The precordial R' wave: A novel discriminator between cardiac sarcoidosis and arrhythmogenic right ventricular cardiomyopathy in patients presenting with ventricular tachycardia

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BACKGROUND Cardiac sarcoidosis (CS) with right ventricular (RV) involvement can mimic arrhythmogenic right ventricular cardiomyopathy (ARVC). Histopathological differences may result in disease-specific RV activation patterns detectable on the 12-lead electrocardiogram. Dominant subepicardial scar in ARVC leads to delayed activation of areas with reduced voltages, translating into terminal activation delay and occasionally (epsilon) waves with a small amplitude. Conversely, patchy transmural RV scar in CS may lead to conduction block and therefore late activated areas with preserved voltages reflected as preserved RV waves.

OBJECTIVE The purpose of this study was to evaluate the distinct terminal activation patterns in precordial leads V1 through V3 as a discriminator between CS and ARVC.

METHODS Thirteen patients with CS affecting the RV and 23 patients with gene-positive ARVC referred for ventricular tachycardia ablation were retrospectively included in a multicenter approach. A non-ventricular-paced 12-lead surface electrocardiogram was analyzed for the presence and the surface area of the R' wave (any positive deflection from baseline after an S wave) in leads V1 through V3.

RESULTS An R' wave in leads V1 through V3 was present in all patients with CS compared to 11 (48%) patients with ARVC (P = .002). An algorithm including a PR interval of ≥220 ms, the presence of an R' wave, and the surface area of the maximum R' wave in leads V1 through V3 of ≥1.65 mm² had 85% sensitivity and 96% specificity for diagnosing CS, validated in a second cohort (18 CS and 40 ARVC) with 83% sensitivity and 88% specificity.

CONCLUSION An easily applicable algorithm including PR prolongation and the surface area of the maximum R’ wave in leads V1 through V3 of ≥1.65 mm² distinguishes CS from ARVC. This QRS terminal activation in precordial leads V1 through V3 may reflect disease-specific scar patterns.

KEYWORDS Arrhythmogenic right ventricular cardiomyopathy; Cardiac sarcoidosis; Right bundle branch block; Twelve-lead surface electrocardiogram; Ventricular tachycardia

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Introduction
Arrhythmogenic right ventricular cardiomyopathy (ARVC) and cardiac sarcoidosis (CS) are the most important underlying etiologies for scar-related ventricular tachycardias (VTs) from the right ventricle (RV). The clinical phenotype of CS can mimic ARVC, although they are histopathologically different. It is important to distinguish the two, as a delayed diagnosis of CS may have harmful consequences. Unfortunately, the diagnostic yield of endomyocardial biopsy for CS is low and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) might be negative in patients with VT referred for ablation. Besides, the Task Force Criteria (TFC), developed for the diagnosis of ARVC, have poor discriminative value as they are fulfilled in up to 63%–100% of patients with CS and RV involvement.

A right bundle branch block (RBBB) pattern on the 12-lead surface electrocardiogram (ECG) has been described in both patients with ARVC and those with CS. A RBBB pattern can be caused by conduction block within the specific conduction system on different levels. However, myocardial RV scar may also influence RV activation, depending on the size, transmurality, and location of the scar. The related ECG changes may therefore mimic RBBB at first sight. It has been suggested that in a RBBB-like pattern in ARVC is caused by intra-RV delay rather than proximal conduction block, reflected as an atypical pattern with R/S ratio < 1 on the ECG.

We hypothesized that the distinct histological scar characteristics of ARVC and CS impact RV activation resulting in different terminal activation patterns in leads V1 through V3. ARVC is characterized by fibrofatty replacement from the subepicardium to the subendocardium beginning at the RV base. As a result, diffuse conduction delay might result in delayed activation of areas with reduced voltages, manifested as terminal activation delay (TAD) and occasionally an (epsilon) wave with a small amplitude. Contrarily, CS is characterized by nonnecrotizing granulomas, creating patchy transmural scars. This may result in local block and delayed activation of areas with preserved voltages, reflected as an R’ wave with a higher voltage. Thus, the aim of this study was to determine whether differences in terminal activation in precordial leads V1 through V3 on the 12-lead surface ECG can distinguish between ARVC and CS in patients presenting with scar-related RV VT.

Methods

Study population
Patients with ARVC (fulfilling TFC or plus pathogenic mutation) and CS with RV involvement (fulfilling Heart Rhythm Society or Japanese criteria) from 7 centers (Boston, Massachusetts; Hokkaido, Japan; Leiden, The Netherlands; Ann Arbor, Michigan; Münster, Germany; Nashville, Tennessee; and Prague, The Czech Republic) who presented with a VT confirmed by a target ablation site in the RV. The study was approved by the Dutch local ethics committee (G19.005) and adhered to the Declaration of Helsinki. All patients provided preprocedural informed consent.

Data collection
From each patient, a resting non-ventricular-paced ECG (25 mm/s and 10 mm/mV) before the first ablation procedure at the institution was obtained from the medical records. Data on imaging (including echocardiography, cardiac magnetic resonance imaging, and 18F-FDG-PET), biopsies, and the presence of cardiac devices were collected. Echocardiography and 18F-FDG-PET performed at the time closest to the ECG (within 6 months) were selected.

Data processing
For detailed analysis of the ECG, Leiden ECG Analysis and Decomposition Software was used. An 8-channel recording in comma-separated value format is input in this MATLAB program (Version 2016a, The Mathworks Inc., Natick, Massachusetts). After the detection of QRST complexes in the spatial velocity signal and baseline correction, Leiden ECG Analysis and Decomposition Software generates a default selection of beats for subsequent averaging. This selection can manually be adjusted, after which selected beats are averaged to generate a representative and low-noise averaged beat, which can be exported in pdf format. Then, measurements per lead were performed using the measurement tool in Adobe Acrobat Pro DC with 1200% zoom. If the 8-channel recording in comma-separated value format was not available, no averaged beat could be generated. In these cases, all measurements were performed for 3 consecutive beats by using Adobe and the measurements subsequently averaged per lead.

Data analysis and definitions
The PR interval and QT interval were determined in lead II or V5. The QRS width was measured from the earliest onset until the latest offset in any lead. RBBB was defined as QRS duration > 120 ms, with either (1) an R’ deflection in lead V1 or V2 and an S wave of greater duration than an R wave in leads I and V6 or (2) a pure dominant (notched) R wave with an R-peak time of >50 ms in lead V1 and normal R-peak time in leads V5 and V6. An atypical RBBB pattern was defined as R/S ratio < 1 in lead V1. A QRS of >120 ms with an R’ wave in lead V1 or V2 but without an S wave of greater duration than an R wave in leads I and V6 was also considered as an atypical RBBB pattern.

Microvoltage was defined as an amplitude of <0.5 mV in all leads for the limb leads and of <1.0 mV for the precordial leads. QRS fragmentation (fQRS) in a QRS of ≤120 ms was defined as notching in the R wave, a notch in the nadir of the S wave, or ≥1 R’ wave in at least 2 contiguous inferior (II and II AVF), lateral (I, AVL, V5, and V6), or RV (V1 through V3) leads. In a QRS of >120 ms, fQRS was present if there...
were >2 R’ waves or >2 notches in the R wave or nadir of the S wave. 20 An R wave was defined as any positive deflection from baseline and a notch as a change in wave front direction.

An epsilon wave was defined as a reproducible low-amplitude signal distinct from the QRS complex in leads V1 through V3.16 TAD was measured from the nadir of the S wave to the end of the QRS in leads V1 through V3 in the absence of RBBB.16 fQRS, epsilon waves, and TAD were assessed by 2 observers.

T-wave inversion (TWI) was evaluated according to the TFC as a major (TWI in leads V1 through V3 in the absence of RBBB) or a minor (TWI in leads V1 and V2 in the absence of RBBB or TWI in leads V1 through V4 in the presence of RBBB) criterion, and in at least 2 contiguous inferior (II, III, and AVF) and lateral (I, AVL, V5, and V6) leads.

Surface area of the R’ wave in leads V1 through V3

As surrogates for the size and voltages of late activated RV areas, the presence and the surface area (SA) of the R’ wave in leads V1 through V3 were measured. An R’ wave was defined as any positive deflection from baseline after an S wave (Figure 1). The SA of the R’ wave was measured by 2 observers.

Derivation cohort vs validation cohort

Patients were consecutively assigned to a derivation and a validation group on the basis of the order of incoming data and ECGs from the centers (Online Supplemental Figure 1). With the results of the first incoming (derivation) cohort, an ECG algorithm was developed to distinguish CS from ARVC and subsequently validated in the second (validation) cohort.

Statistical analysis

Categorical variables are expressed as number and percentage and compared using the χ² test or Fisher exact test. Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) and compared between groups using the Student t test or Mann-Whitney U test. Receiver

Figure 1  Examples and surface area measurement of the R’ wave. Left: Two examples of the atypical R’ wave in patients with cardiac sarcoidosis (CS). Both patients with CS also fulfilled Task Force Criteria for definite diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). Right: Two patients with ARVC with small positive deflections at the end of the QRS and deep inverted T waves.
operating characteristic curve analysis was performed to determine the optimal SA cutoff of the maximum R’ wave in leads V1 through V3. A P value of ≤0.05 was considered significant. Statistical analysis was performed using IBM SPSS version 23 (IBM Corporation, Armonk, NY).

Results
Study population
Thirteen patients with CS affecting the RV and 23 patients with ARVC were included in the derivation cohort (Online Supplemental Figure 1). Baseline characteristics are summarized in Table 1. The median time between ECG and mapping/ablation was 1 day (IQR 1–35 days). At the time of the ECG recording, 46% of patients with CS and 48% of patients with ARVC were on antiarrhythmic drugs.
**ECG parameters**

PR prolongation was present in 4 patients with CS (31%) compared with none of the patients with ARVC (Table 2). Ten patients with CS (77%) and 1 patient with ARVC (4%) fulfilled the definition of RBBB ($P < .001$); 7 of 10 patients with CS and 1 of 1 patient with ARVC had an atypical RBBB pattern with an R/S ratio of <1. In addition, the remaining 3 patients with CS and an additional 3 patients with ARVC had a QRS duration of >120 ms and an R’ wave in lead V1 or V2, but did not have an S wave larger than an R wave in leads I and V6, and therefore also had an atypical RBBB pattern.

Notably, the ECG parameters included in the TFC (epsilon wave, TAD, and repolarization abnormalities) did not differ between groups. The presence of low voltages (<1.0 mV) and/or fQRS in the RV leads (V1 through V3) was present in 8 patients with CS (62%) compared with 9 patients with ARVC ($P = .299$). The results of the interobserver agreement in TAD and fQRS are provided in the Online Supplemental Results and Online Supplemental Tables 1 and 2.

**Presence and SA of the R’ wave in leads V1 through V3**

Any R’ wave in leads V1 through V3 was present in all the 13 patients with CS compared with 11 patients with ARVC (48%) ($P = .002$). In 10 of 13 patients with CS, the R/S ratio was <1 compared with 10 of 11 patients with ARVC. In all RV leads, the SA of the R’ wave was significantly larger in CS than in ARVC (Table 2; Online Supplementary Figure 2). The median SA of the maximum R’ wave in leads V1 through V3 was 3.55 mm² (IQR 2.18–5.81 mm²) in CS and 0.00 mm² (IQR 0.00–0.43 mm²) in ARVC ($P < .001$) (Figure 2A).

**ECG algorithm**

The SA of the maximum R’ wave in leads V1 through V3 was an excellent discriminator between CS and ARVC (area under the curve 0.980; 95% confidence interval 0.945–1.000; $P < .001$) (Figure 2B). An algorithm including a PR interval of ≥220 ms, the presence of an R’ wave, and the SA of the maximum R’ wave of ≥1.65 mm² had 85% sensitivity and 96% specificity for CS (Figure 3). The positive and negative predictive values were both 92%.

There was an excellent agreement between the 2 observers regarding the SA of the maximum R’ wave with an intraclass correlation coefficient of 0.979 (95% confidence interval 0.952–0.991; $P < .001$). The median difference between the 2 observers was 0.02 mm² (IQR −0.05 to 0.04 mm²).

**Validation of the ECG algorithm**

The validation population included 18 patients with CS (mean age 56 ± 12 years; 67% male) and 40 patients with ARVC (mean age 38 ± 17 years; 95% male). In this group, 4 patients (3 CS and 1 ARVC) did not undergo RV mapping and the diagnosis VT of RV origin was based on the 12-lead VT morphology. The median SA of the maximum R’ wave in leads V1 through V3 was 4.71 mm² (IQR 1.14–6.68 mm²) in CS compared with 0.23 mm² (IQR 0.00–0.54 mm²) in ARVC ($P < .001$) (Figure 4A). The ECG algorithm showed 83% sensitivity and 88% specificity for CS (Figure 4B) in

![Figure 2](image-url)

**Figure 2** Surface area of the maximum R’ wave in leads V1 through V3. A: Scatterplot showing the surface area of the maximum R’ wave in leads V1 through V3 between cardiac sarcoidosis (CS) and arrhythmogenic right ventricular cardiomyopathy (ARVC). B: Results of the receiver operator characteristic curve analysis, with an excellent area under the curve (AUC). A surface area cutoff of ≥1.65 mm² had 85% sensitivity 85% and 96% specificity for diagnosing CS.
Discussion

This study aimed to determine the role of the ECG in distinguishing CS from ARVC in patients presenting with scar-related RV VT. The main findings are as follows: (1) an easily applicable algorithm including PR prolongation, the presence of an R’ wave, and the SA of the maximum R’ wave in leads V1 through V3 distinguishes CS from ARVC with excellent sensitivity and specificity in both the derivation and validation cohorts and (2) the “RBBB-like” pattern in CS appears to be often atypical, suggesting that it may be at least partly due to conduction block caused by myocardial scar rather than involvement of the proximal specific conduction system.

Activation sequence of the RV

Normal RV activation starts at the apical anteroseptum and the moderator band and rapidly reaches the basal regions. It progresses from the endocardium to the epicardium, taking 60–70 ms to complete. Myocardial scar might alter this activation sequence and duration, hence changing QRS morphology and (localized) QRS duration on the 12-lead ECG.

The histopathologically and electroanatomically distinct myocardial scars in CS and ARVC may differently impact RV activation and the electroanatomical characteristics of late activated areas. In CS, granuloma formation leads to patchy, well-demarcated, and often transmural RV scars. These confluent granulomas can cause localized conduction block. Subsequently, downstream activated areas with preserved voltages may be delayed activated, leading to a delayed and prolonged deflection on the ECG of considerable size. In ARVC, progressive subepicardial fibrofatty replacement may also cause prolonged RV activation, in particular causing late (independent) activation of the affected low-voltage areas, typically involving the peritricuspid region. This delayed activation may lead to the TAD and occasionally to a late deflection of low amplitude (epsilon wave). Therefore, in order to distinguish between the two etiologies, we analyzed the SA of any positive deflection (R’ wave) after an S wave in leads V1 through V3.

Indeed, an SA of the maximum R’ wave in leads V1 through V3 of ≥1.65 mm² was a good discriminator between CS and ARVC. Although in almost half of the patients with ARVC a late positive deflection was visible, the SA of this deflection was clearly larger in CS. Figure 5 provides an example of electroanatomical activation and voltage mapping in a patient with ARVC, supporting that the small late positive deflection in lead V1 (“epsilon wave”) corresponds to delayed activation of a low-voltage area.

RBBB pattern

Although a RBBB pattern is a relatively common finding in patients without structural heart disease, it has more frequently been described in patients with RV cardiomyopathy. Up to 67% of patients with CS and up to 20% of patients with ARVC (fulfilling TFC) presenting with RV VT have a RBBB-like pattern on their ECG. It is a minor criterion for the diagnosis of CS, while it complicates the diagnosis of ARVC, as TWI and TAD cannot be assessed in the presence of RBBB. Therefore, one prior study aimed to distinguish a RBBB pattern in ARVC from normal controls. In that study, an R/S ratio of <1 showed 88% sensitivity and 86% specificity to distinguish ARVC from normal controls. This atypical RBBB pattern in ARVC has been attributed to intra-RV delay caused by mutations in the cardiac desmosome affecting cell coupling rather than primary conduction disease.

In this context, it is important to mention that all but one study investigating RBBB patterns in ARVC have included patients according to TFC and therefore also patients with right-sided CS with false-positive TFC might have been included.

Intra-RV delay in ARVC has been suggested as explanation for this atypical RBBB pattern. Indeed, in ARVC peritricuspid and subepicardial involvement predominates and delayed transmural activation from the endocardium to the

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**Table 3** Twelve-lead electrocardiographic algorithm distinguishing cardiac sarcoidosis (CS) from arrhythmogenic right ventricular cardiomyopathy (ARVC) in patients with sustained ventricular tachycardia (VT) from the right ventricle (RV). *In all 4 patients with a PR interval of ≥220 ms, the surface area of the maximum R’ wave was ≥1.65 mm². † Defined as any positive deflection after an S wave.

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**Figure 3** Twelve-lead electrocardiographic algorithm distinguishing cardiac sarcoidosis (CS) from arrhythmogenic right ventricular cardiomyopathy (ARVC) in patients with sustained ventricular tachycardia (VT) from the right ventricle (RV). *In all 4 patients with a PR interval of ≥220 ms, the surface area of the maximum R’ wave was ≥1.65 mm². † Defined as any positive deflection after an S wave.

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epicardium has been reported. Delayed transmural activation in affected areas may explain the slurring of the S wave upstroke (Figure 5) or low-amplitude late deflections, but is unlikely to cause a large-sized R' wave, as observed in CS (Figure 6).

Prior studies have described different characteristics in patients with ARVC (fulfilling TFC 2010) with and without a RBBB pattern. Interestingly, patients with RBBB were older, had more RV dilatation, and had a lower RV ejection fraction. Moreover, among patients with RBBB, 77% developed biventricular heart failure during follow-up. Hence, it is interesting to speculate that some previously reported patients with ARVC and a RBBB-like pattern may have had CS, with a known more progressive course and poorer outcome.

**Level of block in patients with CS**

There are 3 types of RBBB, namely, proximal, distal, and terminal. Although in CS a proximal RBBB might be present because of granulomas involving the proximal right fascicle, it is also possible that in CS a RBBB pattern is caused by confluent dense and transmural myocardial RV free wall scar leading to late activation of the preserved pericricuspid region. In more than half of the patients with CS and a RBBB-like pattern on their ECG, this pattern was atypical with an R'/S ratio of <1 or an S wave shorter than an R wave in leads I and V6, suggesting that this might not be typical proximal RBBB. In addition, it is known from postsurgical studies that even block on a distal or terminal level can mimic typical ECG RBBB. Thus, it is interesting to speculate that transmural myocardial scar in CS may mimic typical RBBB, even when the scar location is more distal. However, subtle differences need to be appreciated.

**Clinical implications and future perspectives**

Recognition of the ECG pattern described in this study should raise the suspicion for CS in patients presenting with scar-related RV VT and should prompt further investigations (such as 18F-FDG-PET and/or biopsies) even in the absence of other features related to CS. In addition, the ECG pattern described in this study may indicate RV involvement with a higher propensity for ventricular arrhythmias, warranting careful diagnostic testing and follow-up. Last, in most of the patients, extracardiac...
Figure 5  Right ventricular (RV) endocardial electroanatomic map of a 52-year-old man with arrhythmogenic right ventricular cardiomyopathy. A: Activation map of the RV in 8 isochronals color coded according to the bar. There is no conduction block but evidence for conduction slowing at the basal free wall toward the pericricuspid area (dashed arrow). The insert panel shows a potential from the distal right fascicle (moderator band) excluding proximal right bundle branch block. B: RV activation with adjusted isochronals according to the electrocardiogram (yellow to blue reflects the upstroke of the S wave in lead V1, and purple indicates the epsilon wave) with the corresponding bipolar voltage map. The upstroke of the S wave coincides with slow activation of the free wall. The epsilon wave coincides with late activation of the basoinferior segment with reduced voltages. The propagation map of this patient is available in Online Supplemental Movie 1. Mod PA = modified posteroanterior; Mod RAO = modified right anterior oblique; RAO = right anterior oblique; RL = right lateral.

Figure 6  Right ventricular (RV) endocardial electroanatomic map of a 49-year-old woman with cardiac sarcoidosis. A: Activation map of the RV in 8 isochronals color coded according to the bar. There is a line of conduction block in the septal RV outflow tract (black line). As a result, the infundibulum is activated from the anterior segment. The insert panel shows a potential from the distal right fascicle and therefore proximal right bundle branch block is unlikely. B: RV activation with adjusted isochronals according to the electrocardiogram (yellow to blue reflects the first part of the R' wave in lead V1, and purple indicates the second part of the R' wave) with the corresponding bipolar voltage map. The second R' wave coincides with late activation of the basoinferior segment, with relatively preserved voltages. The propagation map of this patient is available in Online Supplemental Movie 2. Mod LL = modified left lateral; RAO = right anterior oblique; RL = right lateral.
sarcoidosis is asymptomatic and only diagnosed after suspicion of CS. Therefore, (extra)cardiac sarcoidosis needs to be suspected before adequate tests will be initiated. The ECG algorithm may be of help in initializing additional diagnostic tests.

Future longitudinal studies are needed to determine the time course of the development of these specific ECG features. It would be interesting to evaluate if they might predict initial VT occurrence. In this regard, it is important to mention that I study reported worse outcome for patients who developed a RBBB-like pattern compared with those who already had this QRS pattern at baseline.22

Limitations

First, this is a retrospective cross-sectional study. However, it is multicenter and a validation cohort was included. Second, the study included patients referred for VT ablation to tertiary centers, which might reflect a more advanced stage of disease and/or a specific scar pattern related to VT. Third, the cutoff provided in this study (1.65 mm² on an ECG with 25 mm/s) might be difficult to assess visually. However, a cutoff of 2.00 mm² has the same sensitivity and specificity and might be easier to apply in clinical practice (Figures 2 and 4). To use this parameter irrespective of the sweep speed, a cutoff of 6.0 or 8.0 ms·mV can be used, respectively.

Conclusion

The SA of the maximum R’ wave in leads V₁ through V₅ of ≥1.65 mm² discriminates between CS with RV involvement and ARVC in patients presenting with scar-related RV VT. This likely reflects different scar patterns, with transmural RV scars in CS leading to conduction block and subepicardial scars in ARVC leading to conduction delay. The presence of this ECG pattern should prompt careful consideration of diagnostic testing for CS.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.04.032.

References