in absolute and scaled RVOT in both long and short axis views, fulfilling major TFC but in addition these athletes have a significant higher absolute and scaled RVOT2 value suggesting a proportional dilatation of the outflow tract. It is apparent that although the RVOT may be enlarged in these athletes there is a lack of proportional enlargement of the inflow and RVDA with an increased RVOT/RVD1 ratio. This finding is disparate from previous studies in endurance athletes (Oxborough et al., 2012). It is difficult to provide a clear explanation for this, but it must be acknowledged that a disproportionate remodeling occurs as physiological adaptation in some athletes irrespective of training stimulus. We can speculate that this may be driven by individual heterogeneity / genetics, but it is important to note that an increased RVOT/RVD1 ratio (approaching 1) does not indicate pathology.
Our study also highlights the importance of scaling for body size. Some of the NMTFC athletes had high absolute values meeting TFC which normalised once they were scaled to BSA. In view of this, we support D'Ascenzi et al (2017b) by recommending using the major TFC normalized to BSA instead of non-scaled or conventional criteria of RV enlargement from the American Society of Echocardiography (D’Ascenzi, Pelliccia, et al., 2017; D’Ascenzi, Piscicchio, et al., 2017).

Right Ventricular Function

Our conventional echocardiographic data demonstrated no between group difference in global RV systolic function as determined by RV FAC and TAPSE. This supports other athlete RV studies (D’Andrea et al., 2013; Baggish et al., 2008; D’Ascenzi et al., 2017a, 2017b; Moro, Okoshi, Padovani, & Okoshi, 2013; Oxborough et al., 2016; Qasem et al., 2018). Despite this cohort comparability, 6% of NMTFC and MTFC athletes had an RV FAC lower than 33% which is a major echocardiographic criteria for ARVC. This is an important finding in that functional abnormalities are an essential component of the TFC. This is similar to D’Ascenzi, Pelliccia, et al., (2017) whom demonstrated lower RV FAC ≤ 33% in a small population of their athletes raising uncertainty regarding the specificity of RV FAC for the diagnosis of ARVC (D’Ascenzi et al., 2017b). This finding further complicates the differential diagnosis in a minority of athletes. Interestingly, there was borderline normal TDI and ε in the 2 athletes that met the full ARVC criteria in this study. The lack of correlation between RV FAC and longitudinal free and septal wall function further highlights the complex nature of RV function and the problems
of depending on single functional parameters in any assessment process. Furthermore, we provide evidence of reduced TDI RV S' and RV ε in the MTFC group which may exacerbate the diagnostic challenge. Importantly, the difference in RV ε between the groups is significant but small (1% absolute strain and 4% difference in relative terms). This difference sits outside what is currently considered to be clinically meaningful and further highlights the need for a multifactorial assessment. Reduced / low RV function is common in the presence of an enlarged chamber and it would be sensible to consider additional imaging in these populations.

Note that in the current study, 6% of the athletes met functional criteria (RV FAC and TDI S') and 24% have reduced RV ε. Interestingly although systolic function was depressed in some of the athletes regardless of structural criteria, none of the MTFC had reduced diastolic function as determined by RV E' < 10 cm/s suggest a diagnostic role for the assessment of RV diagnostic function in this population.

Previous studies have reported a reduction in RV ε secondary to an increased RVEDA (Elliott & La Gerche, 2015) whilst others have demonstrated a reduction in basal (Teske et al 2009a) and apical function (La Gerche et al., 2012a) in athletes with marked RV dilatation. Teske et al (2009b) also reported lower SR values in the basal and mid segments in athletes with RV enlargement. The base-apex gradient is a normal physiological phenomenon and the current study demonstrates normal values across all athletes with no difference between the groups. This highlights that structural and functional adaptation seen in MTFC athletes fits within the constraints of normal physiology alongside a conventional pattern of function. This may also provide discriminatory capacity in the screening setting. In the current study we
demonstrate lower RV $\varepsilon$ in MTFC compared to NMTFC, which is partly related to absolute and scaled RVOT-PLAX and, therefore, also likely represents normal physiological adaptation to training. An enlarged ventricle will likely lead to a realignment of the myofibre architecture which may influence regional mechanics. In addition, it is apparent that a large chamber requires less myocardial contraction to generate an adequate stroke volume at rest. It is likely that the use of an exercise stimulus (La Gerche et al., 2012b) would provide additional diagnostic information in those athletes that MTFC and have borderline / low systolic function. It is likely that chamber size is a significant contributing factor, however structural enlargement of the outflow only accounted for 5% of RV $\varepsilon$ and SR. This small contribution may reflect the complex RV structure that is only partly being represented by a linear measurement and a more substantive / 3-dimensional assessment of the RV would likely provide greater insight. It is also apparent that due the dependence on load and the inherent intrinsic function of the myocardium other factors such as ventricular interdependence and RV afterload and may also contribute to the lower deformation parameters observed in this study.

Limitations

The MTFC sample size was relatively small and thus further study is warranted in a larger sample size and studies related to different sports discipline, genders and ethnicity specific adaptation. It would have been useful to document pulmonary artery pressures, however we were unable to obtain a CW tricuspid regurgitant signal in a reasonable proportion of the population. That aside, none of our athletes had any
echocardiographic signs (other than RV / RA enlargement) therefore had a low probability of pulmonary hypertension (Galiè et al., 2016).

Conclusion

Athletes that MTFC for RVOT do not develop a proportional increase in the RV inflow dimensions. There are no difference in global conventional RV systolic function by RV FAC and TAPSE between both groups. There are significant lower global RV ε, RVS’ and RVA’ in athletes that MTFC which related partly to the larger RVOT dimension. The complex nature of RV function suggest that a multi-factorial assessment may be informative particularly in those that MTFC.

Declaration of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

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Figure and Table Legends:

Table 1. Participant Demographics.

Table 2. Absolute and Scaled RV Structural Parameters.

Table 3. RV Functional Parameters.

Table 4. Regional RV Strain ($\varepsilon$) and Strain Rate (SR)

Figure 1. Right ventricular temporal curves of (1a) mean longitudinal $\varepsilon$ and (1b) mean strain rate compared between classifications