

Electrocardiographic Features of Arrhythmogenic Right Ventricular Dysplasia

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Background—The purpose of this study was to reevaluate the ECG features of arrhythmogenic right ventricular dysplasia (ARVD). The second objective was to evaluate the sensitivity and specificity of the standard and newly proposed diagnostic ECG markers in the presence of a right bundle-branch block (RBBB).

Methods and Results—One hundred patients with ARVD (57 men; aged 39 ± 15 years) and 57 controls (21 men; aged 40 ± 17 years) were included. Among the 100 patients with ARVD, a complete RBBB was present in 17 patients, and 15 patients had an incomplete RBBB. T-wave inversion through V_3 demonstrated optimal sensitivity and specificity in both ARVD patients without a complete RBBB or incomplete RBBB (71% [95% confidence interval, 58% to 81%] and 96% [95% confidence interval, 81% to 100%], respectively) and in ARVD patients with incomplete RBBB (73% [95% confidence interval, 45% to 92%] and 95% [95% confidence interval, 77% to 100%], respectively). Between ARVD patients and controls with a complete RBBB, the only 2 parameters that differed were the prevalence of T-wave inversion through V_4 (59% versus 12%, respectively; $P < 0.05$) and an r'/s ratio in $V_1 < 1$ (88% versus 14%, respectively; $P < 0.005$). In ARVD patients with complete RBBB, the most sensitive and specific parameter was an r'/s ratio < 1 .

Conclusions—We evaluated comprehensively the diagnostic value of ECG markers for ARVD. On the basis of the findings, we propose an algorithm, with examination of QRS morphology being the first step, for ECG evaluation of ARVD patients. Definite criteria are then applied on the basis of the presence of no RBBB, incomplete RBBB, and complete RBBB to obtain the best diagnostic utility of the ECG. (*Circulation*. 2009;120:477-487.)

Key Words: arrhythmogenic right ventricular cardiomyopathy ■ arrhythmogenic right ventricular dysplasia ■ right bundle-branch block

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy characterized clinically by right ventricular (RV) dysfunction and ventricular arrhythmias of RV origin.^{1,2} The pathological hallmark of ARVD is fibrofatty replacement of the RV myocardium.^{1,3,4} The most common genetic abnormality identified in patients with ARVD is a mutation in 1 or more desmosomal proteins.⁵⁻⁹

Clinical Perspective on p 487

Marcus et al¹ initially described the ECG features of ARVD >25 years ago. Subsequently, the Task Force of the Working Group on Myocardial and Pericardial Diseases of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology included several ECG features of the disease in the diagnostic criteria for ARVD.¹⁰ The ECG parameters included in these diagnostic criteria include T-wave inversion (TWI) in right precordial leads (V_2 and V_3), a prolonged QRS >110 ms in the right precordial leads, and

the presence of an epsilon wave. Since publication of these criteria, several studies have proposed new ECG markers of ARVD that focus on the presence of evidence for delayed RV activation in the right precordial leads. These include the presence of parietal block,¹¹ a delayed S-wave upstroke ≥ 55 ms in leads V_1 through V_3 ,¹² an increased ratio of the QRS duration (DRSd) in the right versus the left precordial leads,^{13,14} and prolonged terminal activation duration (TAD) in leads V_1 through $V_3 \geq 55$ ms.¹⁵ One unusual feature of the Task Force criteria for ARVD is that it is unclear in regard to whether they can be applied to patients with a complete right bundle-branch block (RBBB) (CRBBB). The Task Force criteria specifically state that the TWI criteria cannot be applied to ARVD patients with a RBBB. However, the criteria do not make it clear whether the depolarization criteria of a QRSd in $V_1 > 110$ ms or the presence of an epsilon wave can be used for diagnosis of ARVD in a patient with a RBBB pattern.

The purpose of this study was to reevaluate the ECG features of ARVD. Particular attention is focused on determining the sensitivity and specificity of the newly proposed

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Received December 1, 2008; accepted June 1, 2009.

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The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.838821/DC1>.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.108.838821

Table 1. Clinical Characteristics and Task Force Criteria* of Patients With ARVD

Characteristics	ARVD Without CRBBB/IRBBB (n=68)	ARVD With IRBBB (n=15)	ARVD With CRBBB (n=17)	ARVD (Overall) (n=100)
Clinical characteristics				
Age	39±16	38±11	43±14	39±15
Sex, male†	33 (49)	9 (60)	15 (88)	57 (57)
Task Force criteria				
Family history				
Family history of ARVD confirmed by biopsy or autopsy	15 (22)	1 (7)	1 (6)	17 (17)
Family history of premature sudden death (<35 y) due to suspected ARVD	14 (21)	1 (7)	0 (0)	15 (15)
Family history (clinical diagnosis based on present criteria)	18 (26)	1 (7)	2 (18)	21 (21)
ECG depolarization/conduction abnormalities				
Epsilon waves	5 (7)	0 (0)	0 (0)	5 (5)
Localized QRS duration >110 ms in V ₁ , V ₂ , or V ₃ †	48 (71)	11 (73)	12 (71)	48 (48)
Late potentials on signal-averaged ECG (n1=57, n2=10, n3=11)	42 (74)	9 (90)	10 (91)	61 (78)
Repolarization abnormalities				
Inverted T waves in right precordial leads (V ₂ through V ₃) age >12 y	60 (88)	13 (87)	15 (88)	88 (88)
Tissue characterization of walls				
Fibrofatty replacement of myocardium in endomyocardial biopsy (n1=27, n2=2, n3=4)	9 (33)	2 (100)	2 (50)	13 (39)
Structural or functional abnormalities				
Severe dilatation and reduction of RV ejection fraction with mild or no LV involvement†	10 (15)	6 (40)	6 (35)	22 (22)
Localized RV aneurysm	14 (21)	2 (13)	5 (29)	21 (22)
Mild global RV dilatation and/or ejection fraction reduction (localized RV disease)	40 (59)	7 (47)	9 (53)	56 (56)
Arrhythmias				
Left bundle-branch block VT on ECG, Holter, or exercise tolerance test	46 (68)	14 (93)	14 (82)	74 (74)
Sustained VT (n1=64, n2=15, n3=16)	36 (56)	11 (73)	11 (69)	58 (61)
Nonsustained VT (n1=58, n2=13, n3=16)	41 (71)	12 (92)	13 (81)	66 (76)
Frequent premature ventricular contractions (>1000/24-h Holter) (n1=44, n2=10, n3=9)	30 (68)	7 (70)	5 (56)	42 (67)

Values are n (%) or mean±SD. LV indicates left ventricular; VT, ventricular tachycardia.

*To be diagnosed with ARVD, an individual must have 2 major or 1 major plus 2 minor or 4 minor criteria. n1 indicates sample size of ARVD with no IRBBB/CRBBB; n2, sample size of ARVD with IRBBB; n3, sample size of ARVD with CRBBB (when sample size different from 68, 15, and 17, respectively).

† $P<0.05$ (difference between groups).

diagnostic markers of ARVD that reflect delayed activation of the RV. A second objective of this study is to describe the ECG features of a series of patients with ARVD who have a RBBB pattern and to evaluate the sensitivity and specificity of the standard and newly proposed ECG markers in the diagnosis of ARVD in the presence of a RBBB pattern.

Methods

Study Population

The study population included 100 patients with ARVD (57 men; aged 39±15 years) and 57 controls (21 men; aged 40±17). The study populations were participants in the Johns Hopkins ARVD registry. Per routine protocol, all individuals underwent a series of clinical tests to ascertain the fulfillment of the Task Force criteria. ARVD was diagnosed on the basis of the Task Force criteria.¹⁰ All participants provided written informed consent to participate, and the study protocol was approved by the Johns Hopkins medicine

institutional review board. Each of the 100 patients with ARVD met the Task Force criteria for ARVD. The prevalence of minor and major criteria for ARVD in the 100 patients with ARVD enrolled in this study is summarized in Table 1. None of the patients or controls was receiving antiarrhythmic drugs known to affect the QRS complex at the time of acquisition of the ECG tracings.

The ECGs from 2 control populations were also evaluated. The first control population was a series of 27 patients (10 men; aged 33±17 years) who were evaluated in the ARVD clinic because of a first- or second-degree relative with ARVD. Each of these patients underwent comprehensive testing for ARVD including an ECG, signal-averaged ECG, Holter, magnetic resonance imaging, and stress testing. All of the diagnostic tests were normal in these patients. The second control group was a series of 30 patients (11 men; aged 46±14 years) with a RBBB ECG pattern. Each of the control patients with a RBBB pattern underwent a detailed history and physical examination as well as an echocardiogram. No evidence of cardiovascular disease was identified, other than the RBBB pattern on ECG. Each of the ARVD patients and controls was white.

Table 2. Definitions of ECG Parameters and Measurements Employed in This Study

Variables	Definitions
Right precordial TWI through V ₂	Inverted T wave in leads V ₁ and V ₂
Right precordial TWI through V ₃ ¹⁰	Inverted T wave in leads V ₁ , V ₂ , and V ₃
Right precordial TWI through V ₄	Inverted T wave in leads V ₁ , V ₂ , V ₃ , and V ₄
TWI in inferior leads	Inverted T waves in 2 of 3 inferior leads
Epsilon wave ¹²	Distinct waves of small amplitude that occupy the ST segment in the right precordial leads and are distinct from the QRS complex
QRS prolongation in right precordial leads ¹⁰	QRSd >110 ms in lead V ₁ , V ₂ , or V ₃
Parietal block ¹¹	QRSd in lead V ₁ through V ₃ that exceeds the QRSd in lead V ₆ by >25 ms
Prolonged TAD ¹⁵	Longest value in V ₁ through V ₃ from the nadir of the S wave to the end of all depolarization
Localized right precordial QRS prolongation (increased ratio in the QRSd of the right vs left precordial leads) ^{13,14}	QRSd: (V ₁ +V ₂ +V ₃)/(V ₄ +V ₅ +V ₆) ≥1.2 with QRSd >100 ms in 2 of 3 right precordial leads
CRBBB ¹⁶	QRSd ≥120 ms and: A1: R' or r' in V ₁ or V ₂ A2: S duration >R duration in I and V ₆ A3: S duration >40 ms in I and V ₆ A4: R peak time >50 ms in V ₁ or V ₂ a: A1+A2 b: A1+A3 c: A4+ (A2 or A3)
IRBBB ¹⁶	QRS <120 ms and R peak time in V ₁ or V ₂ >50 ms
R or r' in V ₁ /V ₂	A positive deflection in V ₁ /V ₂ after an S wave
R'/s ratio in V ₁	Ratio of amplitude of r' and S wave in lead V ₁

ECG Parameters and Definitions

Shown in Table 2 are the definitions and criteria used in this study. These ECG parameters include those that are part of the Task Force criteria,¹⁰ newly described measures of conduction delay,^{12,15} and also several additional parameters that have been reported in the literature.^{11,13,14} The criteria for diagnosis of a CRBBB or incomplete RBBB (IRBBB) are the 1985 World Health Organization criteria.¹⁶ It is important to note that an IRBBB was defined in this study as QRS width <120 ms with an R wave peak time in V₁ or V₂ >50 ms. This definition was recommended by the World Health Organization/International Society and Federation for Cardiology Task Force Ad Hoc criteria.¹⁶ According to these criteria, there is no minimal QRSd for IRBBB. It is also important to note that this pattern (ie, IRBBB) has been attributed to causes other than conduction delay in the right bundle branch.

ECG Analysis

The 12-lead ECGs were obtained in the traditional lead positions and recorded at 25 mm/s. All recorded ECGs were scanned with a high-resolution digital scanner and imported into Sigma Scan Pro 5.0 software for further evaluation. To increase the accuracy of measurements, all of the ECGs were enlarged ×2 to obtain a format comparable to 50 mm/s. Digital calipers capable of measuring to within 1 ms (horizontal axis) and 0.01 mV (vertical axis) were used

to determine the intervals with the use of the software. The intervals were measured in 2 consecutive beats in each lead; the mean value of the 2 beats was used. When the difference between the 2 beats was >10 ms, then the mean of 3 beats was taken. Each ECG was analyzed by 2 independent readers, each of whom was blinded to the clinical diagnosis of the patient. Both readers summarized their findings for each ECG on a predesigned paper questionnaire. Differences in the interpretation of the ECG parameters were adjudicated by consensus, and the final diagnosis for each parameter was entered in an electronic database for analysis.

In addition to the analysis of conventional and recently reported ECG markers, we also included a novel ECG marker for use in patients with either a CRBBB or IRBBB. The new parameter that we evaluated is the ratio of the amplitude of r' to s in lead V₁. We developed this parameter in an effort to describe the unique RBBB patterns of patients with and without ARVD. We also evaluated for the first time a novel repolarization parameter that we term *inferior TWI*. This is defined for purposes of this study as the presence of TWI in ≥2 inferior leads.

Data Analysis

Continuous variables were expressed as mean±SD and compared with the use of Student *t* test or ANOVA, and categorical variables were expressed as frequency (%) and compared with a χ^2 or Fisher exact test. Dichotomous variables were created for each ECG marker either on the basis of clinically applicable cutoffs or cutoffs that yielded optimal sensitivity and specificity in a receiver operator characteristic analysis. For each dichotomous variable, sensitivity and specificity were calculated to estimate the diagnostic utility of the variable. As done traditionally, we classified all ECG parameters into repolarization and depolarization abnormalities. The variables were then grouped together on the basis of traditional Task Force recommendations or their individual diagnostic utility. ECG parameters selected for this grouping were based on the original Task Force recommendation as well as the newer parameters that were found to have, in our analysis, sensitivity or specificity >80% for ARVD diagnosis. The diagnostic utility of repolarization and depolarization abnormalities was tested alone and in combination with each other. All analyses were stratified by the QRS morphology, which was classified as no RBBB, IRBBB, and CRBBB. Analyses were performed with the use of STATA statistical software (College Station, Tex), and a *P* value <0.05 was considered statistically significant.

Results

ECG Patterns and Clinical Characteristics in Patients With ARVD and Controls

Among the 100 patients with ARVD, a CRBBB was present in 17 patients, and an IRBBB was present in 15 patients. The clinical characteristics of the overall patient population and these 3 subgroups are shown in Table 1. Patients with a CRBBB pattern were older and more likely to have severe RV dilation or reduction of the RV ejection fraction.

ECG Features of ARVD Compared With Controls

Table 3 presents the prevalence of ECG characteristics in ARVD patients compared with controls. To better define the diagnostic utility of the ECG, we compared each ECG parameter on the basis of whether a CRBBB, IRBBB, or no RBBB pattern was observed.

Characteristics of ARVD in the Absence of an IRBBB or CRBBB Pattern

Shown in Figure 1 is a representative 12-lead ECG obtained from an ARVD patient without a CRBBB or IRBBB pattern. TWI is observed in leads V₁ through V₅, and an epsilon wave can also be seen in lead V₁. Table 3 presents the prevalence of ECG characteristics in ARVD patients in the absence of

Table 3. Relative Prevalence of ECG Features of ARVD and Normal Controls With and Without RBBB

Variables	ARVD Without IRBBB/CRBBB (n=68)	ARVD With IRBBB (n=15)	ARVD With CRBBB (n=17)	Controls Without IRBBB/CRBBB' (n=27)	Controls With IRBBB (n=22)	Controls With CRBBB (n=8)	P*	P†	P‡
Right precordial TWI through V ₂	57 (84)	12 (80)	13 (76)	3 (11)	6 (27)	3 (38)	0.001	0.002	0.058
Right precordial TWI through V ₃	48 (71)	11 (73)	12 (71)	1 (4)	1 (5)	3 (38)	0.001	0.001	0.115
Right precordial TWI through V ₄	35 (51)	9 (60)	10 (59)	1 (4)	0 (0)	1 (12)	0.001	0.001	0.03
TWI in inferior leads (2 of 3)	28 (41)	7 (47)	9 (53)	2 (7)	0 (0)	1 (13)	0.001	0.001	0.088
Epsilon wave	5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.317
QRS prolongation in right precordial leads QRS >110 ms	29 (43)	12 (80)	17 (100)	1 (4)	2 (9)	8 (100)	0.001	0.001	...
Parietal block	9 (13)	6 (40)	8 (47)	1 (4)	0 (0)	4 (50)	0.172	0.03	0.891
Prolonged TAD	31 (46)	12 (80)	17 (100)	3 (11)	8 (36)	7 (88)	0.002	0.009	0.137
Increased ratio in QRSD of the right vs left precordial leads	15 (22)	6 (40)	6 (35)	6 (21)	2 (9)	5 (63)	0.986	0.025	0.201
R'/s ratio <1	...	13 (93)	15 (88)	...	21 (95)	1 (14)	...	0.74	0.001

Values are n (%).

*ARVD without IRBBB/CRBBB vs control without IRBBB/CRBBB pattern.

†ARVD with IRBBB vs control with IRBBB.

‡ARVD with CRBBB vs control with CRBBB.

a CRBBB or IRBBB pattern in comparison to a control population of patients. Six of the 9 ECG parameters that we examined were more commonly observed in ARVD patients compared with controls. The variables that did not differ in frequency between the 2 groups were (1) parietal block, (2) an increased ratio in QRSD of the right versus left precordial leads, and (3) epsilon waves. Epsilon waves were observed in only 5 ARVD patients compared with no controls, a difference that was not statistically significant

likely as a result of small sample size. Table 4 summarizes the sensitivity and specificity of each of these parameters in distinguishing ARVD patients from controls. Among the ECG parameters that differed in the 2 groups, the most sensitive parameter was right precordial TWI through V₂ (84%) (95% confidence interval [CI], 73% to 92%). The most specific parameter was the presence of an epsilon wave (100%) (95% CI, 87% to 100%). The parameter that demonstrated optimal sensitivity and specificity was TWI through



Figure 1. Representative ECG obtained from an ARVD patient without IRBBB or CRBBB. This patient had an advanced form of ARVD. The arrow indicates an epsilon wave. ECG also illustrates TWI in V₁ through V₅, TAD ≥ 55 ms in V₁, and QRSD in V₃ >110 ms. This ECG also demonstrates low voltage, which in our experience is an uncommon finding in patients with ARVD and is usually seen with advanced disease. There was no parietal block or localized right precordial QRS prolongation.

Table 4. Sensitivity and Specificity of ECG Features

Variables	No RBBB		IRBB		CRBBB	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Repolarization criteria						
Right precordial TWI through V ₂	84 (73–92)	89 (71–98)	80 (52–96)	73 (50–89)	76 (50–93)	62 (24–91)
Right precordial TWI through V ₃	71 (58–81)	96 (81–100)	73 (45–92)	95 (77–100)	71 (44–90)	62 (24–91)
Right precordial TWI through V ₄	51 (39–64)	96 (81–100)	60 (32–84)	100 (85–100)	59 (33–82)	88 (47–100)
TWI in inferior leads (2 of 3)	41 (29–54)	93 (76–99)	47 (21–73)	100 (85–100)	53 (28–77)	87 (47–100)
Depolarization criteria						
Epsilon wave	7 (2–16)	100 (87–100)	0 (0–15)	100 (78–100)	0 (0–37)	100 (80–100)
QRS prolongation in right precordial leads QRS >110 ms	43 (31–55)	96 (81–100)	80 (52–96)	91 (71–99)	100 (80–100)	0 (0–37)
Parietal block	13 (6–24)	96 (81–100)	40 (16–68)	91 (70–99)	47 (23–72)	50 (16–84)
Prolonged terminal activation duration	46 (33–58)	89 (71–98)	80 (52–96)	64 (41–83)	100 (80–100)	12 (0.32–53)
Increased ratio in QRSD of the right vs left precordial leads	22 (13–34)	79 (58–91)	40 (16–68)	91 (71–99)	35 (14–62)	37 (9–76)
r'/s ratio <1	93 (66–100)	5 (0.12–23)	88 (64–99)	86 (42–100)

Values are % (95% CI).

V₃ (71% [95% CI, 58% to 81%] and 96% [95% CI, 81% to 100%], respectively).

ECG Characteristics of ARVD in the Presence of IRBBB

Figure 2A shows a representative ECG obtained from an ARVD patient with an IRBBB. Figure 2B shows a representative ECG from a control subject with an IRBBB. Several differences in these 2 ECGs can be appreciated. The major difference is that the ECG obtained from the ARVD patient reveals TWI in leads V₁ through V₅, whereas the ECG from the normal control reveals TWI only through V₂.

Table 3 presents the prevalence of ECG characteristics in ARVD patients with an IRBBB pattern in comparison to a control population with an IRBBB. Nine of the 10 ECG parameters that we examined were more commonly observed in ARVD patients compared with controls. The only parameter that did not differ was our newly proposed parameter for ARVD in the presence of a CRBBB of an r'/s ratio <1. Table 4 summarizes the sensitivity and specificity of these parameters in distinguishing ARVD patients from controls. Among the ECG parameters that differed in the 2 groups, the 3 most sensitive parameters were TWI through V₂ (80%; 95% CI, 52% to 96%), QRS prolongation >110 ms (80%; 95% CI, 52% to 96%), and TAD ≥55 ms (80%; 95% CI, 52% to 96%). Three parameters demonstrated 100% specificity: (1) TWI through V₄ (100%; 95% CI, 85% to 100%); (2) TWI in inferior leads (100%; 95% CI, 85% to 100%); and (3) the presence of an epsilon wave (100%; 95% CI, 78% to 100%). The ECG parameter that demonstrated optimal sensitivity and specificity was again TWI through V₃ (73% [95% CI, 45% to 92%] and 95% [95% CI, 77% to 100%], respectively).

ECG Characteristics of ARVD and Controls in the Presence of CRBBB

Figure 3A shows a representative ECG obtained from ARVD patients with a CRBBB. Figure 3B shows a representative ECG from control subjects with a CRBBB. Several differences in these 2 ECGs can be appreciated. First, the ECG obtained from the ARVD patients reveals TWI in leads V₁

through V₄, whereas the ECG from the patient without ARVD reveals TWI only through V₁. Second, the rsr' pattern in lead V₁ differs significantly in the ECG from the ARVD patient, demonstrating a wide and low-amplitude r' pattern. The r'/s ratio in ECG obtained from the ARVD patient was 0.76 compared with infinity in the control patient.

Table 3 presents the prevalence of ECG characteristics in ARVD patients with a CRBBB pattern in comparison to a control population with a CRBBB. The only 2 parameters that differed in these 2 groups with a CRBBB pattern was the prevalence of TWI in leads V₁ through V₄ and an r'/s ratio <1 in V₁. TWI in V₁ through V₄ was observed in 59% of ARVD patients compared with 12% of controls (P<0.001). Similarly, an r'/s ratio <1 in V₁ was observed more commonly in ARVD patients than controls (88% versus 14%; P<0.005). Table 4 summarizes the sensitivity and specificity of each of these parameters in distinguishing ARVD patients from controls. Among the ECG parameters that differed in the 2 groups, the most sensitive and specific parameter was an r'/s ratio <1. This parameter also demonstrated optimal sensitivity and specificity (88% [95% CI, 64% to 99%] and 86% [95% CI, 42% to 100%], respectively).

Diagnostic Value of Combinations of ECG Parameters

One of the goals of our study was to develop ECG criteria for ARVD that can be used in patients with and without a RBBB pattern. To accomplish this, we studied the repolarization and depolarization criteria alone and in combination to determine their diagnostic utility in ARVD. For determining the parameters that constitute repolarization and depolarization abnormalities, we relied on prior recommendations as well as the sensitivity/specificity associated with the individual parameter in differentiating ARVD patients from controls. In general, we included all parameters with a specificity or sensitivity >80% in addition to the previously recommended criteria.

Patients without a CRBBB or IRBBB pattern and patients with an IRBBB had remarkably similar sensitivity and specificity associated with all ECG parameters. Conse-



Figure 2. A, Representative ECG obtained from an ARVD patient with IRBBB. ECG illustrates TWI in V_1 through V_5 , TAD ≥ 55 ms, QRSd > 110 ms, ratio < 1.2 , and premature ventricular contractions. B, Representative ECG of control with IRBBB illustrating TWI in V_1 through V_2 .

quently, the repolarization and depolarization variables for these 2 subgroups included the same parameters. On the basis of prior recommendation and supported by our present analysis, TWI in leads V_1 through V_3 was considered a repolarization abnormality in these patients. In addition, TWI in inferior leads was found to have $> 80\%$ (96%; 95% CI, 86% to 100%) specificity in this group. Repolarization abnormalities in this group were therefore defined as presence of TWI in the right precordial or inferior leads. A depolarization abnormality in these groups was defined as presence of QRS duration > 110 ms, presence of epsilon wave, or presence of TAD. Among patients with no CRBBB/IRBBB, optimal sensitivity and specificity was noted when a combination of depolarization and repolarization was used. In patients with an IRBBB, the optimal sensitivity and specificity were observed by using repolarization alone (Table 5).

Previously published criteria are not applicable to patients with CRBBB. In the present analysis, TWI in leads V_4 or beyond had a specificity of 88% (95% CI, 47% to 100%) in diagnosing ARVD among patients with CRBBB. In addition, TWI in inferior leads was found to have 87% (95% CI, 47% to 100%) specificity in this group. Consequently, TWI beyond V_4 or in the inferior leads was included as a repolarization abnormality in this subgroup. The only depolarization abnormality that stood out in this subgroup was r'/s ratio < 1 in lead V_1 . On examination of individual repolarization and depolarization abnormalities and the combination thereof, it was noted that the r'/s ratio by itself yielded a sensitivity of 88% (95% CI, 64% to 99%) and a specificity of 88% (95% CI, 42% to 100%) (Table 5).

On the basis of these findings, we propose a clinical algorithm for ECG evaluation of ARVD (Figure 4). On the

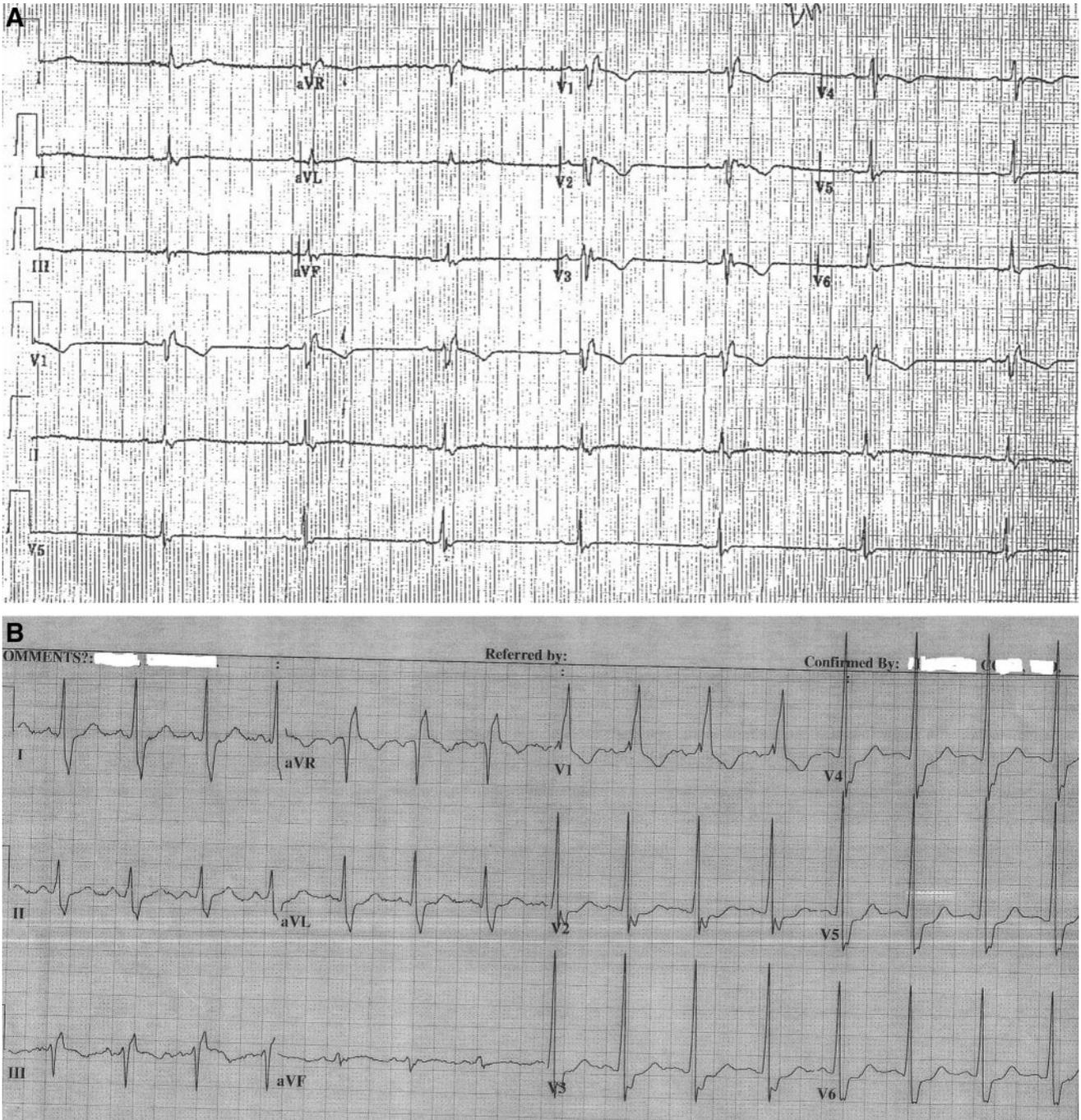


Figure 3. A, Representative ECG obtained from an ARVD patient with CRBBB. It shows TWI in V_1 through V_4 and r'/s ratio < 1 . B, Representative ECG of control with CRBBB. It shows TWI in V_1 and $r'/s > 1$.

basis of this algorithm, we recommend that the QRS morphology be examined as a first step when evaluating a patient for ARVD diagnosis. A fixed set of criteria is then applied to patients on the basis of the presence of no RBBB, IRBBB, and CRBBB to obtain the best diagnostic utility of the ECG.

Discussion

Main Findings

In this study, we performed a systematic analysis of the 12-lead ECG in ARVD patients compared with controls and investigated the diagnostic value of ECG criteria that are

included in the Task Force criteria, other previously described ECG markers of ARVD including those that were developed as markers of RV conduction delay, and also new markers of ARVD in patients with a RBBB pattern. This is the first study to evaluate the ECG features of ARVD patients on the basis of the presence or absence of a CRBBB or IRBBB. This is of particular importance because IRBBB or CRBBB patterns are commonly observed in patients with ARVD. There are 3 main findings of this study. First, in the absence of a CRBBB or IRBBB, TWI through V_3 is the single ECG parameter that demonstrates optimal sensitivity and specificity. The use of a

Table 5. Prevalence and Diagnostic Utility of ECG Features Based on Combination of Criteria

Parameter	Prevalence		Diagnostic Utility	
	ARVD (n=100)	Controls (n=57)	Sensitivity	Specificity
No RBBB				
Depolarization criteria (QRSd >110 ms, TAD, epsilon wave)*	37 (54)	3 (11)	54 (42–67)	89 (71–98)
Repolarization criteria (TWI through V ₃ , TWI in inferior leads [2 of 3])*	52 (76)	2 (7)	76 (65–86)	93 (76–99)
(Combination of repolarization and depolarization criteria)				
1 Criterion*	60 (88)	5 (19)	88 (78–95)	81 (62–94)
2 Criteria*	29 (43)	0 (0)	43 (31–55)	100 (87–100)
IRBBB				
Depolarization criteria (QRSd >110 ms, TAD, epsilon wave)*	13 (87)	8 (36)	87 (60–98)	64 (41–83)
Repolarization criteria (TWI through V ₃ , TWI in inferior leads [2 of 3])*	13 (87)	1 (5)	87 (60–98)	95 (77–100)
Combination of repolarization and depolarization criteria				
1 Criterion*	15 (100)	9 (41)	100 (78–100)	59 (36–79)
2 Criteria*	11 (73)	0 (0)	73 (45–92)	100 (85–100)
CRBBB				
Depolarization criteria (r'/s amplitude <1)*	15 (88)	1 (13)	88 (64–99)	88 (47–100)
Repolarization criteria (TWI through V ₄ , TWI in inferior leads [2 of 3])†	13 (76)	2 (25)	76 (50–93)	75 (35–97)
Combination of repolarization and depolarization criteria				
1 Criterion*	17 (100)	3 (38)	100 (80–100)	63 (24–91)
2 Criteria*	11 (65)	0 (0)	65 (38–86)	100 (63–100)

Prevalence data are expressed as frequency (%); diagnostic utility data are expressed as point estimate (95% CI).

*P<0.01.

†P<0.05.

simple scoring system that screens for depolarization and/or repolarization criteria improves sensitivity with a slight decrease in specificity. Second, for patients with an IRBBB pattern, TWI through V₃ is also the single ECG parameter that demonstrates optimal sensitivity and specificity. The use of a simple scoring system that screens for depolarization and/or repolarization criteria improves sensitivity with no decrease in specificity. Third, for patients with a CRBBB pattern, an r'/s ratio <1 in V₁ was the single ECG parameter that demonstrates optimal sensitivity and specificity. The use of a simple scoring system that screens for depolarization and/or repolarization criteria did not improve sensitivity and specificity compared with this single parameter alone.

ECG Features of ARVD Identified in the International Task Force Criteria

The Task Force criteria include 3 ECG features of the disease in the diagnostic criteria for ARVD.¹⁰ One of the criteria, which is identified as a minor criterion under the category of repolarization abnormalities, is the presence of TWI in leads V₂ and V₃ in the absence of a CRBBB. The prevalence of TWI in leads V₁ through V₃ in ARVD patients has been reported to be between 55% and 85% in the literature^{1,12–14,17–20} and has been shown to be more common in patients with greater RV dysfunction.^{12,21} This parameter has not been studied in ARVD patients with a CRBBB in any of the aforementioned studies. The results of our study confirm and

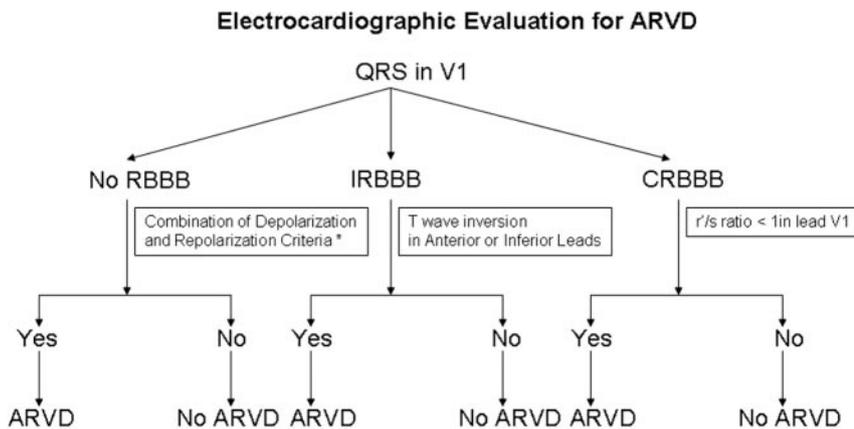


Figure 4. Flow chart summarizing an algorithm that can be used on the basis of the presence or absence of an IRBBB or CRBBB to identify patients with ARVD.

*The depolarization criteria used to screen patients with either an IRBBB or no RBBB are QRSd in V₁ through V₃ >110 ms, TAD, and epsilon wave. Repolarization criteria used in the patients with either IRBBB or no RBBB are TWI in V₁ through V₃, TWI in 2 of the 3 inferior leads, or both. In ARVD patients with CRBBB, the depolarization criterion used is r'/s ratio <1 in lead V₁. The repolarization criteria used in ARVD patients with CRBBB are TWI through V₄ and/or TWI in 2 of the 3 inferior leads.

* Depolarization Criteria: QRSd ≥ 110ms or TAD or Epsilon wave
 Repolarization Criteria: TWI thru V3 or TWI in 2 out of 3 inferior leads

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extend the findings of these prior studies. Consistent with these prior studies, TWI in our study was present in 59 of 83 patients with ARVD who did not have a CRBBB versus 2 of 49 controls, giving a sensitivity of 71% (95% CI, 60% to 81%) and specificity of 96% (95% CI, 86% to 100%). We found that the sensitivity and specificity of this parameter did not differ on the basis of the presence or absence of an IRBBB. A new finding of our study was that TWI in leads V₁ through V₃ does not differ in ARVD patients with a CRBBB versus a control population of patients with a CRBBB. However, TWI in leads V₁ through V₄ is more common in ARVD patients with a RBBB pattern than controls. The sensitivity and specificity of this new criterion for ARVD in the presence of a CRBBB were 59% (95% CI, 33% to 82%) and 88% (95% CI, 47% to 100%), respectively.

The other 2 criteria that were included as diagnostic criteria in the International Task Force criteria under the category of depolarization abnormalities were the presence of an epsilon wave and the presence of a prolonged QRS >110 ms in the right precordial leads. The presence of either of these parameters was identified as major criteria for ARVD. Prior studies have reported that epsilon waves are present in between 10% and 35% of ARVD patients.^{12–15} This wide difference in the prevalence of epsilon waves likely reflects differences in the severity of ARVD in different studies as well as varying definitions of an epsilon wave. In this study, we defined an epsilon wave as a distinct wave of small amplitude that occupies the ST segment in the right precordial leads and is distinct from the QRS complex. In the present study, we report an epsilon wave in 5 of 68 ARVD patients (7%). This finding is very similar to that of Cox et al,¹⁵ who used a definition of epsilon waves virtually identical to that used in the present article and reported a prevalence of 10%. We did not identify epsilon waves in any of the ARVD patients or controls with a CRBBB pattern.

Perhaps the most controversial and poorly defined diagnostic parameter for ARVD identified in the original Task Force criteria was the presence of a QRSd >110 ms in the right precordial leads. One of the most confusing aspects of the 1994 criteria¹⁰ is that they do not specify whether this parameter can be applied to patients with a CRBBB or IRBBB pattern. Reflecting this uncertainty in the diagnostic criteria is an extremely wide variation from 26% to 75% in the prevalence of this parameter in prior studies.^{13–15} Not surprisingly, the prevalence of a QRSd >110 ms differed markedly depending on whether there was no IRBBB or CRBBB pattern, an IRBBB pattern, or a CRBBB pattern (43%, 80%, and 100%, respectively). Marked differences in the sensitivity and specificity of this criterion were observed depending on the baseline conduction pattern.

Other ECG Markers of ARVD

In addition to the 3 ECG parameters that have been relied on as part of the Task Force criteria for ARVD, we have evaluated 5 other ECG markers of ARVD. Three of these have been reported to be of diagnostic value in prior reports (parietal block, localized right precordial QRS prolongation, and TAD), and 2 are novel ECG parameters (inferior TWI and r'/s ratio in V₁ <1). In this section, we will identify each

of these parameters in the order that they were first reported, provide a brief review of prior studies, and then review the results of the present study.

Parietal Block

The concept that the conduction abnormalities observed in patients with ARVD result from parietal block without definite alteration of conduction in the bundle branches was first proposed by Fontaine et al.¹¹ He proposed that a QRSd in leads V₁ through V₃ that exceeds the QRSd V₆ by ≥ 25 ms in the presence of a RBBB block is a marker of parietal block and therefore can be used as a diagnostic criterion for ARVD patients who demonstrate a CRBBB pattern. In the present study, we evaluated, for the first time, the prevalence of parietal block in patients and controls with and without a CRBBB or IRBBB pattern. An important new finding of this study was that the prevalence of parietal block differed markedly depending on whether there was no IRBBB or CRBBB pattern, an IRBBB pattern, or a CRBBB pattern (13%, 40%, and 47%, respectively). Of particular importance was our finding that in the presence of a RBBB, this parameter was of no value in distinguishing ARVD patients from controls. We therefore conclude that this parameter is not of diagnostic value in patients being evaluated for ARVD. This likely reflects the error involved in measurement of QRSd in multiple leads.

Localized Right Preordial QRS Prolongation (Increased Ratio)

Peters and Trummel¹³ first proposed localized right precordial QRS prolongation (defined as the ratio of the sum of the QRSd in leads V₁ through V₃ versus V₄ through V₆ of ≥ 1.2) as an ECG marker for ARVD in 2003. In this initial study, they reported that 98% of ARVD patients had localized right precordial QRS prolongation. Importantly, no control population was included in this study. In the present study, we evaluated, for the first time, the prevalence of localized right precordial QRS prolongation in patients and controls with and without a CRBBB or IRBBB pattern. An important new finding of this study was that the prevalence of localized right precordial QRS prolongation differed depending on whether there was no IRBBB or CRBBB, an IRBBB, or a CRBBB (22%, 40%, and 47%, respectively). We did not find this parameter to be of diagnostic value when compared with a control population of patients with and without a CRBBB or IRBBB pattern.

Prolonged TAD

TAD was first described by Cox et al¹⁵ as a marker of delayed RV activation. This parameter is an extension to delayed S-wave upstroke, which was proposed by Nasir et al.¹² Cox et al reported TAD in 30 of the 42 ARVD patients (71%) versus in 1 of 27 controls (4%). In the present study, we evaluated, for the first time, the prevalence of TAD in patients and controls with and without a CRBBB or IRBBB pattern. An important new finding of this study was that the prevalence of TAD differed depending on whether there was no IRBBB or CRBBB pattern, an IRBBB pattern, or a CRBBB pattern (46%, 80%, and 100%, respectively). As in prior studies, we found that this parameter was of value in identifying ARVD patients. Importantly, the sensitivity, specificity, and diagnostic value of this parameter were greatest in patients without an

IRBBB or CRBBB. TAD was not of diagnostic value in patients with a CRBBB pattern.

TWI in Inferior Leads

One of the novel ECG parameters that we investigated in this study is inferior TWI, which we defined as TWI in 2 of 3 inferior ECG leads. We report the presence of inferior TWI in 41%, 47%, and 53% of ARVD versus in 7%, 0%, and 13% of control patients with no CRBBB or IRBBB, an IRBBB, and a CRBBB, respectively. This parameter is an insensitive but specific marker of ARVD in patients without a CRBBB pattern. Because of its diagnostic value, inferior TWI has been included in our ECG scoring system.

r'/s Ratio <1 in Lead V₁

The second novel marker of ARVD included in this study is the r'/s ratio <1 in V₁, which is a parameter that we developed for use in ARVD patients with a CRBBB pattern. In the present study, we report this parameter to be the best diagnostic marker of ARVD in the setting of a CRBBB pattern, with a sensitivity and specificity of 88% (95% CI, 64% to 99%) and 86% (95% CI, 42% to 100%), respectively.

Diagnostic Value of Combinations of ECG Parameters

One of the goals of our study was to develop ECG criteria for ARVD that can be used in patients with and without a RBBB pattern. To accomplish this, we studied the repolarization and depolarization criteria alone and in combination to determine their diagnostic utility in ARVD. The results of our analysis reveal that in the absence of a CRBBB or IRBBB pattern, TWI through V₃ is the single ECG parameter that demonstrates the most optimal sensitivity and specificity for identifying patients with ARVD. The use of a simple scoring system that screens for depolarization criteria (QRSd >110 ms, epsilon wave, TAD, or some combination of the 3) and repolarization criteria (TWI in the anterior or inferior leads) improves sensitivity with a slight decrease in specificity (88% [95% CI, 78% to 95%] and 81% [95% CI, 62% to 94%], respectively). For patients with an IRBBB pattern, TWI through V₃ is also the single ECG parameter that demonstrates the most optimal sensitivity and specificity. The use of a simple scoring system that screens for the depolarization and repolarization criteria listed above improves sensitivity with marked decrease in specificity (100% [95% CI, 78% to 100%] and 59% [95% CI, 36% to 79%], respectively). For this reason, our proposed algorithm suggests that repolarization criteria alone be used in screening patients with an IRBBB pattern. For patients with a CRBBB pattern, an r'/s ratio of <1 in V₁ was the single ECG parameter that demonstrates the most optimal sensitivity and specificity (88% [95% CI, 64% to 99%] and 86% [95% CI, 42% to 100%], respectively). The use of a simple scoring system that screens for depolarization and repolarization criteria did not improve sensitivity and specificity compared with this single parameter alone. The scoring system needs validation in further studies with larger sample size of patients with IRBBB.

Study Limitations

There are several limitations of this study. First, there is currently no absolute "gold standard" for diagnosis of ARVD. In the absence of a true gold standard, we and others in the

field have relied on the 1994 International Task Force criteria.¹⁰ Although the criteria have proved enormously helpful in standardizing research on ARVD and patient care, they are imperfect and are currently undergoing revision. Because of the absence of a true gold standard for diagnosis of ARVD, it is difficult to estimate the true sensitivity and specificity of any diagnostic test, including the ECG. In this study, we relied on the 1994 Task Force criteria as our gold standard. This may have resulted in overestimation of sensitivity and specificity of the ECG parameters tested, particularly those that are included in the 1994 Task Force criteria. Because of a possible correlation between the ECG parameters not included and those included in the 1994 Task Force criteria, the sensitivity and specificity of such parameters may also have been overestimated in our analyses. This is a limitation of our study as well as all other studies that have relied on these criteria. A second limitation of our study is that the control patients with RBBB pattern did not undergo contrast echocardiogram to screen for atrial septal defects. These control patients also did not undergo magnetic resonance imaging. A third limitation of this study is that it is a small study. This is particularly true in regard to the new algorithm that we propose when ECGs that have an IRBBB or CRBBB pattern are interpreted. In this study, we analyzed ECGs from 17 and 15 ARVD patients with a CRBBB and IRBBB pattern, respectively. The small sample sizes may have resulted in low precision for estimating sensitivity and specificity (as noted by the wide CIs) in these subgroups. It is clear that the criteria proposed in this report will need prospective validation before they can be relied on to make or exclude the diagnosis of ARVD.

Conclusions

The value of the ECG in the diagnosis of ARVD cannot be underestimated, although definite diagnosis is only possible after a comprehensive evaluation that includes evaluation of the family history, the structure and function of the RV, and screening for arrhythmias. In this study, we have critically and comprehensively evaluated the diagnostic value of various ECG markers for ARVD and presented an algorithm for ECG screening for ARVD that is based on the presence or absence of a CRRB or an IRBBB. It is our hope that the findings of our study will be confirmed in other populations of ARVD patients and that in the future, the ECG can be relied on with greater confidence as a screening tool for ARVD.

Sources of Funding

The Johns Hopkins ARVD program is supported by the Bogle Foundation, Healing Hearts Foundation, Campanella family, and Wilmerding Endowment. We also acknowledge funding from the National Heart, Lung, and Blood Institute (K23HL093350 to Dr Tandri and 1 U01 HL65594-01A1), National Institutes of Health grant HL088072, Boston Scientific Corp, St Jude Medical Inc, and Medtronic Inc.

Disclosures

We acknowledge funding from the National Heart, Lung, and Blood Institute (K23HL093350 to Dr Tandri and 1 U01 HL65594-01A1), National Institutes of Health grant HL088072, Boston Scientific Corp, St Jude Medical Inc, and Medtronic Inc. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) relies on results of diagnostic tests that screen for structural abnormalities of the right ventricle, ventricular arrhythmias, a family history of sudden death or ARVD, and ECG abnormalities that have been linked to ARVD. Among the many diagnostic tests that are used to screen patients for ARVD, the ECG is of particular importance because of its widespread availability and low cost. In this study, we performed a systematic analysis of the 12-lead ECG in ARVD patients compared with controls. To our knowledge, this is the first study to evaluate the ECG features of ARVD patients on the basis of the presence or absence of a complete or incomplete right bundle-branch block (RBBB). This is of particular importance because incomplete RBBB or complete RBBB patterns are commonly observed in patients with ARVD. The results of this study reveal that in the absence of a complete RBBB or incomplete RBBB, T-wave inversion through V_3 is the single ECG parameter that demonstrates optimal sensitivity and specificity. Second, for patients with an incomplete RBBB pattern, T-wave inversion through V_3 is also the single ECG parameter that demonstrates optimal sensitivity and specificity. Third, for patients with a complete RBBB pattern, an r'/s ratio of <1 in V_1 was the single ECG parameter that demonstrates optimal sensitivity and specificity. It is our hope that the findings of our study will be confirmed in other populations of ARVD patients and that, in future, the ECG can be relied on with greater confidence as a screening tool for ARVD.

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Circulation. 2009;120:477-487; originally published online July 27, 2009;
doi: 10.1161/CIRCULATIONAHA.108.838821

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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