FULL RESEARCH PAPER
Sports cardiology

Electrocardiographic predictors of left ventricular scar in athletes with right bundle branch block premature ventricular beats

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Aims	Right bundle branch block (RBBB) morphology non-sustained ventricular arrhythmias (VAs) have been associated with the presence of non-ischaemic left ventricular scar (NLVS) in athletes. The aim of this cross-sectional study was to identify clinical and electrocardiogram (ECG) predictors of the presence of NLVS in athletes with RBBB VAs.
Methods and results	Sixty-four athletes [median age 39 (24–53) years, 79% males] with non-sustained RBBB VAs underwent cardiac magnetic resonance (CMR) with late gadolinium enhancement in order to exclude the presence of a concealed structural heart disease. Thirty-six athletes (56%) showed NLVS at CMR and were assigned to the NLVS positive group, whereas 28 athletes (44%) to the NLVS negative group. Family history of cardiomyopathy and seven different ECG variables were statistically more prevalent in the NLVS positive group. At univariate analysis, seven ECG variables (low QRS voltages in limb leads, negative T waves in inferior leads, negative T waves in limb leads I–aVL, negative T waves in precordial leads V4–V6, presence of left posterior fascicular block, presence of pathologic Q waves, and poor R-wave progression in right precordial leads) proved to be statistically associated with the finding of NLVS; these were grouped together in a score. A score ≥2 was proved to be the optimal cut-off point, identifying NLVS athletes in 92% of cases and showing the best accuracy (86% sensitivity and 100% specificity, respectively). However, a cut-off ≥1 correctly identified all patients with NLVS (absence of false negatives).
Conclusion	In athletes with RBBB morphology non-sustained VAs, specific ECG abnormalities at 12-lead ECG can help in detecting subjects with NLVS at CMR.
Lay summary	In athletes with right bundle branch block (RBBB) morphology non-sustained ventricular arrhythmias (VAs), the presence of a non-ischaemic left ventricular scar (NLVS) may be highly suspected if one or more of the following electrocardiogram (ECG) characteristics are present at the 12-lead resting ECG: low QRS voltages in limb leads, negative T waves in inferior leads, negative T waves in limb leads I–aVL, negative T waves in precordial leads V4–V6, presence of left posterior fascicular block, presence of pathologic Q waves, and poor R-wave progression in right precordial leads. This score should be externally validated in a larger population of athletes with VAs.

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- In athletes with RBBB morphology non-sustained Vas, attention should be placed on the 12-lead resting ECG to suspect the presence of an NLVS.
- In athletes with RBBB VAs and the presence of one or more of the identified ECG characteristics, a cardiac magnetic resonance with late gadolinium enhancement is useful to rule out an NLVS.

Graphical Abstract

12-lead resting ECG parameters associated with the presence of LV scar at CMR

1. Low QRS voltages in limb leads
2. Negative T-waves in inferior limb leads
3. Negative T-waves in limb leads I-aVL
4. Negative T waves in precordial leads V4-V6
5. Presence of left posterior fascicular block
6. Presence of pathologic Q waves
7. Poor R-wave progression in right precordial leads

Keywords   ECG • Athletes • Ventricular arrhythmias • Predictors • Non-ischaemic left ventricular scar

Introduction

Premature ventricular beats (PVBs) are not an uncommon finding in young athletes undergoing pre-participation screening.[1] Although generally considered a benign phenomenon,[2,3] in a minority of cases, they may be the expression of a structural heart disease (SHD). Premature ventricular beats are therefore a matter of concern in athletes because the presence of an unrecognized SHD carries a risk of sudden cardiac death during sports activity.[4]

An SHD can be identified at pre-participation evaluation in many cases, because of abnormal clinical and electrocardiographic findings that point to a specific disease or prompt further diagnostic exams (mainly echocardiography), which may be effective in defining a diagnosis.[5,6] However, in subjects with frequent PVBs, the standard diagnostic workup often fails to identify signs of SHD, being the arrhythmias an isolated abnormal finding. In recent years, cardiac magnetic resonance (CMR) has gained momentum as an invaluable tool to identify a concealed SHD in apparently healthy subjects with frequent PVBs or non-sustained ventricular arrhythmias (VAs).[7,8] Non-ischaemic left ventricular scar (NLVS) is the most frequent pathological finding at CMR in subjects with VA and an otherwise negative diagnostic workup.[9,10] Non-ischaemic left ventricular scar can be

also found in association with well-defined forms of SHD, including cardiomyopathies, infiltrative heart diseases, and myocarditis.[11–13] Most importantly, the presence of NLVS has been strongly associated with the occurrence of malignant VA and an adverse prognosis.[10,14–17] The likelihood that NLVS may be found at CMR in an apparently healthy subject with frequent PVBs mainly depends on the electrocardiographic morphology of the ectopic beats. Idiopathic or common pattern PVBs, i.e. those occurring in the absence of SHD, more often present with an 'infundibolar' [left bundle branch block (LBBB) and inferior axis] or a 'fascicular' [typical right bundle branch block (RBBB) and duration <130 ms] QRS pattern. On the other hand, different and uncommon QRS morphologies, such as LBBB with a superior axis or atypical RBBB, may be more likely the expression of an SHD.[9,10,18–21] Moreover, despite some left ventricular (LV) sites as the mitral valve annulus and papillary muscles can give rise to idiopathic forms of VA, atypical RBBB morphology arrhythmias (almost always originating from the LV) have been strongly linked to the presence of NLVS.

Besides the analysis of the PVBs features, the role of a 12-lead surface electrocardiogram (ECG) in predicting the presence of NLVS at CMR is not well defined. Several abnormalities, mainly inferolateral T-wave inversion and low QRS voltages in limb leads, have been described in

athletes with NLVS,[9,14,20] but the prevalence of these findings has been reported to be low, having most subjects a normal ECG.

The aim of our study was to investigate the ECG characteristics of apparently healthy athletes with non-sustained VA presenting with at least one RBBB morphology ventricular premature beat, in relation to the presence of NLVS at CMR.

Methods

Study population and clinical evaluation

Our study population includes consecutive athletes with frequent PVBs (>500/24 h) and/or repetitive VAs such as couplets or non-sustained ventricular tachycardia. Only subjects with PVBs consistent with LV origin, based on QRS morphology at 12-lead ECG (RBBB with superior/intermediate or inferior axis), were included.

The athletes were enrolled between 2018 and 2020, among those undergoing pre-participation screening or those who were referred to our out-patient centre for VAs, dedicated to the clinical management of athletes with suspected or ascertained arrhythmic diseases.

Athletes younger than 18 years were excluded. In order to avoid the confounding effect of obesity on ECG parameters, only subjects with a body mass index <25 kg/m^2 were included. Both competitive and non-competitive athletes were enrolled. Non-competitive athletes could be included in the study only if their training could meet some requirements: at least three training sessions per week and at least 5 h of training a week. According to the Italian classification, athletes over 40 years of age were considered as 'master' athletes.

Every subject underwent clinical basic evaluation (including familiar and personal medical history, physical examination), 12-lead surface standard ECG, bidimensional trans-thoracic echocardiography, and 24 h ECG Holter monitoring. A cycle ergometer exercise test with step increments of 30 W every 2 min was performed as well. Cardiac/coronary arteries computed tomography scan, coronary angiography, and electrophysiologic invasive study were performed in selected cases.

Only athletes without an overt SHD at routine clinical workup were enrolled in the study. Subsequently, every athlete underwent CMR in order to further investigate the presence of a concealed SHD, as a possible cause of clinical arrhythmias. According to the presence or absence of late gadolinium enhancement (LGE) at CMR without other features of a concealed cardiomyopathy, the patients were divided into two groups: Group A, athletes with evidence of LGE at CMR, and Group B, athletes without evidence of LGE at CMR.

All athletes gave signed informed consent after counselling in accordance with the Declaration of Helsinki of 2001 and under the recommendation of the institutional ethical review board.

Electrocardiogram analysis

Electrocardiograms were recorded at a paper speed of 25 mm/s, filter range of 0.15–50 Hz, AC filter of 60 Hz, and gain setting of 10 mm/mV. The ECG tracings were manually analysed by two separate expert cardiologists (L.S. and A.S.), unaware of the study objectives, and differences were solved by consensus.

The following ECG data were collected: rhythm type, heart rate, PR interval, QRS axis in the frontal plane, presence of any intraventricular conduction delay: LBBB, anterior or posterior left fascicular block, complete RBBB, and non-specific intraventricular conduction delay. The presence of seven additional potentially abnormal ECG features was also evaluated: (i) pathologic Q waves defined as Q/R ratio ≥0.25 or ≥40 ms in duration in two or more leads, excluding III and aVR[22]; (ii) poor R-wave progression in right precordial leads, defined as an R-wave amplitude of 3 mm or less in precordial lead V3. The ECG was standardized, so that a 10 mm deflection was equal to 1 mV and when the R-wave amplitude in lead V2 was equal to or smaller than the R-wave amplitude in V3[23]; (iii) negative T waves ≥1 mm in depth, except in limb leads aVR and III and in precordial lead V1 in at least in two or more inferior limb leads II, III, and aVF; (iv) negative T waves in limb leads I and/or aVL; (v) negative T waves in right precordial leads V1–V3; (vi) negative T waves in at least two adjacent leads between precordial leads V4 and V6[24]; and (vii) low voltages in limb leads (defined as the amplitude of

the QRS complex measured from nadir to zenith of QRS <0.5 mV in limb leads with a total limb lead QRS amplitude of <30 and/or <1.0 mV in all precordial leads and/or SV1 +RV5 or V6 <1.5 mV.[25]

Cardiac magnetic resonance imaging

Scan protocol

Cardiac magnetic resonance imaging was performed with 1.5 T systems (Prodiva, Philips Healthcare, Amsterdam, The Netherlands) using dedicated cardiac software, a phased array surface receiver coil, and vectorcardiogram triggering. All patients underwent detailed contrast-enhanced CMR study protocol including post-contrast sequences. Images were acquired using a two-dimensional (2D) steady-state free precession (cine-SSFP) sequence in sequential short-axis views (slice thickness 8 mm, gap 0 mm, repetition time 2.6–3.8 ms, echo time 1.1–1.7 ms, average in-plane resolution 2 × 2.4 mm, flip angle 45°–60°, and temporal resolution 30–50 ms) and long-axis views (two-chamber, three-chamber, and four-chamber views).

Also, T$_2$-weighted turbo spin echo BlackBlood imaging (repetition time 60 ms, echo time 2600–2900 ms, average in-plane spatial resolution 2.2 × 3.0 mm, slice thickness 8 mm, gap 2–4 mm, and flip angle 90°) was acquired in sequential short-axis views and four-chamber long-axis views.

At least 10 min after intravenous administration of 0.2 mmol/kg gadolinium, 2D inversion recovery turbo field echo sequences (repetition time 5.2–7.7 ms, echo time 1.3–3.8 ms, average in-plane spatial resolution 2.4 × 3.3 mm, slice thickness 10 mm, gap 0 mm, and flip angle 20°–25°) were acquired in short-axis views (9–13 images covering the entire LV) and long-axis views (two-chamber and four-chamber views). Inversion times were adjusted to null normal myocardium using the look-locker sequence.

Image analysis

Right ventricular and LV volumes and systolic functions and absolute and index LV myocardial mass, excluding papillary muscles from the myocardium, were calculated from the short-axis cine images, using a dedicated workstation (IntelliSpace Portal, Philips Healthcare).

For qualitative reporting, LV was divided into five regions: anterior wall, lateral wall, posterior–inferior wall, septum, and apex. The presence of LGE in each segment was determined by an expert radiologist with the Society of Cardiovascular Magnetic Resonance level-3 experience (M.D.R.), who was blinded to the clinical data and to the study protocol purpose. Late gadolinium enhancement was quantified only if present in two orthogonal views, using a signal intensity threshold of >2 SD above a remote reference region, and quantified by a semi-automatic detection and was expressed as a per cent of total LV mass, as previously described.[20] The pattern of LGE distribution and morphology was characterized as either epicardial/mid-myocardial or patchy/junctional spotty.

Statistical analysis

For descriptive statistics, continuous variables were reported as median (inter-quartile range) and categorical variables as percentage, calculated using known non-missing values. Differences between the groups LGE+ and LGE− were tested using the Mann–Whitney for continuous variables. For categorical variables, between-group differences were assessed using the Pearson χ^2 test or Fisher's exact test for large-expected or small-expected counts, respectively. Significance level was set at $P = 0.05$. Univariate logistic regression was performed, including the baseline characteristics of the patients and ECG parameters (any anomalous findings such as conduction delays and the seven additional potentially pathological ECG features evaluated) in order to define their relationship with LGE. Electrocardiogram characteristics showing statistical significance (P-value <0.05) in univariate analysis and those exclusively observed in the LGE+ group, with no instances in the LGE− group, were combined together in order to generate a score to predict the presence of LGE at CMR.

The prediction performance of the score was estimated with a receiver operating curve (ROC) analysis. The cut-off value of the score was selected by the maximization of the proportion of correctly classified observations, choosing the best compromise between sensitivity and specificity. For the proposed cut-off value of the score, positive predictive value and negative predictive value were calculated.

Table 1 Patients' anthropometric and clinical characteristics

	Overall (N = 64)	Athletes with CMR LGE+ (N = 36)	Athletes with CMR LGE− (N = 28)	P-value[a]
Male gender, n (%)	50 (79)	29 (82.9)	21 (75.0)	0.444
Age (years)	39 (24–53)	42 (27–54)	38 (24–53)	0.409
Sport				
Soccer	13 (20)	8 (22)	5 (18)	0.667
Running	11 (17)	6 (17)	5 (18)	0.900
Cycling	10 (16)	6 (17)	4 (14)	0.795
Volley	7 (11)	2 (6)	5 (18)	0.118
Swimming	4 (6)	3 (8)	1 (4)	0.435
Boxe/kick boxing	3 (5)	1 (3)	2 (7)	0.709
Other	17 (27)	11 (31)	6 (21)	0.134
Competitive activity	33 (52)	17 (47)	16 (57)	0.431
Master athletes (age over 40 years)	35 (55)	21 (58)	14 (50.0)	0.506
Family history				
Family history of sudden death	6 (9)	5 (14)	1 (4)	0.160
Family history of cardiomyopathy	5 (8)	5 (14)	0 (0)	—
Clinical history				
Symptoms present	33 (52)	20 (56)	13 (46)	0.469
Palpitations	23 (36)	12 (34)	11 (39)	0.682
Syncope	4 (6)	4 (11)	0 (0)	—
Cardiac arrest	3 (5)	3 (8)	0 (0)	—
Other	8 (12)	5 (14)	3 (11)	0.703
Regional LV wall motion abnormalities at echocardiogram	2 (3)	1 (3)	1 (4)	0.887
CMR features				
Moderate to severe LV EF depression	0	0	0	—
Mild LV EF (45–50%) depression	4 (6)	3 (8)	1 (4)	0.547
Mild LV dilatation	5 (8)	3 (9)	2 (7)	0.691
Mild RV dilatation	4 (6)	2 (6)	2 (7)	0.819

The P-value has been omitted when one of the comparators was zero.

EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; CMR, cardiac magnetic resonance; RV, right ventricular.

[a]The Mann–Whitney U test or the Pearson χ^2 for differences between groups LGE+ and LGE− for continuous and categorical variables as appropriate.

Results

Patients' population characteristics

Sixty-four athletes with non-sustained RBBB VAs [median age 39 years, range 24–53 years, 50 (79%) males] and a negative first-line diagnostic workup underwent CMR and were divided into two groups according to the presence or absence of LGE with non-ischaemic distribution (mid-myocardial and/or sub-epicardial): (i) LGE+ group: 36 athletes (56%) with evidence of LGE (29 males, 83%) and (ii) LGE− group: 28 athletes (44%) without evidence of LGE (21 males, 75%). As shown in *Table 1*, there were no statistically significant differences among groups regarding gender, age, type of sport, and competitive activity prevalence. Master athletes were equally distributed in the two groups. A significant prevalence of a family history of cardiomyopathy and a non-significant trend towards a higher percentage of patients with a family history of sudden death were observed in the LGE+ group. The presence of symptoms was not statistically different between groups, but three patients in the LGE+ group had experienced cardiac arrest. A non-significant trend towards a higher prevalence of syncope was observed in the LGE+ group. The study flowchart is presented in *Figure 1*.

Prevalence of electrocardiogram abnormalities

The prevalence of ECG abnormalities was compared between LGE+ and LGE− groups (*Table 2*). Low QRS voltages in limb leads, negative T waves in inferior leads, negative T waves in limb leads I and aVL, negative T waves in precordial leads V4–V6, pathologic Q-waves, and poor R-wave progression in precordial leads resulted to be significantly prevalent in the LGE+ group.

Cardiac magnetic resonance

In the LGE+ group, in 35 athletes out of 36 (97%), LGE was present in the lateral wall. Twenty-five athletes (69%) showed LGE in the infero-posterior wall. In seven athletes (19%), LGE was localized in the anterior wall. An apical or septal LGE distribution was observed in four (11%) and seven athletes (19%), respectively.

All patients with LGE+ showed a sub-epicardial and/or mid-myocardial pattern, compatible with NLVS. In 29 athletes (80%), NLVS was located in at least two different walls. In many cases, a 'stria' pattern, defined as sub-epicardial and/or mid-myocardial linear LGE detectable in at least three contiguous segments in the same short-axis slice,[19–21] was also recognizable.

Sixty-four athletes (50 males (79.4%); median age 39 years (24.5-53 years) with non-sustained VAs and at least one RBBB morphology

No evidence of SHD at routine diagnostic work-up including echocardiography

All underwent CMR with LGE

36 athletes (56%) showed NLVS at CMR

28 athletes (44%) without NLVS at CMR

7 ECG variables proved to be statistically associated with NLVS
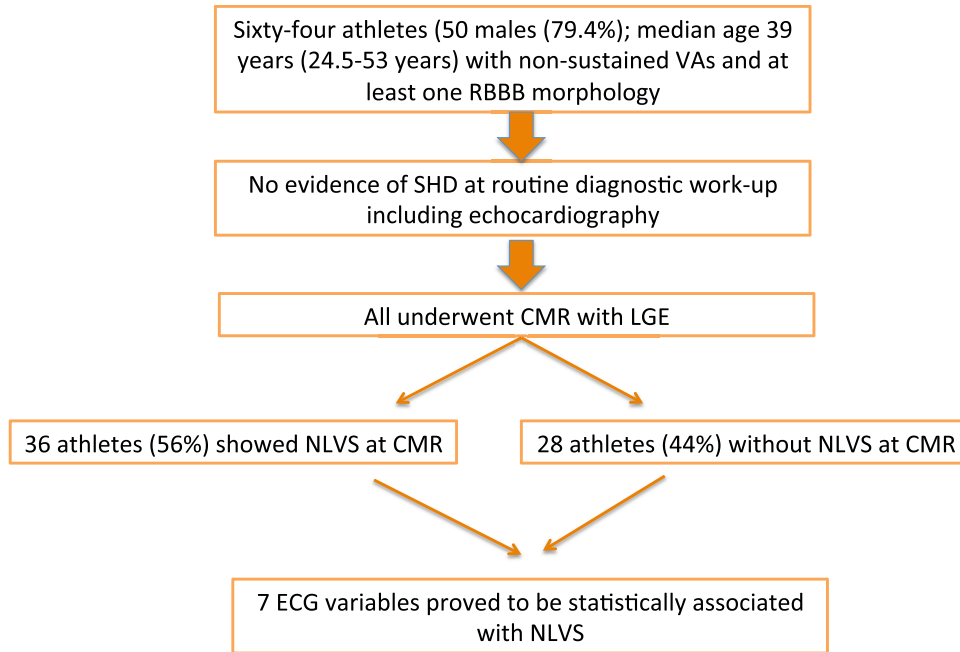
Figure 1 Diagram of the study protocol. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; NLVS, non-ischaemic left ventricular scar; RBBB, right bundle branch block; SHD, structural heart disease; VAs, ventricular arrhythmias.

Table 2 Prevalence of electrocardiogram anomalies by the presence of late gadolinium enhancement at cardiac magnetic resonance

	All (N = 64)	LGE+ (N = 36)	LGE− (N = 28)	P-value[a]
Low voltages in limb leads	20 (31)	20 (56)	0 (0.0)	—
Negative T-wave in inferior leads	17 (27)	16 (44)	1 (4)	<0.001
Negative T-wave in limb leads I–aVL	18 (28)	14 (39)	4 (14)	0.030
Negative T-wave in precordial leads V4–V6	12 (19)	12 (33)	0 (0.0)	—
Negative T-wave in precordial leads V1–V3	8 (12)	7 (19)	1 (4)	0.057
Left posterior fascicular block	4 (6)	4 (11)	0 (0.0)	—
Left anterior fascicular block	6 (9)	5 (14)	1 (4)	0.160
Pathologic Q waves	7 (11)	7 (19)	0 (0.0)	—
Poor R-wave progression	14 (22)	11 (31)	3 (11)	0.034

[a]The Pearson χ^2 for differences between the groups LGE+ and LGE− for categorical variables. The P-value has been omitted when one of the comparators was zero.

In three athletes (8%) with NLVS, a junctional pattern was documented, as well. Other CMR features are shown in Table 1.

Positive late gadolinium enhancement predictors

Predictive factors for the presence of LGE are shown in Table 3. At univariate logistic regression analysis, among the patients' clinical characteristics only a family history of cardiomyopathy resulted to be strongly associated with LGE finding at CMR, whereas male gender, age, family history of sudden death, condition of master athlete, competitive activity practicing, and presence of symptoms were not.

According to ECG features, four variables were present only in the LGE+ group: low QRS voltages in limb leads, negative T waves in precordial leads V4–V6, presence of left fascicular posterior block, and presence of pathologic Q waves. A significant correlation with LGE at CMR was found for negative T waves in inferior leads, negative T waves in limb leads I and aVL, and poor R-wave progression in precordial leads.

Electrocardiogram score

All ECG variables present only in the LGE+ group, and those proved to be statistically associated with the presence of LGE at univariate analysis were selected to build a score, aimed to predict the presence of LGE. Precisely, seven variables were considered: low QRS voltages in limb leads,

Table 3 Univariate logistic regression for predictors of late gadolinium enhancement

	Odds ratio	Confidence interval (95%)	P-value[a]
Male	0.62	(0.18–2.12)	0.446
Age (years)	1.03	(0.99–1.06)	0.148
Familiarity for sudden death	4.35	(0.48–39.62)	0.192
Familiarity for cardiomyopathy	—		
Master athletes (age over 40 years)	1.40	(0.51–3.78)	0.507
Competitive activity	0.67	(0.25–1.81)	0.432
Symptoms present	1.44	(0.53–3.89)	0.469
Low voltages in limb leads[a]	—		
Inferior negative T waves	24.1	(2.96–197.36)	0.003
Negative T-wave in limb leads I–aVL	4.28	(1.23–14.94)	0.022
Negative T-wave in precordial leads V4–V6[a]	—		
Negative T-wave in precordial leads V1–V3	6.52	(0.75–56.58)	0.089
Left posterior fascicular block[a]	—		
Left anterior fascicular block	4.35	(0.49–40.98)	0.182
Pathologic Q wave[a]	—		
Poor R-wave progression in right precordial leads	4.17	(1.04–16.62)	0.043

The components of prediction score are as follows: low QRS voltage, inferior negative T-wave, negative T-wave in limb leads I–aVL, negative T-wave in precordial leads V4–V6, negative T-wave in precordial leads V1–V3, left posterior fascicular block, left anterior fascicular block, pathologic Q wave, and poor R-wave progression in precordial leads.
[a]Odds ratio has been omitted.

negative T waves in inferior leads, negative T waves in limb leads I and aVL, negative T waves in precordial leads V4–V6, presence of left posterior fascicular block, presence of pathologic Q waves, and poor R-wave progression in right precordial leads. The weight associated with each variable was assigned the value of 0 if absent and 1 if present. Therefore, the score could range from a minimum of 0 to a maximum of 7.

Based on the analysis of ROC curves, an optimal cut-off point ≥2 to identify athletes with LGE at CMR based on the ECG was extrapolated. In fact, a score ≥2 correctly classified the 34 athletes of Group A as carriers of NLVS in 92% of cases, showing the best sensitivity and specificity (86 and 100%, respectively). However, a cut-off ≥1 rendered it possible to optimize sensitivity, correctly identifying all patients with NLVS (absence of false negatives). *Figure 2* summarizes the data relative to each score model cut-off point and shows the ROC curve relating to the score prediction performance.

Discussion

We studied a population of apparently healthy athletes with RBBB morphology non-sustained VAs, to evaluate the association between the presence of 12-lead ECG abnormalities and the finding of NLVS at CMR. The main results of the study were as follows: (i) the presence of NLVS was identified at CMR in 56% of the study population; (ii) at univariate analysis, some electrocardiographic abnormalities proved to be associated with the presence of NLVS; (iii) when such variables were grouped to build a score, in order to predict the presence of NLVS, a cut-off point of two yielded optimized sensitivity and specificity values of 86 and 100%, respectively; and (iv) lowering the cut-off point of the score to 1, increased the sensitivity to 100%, while maintaining an acceptable specificity, which means that none of the subjects with NLVS were classified as a negative ECG.
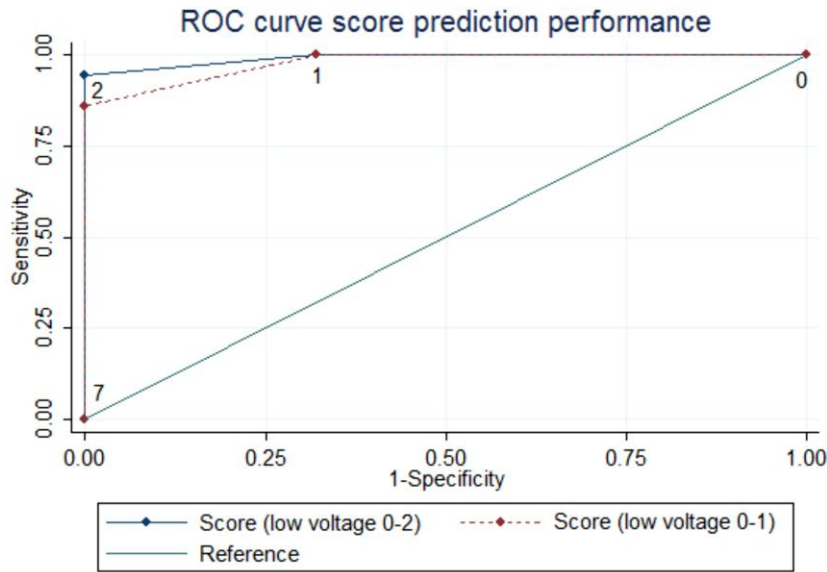
Ventricular arrhythmias and left ventricular scar in athletes

Systematic pre-participation screening in competitive athletes has been established in Italy since 1982. This approach has proved capable of

reducing the incidence of sport-related sudden death in the screened population by up to 89%.[5] Mortality reduction was predominantly due to the increased identification of clinically silent SHD, mainly hypertrophic cardiomyopathy and arrhythmogenic cardiomyopathy. Since cardiomyopathies, as well as some inheritable non-SHDs, may present with a specific ECG pattern, their presence can be suspected at pre-participation screening that is essentially based on ECG evaluation (*Figure 3*).

Frequent PVBs may be encountered in athletes undergoing systematic resting and exercise ECGs. When the presence of SHD is subsequently ruled out (which has been usually intended as the absence of pathological findings at clinical examination, echocardiogram, and stress testing), PVBs have long been considered a benign phenomenon and a possible manifestation of athlete's heart.[2,3,26–28] However, evidence has grown that in a non-negligible percentage of cases, PVBs are the expression of a concealed SHD.[29–31] In recent years, CMR by means of different techniques has been able to identify a number of cardiac structural and functional abnormalities that are not detectable at echocardiography. The most frequent structural abnormality found at CMR in subjects with frequent VA is NLVS,[9,10] which has been defined as the presence of LGE in the LV with a mid-ventricular or sub-epicardial distribution, in the absence of significant coronary artery disease.[14] It may present both as an isolated finding[27] or in the setting of a definite SHD.[8] The main determinant of NLVS prevalence in patients with frequent non-sustained VAs is the ventricular site of the origin of the PVBs, when dichotomized as right or left. Muser et al.[10] found LGE in the LV in 15% of patients with frequent PVBs and a negative diagnostic workup; however, patients with RBBB pattern PVBs more often had abnormalities at CMR (mainly NLVS) than patients with LBBB pattern PVBs (51 vs. 5%). Similarly, Nucifora et al.[19] found that the prevalence of LV fibrosis in patients with VA and no evidence of SHD was higher in an RBBB than in an LBBB subset (41 vs. 4%). Since we evaluated subjects who had at least one ectopic QRS morphology consistent with an LV origin and repetitive PVBs, our finding of a 56% prevalence of NLVS at CMR appears to be in line with previous studies.

Non-ischaemic left ventricular scar, which mostly presents with a sub-epicardial and/or mesomyocardial pattern and a 'stria' appearance,

Figure 2 The receiver operating characteristic curve is the plot of the true-positive rate against the false-positive rate, and it illustrates the performance of the model at varying threshold values for the prediction of non-ischaemic left ventricular scar at cardiac magnetic resonance with late gadolinium enhancement.

was the most frequent pathological finding in sudden deaths occurring during sports.[14] Together with the presence of RBBB pattern VA, a stria pattern NLVS has been considered the hallmark of the left-dominant form of arrhythmogenic cardiomyopathy (LDAC).[32,33] Recently, a stria pattern NLVS has been associated with mutations in desmoplakin and filamin C genes, further detailing the diagnostic framework of LDAC.[26,34,35] However, when genetic typing is not available and a clear family history of cardiomyopathy or sudden death is lacking, the diagnosis of LDAC is often difficult, even considering that a stria pattern NLVS may also be encountered in other conditions, mainly in chronic or healed myocarditis.[36]

In patients with LDAC, lateral *T*-wave inversion[32] and low QRS voltages in limb leads[14] have been reported. In analogy with arrhythmogenic right ventricular cardiomyopathy, which presents ECG abnormalities in the vast majority of cases,[37] ECG would be expected to manifest a wide range of abnormalities in LDAC as well. However, if we consider subjects with RBBB VAs and NLVS, in the absence of a definite diagnosis of SHD, the prevalence and type of ECG anomalies are not clearly defined.

Zorzi *et al.*[20] studied 35 athletes with non-sustained and sustained VA and NLVS; they found evident abnormalities of the surface ECG in 37% of subjects, among which the most common were low QRS voltages in limb leads and *T*-wave inversion in inferolateral leads; 28/35 (80%) of the athletes had VA with a predominant RBBB morphology, whereas 27/35 (77%) showed a stria pattern NLVS at CMR. In the latter subgroup, the prevalence of repolarization abnormalities was higher, reaching 48%.[20] Differently from Zorzi *et al.*,[20] we selected only athletes who had at least one VA morphology consistent with an LV origin;

therefore, in this highly selected study population, we identified ECG predictors more easily. We found in our patients at least one abnormal ECG finding, among those included in the score, in 70% of 64 athletes with non-sustained VA; in those who had NLVS, an abnormal ECG was present in 100% of cases. Other authors who evaluated the association between LV scar and VA preventively excluded from their analysis the patients with an abnormal ECG[10,19,21]; in other cases, surface ECG features, with regards to the possible presence of abnormalities, were not specified.[8,18]

Prediction of ventricular scar by electrocardiogram

Several attempts have been made to predict the presence of ventricular scar by surface ECG analysis. The Selvester QRS score predicts the presence of a ventricular scar based on QRS features at 12-lead surface ECG; it was first proposed in 1972 and has undergone gradual improvements over the following years.[38] Although the Selvester score has been extensively validated first in comparison with autopsy findings and more recently with CMR,[38,39] it was originally validated for the prediction of size and location (and not just the presence) of ischaemic scars (that are sub-epicardial/transmural). Moreover, the accuracy of the Selvester score in the presence of ECG confounders, mainly LBBB, proved to be limited.[39,40]

Fractionated QRS has been associated with both myocardial scar and an adverse prognosis.[41] However, it is frequently found in apparently
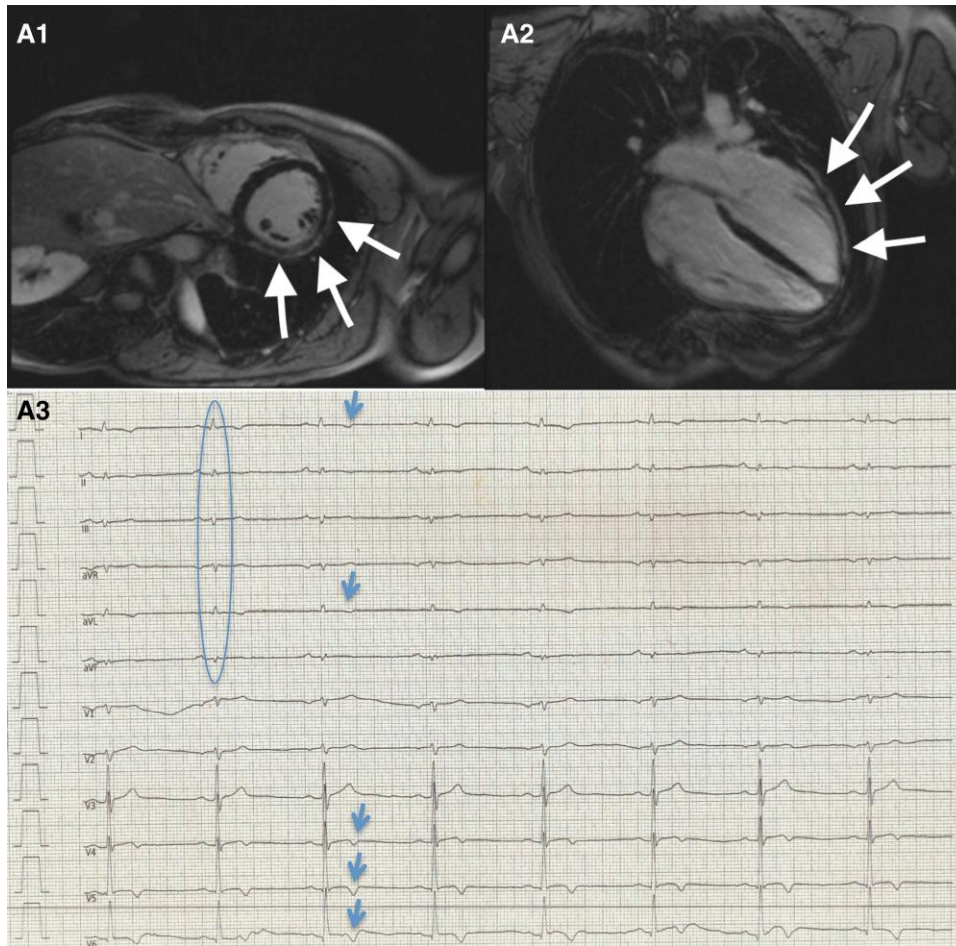
Figure 3 Images refer to a 40-year-old cyclist with right ventricular bundle branch block ventricular arrhythmias. (*A1* and *A2*) Cardiac magnetic resonance images. The arrows show a wide sub-epicardial stria of late gadolinium enhancement in the inferior and lateral left ventricular walls. (*A3*) The 12-lead electrocardiogram is presented. Low voltages in peripheral leads are evident (circle). Moreover, it can be noted a negative *T* wave in limb leads I–aVL and in precordial leads V4–V6 (arrows). According to our proposed evaluation, this patient shows a score equal to 3 points.

healthy individuals, and criteria to distinguish between benign forms and those associated with scars have not been clearly established.

Diagnosing scar at pre-participation screening

In the last few years, CMR has demonstrated high accuracy in the study of cardiac structure and function, in addition to its unique ability to perform cardiac tissue characterization becoming the gold standard method in this field. Accordingly, CMR has become a diagnostic standpoint in the evaluation of athletes with VAs.[1,42] In daily clinical practice, however, CMR has some limitations: it is expensive and not yet widely available; claustrophobic patients and those with metal inserts may be unable to undergo the examination. For these reasons, it is difficult to systematically include CMR as part of the clinical workout of athletes who have VAs.

The pre-participation screening for competitive activity in Italy[43] and in Europe[44] is mainly based on clinical evaluation and 12-lead standard surface ECG interpretation. Therefore, it is important to define the diagnostic power of ECG in identifying subjects who could have clinically silent cardiac abnormalities, which is particularly important also in emerging athletic populations such as paediatric and master athletes.[45–47]

We found that several ECG abnormalities were associated with the presence of NLVS; based on this result, we built an electrocardiographic score to predict the presence of NLVS. The index range extends from 0 to 7, and a score of 2 or more points allowed to optimize sensitivity and specificity, which reached values of 86 and 100%, respectively. Moreover, a score equal to 0 points was present in no athlete with NLVS. This suggests the possibility of applying the score with a cut-off point of 1 as a first step and then submitting those who get a score of 1 or more to CMR, in order to rule out false positives. Such a two-step approach, based on the systematic application of an ECG score, could improve the screening of athletes in terms of cost-effectiveness, by optimizing the diagnostic power of ECG and, as a consequence, reducing the number of subjects who need to undergo CMR. The clinical accuracy of this approach, and in particular its ability to identify the subjects without NLVS, needs to be thoroughly verified in wider populations of athletes with RBBB VA.

Study limitations

Our study has several limitations. First, this is a retrospective cross-sectional study, and the results relate to a subpopulation of adult athletes with RBBB VAs (i.e. a high probability of NLVS because VAs originate from the LV); therefore, the results cannot be extrapolated and

applied to a population with different characteristics such as athletes with LV bundle branch block VAs or athlete without evidence of RBBB VAs or a population of non-athletes or children and adolescents; they would probably need other ECG criteria, as they show different normal ECGs. Second, the results need an external validation in a prospective cohort of consecutive athletes. Third, the number of patients is limited, and no genetic testing was performed at the time of the manuscript drafting to improve the diagnosis of the underlying disease and subsequent risk stratification. Moreover, the use of different weights in the ECG score must be assessed in a validation study. Importantly, some subtle changes in the 12-lead ECG of uncertain significance but possibly related to SHD (e.g. low voltage or flat *T* waves) may not be recognized as abnormal according to the set of parameters we have adopted. Another limitation of our study is the lack of comparison with other established scores. However, we must underline that at present, no specific ECG score has been proposed in the setting of LV non-ischaemic scar prediction.

Conclusions

In a highly selected population of athletes with RBBB VAs, seven electrocardiographic predictors for the presence of an NLVS were identified at 12-lead resting ECG and coupled in a score, which should be further validated in a larger population of athletes and eventually in non-athletes with VAs. Hence, in athletes with RBBB VAs, the presence of >1 ECG predictors at 12-lead resting ECG cannot be simply dismissed as a benign condition but should prompt an imaging study such as CMR with LGE to rule out the presence of an NLVS. The most appropriate management strategy for RBBB VAs athletes remains to be clearly defined, but this simple ECG score can support the initial diagnosis.

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Author contribution

L.S. conceived the study. P.G., E.C., A.S., A.G.R., M.D.M., A.B., M.D.R., A.D, S.G., F.R., P.D., M.N., Z.P., and S.R. contributed to data acquisition, analysis, and interpretation. E.C. and P.G. performed statistical analyses. A.G.R., E.C., and L.S. drafted the manuscript. L.S., P.G., E.C., A.S., A.G.R., M.D.M., A.B., M.D.R., A.D., S.G., F.R., P.D., M.N., Z.P., A.Z., L.C., and S.R. critically revised the manuscript for key intellectual content. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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Data availability

Data are available after motivated request to the corresponding author.

References

1. Zorzi A, D'Ascenzi F, Andreini D, Castelletti S, Casella M, Cavarretta E, *et al.* Interpretation and management of premature ventricular beats in athletes: an expert opinion document of the Italian Society of Sports Cardiology (SICSPORT). *Int J Cardiol* 2023;**391**:131220.
2. Biffi A, Pelliccia A, Verdile L, Fernando F, Spataro A, Caselli F, *et al.* Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. *J Am Coll Cardiol* 2002;**40**:446–452.
3. Delise P, Sitta N, Lanari E, Berton G, Centa M, Allocca G, *et al.* Long-term effect of continuing sports activity in competitive athlete with frequent ventricular premature complexes and apparently normal heart. *Am J Cardiol* 2013;**112**:1396–1402.
4. Robles AG, Palamà Z, Nesti M, Tunzi RM, Delise P, Cavarretta E, *et al.* Sport related sudden death: the importance of primary and secondary prevention. *J Clin Med* 2022;**11**:4683.
5. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA* 2006;**296**:1593–1601.
6. Calò L, Sperandii F, Martino A, Guerra E, Cavarretta E, Quaranta F, *et al.* Echocardiographic findings in 2261 peri-pubertal athletes with or without inverted T waves at electrocardiogram. *Heart* 2015;**101**:193–200.
7. White JA, Fine NM, Gula L, Yee R, Skanes A, Klein G, *et al.* Utility of cardiovascular magnetic resonance in identifying substrate for malignant ventricular arrhythmias. *Circ Cardiovasc Imaging* 2012;**5**:12–20.
8. Andreini D, Dello Russo A, Pontone G, Mushtaq S, Conte E, Perchinunno M, *et al.* CMR for identifying the substrate of ventricular arrhythmia in patients with normal echocardiography. *JACC Cardiovasc Imaging* 2020;**13**:410–421.
9. Cipriani A, Zorzi A, Sarto P, Donini M, Rigato I, Bariani R, *et al.* Predictive value of exercise testing in athletes with ventricular ectopy evaluated by cardiac magnetic resonance. *Heart Rhythm* 2019;**16**:239–248.
10. Muser D, Santangeli P, Castro SA, Casado Arroyo R, Maeda S, Benhayon DA, *et al.* Risk stratification of patients with apparently idiopathic premature ventricular contractions: a multicenter international CMR registry. *J Am Coll Cardiol Clin Electrophysiol* 2020;**6**:722–735.
11. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M. Late gadolinium enhancement on CMR predicts adverse cardiovascular outcomes in non-ischemic cardiomyopathy: a systematic review and meta-analysis. *Circ Cardiovasc Imaging* 2014;**7**:250–258.
12. Seward JB, Casaclang-Verzosa G. Infiltrative cardiovascular diseases: cardiomyopathies that look alike. *J Am Coll Cardiol* 2010;**55**:1769–1779.
13. Zagrosek A, Abdel-Aty H, Boyé PB, Wassmuth R, Messroghli D, Utz W, *et al.* Cardiac magnetic resonance monitors reversible and irreversible myocardial injury in myocarditis. *J Am Coll Cardiol Cardiovasc Imaging* 2009;**2**:131–138.
14. di Gioia CR, Giordano C, Cerbelli B, Pisano A, Perli E, De Dominicis E, *et al.* Nonischemic left ventricular scar and cardiac sudden death in the young. *Hum Pathol* 2016;**58**:78–89.
15. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, *et al.* Myocardial fibrosis assessment by LGE is a powerful predictor of ventricular tachyarrhythmias in ischemic and nonischemic LV dysfunction. A meta-analysis. *J Am Coll Cardiol Cardiovasc Imaging* 2016;**9**:1046–1055.
16. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, *et al.* Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail* 2017;**5**:28–38.
17. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *J Am Coll Cardiol Cardiovasc Imaging* 2018;**11**:1274–1284.
18. Oebel S, Dinov B, Arya A, Hilbert S, Sommer P, Bollmann A, *et al.* ECG morphology of premature ventricular contractions predicts the presence of myocardial fibrotic substrate on cardiac magnetic resonance imaging in patients undergoing ablation. *J Cardiovasc Electrophysiol* 2017;**28**:1316–1323.
19. Nucifora G, Muser D, Masci PG, Barison A, Rebellato L, Piccoli G, *et al.* Prevalence and prognostic value of concealed structural abnormalities in patients with apparently idiopathic ventricular arrhythmias of left versus right ventricular origin. A magnetic resonance imaging study. *Circ Arrhythm Electrophysiol* 2014;**7**:456–462.
20. Zorzi A, Perazzolo Marra M, Rigato I, De Lazzari M, Susana A, Niero A, *et al.* Nonischemic left ventricular scar as a substrate of life-threatening ventricular arrhythmias and sudden cardiac death in competitive athletes. *Circ Arrhythm Electrophysiol* 2016;**9**:e004229.
21. Crescenzi C, Zorzi A, Vessella T, Martino A, Panattoni G, Cipriani A, *et al.* Predictors of left ventricular scar using cardiac magnetic resonance in athletes with apparently idiopathic ventricular arrhythmias. *J Am Heart Assoc* 2021;**10**:e018206.
22. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, *et al.* International recommendations for electrocardiographic interpretation in athletes. *Eur Heart J* 2018;**39**:1466–1480.
23. DePace NL, Colby J, Hakki AH, Manno B, Horowitz LN, Iskandrian AS. Poor R wave progression in the precordial leads: clinical implications for the diagnosis of myocardial infarction. *J Am Coll Cardiol* 1983;**2**:1073–1079.

24. Augusto JB, Eiros R, Nakou E, Moura-Ferreira S, Treibel TA, Captur G, *et al.* Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: a comprehensive genotype-imaging phenotype study. *Eur Heart J Cardiovasc Imaging* 2020;**21**: 326–336.

25. Pelliccia A, Tatangelo M, Borrazzo C, Zampaglione D, Mango F, Fedele E, *et al.* Low QRS voltages and left ventricular hypertrophy: a risky association. *Eur J Prev Cardiol* 2023;**30**: 1132–1138.

26. Biffi A, Maron BJ, Verdile L, Fernando F, Spataro A, Marcello G. Impact of physical deconditioning on ventricular tachyarrhythmias in trained athletes. *J Am Coll Cardiol* 2004; **44**:1053–1058.

27. Sciarra L, Cavarretta E, Siciliani S, Sette A, Scarà A, Grieco D, *et al.* Managing athletes with palpitations of unknown origin with an external loop recorder: a cohort study. *J Sports Med Phys Fitness* 2022;**62**:554–559.

28. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Frederiksen BS, Davanlou M, *et al.* Ventricular arrhythmias and risk of death and acute myocardial infarction in apparently healthy subjects of age ≥55 years. *Am J Cardiol* 2006;**97**:1351–1357.

29. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, *et al.* Left-dominant arrhythmogenic cardiomyopathy. An under-recognized clinical entity. *J Am Coll Cardiol* 2008;**52**:2175–2187.

30. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, *et al.* Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J* 2020;**41**:1414–1427.

31. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, *et al.* Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *J Am Coll Cardiol* 2016;**68**:2440–2451.

32. Smith ED, Lakdawala MK, Papoutsidakis N, Aubert G, Mazzanti A, McCanta AC, *et al.* Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2020;**141**:1872–1884.

33. Graziano F, Cipriani A, Balla D, Bondarev S, Marra MP, Bauce B, *et al.* Evolving spectrum of arrhythmogenic cardiomyopathy: implications for Sports Cardiology. *Clin Cardiol* 2023;**46**:1072–1081.

34. Zhang L, Liu L, Kowey PR, Fontaine GH. The electrocardiographic manifestations of arrhythmogenic right ventricular dysplasia. *Curr Cardiol Rev* 2014;**10**:237–245.

35. Strauss DG, Selvester RH. The QRS complex—a biomarker that "images" the heart: QRS scores to quantify myocardial scar in the presence of normal and abnormal ventricular conduction. *J Electrocardiol* 2009;**42**:85–96.

36. Sevilla DC, Wagner NB, White RD, Peck SL, Ideker RE, Hackel DB, *et al.* Anatomic validation of electrocardiographic estimation of the size of acute or healed myocardial infarcts. *Am J Cardiol* 1990;**65**:1301–1307.

37. Strauss DG, Selvester RH, Lima JAC, Arheden H, Miller JM, Gerstenblith G, *et al.* ECG quantification of myocardial scar in cardiomyopathy patients with or without conduction defects. Correlation with cardiac magnetic resonance and arrhythmogenesis. *Circ Arrhythm Electrophysiol* 2008;**1**:327–336.

38. Wieslander B, Xia X, Jablonowski R, Axelsson J, Klem I, Nijveldt R, *et al.* The ability of the electrocardiogram in left bundle branch block to detect myocardial scar determined by cardiovascular magnetic resonance. *J Electrocardiol* 2018;**51**:779–786.

39. Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. *Heart Rhythm* 2009;**6**:S8–S14.

40. Nesti M, Perini AP, Bani R, Cartei S, Checchi L, Ricciardi G, *et al.* Myocardial scar on surface ECG: Selvester score, but not fragmentation, predicts response to CRT. *Cardiol Res Pract* 2020;**2020**:2036545.

41. Haukilahti MAE, Eranti A, Kenttä T, Huikuri HV. QRS fragmentation patterns representing myocardial scar need to be separated from benign normal variants: hypotheses and proposal for morphology based classification. *Front Physiol* 2016;**7**:1–10.

42. Galderisi M, Cardim N, D'Andrea A, Bruder O, Cosyns B, Davin L, *et al.* The multimodality cardiac imaging approach to the Athlete's heart: an expert consensus of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**:353.

43. Delise P, Mos L, Sciarra L, Basso C, Biffi A, Cecchi F, *et al.* Italian cardiological guidelines (COCIS) for competitive sport eligibility in athletes with heart disease: update 2020. *J Cardiovasc Med (Hagerstown)* 2021;**22**:874–891.

44. Corrado D, Pelliccia A, Bjornstad HH, Vanhees L, Biffi A, Borjesson M, *et al.* Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005;**26**:516–524.

45. Cavarretta E, Sciarra L, Biondi-Zoccai G, Maffessanti F, Nigro A, Sperandii F, *et al.* Age-related electrocardiographic characteristics of male junior soccer athletes. *Front Cardiovasc Med* 2022;**8**:784170.

46. Cavarretta E, Pingitore A, Peruzzi M, Sciarra L. Cardiovascular screening of master athletes: insights from the Master Athletes Screening Study. *Eur J Prev Cardiol* 2023;**30**: 884–886.

47. Morrison BN, Isserow S, Taunton J, Oxborough D, Moulson N, Warburton DER, *et al.* Masters athlete screening study (MASS): incidence of cardiovascular disease and major adverse cardiac events and efficacy of screening over five years. *Eur J Prev Cardiol* 2023; **30**:887–899.