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NEW RESEARCH PAPERS

Electrocardiographic Features Differentiating Arrhythmogenic Right Ventricular Cardiomyopathy From an Athlete's Heart

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) identify ECG parameters and features that are differentially expressed in patients with ARVC and healthy athletes; and 2) determine which ECG features are the strongest independent predictors of ARVC.

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Electrocardiographic Features Differentiating Arrhythmogenic Right Ventricular Cardiomyopathy From an Athlete's Heart

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ABSTRACT

OBJECTIVES This study sought to compare electrocardiogram (ECG) variants in athletic and arrhythmogenic right ventricular cardiomyopathy (ARVC) cohorts matched for the confounders of age, sex, and ethnicity.

BACKGROUND Anterior T-wave inversion (TWI_{V1-V4}) is a common electrocardiographic finding in both athletes and patients with ARVC, and is a frequent conundrum in the setting of pre-participation screening. J-point elevation (JPE) has been proposed as an accurate means of identifying athletes, whereas disease markers, including premature ventricular contractions (PVCs) and low-voltage signals, have been associated with ARVC.

METHODS This study examined 200 subjects with TWI_{V1-V4}, including 100 healthy athletes and 100 ARVC patients matched 1:1 for age, sex, and ethnicity (age: 21 ± 5 years for athletes vs. 22 ± 5 years for ARVC patients; 47% male; 97% Caucasian). The presence of TWI, JPE, PVCs, and left ventricular hypertrophy (LVH) were assessed.

RESULTS JPE was observed in 27% of athletes versus 16% of ARVC patients ($p = 0.09$). Thus, JPE had poor specificity (27%) and accuracy (60%) in identifying healthy athletes. In contrast, ARVC patients demonstrated a greater prevalence of precordial TWI beyond lead V_3 (34% vs. 8%; $p < 0.001$), inferior TWI (31% vs. 3%; $p < 0.001$), PVCs (18% vs. 0%; $p < 0.001$), and lower LVH scores ($S_{V1} + R_{V5}$; 19 ± 1 mm vs. 30 ± 1 mm; $p < 0.001$). These combined factors provided more reliable differentiation between health and disease (specificity 82%, accuracy 81%).

CONCLUSIONS PVCs and low QRS voltages are more prevalent among ARVC patients than athletes, whereas JPE is a relatively poor discriminator of health and disease when the confounders of age, sex, and ethnicity are considered. (J Am Coll Cardiol EP 2018;4:1613–25) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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Screening with 12-lead electrocardiography is being adopted by an increasing number of organizations to identify athletes at risk of sudden cardiac death due to a subclinical channelopathy or cardiomyopathy. One of the greatest areas of ambiguity in the interpretation of electrocardiograms (ECGs) in athletes is anterior T-wave inversion (TWI) (TWI in leads V_1 to V_4 [TWI_{V1-V4}]) because it is common in both arrhythmogenic right ventricular cardiomyopathy (ARVC) and healthy athletes (1-3). Furthermore, the 2 entities may not be mutually exclusive because endurance exercise can accelerate the ARVC phenotype, which can lead to a higher incidence of life-threatening arrhythmias (4-7). Thus, there has been a concerted effort to find a simple way of accurately differentiating between healthy athletes and patients with ARVC.

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TWI confined to leads V_1 to V_4 has been observed in up to one-quarter of endurance athletes of both sexes (1,2). It is preceded by J-point elevation (JPE) in almost one-fifth of black male athletes of African/Afro-Caribbean descent, and expert consensus guidelines now recommend that this combination of findings be considered normal among this ethnic group (8,9). Recent evidence has suggested that JPE may accurately differentiate health from ARVC in the broader athletic population with TWI_{V1-V4}, irrespective of ethnicity (10). However, these conclusions were drawn from an athletic cohort of predominantly young males of black ethnicity compared with an ARVC cohort of predominantly older male Caucasians; therefore, the confounding of age, sex, and ethnicity might not have been adequately addressed. Each of these factors has been demonstrated to influence the prevalence of JPE (1,11-17). Furthermore, there are other ECG features that are associated with ARVC that have not been well assessed in athlete populations. These include the prevalence of premature ventricular complexes (PVCs), low voltages in precordial and limb leads, and extensive TWI.

In the first study to compare athletes and ARVC subjects carefully matched for age, sex, and ethnicity, we aimed to: 1) compare the prevalence of JPE and extent of TWI in ARVC patients and healthy athletes; 2) identify novel ECG parameters that are differentially expressed between athletes and ARVC; and 3) determine which of these ECG markers are the strongest independent predictors of ARVC.

METHODS

STUDY POPULATION. The study compared a cohort of asymptomatic athletes who underwent ECG screening and an age-, sex-, and ethnicity-matched cohort of subjects diagnosed with ARVC according to the 2010 Task Force Criteria. In both groups, only individuals who: 1) had TWI ≥1 mm in at least 2 anterior ECG leads (leads V_1 to V_4); and 2) did not have a complete right (RBBB), left bundle branch block (LBBB), or pre-excitation were eligible for inclusion in the study. A CONSORT diagram illustrating recruitment of the study population is presented in **Figure 1**.

Healthy athletes. Between June 2011 and November 2015, 1,658 consecutive elite athletes aged 15 to 35 years underwent pre-participation screening that included a detailed family and personal history, physical examination, and a 12-lead ECG. The methodology and a large subset of the cohort was previously described in detail (1). Among all screened athletes, 152 had ECG evidence of TWI_{V1-V4}. These 152 athletes underwent clinical-guided investigations that included transthoracic echocardiography, stress ECG, Holter monitoring, and cardiac magnetic resonance imaging. Two athletes with TWI_{V1-V4} were subsequently diagnosed with a cardiac disorder and were thus excluded from this analysis (1 with hypertrophic cardiomyopathy, 1 with myocarditis). Thus, 150 (90 males, 60 females) ECGs from athletes were eligible for inclusion in the study.

ARVC patients. ARVC patients were ascertained from 2 large ARVC Registries: The Johns Hopkins ARVD/C Registry (Baltimore, Maryland) and the Netherlands ACM (ARVC) Registry. Registry protocols were previously described (18). From this cohort, we

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy
CI = confidence interval
ECG = electrocardiogram
JPE = J-point elevation
LBBB = left bundle branch block
LVH = left ventricular hypertrophy
OR = odds ratio
PVC = premature ventricular complex
RBBB = right bundle branch block
TWI = T-wave inversion

CVON2015-12 eDETECT). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Katja Zeppenfeld, MD, served as Guest Editor for this paper.
All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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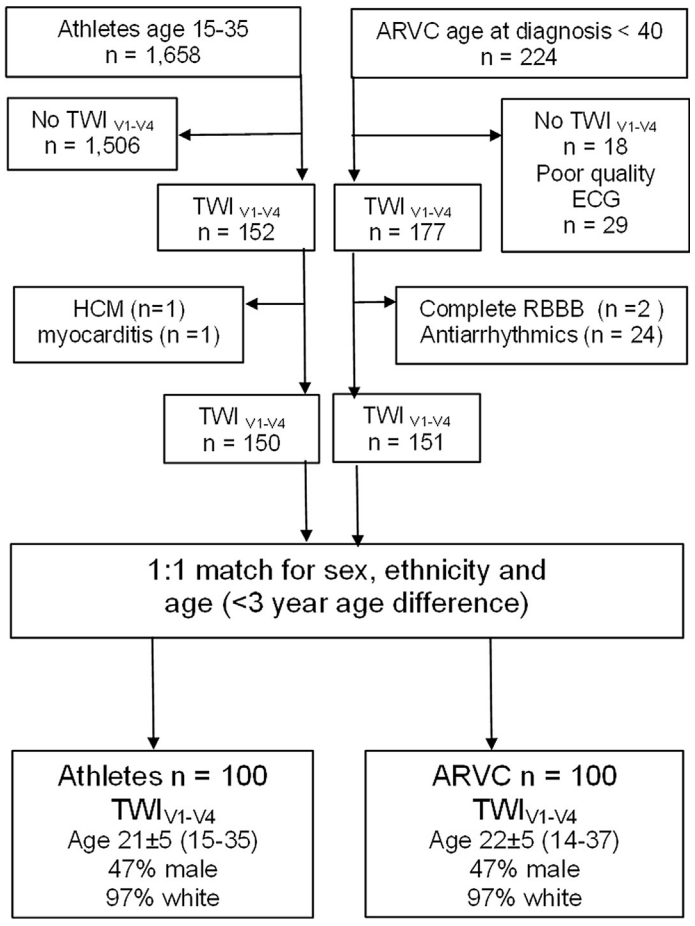
FIGURE 1 CONSORT Diagram



CONSORT diagram: selection of study population. ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; TWI_{V1-V4} = T-wave inversion ≥ 1 mm in at least 2 precordial ECG leads V_1 to V_4.

identified 224 patients diagnosed with ARVC by the 2010 Task Force Criteria who were between the ages of 15 and 40 years, among whom 177 patients had a good quality ECG available within 6 months of diagnosis that demonstrated TWI_{V1-V4}. Subsequently, 2 patients were excluded because of a complete RBBB, and 24 patients were excluded because they used class I or class III antiarrhythmic medications at the time of ECG acquisition. As a result of these exclusions, 151 ARVC patients (65 males, 86 females) were eligible for inclusion in the study. If multiple ECGs were available for the same patient, the ECG closest to the date of diagnosis was used for analysis.

Matching of the study population. A case–control study design was subsequently obtained using a 1:1 match of ARVC patients with healthy athletes for age, sex, and ethnicity. A 100% match was pursued for sex and ethnicity; for age, a difference of 3 years was allowed for matching. As shown in Figure 1, using these criteria, a total of 100 young ARVC subjects were matched to 100 healthy athletes and included in the analysis. All individuals provided informed consent, and the study was approved by the respective institutional review boards.

ECG ANALYSIS. All ECGs were performed with subjects resting in the supine position, recorded at a paper speed of 25 mm/s and 10-mm/1-mV calibration, and stored in electronic and hard copy format. Only ECG recordings while subjects were off class I, III, and IV antiarrhythmic medications, as well as medications known to affect cardiac depolarization and repolarization, were included in the study.

Standard measurements included heart rate, rhythm, QRS axis, PR interval, QT interval, and QRS duration. The QTc was calculated using Bazett's (QTc B) formula using the tangent method in lead II or lead V_5 (whichever provided the best delineation of the T-wave) (19). In addition, Sokolow-Lyon voltage criteria for left ventricular hypertrophy (LVH) (S_{V1} + R_{V5}, in millimeters) and right ventricular hypertrophy (R_{V1} + S_{V5} in mm) were measured. Pathological Q waves were considered to be present if there were Q waves in ≥2 leads, except leads III and aVR (defined as Q >40 ms in duration and/or a Q/R ratio of ≥0.25). Other ECG measures included pathological ST depression, which was defined as ≥0.5 mm in any 2 adjacent leads; an abnormal QRS axis, which was defined as QRS axis more negative than -30 degrees or more positive than 110 degrees; complete RBBB, which was defined as an rSR′ pattern in lead V_1 with a slurred S wave in lead V_6 and a QRS duration of >120 ms; and complete LBBB, which was defined as a QS or rS complex in lead V_1 and RsR′ in lead V_6, with a QRS duration of >120 ms and absence of a Q wave in leads I, aVL, and V_6. The R:S transition zone was defined as the first precordial lead (leads V_1 to V_6) in which the R-wave amplitude exceeded the S-wave amplitude. Low limb voltage was defined as a QRS amplitude of <5 mm in all limb leads. When present, the count of PVCs on each 10-s trace was also noted.

TWI_{V1-V4} was defined as the presence of TWI ≥1 mm in at least 2 ECG leads in the anterior leads V_1 to V_4. When TWI_{V1-V4} was present, the maximum T-wave depth below the isoelectric line (PR segment) was measured in millimeters in the lead of greatest negativity (Figure 2). In cases of biphasic TWI, the depth of the negative portion of the T-wave was considered. Biphasic TWI was considered to be present when part of the T-wave was above and part below the isoelectric line in any of the leads V_1 to V_4

with TWI. Inferior TWI was defined as ≥1 mm in at least 2 inferior leads (leads II, III, and aVF).

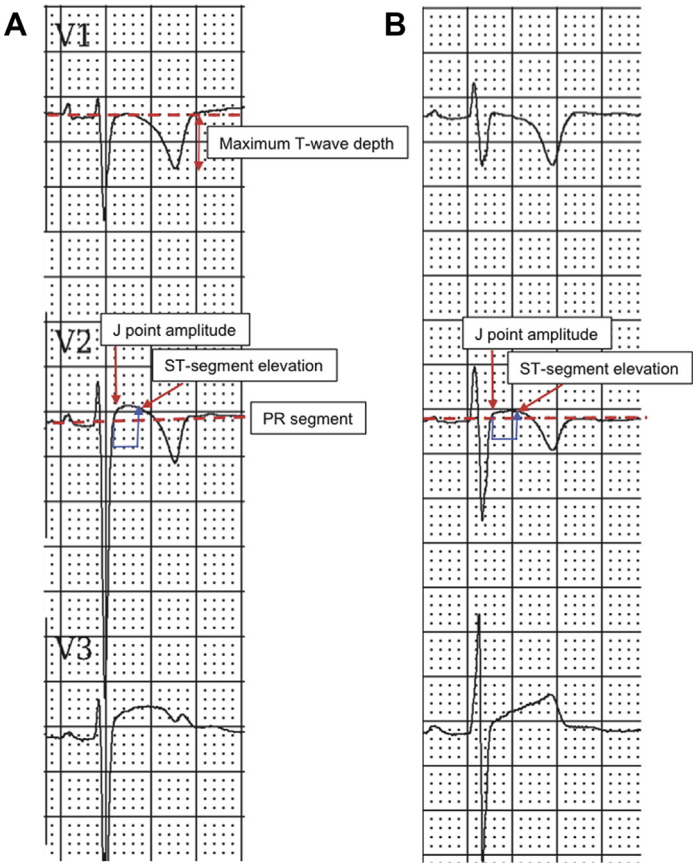
The J-point was defined as the junction between the termination of the QRS complex and the beginning of the ST segment. The amplitude of the J-point was measured using the preceding PR segment as the baseline (in millimeters, where 10 mV = 1 mm). ST-segment elevation was measured 100 ms after the merging of the J-point and the ST segment (Figure 2). According to previous studies (10), JPE was considered to be present if ≥1 mm of JPE was measured in at least 1 of the leads V_1 to V_4 in which TWI was also present. Similarly, ST-segment elevation was considered to be present if ≥1 mm of ST-segment elevation was present in at least 1 lead of leads V_1 to V_4 in which TWI was also present.

All ECGs were analyzed for the presence of $TWI_{V1–V4}$, inferior TWI, JPE, and ST-segment elevation by 2 independent observers experienced in ECG screening for ARVC (M.B. and A.T.R.). Although all of the ECGs were de-identified, true blinding from disease status was not possible because of other features, such as machine type or age of the trace. In cases of disagreement, consensus was obtained from a third cardiologist (A.L.G.).

STATISTICAL ANALYSIS. Values are displayed as mean ± SD and as number (percentage), as appropriate. Continuous variables were compared between groups using independent sample *t*-tests and categorical variables using the chi-square test or the Fisher exact test, when appropriate. Univariable logistic regression analysis was performed to assess demographic and ECG predictors of JPE and to determine ECG predictors of ARVC disease status. Variables with a p value <0.15 at univariable analysis were selected for multivariable conditional logistic regression analysis. A backward selection method with an exclusion criterion of p ≥0.10 was used. All analyses were performed using SPSS version 21 software (IBM, Armonk, New York). A p value of <0.05 was considered significant throughout.

Diagnostic performance. The diagnostic performance of JPE and pre-defined ECG markers of interest (extensive TWI, PVCs, and LVH score) were expressed as sensitivity and/or specificity and accuracy. In addition, the diagnostic performance of the previously proposed Calore et al. (10) criteria (combination of JPE and TWI confined to leads V_1 to V_4) was specifically evaluated. For LVH score, receiver-operating characteristic analysis was performed to determine the LVH score (in millimeters) with the best predictive value for disease status.

FIGURE 2 Methodology for Measurement of J-Point Amplitude, ST-Segment Elevation, and T-Wave Depth



All measurements were made with reference to the baseline (PR segment) and expressed in millimeters, where 1 mm = 1 mV and 40 ms. ST-segment elevation was measured 100 ms after the J-point. **(A)** Athlete electrocardiographic example with T-wave inversion in lead V_2 with associated J-point and ST-segment elevation of >1 mm. **(B)** Athlete electrocardiographic example of T-wave inversion in lead V_2 with <1 mm of J-point elevation and 1 mm of ST-segment elevation.

Interobserver reproducibility. Interobserver reproducibility analyses were performed using the κ statistic to determine consistency for interpretation of the presence of $TWI_{V1–V4}$, JPE, ST-segment elevation, and inferior lead TWI. A κ value of > 0.61 was categorized as substantial agreement, and κ >0.81 was categorized as excellent agreement (20).

RESULTS

SUBJECT CHARACTERISTICS. Demographic and ECG characteristics of the 100 healthy athletes with $TWI_{V1–V4}$ and 100 ARVC subjects with $TWI_{V1–V4}$ are outlined in Table 1. By study design, the groups were matched for age (21 ± 5 years for athletes vs. 22 ± 5 years for ARVC patients), sex (both groups 47%

TABLE 1 Comparison of Demographics and ECG Findings Between Subjects With ARVC and Healthy Athletes Both With $TWI_{V1–V4}$

	ARVC (n = 100)	Healthy Athletes (n = 100)	p Value
Age, yrs	22 ± 5 (14–37)	21 ± 5 (15–35)	0.35
Sex (male)	47 (47)	47 (47)	1.00
Ethnicity (white)	97 (97)	97 (97)	1.00
Heart rate (beats/min)	60 ± 11	56 ± 10	0.01
PR interval (ms)	148 ± 29	155 ± 23	0.04
QRS duration (ms)	91 ± 11	95 ± 11	0.03
QTcB (ms)	429 ± 26	399 ± 29	<0.001
Axis (degrees)	56 ± 44	72 ± 19	0.001
Abnormal axis	11 (11)	1 (1)	0.01
iRBBB	13 (13)	39 (39)	<0.001
Sokolow-Lyon LVH (mm)	19 ± 1	30 ± 1	<0.001
Sokolow-Lyon score ≥35 mm	5 (5)	24 (24)	<0.001
Sokolow-Lyon RVH (mm)	4 ± 3	4 ± 3	0.47
Low limb lead voltage	21 (21)	1 (1)	<0.001
Q waves	2 (2)	0 (0)	0.50
R:S transition	V_4 ± 1	V_4 ± 1	0.35
J-point elevation			
≥1 mm	16 (16)	27 (27)	0.09
≥2 mm	2 (2)	20 (20)	<0.001
ST-segment elevation			
≥1 mm	21 (21)	41 (41)	0.002
≥2 mm	4 (4)	21 (21)	<0.001
ST-segment depression	4 (4)	0 (0)	0.12
Negative T waves (leads)			
V_1–V_2 only*	14 (14)	62 (62)	<0.001
V_3	34 (34)	30 (30)	0.65
V_4	32 (32)	8 (8)	<0.001
V_5	5 (5)	0	0.06
V_6	15 (15)	0	<0.001
Inferior TWI	31 (31)	3 (3)	<0.001
Maximal depth TWI	3.8 ± 2	3.3 ± 1	0.04
TWI depth ≥5 mm	8 (8)	14 (14)	0.26
Biphasic TWI	21 (21)	18 (18)	0.72
Premature ventricular complexes			
At least 1	18 (18)	0	<0.001
At least 2	8 (8)	0	0.01

Values are mean ± SD (range) or n (%). *T-wave inversion (TWI) isolated to leads V_1 to V_2 only.

ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiography; iRBBB = incomplete right bundle branch block; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; $TWI_{V1–V4}$ = T-wave inversion ≥1 mm in at least 2 precordial ECG leads V_1 to V_4.

male), and ethnicity (both groups 97% white). All ARVC subjects fulfilled 2010 diagnostic criteria for ARVC at time of ECG collection. A pathogenic gene variant was identified in 77 (77%) of the ARVC subjects, and 22 (22%) were on beta-blockers at the time of ECG collection. No individual used class I, III, or IV antiarrhythmic medications.

COMPARISON OF ECG FINDINGS IN HEALTHY ATHLETES AND ARVC SUBJECTS. A comparison of ECG findings in healthy athletes and ARVC subjects is provided in Table 1. Compared with healthy athletes, ARVC subjects had higher heart rates, shorter PR intervals, shorter QRS duration, longer corrected QT intervals, higher prevalence of an abnormal QRS axis, lower prevalence of incomplete right bundle branch block (iRBBB), and lower voltage scores for LVH. Voltage scores for right ventricular hypertrophy, and R:S transition zone were similar between athletes and ARVC subjects, and biphasic TWI was observed with a similar prevalence in both groups.

AIM 1: COMPARISON OF J-POINT AND ST-SEGMENT ELEVATION IN HEALTHY ATHLETES AND ARVC SUBJECTS. As shown in Table 1, there was no significant difference in the overall prevalence of JPE ≥1 mm between the athletes and ARVC subjects (27% vs. 16%, respectively; p = 0.09). However, when JPE was present, it tended to be more marked in the athletes than the ARVC subjects (J-point ≥2 mm: 20% vs. 2%, respectively; p < 0.001). Both of the ARVC patients with JPE ≥2 mm were athletes (1 a long-distance runner, the other a competitive swimmer). ST-segment elevation ≥1 mm, as well as marked ST-segment elevation (≥2 mm) was also observed with higher prevalence in athletes than in ARVC subjects (41% vs. 21% for elevation ≥1 mm; p = 0.002, and 21% vs. 4% for elevation ≥2 mm; p < 0.001, respectively). Overall, 8 of 41 (20%) athletes and 3 of 21 (14%) ARVC subjects with ST-segment elevation did not demonstrate JPE (p = 0.73). The ECGs from the 16 ARVC patients with JPE are provided as a supplement to the on-line version of this paper (Online Appendix).

When males were considered separately, male athletes demonstrated a greater prevalence of JPE than male ARVC subjects (22 of 47 [47%] vs. 11 of 47 [23%]; p = 0.03). The prevalence of JPE was similarly low in both female athletes and female ARVC subjects (5 of 53 [9%] vs. 3 of 53 [6%], respectively; p = 0.72). Both JPE ≥1 mm (35 of 94 [37%] vs. 8 of 106 [8%]; p < 0.001) and ST-segment elevation ≥1 mm (43 of 94 [46%] vs. 19 of 106 [18%]; p < 0.001) were more prevalent in male subjects versus female subjects.

Table 2 shows predictors of JPE using univariable and multivariable logistic regression analyses. Univariable analysis confirmed the association between male sex and JPE (odds ratio [OR]: 7.3; 95% confidence interval [CI]: 3.2 to 16.7; p < 0.001). Although athletic status was not significantly associated with JPE (p = 0.06), predictors of JPE were LVH score (p < 0.001) and a lower heart rate (p = 0.002). At multivariable conditional logistic regression, a trend remained visible for the association between LVH score and JPE (p = 0.06).

The fact that JPE ≥1 mm was similarly prevalent in the athletes and ARVC subjects had implications for the accuracy of the Calore et al. (10) criteria (combination of JPE and TWI confined to leads V_1 to V_4) (Figure 3). In 73 (73%) athletes, TWI was confined to leads V_1 to V_4, but JPE was absent, which corresponded to an incorrect classification of suspected ARVC by the Calore et al. (10) criteria. Therefore, the specificity of the Calore et al. (10) criteria was relatively poor at 27%. Conversely, 8 (8%) ARVC patients had TWI confined to leads V_1 to V_4 with concomitant JPE, which corresponded to an incorrect classification of normal on the basis of the algorithm proposed by Calore et al. (10). Figure 4C provides a representative example of an ECG of an ARVC subject that would have been incorrectly classified as healthy. The combination of these findings led to an accuracy of 60% for the Calore et al. (10) criteria.

AIM 2: IDENTIFY NOVEL ECG PARAMETERS THAT ARE DIFFERENTIALLY EXPRESSED BETWEEN ATHLETES AND ARVC. Extensive TWI (extending beyond lead V_3) was less common in athletes than in ARVC subjects (8% vs. 52%; $p < 0.001$) (Table 1). Precordial TWI beyond lead V_4 was not observed in any athlete but was seen in 20% of subjects with ARVC ($p < 0.001$). Inferior TWI was rare in athletes compared with ARVC subjects (3% vs. 31%; $p < 0.001$). Maximum T-wave depth was greater in the ARVC patients versus athletic patients (3.8 mm vs. 3.3 mm; $p = 0.039$); however, profound (≥5 mm depth) TWI was seen with similar prevalence in both groups.

PVCs were not observed in any of the athletes compared with 18% of ARVC subjects ($p = 0.002$) (Table 1). Ten ARVC subjects had a single PVC, and 8 subjects had multiple PVCs (range 2 to 6) on a 10-s ECG recording.

Voltage scores for LVH were higher in athletes compared with ARVC patients (30 ± 1 mm vs. 19 ± 1 mm; $p < 0.001$) (Table 1). Low limb lead voltages were observed in only 1 (1%) athlete but were observed in 21 (21%) ARVC subjects ($p < 0.001$). A strong association between LVH score and low limb lead voltages was identified, with an LVH score in those with low limb lead voltages of 1.4 ± 0.7 mm versus 2.6 ± 1.0 mm in those without ($p < 0.001$). An LVH score of <20 mm was identified as the optimal cutoff for differentiating between athletes and ARVC subjects after receiver-operating characteristic analysis, with a sensitivity of 84% and specificity of 63% (area under the curve: 0.815).

To address whether ECG variables could discriminate between athletic ARVC patients and healthy athletes, we evaluated exercise participation data on 33 ARVC patients who underwent a structured telephone or in-person interview. Overall, 30 of 33 (91%) of these subjects were considered class C athletes, which was defined as participation in vigorous intensity endurance athletics (>70% maximum oxygen; class C athletics as defined by the 36th Bethesda Conference Classification of Sports) for at least 50 h/year. ARVC athletes had similar features with the overall ARVC population; consequently, distinguishing features between ARVC athletes and healthy athletes were similar. Although JPE

TABLE 2 Univariable and Multivariable Logistic Regression Analysis for Predictors of the Presence of JPE ≥1 mm

	Univariable Model		Multivariable Model	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
Male	7.3 (3.2–16.7)	<0.001	*	*
Age (yrs)	1.0 (0.9–1.1)	0.35	*	*
Non-Caucasian ethnicity	3.9 (0.8–19.8)	0.11	*	*
LVH score (cm)	3.3 (2.1–4.9)	<0.001	1.9 (0.9–3.8)	0.06
Heart rate (beats/min)	0.94 (0.91–0.98)	0.002	0.98 (0.92–1.05)	0.60
Athlete	1.9 (0.9–3.9)	0.06	1.0 (0.4–2.7)	1.00

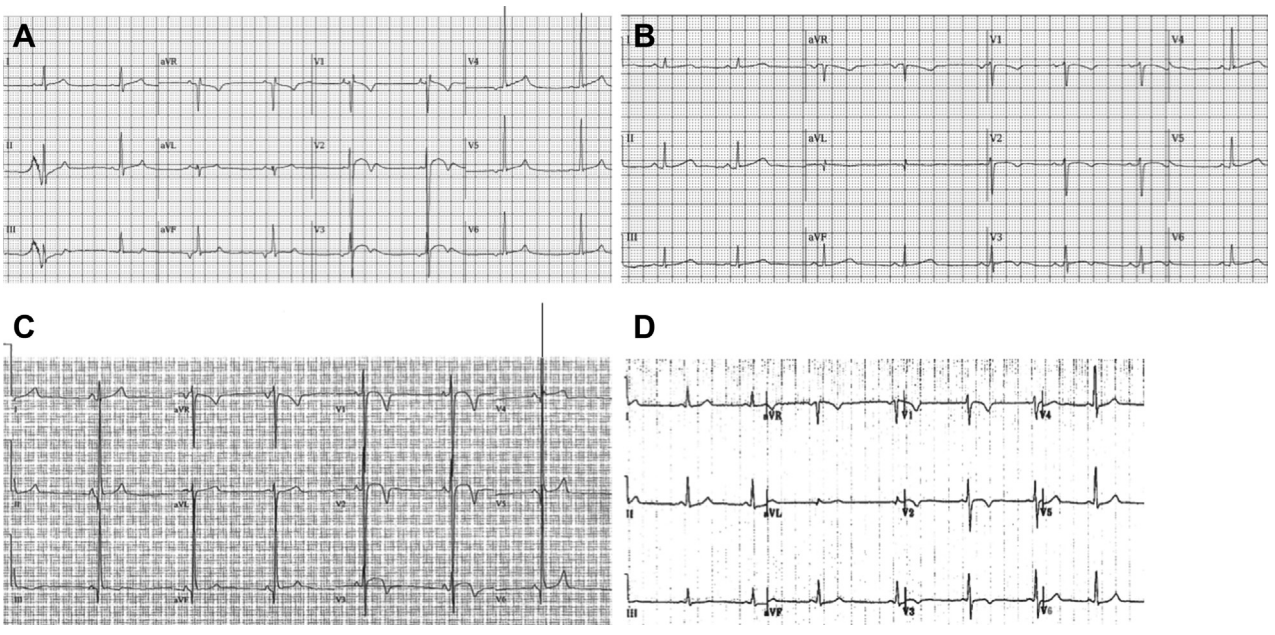
*Age, sex, and ethnicity were not entered in the multivariable conditional logistic regression because groups were matched on these variables.

CI = confidence interval; JPE = J-point elevation; other abbreviation as in Table 1.

FIGURE 3 Diagnostic Accuracy of the Calore et al. (10) Criteria (<1 mm JPE and/or TWI beyond lead V_4) in Identifying Patients With ARVC

Applying this algorithm, 73% of athletes were incorrectly classified as having suspected ARVC, and 8% of subjects with ARVC were incorrectly classified as being normal. The overall accuracy of the proposed algorithm was 60%. JPE = J-point elevation ≥1 mm in at least 1 lead in leads V_1 to V_4 demonstrating TWI-wave inversion; +ve = positive; −ve = negative; other abbreviations as in Figure 1.

FIGURE 4 Representative ECG Examples



ECGs from **(top)** 2 healthy athletes and **(bottom)** 2 ARVC patients. **(A)** ECG from 23-year-old male cross-country ski athlete demonstrating TWI in leads V_1 to V_3 with J-point elevation. Incidental note is made of low atrial rhythm (a normal variant). **(B)** ECG from 16-year-old female rower demonstrating TWI in leads V_1 to V_3 without J-point elevation. **(C)** ECG from 16-year-old male ARVC patient who was a competitive swimmer demonstrating TWI in leads V_1 to V_3 with J-point elevation. **(D)** ECG from 20-year-old female ARVC patient subject who played collegiate soccer demonstrating TWI in leads V_1 to V_3 without J-point elevation. Abbreviations as in Figure 1.

≥1 mm and ST-segment elevation ≥1 mm were not significantly different in ARVC athletes compared with healthy athletes, low limb voltage and/or LVH scores, inferior lead TWI, and presence of PVCs significantly distinguished the 2 groups ($p < 0.0001$). These comparisons are presented in Online Table 1.

TABLE 3 Univariable and Multivariable Logistic Regression Analysis for Predictors of ARVC Disease Status

	Univariable Model		Multivariable Model	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
TWI > V_3 or inferior	10.7 (5.1–22.5)	<0.001	8.2 (2.5–26.9)	<0.001
PVCs (≥1)	21.7 (2.8–166)	0.003	26.9 (1.7–427)	0.02
LVH score <20 mm	11.0 (5.1–23.6)	<0.001	11.6 (3.1–43.4)	<0.001
LVH score (cm)	0.3 (0.2–0.4)	<0.001	*	*
Low limb lead voltages	26.3 (3.4–199)	0.002	*	*
JPE <1 mm	1.9 (0.9–3.9)	0.06	2.9 (0.9–9.9)	0.09

*LVH score <20 mm, continuous score for LVH and low limb lead voltages were strongly correlated, among which a LVH score of <20 mm was most strongly associated with disease status. Therefore, only a LVH score of <20 mm rather than a continuous LVH score and low limb lead voltages was considered in the multivariable regression analysis.

LVH score = sum of S_{V1} and R_{V5} (in centimeters); TWI > V_3 or inferior = T-wave inversion beyond precordial lead V_3 (into leads V_4 to V_6, I, aVL) and/or in ≥2 inferior leads (II, III, aVF); PVCs = premature ventricular complexes; other abbreviations as in Tables 1 and 2.

AIM 3: IDENTIFY THE STRONGEST INDEPENDENT ECG PREDICTORS OF ARVC. Table 3 shows the association between ECG characteristics and ARVC disease status derived from univariable and multivariable logistic regression analyses. For univariable analysis, all alternative ECG characteristics (extensive TWI, PVCs, LVH score, and low limb lead voltages) were significantly associated with ARVC disease status, whereas JPE showed a trend. In multivariable conditional logistic regression, TWI beyond lead V_3 or in inferior leads (OR: 8.2; 95% CI: 2.5 to 26.9; $p < 0.001$), presence of PVCs (OR: 26.9; 95% CI: 1.7 to 42.7; $p = 0.02$), and LVH score <20 mm (OR: 11.6; 95% CI: 3.1 to 43.4 ± 1; $p < 0.001$) were independent predictors of ARVC disease status (Table 3). The combination of TWI beyond lead V_3 or inferior, PVCs, and/or LVH score <20 mm had an overall sensitivity of 80%, specificity of 82%, and accuracy of 81% for ARVC disease status.

INTEROBSERVER VARIABILITY IN ELECTROCARDIOGRAPHIC INTERPRETATION. Interobserver agreement on the presence of JPE and ST-segment elevation was substantial ($\kappa = 0.687$ and $\kappa = 0.662$, respectively) and excellent for inferior TWI ($\kappa = 0.821$). There was 99% agreement on the presence of

TABLE 4 Interobserver Agreement in ECG Interpretation

	Agreement	κ	p Value
JPE	178 (89)	0.687	<0.0001
ST-segment elevation	172 (86)	0.662	<0.0001
Inferior TWI	191 (96)	0.821	<0.0001
$TWI_{V1–V4}$	197 (99)	0.566	<0.0001

Values are n (%).
Abbreviations as in Tables 1 and 2.

$TWI_{V1–V4}$, which translated into only moderate agreement (κ = 0.566) due to the sensitivity of the κ score to low prevalence disagreement in high prevalence conditions (Table 4).

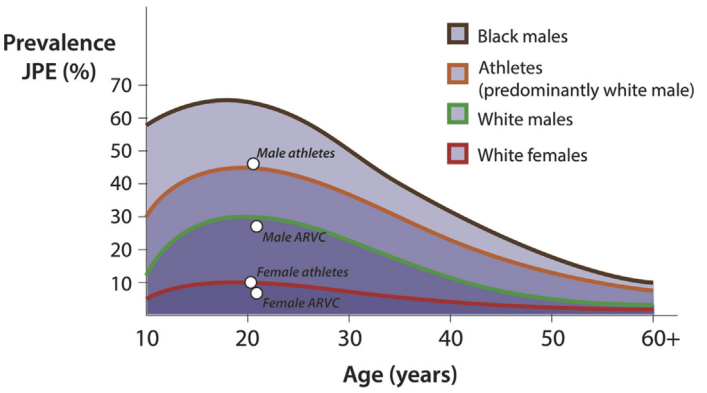
DISCUSSION

Our study confirmed that the presence or absence of JPE did not reliably discriminate between pathological and physiological anterior TWI for ARVC evaluation in subjects of similar age, sex, and ethnicity. Rather, we identified 3 alternative ECG markers (extensive TWI [beyond lead V_3 and/or inferior], the presence of PVCs, and Sokolow-Lyon LVH score <20 mm) that were independent predictors of disease status. In athletes and ARVC subjects with $TWI_{V1–V4}$, these 3 combined ECG features differentiated health from disease with 81% accuracy.

LIMITED ROLE OF JPE FOR DIFFERENTIATING BETWEEN ARVC SUBJECTS AND HEALTHY ATHLETES. We observed JPE preceding TWI in only 27% of the athletes (47% of males and 9% of females). Thus, more than one-half of the male athletes and 90% of the female athletes in our study would not have been differentiated from ARVC on the basis of the algorithm proposed by Calore et al. (10), who observed JPE in 80% in their athletic cohort. In the present study, almost all of the athletes were white and approximately half were female, whereas 66% of the athletes studied by Calore et al. were black, and 75% were male. The prevalence of JPE in the anterior leads was consistently observed, with a greater prevalence in blacks versus whites, and male subjects versus female subjects (as shown in Figure 5). A prevalence of anterior JPE in 63% of black male soccer players versus 33% of white male soccer players was observed by Biasco et al. (21). We previously observed that the prevalence of JPE in any lead (including leads V_1 to V_4) in male athletes was almost twice that of female athletes of similar age (1). Similarly, marked sex-related differences in nonathletic cohorts were reported, with JPE up to 5 times more prevalent in male subjects versus female subjects (14,17,22). Consistent with these studies, we observed that JPE was 4 times more common in male subjects versus female subjects. Thus, the marked differences in prevalence of JPE in the athlete cohort in the present study compared with that of the Calore et al. (10) criteria can be largely accounted for by differences in sex and ethnicity. The most recent International Recommendations for ECG interpretation in athletes (9) considers JPE combined with TWI in black athletes to be common and therefore unlikely to represent ARVC. Although this seems appropriate, the data presented here suggested that this recommendation should not be expanded to athletes of all races.

Another important confounder in the appraisal of JPE was age. We observed a much greater prevalence of JPE preceding $TWI_{V1–V4}$ among ARVC subjects than that seen in the Calore et al. (10) study (16% compared with 2%); this might be explained by the substantial differences in the ages of the subjects between the 2 studies. As shown in Figure 5, previous research demonstrated that the association between age and JPE was not linear, with prevalence peaking in the second decade of life and declining sharply thereafter

FIGURE 5 Prevalence of JPE in Leads V_1 to V_4 According to Age, Sex, and Ethnicity



The **colored lines** represent the reported prevalence in black males, athletes (predominantly white males), white males (non-athletes), and white females according to age; because of the limited data on black females and female athletes, these groups are not represented. The **open white circles** represent the observed prevalence of JPE in the athlete and ARVC cohorts in the present study. By study design, the athlete and ARVC groups were of similar age and ethnicity. The reported data in the literature show that prevalence of JPE peaks in the second decade of life and declines thereafter, with a greater prevalence in athletes versus non-athletes reported (7,10,13–16). It is up to 5 times more prevalent in males than females, and most common in males of black African/Afro-Caribbean descent (9,10,14,15,17). Observed data in the present study showed that male athletes had a greater prevalence of JPE than male ARVC subjects (47% vs. 23%; p = 0.03), whereas the prevalence of JPE in the female athlete and ARVC groups was similarly low (9% vs. 6%; p = 0.72). Abbreviations as in Figures 1 and 3.

(1,8,12,21-23). JPE is common among young people, especially young males, regardless of disease status. The assertion that TWI preceded by JPE might be considered a benign trait raises significant concern. In the present study, JPE was seen in almost one-quarter of young male subjects with ARVC, and in 8% of subjects, TWI_{V1-V4} was the only ECG abnormality; thus, these young subjects with proven ARVC would have been falsely assured of being disease free.

SIGNIFICANT ROLE FOR NOVEL ECG PREDICTORS OF DISEASE STATUS. We identified 3 ECG markers that were effective at differentiating ARVC subjects from athletes matched for age, sex, and ethnicity: TWI extending beyond lead V_3, the presence of PVCs, and LVH voltage score <20 mm. It was not surprising that the extent of TWI was identified as a significant predictor of disease in our study. Diffuse TWI is a well-established marker of disease severity in ARVC (24-26). Furthermore, TWI beyond lead V_3 is uncommon in the general population (27) and in athletes (1-3) but occurs in a significant subset of ARVC patients (25,28,29). Thus, it is to be expected that the specificity for underlying myocardial pathology will increase with more extensive TWI. This is already recognized among contemporary recommendations for ECG interpretation in which TWI beyond lead V_2 should evoke consideration of potential disease.

Isolated PVCs were common among the ARVC patients in our study. In contrast, not a single PVC was observed among the 100 athlete ECGs. Others also reported the rarity of isolated PVCs in healthy athletes compared with subjects with ARVC (3). The ECG and clinical manifestations of ARVC in young subjects with a mean age of 15 years were described by Te Riele et al. (28), who reported that TWI isolated to leads V_1 to V_3 and frequent PVCs on Holter monitoring were the most commonly observed electrical manifestations of the disease, seen in approximately three-quarters of young ARVC subjects. Because this is the age at which pre-participation screening generally commences, ventricular ectopy may be a more sensitive marker of early disease than other ECG criteria in this age group. The striking association between PVCs and ARVC (100% specificity) in this derivation cohort likely represented an over estimate and would not be expected to hold true in the general athletic population. However, it did raise questions as to whether PVCs should be dismissed as benign in athletes with an otherwise normal ECG. Current ECG screening recommendations for athletes suggest that 1 PVC on a 12-lead ECG does not warrant further evaluation (9). We would argue that there is a need to validate the potential association between PVCs and structural heart disease in a larger cohort of athletes undergoing screening because our preliminary experience suggested that it was a robust red flag as many other ECG changes that currently prompt further investigations for underlying cardiac pathology.

Isolated voltage criteria for LVH is widely accepted as a reflection of healthy adaptation to exercise in athletes, and as such, is considered a normal finding in current athlete ECG interpretation criteria (9). The lower voltage scores observed in subjects with ARVC may reflect an underlying disease process, such as ventricular dilatation and fibro-fatty replacement of myocardium. Low QRS voltages have been associated with diffuse myocardial fibrosis as assessed by an elevated myocardial extracellular volume fraction with cardiac magnetic resonance imaging (30) and with more advanced right ventricular pathological remodeling (31). Although not specific for ARVC, and subject to influence of factors, including body habitus (32), low limb or precordial lead voltages may be a useful potential marker of underlying myocardial disease, particularly when seen in combination with other ECG abnormalities, such as TWI and PVCs.

CLINICAL IMPLICATIONS. ECG evaluation is being incorporated into pre-participation screening of athletes with increasing frequency. Precordial TWI is prevalent in both endurance athletes and those with ARVC, and this diagnostic overlap continues to be one of the limitations in ECG interpretation. Thus, there is great interest in identifying additional ECG markers that may assist in further differentiation. Our study was the first to compare sizeable cohorts of ARVC and athletic subjects who were carefully matched to exclude confounding from age, sex, and ethnicity. This enabled us to clarify recent contentions and establish that JPE is not useful in distinguishing health from disease. The current international guidelines for athlete ECG interpretation argue that precordial TWI associated with J-point and ST-segment elevation can be considered a normal variant in athletes of Afro-Caribbean ethnicity and that there is no need for further investigations. We were unable to confirm or refute this because our cohort of ARVC patients included mostly Caucasian subjects. This ethnic disparity was representative of the larger ARVC populations at Johns Hopkins and the Netherlands Heart Institute. It was also consistent with the world-wide experience in which ARVC

genetic mutations, and particularly in those with the plakophilin (PKP-2) gene, appear to have a common European founder. This might explain why ARVC appears to be far less prevalent among black populations. For example, Watkins et al. (33) reported that ARVC was 10 times more common among white South Africans despite the reverse in the ethnic representation in that country, which again identified common mutations and allele segregation that suggested a common founder effect. In contrast, it was possible that these observations reflected disparities in health access, which led to under-diagnosis in black populations. We were unable to address these issues in our study and were confined by the demographics of the ARVC cohorts at our institutions. Thus, our findings should not be generalized to other ethnic groups, and, particularly, should not be generalized to athletes of Afro-Caribbean descent in whom precordial TWI is particularly prevalent (8,34,35).

Although we found JPE and ST elevation to be poorly predictive in our population, we were able to identify 3 novel ECG markers that might be useful in distinguishing between athletes and ARVC. Two of these criteria, PVCs and low voltage scores, are not considered as possible markers of disease in the current international guidelines. We would argue that this should be re-considered.

Although most ARVC subjects in the present study had multiple ECG abnormalities, it is important to note that 14% had TWIs isolated to leads V_1 to V_2, and another 3% aged younger than 16 years had TWI isolated to leads V_1 to V_3 as a solitary ECG abnormality. These subjects would thus be considered normal if subjected to ECG screening in the context of sports participation (9). Because of the low community prevalence of ARVC of ~1:5,000, many thousands of athletes would need to be screened for these missed diagnoses to become apparent. There has been a concerted push to refine ECG interpretation to minimize the burden of false positives (36). Our data would suggest that some additional cases of ARVC might be missed as a consequence. Although these cases are likely to be few, and may be considered acceptable against the potential harm associated with false positives in the setting of screening asymptomatic athletes, it is pertinent to remember that so-called benign ECG features associated with athletic training should not provide reassurance when the pre-test probability is high, such as in the assessment of young athletes with symptoms, arrhythmias, a positive family history, or a known pathogenic variant.

STUDY LIMITATIONS. To the best of our knowledge, this study represented the largest cohort of age-, sex-, and ethnicity-matched ARVC patients and athletes. As discussed previously, our institutional cohorts of ARVC included mostly Caucasian subjects, and our results should not be generalized to other ethnic groups. It seems reasonable to argue that it was not possible to anticipate the predictive value of ECG screening in ethnic groups in which there is a limited understanding of the population prevalence of disease. This was not only a limitation of this study but also of the process of athletic screening in general. Sporting authorities are recommending screening athletes of all racial groups despite our limited knowledge about ECG variants, as well as potential differences in disease and the prevalence of sudden death.

Matching for exercise participation was unfortunately not possible because in-depth exercise interviews were not available for all ARVC subjects. ECG findings of RV and LV morphology among ARVC patients who were avid exercisers might differ considerably from the general ARVC population included in our present analysis. This represented an essential element of future work. JPE and ST-segment elevation had moderate reproducibility, which suggested that the clinical use of these parameters was limited, regardless of their predictive value.

CONCLUSIONS

The prevalence of JPE is influenced by age, sex, and ethnicity, and is not an adequately specific finding to be useful in ECG screening of athletes. In contrast, TWI, spontaneous PVCs, and low QRS voltages were more strongly associated with ARVC, and it could be argued that the absence of these novel markers was of sufficiently robust negative predictive value to be useful for screening. The latter 2 of these 3 markers are not currently considered in criteria for differentiation between the heart and pathology in athletes. Our data would argue for their inclusion in future revisions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There is considerable overlap in ECG features among athletes and patients with ARVC. This presents a significant challenge for screening strategies in which ECG variants are common among athletes (especially endurance athletes), whereas the community prevalence of ARVC is decidedly uncommon. Thus, highly predictive ECG markers are necessary to ensure that ECG screening strategies do not result in inappropriate investigations and incorrect diagnoses.

TRANSLATIONAL OUTLOOK: PVCs and low ECG voltages are relatively common among ARVC patients but rare among athletes, whereas JPE is similarly prevalent. While these features were able to differentiate between these 2 groups with reasonable accuracy, these markers might be expected to perform less well when screening unselected athletic populations with lower disease prevalence. Thus, although these novel ECG criteria may assist in refining the diagnostic accuracy of ECG criteria, there are no features that are expected to entirely circumvent the underlying fact that there are multiple similarities between the ECGs of athletes and ARVC patients.

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KEY WORDS arrhythmogenic right ventricular cardiomyopathy, athlete, ECG, pre-participation screening, T-wave inversion

APPENDIX For the supplemental table and the ECGs of all 16 ARVC patients with J-point elevation, please see the online version of this paper.

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