1 **Right Ventricular Function in Elite Male Athletes Meeting the Structural**

2 **Echocardiographic Task Force Criteria for Arrhythmogenic Right Ventricular**

3 **Cardiomyopathy**

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21   **Abstract**

22   Athlete pre-participation screening is focused on detecting pathological conditions

23   like arrhythmogenic right ventricular cardiomyopathy (ARVC). The diagnosis of

24   ARVC is established by applying the revised 2010 ARVC Task Force Criteria (TFC)

25   that assesses RV structure and function. Some athletes may meet structural TFC

26   without having ARVC but we do not know the consequences for RV function. This

27   study compared RV structural and functional indices in male athletes that meet the

28   structural TFC (MTFC) for ARVC and those that do not (NMTFC). We recruited

29   214 male elite athletes. All participants underwent 2D, Doppler, tissue Doppler and

30   strain (ε) echocardiography with a focused and comprehensive assessment of the

31   right heart. Athletes were grouped on RV structural data: MTFC n=34; NMTFC

32   n=180. Functional data were compared between groups. By selection, MTFC had

33   larger absolute and scaled RV outflow tract (RVOT) diameter compared to NMTFC

34   (P <0.05) but these athletes did not develop a proportional increase in the RV inflow

35   dimensions. There was no difference in global conventional RV systolic function

36   between both groups however, there was significantly lower global RV ε in athletes

37   that MTFC which can be explained, in part, by the RVOT dimension.

38

39   **Key Words:** echocardiography; arrhythmogenic right ventricular cardiomyopathy;

40   Athletes; strain; ARVC

41

Introduction

43   Arrhythmogenic right ventricular cardiomyopathy (ARVC) accounts for

44   approximately 14% of sudden cardiac deaths (SCD) in athletes aged between 18 and

45   35 years (Finocchiaro et al., 2016). Athlete pre-participation screening is focused on

46   detecting and diagnosing conditions like ARVC and this is aided by applying the

47   revised 2010 ARVC Task Force Criteria (TFC) (Marcus et al., 2010; Pelliccia et al.,

48   2017) related to family history, electrocardiographic (ECG) abnormalities, tissue

49   characterisation and RV structural and functional indices (Marcus et al., 2010;

50   McKenna et al., 1994). Both major and minor ARVC TFC can be assessed via

51   echocardiography including the presence of an enlarged RV outflow tract in

52   association with a reduction in RV functional indices such as tricuspid annular plane

53   systolic excursion (TAPSE) and right ventricular fractional area change (RV FAC).

54

55   Chronic exercise training in the athlete causes physiological remodelling of the heart

56   due to frequent exposure to elevated preload (D'Andrea et al., 2013; Oxborough et

57   al., 2012; Pagourelias et al., 2013; Teske et al., 2009a). This adaptation often occurs

58   beyond normal limits, particularly with regards to the RV (Maron & Pelliccia 2006;

59   D'Andrea et al. 2010; Utomi et al. 2013; D'Ascenzi et al., 2017a, 2017b). The size of

60   the RV outflow tract (RVOT) met the structural criteria for ARVC in 6% of

61   endurance athletes (Oxborough et al., 2012) and D'Ascenzi, Pisicchio, et al. (2017)

62   established that 3% of Olympic athletes met the structural RVOT criteria for ARVC

63   (D'Ascenzi et al., 2017a). There is also evidence to suggest that athletes with dilated

64   RV cavities may have some depression in function (D'Andrea et al., 2015; La Gerche,

65   Macisaac, & Prior, 2012a; Teske et al., 2009a). To further compound diagnostic

66   dilemmas a recent meta-analysis demonstrated that RV functional indices identified

67   in the TFC, such as RV fractional area change (RV FAC), are often normal in

68   patients with ARVC (Qasem et al., 2016).

69

70   The assessment of regional measures of RV mechanics using speckle tracking

71   echocardiography (STE) have been reported in athletic heart studies with disparate

72   findings (Mirea, Duchenne, & Voigt, 2016; Utomi et al., 2013). Some studies have

73   demonstrated normal function (D'Andrea et al., 2013; Oxborough et al., 2016;

74   Qasem et al., 2018) whilst others presented regional dysfunction particularly in those

75   athletes with a marked RV phenotype (La Gerche et al., 2012a; Teske et al., 2009a,b).

76   Qasem et al. (2016) identified that RV strain (ε) is likely to be depressed in patients

77   with ARVC with a purported cut-off for global RV ε of -21%. Based on the

78   importance of RV function in diagnosing ARVC, a more detailed functional

79   assessment in those athletes with large RV cavities that meet the structural TFC is

80   required.

81

82   In view of this, the aim of this study was to compare conventional RV functional

83   indices and STE measures of RV mechanics in male athletes that meet the structural

84   TFC for ARVC and those that do not meet the structural ARVC TFC. We

85   hypothesize that athletes that meet structural TFC may have lower global and

86   regional RV mechanics.

87

Methods

Participants

90 Two hundred and fourteen elite male athletes (mean ± SD age: 23 ± 6 years) who

91 presented for cardiac pre-participation screening were included in the study.

92 Inclusion criteria were; (1) competitive at National level in their specific sporting

93 discipline and (2) no personal or early family history of cardiovascular, respiratory,

94 renal and/or metabolic disease. Athletes were excluded if; (1) they were currently

95 taking prescribed medication and/or (2) had non-training related ECG findings upon

96 screening (Drezner et al., 2017; Sharma et al., 2017). After analysis of RV structure

97 the athletes were split into two groups: 1) those that met the echocardiographic

98 structural TFC (MTFC); indexed RVOT (from the parasternal long axis view;

99 RVOT-PLAX $\geq$ 19 mm/m^2) and indexed RVOT (from the parasternal short axis

100 view; RVOT-PSAX $\geq$ 21 mm/m^2] and 2) those athletes that did not meet

101 echocardiographic structural TFC (NMTFC). Ethics approval was obtained by the

102 Ethics Committee of Liverpool John Moores University and all the athletes provided

103 written informed consent.

104

Study Design and Procedures

106 A prospective cross-sectional study design was utilised with the athletes attending

107 for a single testing / screening session. Each session involved the athlete completing

108 a personal health questionnaire, undergoing anthropometric assessment of body mass

109 and height, measurement of brachial artery blood pressure, a 12-lead ECG and a

110   resting transthoracic echocardiogram. All assessments were overseen by an

111   experienced consultant sports cardiologist. All athletes refrained from alcohol and

112   caffeine consumption for 24 hours prior to testing and did not undertake any exercise

113   training 6 hours prior to assessment. Athletes were excluded if they had a definitive

114   or suggestive diagnosis of cardiovascular disease after full cardiac screening

115   examination and/or any other clinically relevant follow-up test.

116

117   *Anthropometric Assessment*

118   All athletes' height and body mass were assessed by using a standard scale and

119   stadiometer (SECA 764, Birmingham, UK). Body surface area (BSA) was calculated

120   using the Mosteller standard formula (Mosteller, 1987). Blood pressure was recorded

121   using an automated sphygmomanometer (DINAMMAP 300, GE Medical System,

122   Milwaukee, Wisconsin, USA).

123

124   *12-Lead Electrocardiogram*

125   A standard resting 12-lead electrocardiogram (CardioExpress SL6, Spacelabs

126   Healthcare, Washington US) was undertaken in accordance with the American heart

127   Association (Mason, Hancock, & Gettes, 2007). Interpretation was made in

128   agreement with the international criteria for electrocardiographic interpretation in

129   athletes (Drezner et al., 2017; Sharma et al., 2017).

130

131   *Transthoracic Echocardiography*

132   The echocardiographic examination was performed by one of two experienced

133   echocardiographers (DO / LF) using a Vivid Q ultrasound machine (GE Healthcare,

134   Horten, Norway) with a 2.5-5 MHz transducer. All images were acquired using an

135   echocardiography protocol, in accordance with the American Society of

136   Echocardiography (ASE) (Lang et al., 2015; Rudski et al., 2010), at end expiration

137   over a minimum of 3 cardiac cycles and stored in a raw Digital Imaging and

138   Communications in Medicine format. Images were exported to the offline analysis

139   system (EchoPac V.110.0.2; GE Healthcare, Horton, Norway) and analysis was

140   undertaken by the same sonographers in accordance with ASE guidelines (Lang et

141   al., 2015).

142

143   *Conventional 2D and Tissue Doppler:* The RV outflow tract dimension was assessed

144   at 3 specific locations. The proximal aspect was measured from a parasternal long

145   and short axis orientation (RVOT-PLAX and RVOT-SAX respectively) and the

146   distal level from a parasternal short axis view (RVOT2). The RV inflow was

147   assessed using a modified apical four chamber orientation (Rudski et al., 2010), with

148   minor dimensions taken at the basal and mid levels (RVD1 and RVD2 respectively).

149   RV length was measured from apex to the tricuspid annulus (RVD3). To establish

150   relative outflow and inflow dimensions the ratio RVOT-SAX/RVD1 was calculated.

151   RV area was measured in diastole (RVDA) and systole (RVSA) by tracing the RV

152   endocardium using the same modified apical four chamber view and RVFAC was

153   calculated. From a subcostal view, RV wall thickness (RVWT) was measured at mid

154   wall level.

155

156   RVOT-PLAX and RVOT-SAX were indexed linearly to BSA in accordance with the

157   TFC but in addition all structural variables were scaled allometrically to BSA

158   according to the law of geometric similarity. Linear dimensions were scaled to

159    $BSA^{0.5}$ area measurements were scaled directly to BSA (Batterham, George, Whyte,

160   Sharma, & McKenna, 1999).

161

162   RV longitudinal function was assessed using pulsed wave tissue Doppler imaging

163   (TDI) and this allowed the derivation of peak myocardial velocities in systole (S'),

164   early diastole (E') and late diastole (A'). M-mode derived tricuspid annular plane

165   systolic excursion (TAPSE) of the RV lateral wall.

166

167   *Speckle tracking Echocardiography:* Longitudinal RV lateral wall and septal ε and

168   strain rate (SR) were assessed from the modified apical four chamber view. Images

169   were optimised to provide an optimal endocardial delineation. To reduce the impact

170   of the beam divergence, the focal point was positioned at mid cavity of the RV.

171   Frame rates were set between 80 and 90 frames per second. Pulmonary valve closure

172   (PVC) was acquired for offline analysis at the RV outflow tract from the pulsed

173   Doppler signal. A narrow region of interest was placed around the RV basal lateral

174   wall through to basal septum. The tracking of the base, mid and apex segments was

175   automatically derived by the software, however, where segments appeared to not

176   track appropriately they were excluded from the subsequent analysis. The 6

177   myocardial segments provided regional peak and time to peak RV ε, peak systolic

178   SR (SRS'), peak early diastolic SR (SRE') and peak late diastolic SR (SRA'). An

179   average of the 6 segments provided a global value of the same deformation indices.

180   The difference in ε between the basal and apical segment was calculated at both the

181   septum and the lateral wall to provide a base to apex ε gradient.

182

183   In addition to the peak data, the raw data was exported to an excel spreadsheet

184   (Excel, Microsoft Corp, Washington, US), where it underwent cubic spline

185   interpolation to correct for variations in heart rates providing 300 ε and SR points in

186   systole and 300 points in diastole. This data was then split into 5% increments to

187   provide a comprehensive temporal assessment of RV ε across the cardiac cycle.

188

189   *Statistical Analysis*

190   Statistical analysis was performed using Statistical Package for the Social Sciences

191   (SPSS) (version 23.0, Chicago IL, USA), and the critical α was set a $p<0.05$. All

192   parameters were presented as mean ± SD. Normal distribution was tested using a

193   Kolmogorov-Smirnov test. Analysis between both groups was undertaken using

194   independent t-tests, where normal distribution was presented, and Mann-Whitney U

195   tests when the distribution was not normal. Supplementary analysis included

196   Pearson's correlation analysis of the association between RV functional indices and

197   ARVC structural TFC criteria. A multi–linear regression was undertaken to

198   determine the relative contribution of each independent parameters (i.e. absolute and

199   scaled RVOT-PLAX) on the dependent variable (i.e. global peak RV ε).

200

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 m^2) 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 m^2). 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].

INSERT TABLE 1

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.

223

224   RV structural parameters are presented in table 2. As per group allocation, MTFC

225   had larger absolute and scaled RVOT-PLAX compared to NMTFC (P=0.001 and

226   P=0.001, respectively) and RVOT-SAX (P=0.001 and P=0.001, respectively). In

227   addition, MTFC had larger absolute and scaled RVOT2 (P=0.019 and P=0.009,

228   respectively) as well as RVOT-SAX/RVD1 compared to NMTFC (P=0.001 and

229   P=0.001, respectively).　The RV: LV ratio was larger in the NMTFC group

230   (P=0.016).

231

232   INSERT TABLE 2

233

234   Standard RV functional indices, tissue Doppler velocities and STE data are presented

235   in Tables 3 and 4. There were no between group differences for TAPSE or RVFAC,

236   however 6% of both groups (n=2 and n=10 in MTFC and NMTFC respectively) had

237   a RVFAC ≤ 33%. Both RVS' and RVA' were lower in MTFC compared to NMTFC

238   (P= 0.021 and P=0.010, respectively). MTFC also had significantly lower global

239   RVε than NMTFC that persisted across the cardiac cycle between 25-85% of systole

240   (Figure 1). There were no differences in global SRS', SRE' and SRA' between groups.

241   MTFC had significantly lower SRE' in the mid lateral wall segment (P=0.026), but

242   with no differences in the base-apex gradient (see table 4). 24% and 6% of MTFC

243   and 7% and 2% of NMTFC had RV ε < 21% and RV S' < 10 cm/s respectively. The

244   2 athletes that met the full TFC i.e. structural and functional (RVFAC) had RV S' >

245   10cm/s, RV ε ≥ 21% had a normal ECG.

246

247   INSERT TABLES 3, 4 AND FIGURE 1

248

249   There was a small but significant correlation between global peak RV ε and both

250   absolute and scaled RVOT-PLAX (r= 0.21, P= 0.009 ; r= 0.16, P= 0.044, respectively). Peak

251   RVS' correlated with absolute and scaled RVOT-PLAX (r= -0.17, P= 0.012, r= -0.18, P=

252   0.008, respectively). Following multi-linear regression, Absolute and scaled RVOT-

253   PLAX account for 5% ($R^2 = 0.047$) of global peak RV ε and absolute and scaled

254   RVOT-PLAX account for 3% ($R^2 = 0.032$) of RV S'.

255

256   **Discussion**

257   The key findings from this study were (1) athletes that MTFC have larger absolute

258   and scaled RV structural values at inflow and outflow tracts compared to NMTFC,

259   (2) there are no differences between both groups for RV FAC and TAPSE with

260   absolute RV FAC meeting TFC in a small proportion of the athletes, (3) athletes that

261   MTFC have lower global RV ε, SRS' and SRA' compared to NMTFC that may, in

262   part, be explained by the larger RVOT dimension.

263

264   *Right Ventricular Structure*

265   ARVC is an inherited genetic disease that is characterized by a fibrofatty

266   replacement of the RV myocardium (Marcus et al., 2010). Due to the variable

267   phenotypical expression and clinical manifestation of the disease, its diagnosis

12

268 remains challenging, particularly, in its early stages. The structural changes in

269 ARVC may be absent or subtle and limited to a localized region of the RV called the

270 'triangle of dysplasia' (Marcus et al., 2010; Rojas & Calkins, 2015), RV inflow tract

271 (sinus), the RV apex, RV outflow tract (Aneq, 2011; Te Riele et al., 2013) or

272 infundibulum (RVOT2) (Basso et al., 1996). Many studies have demonstrated that

273 chronic exercise training leads to RV dilation and acute exercise causes

274 disproportionate wall stress (Douglas & O'Toole, 1990; Heidbuchel, Prior, & La

275 Gerche, 2012; Rojas & Calkins, 2015). Thus, previous athlete heart studies have

276 demonstrated RV enlargement that exceeds the normal cut-off values and fulfill

277 ARVC structural TFC (D'Ascenzi et al., 2017a, 2017b; Oxborough et al., 2012;

278 Zaidi et al., 2013). The current study reports a significant enlargement in absolute

279 and scaled RVOT in both long and short axis views, fulfilling major TFC but in

280 addition these athletes have a significant higher absolute and scaled RVOT2 value

281 suggesting a proportional dilatation of the outflow tract. It is apparent that although

282 the RVOT may be enlarged in these athletes there is a lack of proportional

283 enlargement of the inflow and RVDA with an increased RVOT/RVD1 ratio. This

284 finding is disparate from previous studies in endurance athletes (Oxborough et al.,

285 2012). It is difficult to provide a clear explanation for this, but it must be

286 acknowledged that a disproportionate remodeling occurs as physiological adaptation

287 in *some* athletes irrespective of training stimulus. We can speculate that this may be

288 driven by individual heterogeneity / genetics, but it is important to note that an

289 increased RVOT/RVD1 ratio (approaching 1) does not indicate pathology.

290

291 Our study also highlights the importance of scaling for body size. Some of the

292 NMTFC athletes had high absolute values meeting TFC which normalised once they

293 were scaled to BSA. In view of this, we support D'Ascenzi et al (2017b) by

294 recommending using the major TFC normalized to BSA instead of non-scaled or

295 conventional criteria of RV enlargement from the American Society of

296 Ecohcardiography (D'Ascenzi, Pelliccia, et al., 2017; D'Ascenzi, Pisicchio, et al.,

297 2017).

298

299 *Right Ventricular Function*

300 Our conventional echocardiographic data demonstrated no between group difference

301 in global RV systolic function as determined by RV FAC and TAPSE.   This

302 supports other athlete RV studies (D'Andrea et al., 2013; Baggish et al., 2008;

303 D'Ascenzi et al., 2017a, 2017b; Moro, Okoshi, Padovani, & Okoshi, 2013;

304 Oxborough et al., 2016; Qasem et al., 2018). Despite this cohort comparability, 6%

305 of NMTFC and MTFC athletes had an RV FAC lower than 33% which is a major

306 echocardiographic criteria for ARVC. This is an important finding in that functional

307 abnormalities are an essential component of the TFC. This is similar to D'Ascenzi,

308 Pelliccia, et al., (2017) whom demonstrated lower RV FAC $\leq$ 33% in a small

309 population of their athletes raising uncertainty regarding the specificity of RV FAC

310 for the diagnosis of ARVC (D'Ascenzi et al., 2017b). This finding further

311 complicates the differential diagnosis in a minority of athletes. Interestingly, there

312 was borderline normal TDI and ε in the 2 athletes that met the full ARVC criteria in

313 this study. The lack of correlation between RV FAC and longitudinal free and septal

314 wall function further highlights the complex nature of RV function and the problems

14

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

339 demonstrate lower RV ε in MTFC compared to NMTFC, which is partly related to

340 absolute and scaled RVOT-PLAX and, therefore, also likely represents normal

341 physiological adaptation to training. An enlarged ventricle will likely lead to a

342 realignment of the myofibre architecture which may influence regional mechanics.

343 In addition, it is apparent that a large chamber requires less myocardial contraction to

344 generate an adequate stroke volume at rest. It is likely that the use of an exercise

345 stimulus (La Gerche et al., 2012b) would provide additional diagnostic information

346 in those athletes that MTFC and have borderline / low systolic function. It is likely

347 that chamber size is a significant contributing factor, however structural enlargement

348 of the outflow only accounted for 5% of RV ε and SR. This small contribution may

349 reflect the complex RV structure that is only partly being represented by a linear

350 measurement and a more substantive / 3-dimensional assessment of the RV would

351 likely provide greater insight. It is also apparent that due the dependence on load and

352 the inherent intrinsic function of the myocardium other factors such as ventricular

353 interdependence and RV afterload and may also contribute to the lower deformation

354 parameters observed in this study.

355

356 *Limitations*

357 The MTFC sample size was relatively small and thus further study is warranted in a

358 larger sample size and studies related to different sports discipline, genders and

359 ethnicity specific adaptation. It would have been useful to document pulmonary

360 artery pressures, however we were unable to obtain a CW tricuspid regurgitant signal

361 in a reasonable proportion of the population. That aside, none of our athletes had any

16

362 echocardiographic signs (other than RV / RA enlargement) therefore had a low

363 probability of pulmonary hypertension (Galiè et al., 2016).

364

365 **Conclusion**

366 Athletes that MTFC for RVOT do not develop a proportional increase in the RV

367 inflow dimensions. There are no difference in global conventional RV systolic

368 function by RV FAC and TAPSE between both groups. There are significant lower

369 global RV ε, RVS' and RVA' in athletes that MTFC which related partly to the

370 larger RVOT dimension. The complex nature of RV function suggest that a multi-

371 factorial assessment may be informative particularly in those that MTFC.

372

373 **Declaration of Interest**

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

375 of the research reported

376

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379

380

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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 (ε) and Strain Rate (SR)

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