


# Electrocardiographic findings in patients with arrhythmogenic cardiomyopathy and right bundle branch block ventricular tachycardia

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## Aims

Little is known about patients with right bundle branch block (RBBB)-ventricular tachycardia (VT) and arrhythmogenic cardiomyopathy (ACM). Our aims were: (i) to describe electrocardiogram (ECG) characteristics of sinus rhythm (SR) and VT; (ii) to correlate SR with RBBB-VT ECGs; and (iii) to compare VT ECGs with electro-anatomic mapping (EAM) data.

## Methods and results

From the European Survey on ACM, 70 patients with spontaneous RBBB-VT were included. Putative left ventricular (LV) sites of origin (SOOs) were estimated with a VT-axis-derived methodology and confirmed by EAM data when available. Overall, 49 (70%) patients met definite Task Force Criteria. Low QRS voltage predominated in lateral leads ( $n = 37$ , 55%), but QRS fragmentation was more frequent in inferior leads ( $n = 15$ , 23%). T-wave inversion (TWI) was equally

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frequent in inferior ( $n = 28, 42\%$ ) and lateral ( $n = 27, 40\%$ ) leads. TWI in inferior leads was associated with reduced LV ejection fraction (LVEF;  $46 \pm 10$  vs.  $53 \pm 8, P = 0.02$ ). Regarding SOOs, the inferior wall harboured 31 (46%) SOOs, followed by the lateral wall ( $n = 17, 25\%$ ), the anterior wall ( $n = 15, 22\%$ ), and the septum ( $n = 4, 6\%$ ). EAM data were available for 16 patients and showed good concordance with the putative SOOs. In all patients with superior-axis RBBB-VT who underwent endo-epicardial VT activation mapping, VT originated from the LV.

## Conclusions

In patients with ACM and RBBB-VT, RBBB-VTs originated mainly from the inferior and lateral LV walls. SR depolarization and repolarization abnormalities were frequent and associated with underlying variants.

## Keywords

Ventricular arrhythmia • Arrhythmogenic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy • ECG • Site of origin

## What's new?

- Patients with arrhythmogenic cardiomyopathy (ACM) and right bundle branch block (RBBB)-ventricular tachycardia (VT) display electrocardiogram abnormalities in sinus rhythm suggestive of left ventricle (LV) involvement
- The most common RBBB-VT site of origins are the inferior and the lateral LV walls.
- Further studies addressing invasive mapping of RBBB-VT in ACM will shed further light on the underlying substrate, electrophysiological characteristics of RBBB-VT and outcomes following catheter ablation of RBBB-VT in ACM.
- This work contributes to the ongoing efforts to redefine the spectrum of arrhythmic cardiomyopathies, of which RBBB-VTs originating from the LV are an important feature.

## Introduction

Arrhythmogenic cardiomyopathy (ACM) is characterized by fibro-fatty infiltration of the right ventricle (RV) or left ventricle (LV) alone or together.<sup>1</sup> Classification of ACM into three subtypes has been suggested: (i) the *classical form*, mainly affecting the RV; (ii) the *left dominant form*; and (iii) the *biventricular form*.<sup>2</sup> ACM predisposes to ventricular arrhythmias including monomorphic re-entrant ventricular tachycardia (VT). In the classical form of ACM, monomorphic VT almost always exhibits a left bundle branch block (LBBB) pattern. Although the LV is frequently involved in all forms of ACM, cases of sustained monomorphic VT with a right bundle branch block (RBBB) morphology have been scarcely reported.<sup>3</sup>

In our recently published European Survey on ACM involving 954 ACM patients with at least 1 documented episode of sustained VT, we found that 72 (7.5%) of these patients exhibited a RBBB morphology during VT, which suggests a LV arrhythmia origin.<sup>4</sup> However, recent data from Marchlinski et al.<sup>5</sup> suggest that up to half of RBBB-VT cases may originate from the inferior RV.

The present study has three objectives: (i) to extensively describe the electrocardiogram (ECG) characteristics during VT and sinus rhythm (SR) in patients with ACM and documented spontaneous RBBB-VT; (ii) to establish any correlations between SR-ECGs and the putative VT site of origin (SOO); and (iii) to compare the VT-ECG to electro-anatomic mapping (EAM) in patients with available EAM data.

## Methods

The Sheba Medical Center Institutional Review Board committee approved the study. All centres complied with local institutional review board registry protocols. The cases of 3 patients with RBBB-VT and one patient with both LBBB- and RBBB-VT were previously published.<sup>3</sup>

## Study population

The study population consisted of patients enrolled in the European Survey on ACM with RBBB-VT documented in a 12-lead ECG during the disease course.<sup>4</sup> Briefly, patients were eligible if they fulfilled the following two conditions: (i) a diagnosis of definite, probable or borderline ACM according to the revised 2010 Task Force Criteria (TFC)<sup>6</sup> and (ii) experiencing at least one spontaneous episode of sustained ( $\geq 30$  s) RBBB-VT. RBBB was defined as mono-, bi-, or triphasic R wave in V1 or a qR in V1. In patients with a probable or borderline ACM diagnosis, the modified Padua criteria for arrhythmogenic left ventricular cardiomyopathy (ALVC) were retrospectively assessed.<sup>7</sup> Study exclusion criteria included (i) patients with ventricular flutter or non-sustained VT ( $< 30$  s); (ii) patients with VT induced only by electrophysiologic study; (iii) patients in whom VT could be related to a different heart disease; and (iv) patients in whom 12-lead ECG during VT were not of optimal quality for accurate analysis ( $n = 2$ ). All genetic assays sequenced at least five desmosomal genes. Specialists of cardiac genetics at each centre reviewed genetic variants associated with ACM, and their pathogenicity was classified by using American College of Medical Genetics criteria.

## Electrocardiogram analyses

Twelve-lead baseline (sinus or atrial paced rhythms) and VT ECG readouts were analysed by using Compas EP v2.3 (EP Studios Inc., Parker, CO). All measurements were independently performed by three experienced electrophysiologists (M.L., O.T.B., Y.M.). In case of discordance, the senior investigator (B.B.) adjudicated the conflicting value. Low QRS voltage in limb leads was defined as mean amplitude limb leads  $< 0.6$  mV. The baseline ECG in SR or atrial paced rhythm was obtained  $< 1$  year before or after the first documented RBBB-VT.

## Baseline electrocardiogram

QRS amplitude was measured for each lead and averaged within lateral leads (V4, V5, V6, I, aVL) and inferior leads (II, III, aVF). Low QRS voltage in inferior leads was defined as QRS amplitude  $< 0.6$  in  $\geq 2$  leads among DII, vF, and DIII, and low QRS voltage in lateral leads was defined as QRS amplitude  $< 0.6$  in  $\geq 2$  leads among D1, vL, V5, and V6. QRS fragmentation was defined using adapted criteria for classical ARVC<sup>8,9</sup> by the presence of  $\geq 1$  of the following criteria in  $\geq 2$  contiguous leads: presence of an additional R wave (R'), notching on the top of the R wave, notching at the nadir of the S wave, and presence of a deflection at the beginning of the QRS complex. A notch was defined as an abnormal deflection within or immediately after the QRS yet not reaching the criteria for QRS fragmentation. The epsilon-wave was defined as a reproducible low-amplitude signal between the end of QRS complex and the T wave in  $\geq 1$  right precordial lead (V1 to V3). A notch or QRS fragmentation in V1-V3 could be ignored in the presence of an epsilon-wave. Terminal activation duration was measured from the nadir of the S-wave to the end of the QRS in the absence of complete RBBB.

## Right bundle branch block-ventricular tachycardia electrocardiogram

Putative LV site of origin was estimated based on the VT axis using the methodology established by Andreu et al.<sup>10</sup> RBBB-VTs with a superior

**Table 1** Patient characteristics (n = 70)

Age at diagnosis, years	45.0 ± 14.2
Age at first documented RBBB-VT, years	46.3 ± 14.5
Male sex	54 (77)
Proband	63 (90)
2010 TFC diagnostic criteria	
Definite	49 (70)
Borderline	11 (16)
Possible	10 (14)
Pathogenic mutation in the ACM spectrum <sup>a</sup>	32 (67)
<i>DSP</i>	11 (23)
<i>PKP2</i>	8 (17)
<i>PLN</i>	5 (8)
<i>DSG2</i>	3 (6)
<i>DSC2</i>	1 (2)
<i>TTN</i>	1 (2)
<i>JUP</i>	1 (2)
<i>FLNC</i>	1 (2)
<i>MYH7</i>	1 (2)
Imaging	
LVEF by MRI, % <sup>b</sup>	49.2 ± 9.9
LVEF < 50% <sup>b</sup>	27 (53)
LVEF < 35% <sup>b</sup>	2 (4)
LV late gadolinium enhancement <sup>c</sup>	33 (79)
RVEF by MRI, % <sup>d</sup>	40.4 ± 12.5
RVEF < 40% <sup>d</sup>	23 (53)
RV late gadolinium enhancement <sup>c</sup>	21 (50)
Documented clinical VT	
RBBB-VT alone	43 (61)
RBBB-VT and LBBB-VT	27 (39)
Programmed ventricular stimulation <sup>e</sup>	
Sustained RBBB-VT	28 (50)
Sustained LBBB-VT	8 (14)
Sustained RBBB-VT + RBBB-VT	12 (56)
No sustained VT	7 (13)
Anti-arrhythmic drug treatment <sup>f</sup>	
Beta-blockers only	19 (28)
Sotalol	24 (35)
Flecainide	6 (9)
Amiodarone	3 (4)
ICD	65 (93)

Data are n (%), median (interquartile range), or mean ± SD.

ACM, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; RBBB, right bundle branch block; LV, left ventricular; LVEF, LV ejection fraction; RV, right ventricular; RVEF, RV ejection fraction; TFC, Task Force Criteria; VT, ventricular tachycardia.

<sup>a</sup>Among 48 patients with a genetic test performed; including class IV (likely pathogenic) and class V (pathogenic) variants.

<sup>b</sup>Data available for 51 patients.

<sup>c</sup>Data available for 42 patients.

<sup>d</sup>Data available for 43 patients.

<sup>e</sup>Data available for 56 patients.

<sup>f</sup>Data available for 68 patients.

**Table 2** Baseline ECG characteristics (n = 70)

Rhythm	
Sinus rhythm	65 (93)
Ventricular pacing	4 (6)
Atrial fibrillation	1 (1)
Bundle branch block	
Absent	37 (53)
Complete RBBB	12 (17)
Incomplete RBBB	6 (9)
Complete LBBB	2 (3)
Incomplete LBBB	3 (4)
Intraventricular conduction disease	6 (9)
Ventricular pacing	4 (6)
QRS axis <sup>a</sup>	
≤ -90°	4 (6)
> -90° and ≤ 0°	30 (46)
> 0° and ≤ 90°	22 (33)
> 90°	10 (15)
QRS duration <sup>b</sup> , ms	122 (110–140)
QRS amplitude <sup>c</sup>	
Amplitude in limb leads, mV	0.55 (0.42–0.72)
Amplitude in all limb leads < 0.6 mV	19 (28)
Mean amplitude in all limb leads < 0.6 mV	34 (51)
Amplitude in inferior limb leads, mV	0.57 (4.00–7.50)
Amplitude in all inferior limb leads < 0.6 mV	21 (31)
Mean amplitude in inferior limb leads < 0.6 mV	33 (49)
Amplitude in lateral limb leads, mV	0.49 (0.38–0.69)
Amplitude in all lateral limb leads < 0.6 mV	37 (55)
Mean amplitude in lateral limb leads < 0.6 mV	44 (67)
R-wave amplitude in V1, mV	0.16 (0.12–0.23)
R-wave amplitude in V2, mV	0.36 (0.18–0.56)
R-wave amplitude in V3, mV	0.49 (0.31–0.79)
R-wave amplitude in V4, mV	0.70 (0.34–0.98)
R-wave amplitude in V5, mV	0.67 (0.37–1.02)
R-wave amplitude in V6, mV	0.53 (0.27–0.78)
QRS fragmentation and Epsilon-wave <sup>a</sup>	
Notch within QRS in inferior limb leads (≥ 2/3 leads)	12 (18)
Notch after QRS in inferior limb leads (≥ 2/3 leads)	6 (9)
QRS fragmentation in inferior limb leads (≥ 2/3 leads)	15 (23)
Notch within QRS in lateral limb leads (≥ 2/3 leads)	8 (12)
Notch after QRS in lateral limb leads (≥ 2/3 leads)	5 (8)
QRS fragmentation in lateral limb leads (≥ 2/3 leads)	10 (15)
Epsilon-wave in V1–V3 (≥ 1/3 leads)	10 (15)
Notch within QRS in V1–V3 (≥ 2/3 leads) <sup>d</sup>	29 (52)
QRS fragmentation in V1–V3 (≥ 2/3 leads) <sup>d</sup>	10 (15)
Repolarization abnormalities <sup>a</sup>	
TWI in inferior leads (≥ 2/3 leads)	28 (42)
TWI in lateral leads (≥ 2/4 leads)	27 (41)
TWI in V1–V3 (3/3 leads)	10 (15)
Precordial progression toward deeper negative T-waves	16 (24)
ST segment modifications (≥ 2 leads)	9 (14)

Data are n (%), median (interquartile range), or mean ± SD.

ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block.

<sup>a</sup>Among 66 patients with an intrinsic QRS.

<sup>b</sup>Data available for 65 patients with an intrinsic QRS.

<sup>c</sup>For 54 patients without complete RBBB or ventricular pacing.

<sup>d</sup>Data available for 56 patients with an intrinsic QRS and no epsilon-wave in V1–V3.

axis were assessed according to the description from Marchlinski et al.<sup>5</sup> for a possible inferior RV origin.<sup>5</sup> Superior-axis RBBB-VTs with an early precordial R-wave transition ( $\leq V3$ ) were classified as consistent with the description from Marchlinski et al.<sup>5</sup>

## Electro-anatomic mapping

Among the study population, 19 patients underwent VT ablation with an EAM system. When the hemodynamic status allowed for VT mapping, ECG tracings of mapped VT were carefully compared to clinical VTs recorded on surface ECG to ensure their similarity. Low-bipolar voltage was defined as local electrogram bipolar voltage amplitude  $<1.5$  mV. Participating centres were asked to describe the low-bipolar voltage areas based on an endo-epicardial simplified segmentation including five segments for the endocardial RV, five for the epicardial RV, nine for the endocardial LV, and nine for the epicardial LV. All centres were asked to provide images of bipolar voltage mapping, which, when available, were compared to the data mentioned above.

## Statistical analyses

The data are presented as mean (SD), median [interquartile range (IQR)] or count (percentage), depending on their distribution. Non-parametric statistical tests were systematically used for comparisons because of small sample sizes. Fisher's exact, Mann-Whitney *U* and Kruskal-Wallis tests were used as appropriate. Correlation analyses of continuous variables involved linear regression with *P* values for Pearson's correlation coefficients. Statistical analyses were performed with JMP v15.2.1 (SAS Institute Inc., Cary, NC) and PRISM v7 (GraphPad, San Diego, CA). *P* < 0.05 was considered statistically significant.

## Results

### Study population

From the population of the European Survey on ACM (*n* = 954 patients with ACM and documented VT), we included 70 with documented RBBB-VT fulfilling study inclusion criteria. Clinical characteristics are in *Table 1*. RBBB-VT was the only documented VT in 43 (61%) patients, but 27 (39%) patients had both RBBB- and LBBB-VT documented in their clinical history. Detailed characteristics and Padua criteria for ALVC diagnosis of the 21 (30%) patients with borderline or possible 2010 TFC ARVC diagnosis are in [Supplementary material online, Table S1](#).<sup>6,7</sup> Most of these patients had several ALVC criteria. On 24-hr Holter monitoring (available in 54 patients), 29 (54%) patients had >1000 ventricular premature complexes, 37 (69%) >400 complexes and 4 (7%) sustained VT. Exercise test was performed in 33 (47%) patients. Sustained RBBB-VT was induced in 2 (6%) patients, RBBB-PVCs were present in 7 (21%) and LBBB-PVC in 6 (18%). In total, 54 patients underwent coronary angiography; 53 (98%) patients had no or non-significant coronary artery disease, and one (2%) patient exhibited 70% circumflex artery stenosis that did not require revascularization. Echocardiography revealed LV and RV wall motion abnormalities in 40 (57%) and 44 (63%) patients, respectively. The first ventricular arrhythmia was RBBB-VT in 52 (74%) patients, LBBB-VT in 10 (14%) and aborted cardiac arrest in 8 (11%). Circumstances during which the first RBBB-VT occurred [data available in 39 (55%) patients] included: exercise in 20 (51%) patients, rest in 14 (36%), emotional stress in 3 (8%), and myocarditis in 2 (5%) patients

Median follow-up after ACM diagnosis was 8.6 (IQR 4.3–16.3) years. Overall, eight patients died or underwent heart transplantation. Cumulative survival without death or heart transplantation was estimated at 95% [95% confidence interval (CI) 86–98], 92% (95% CI 79–97), and 82% (95% CI 59–93) at 1, 5, and 10 years, respectively, after ACM diagnosis (see [Supplementary material online, Figure S1](#)).

**Table 3** Ventricular tachycardia ECG characteristics (*n* = 70)

Pattern in ECG lead I	
Q	21 (30)
R or Rs	29 (42)
rS	11 (16)
qrs	3 (4)
rs or RS	5 (7)
Pattern in ECG lead II	
Q	38 (54)
R or Rs	26 (38)
rS	2 (3)
qrs or qr	1 (1)
rs, rsr or RS	3 (4)
Compatibility with the description from Marchlinski et al. <sup>5</sup>	
No	60 (86)
Yes, infero-median	6 (9)
Yes, infero-apical	4 (6)
Maximum QRS duration <sup>b</sup>	200 (155–218)
Precordial transition pattern <sup>a</sup>	
Dominant (positive concordance)	17 (25)
Early reverse	16 (24)
Late reverse	15 (63)
Abrupt loss	10 (15)
Regression growth (double transition)	11 (17)
Precordial transition	
None (positive concordance)	17 (25)
V2	6 (9)
V3	13 (19)
V4	11 (16)
V5	6 (9)
V6	6 (9)
Double transition	11 (17)
V2 and V3	1 (1)
V2 and V4	3 (4)
V2 and V5	4 (6)
V3 and V4	1 (1)
V4 and V5	1 (1)
V4 and V6	1 (1)

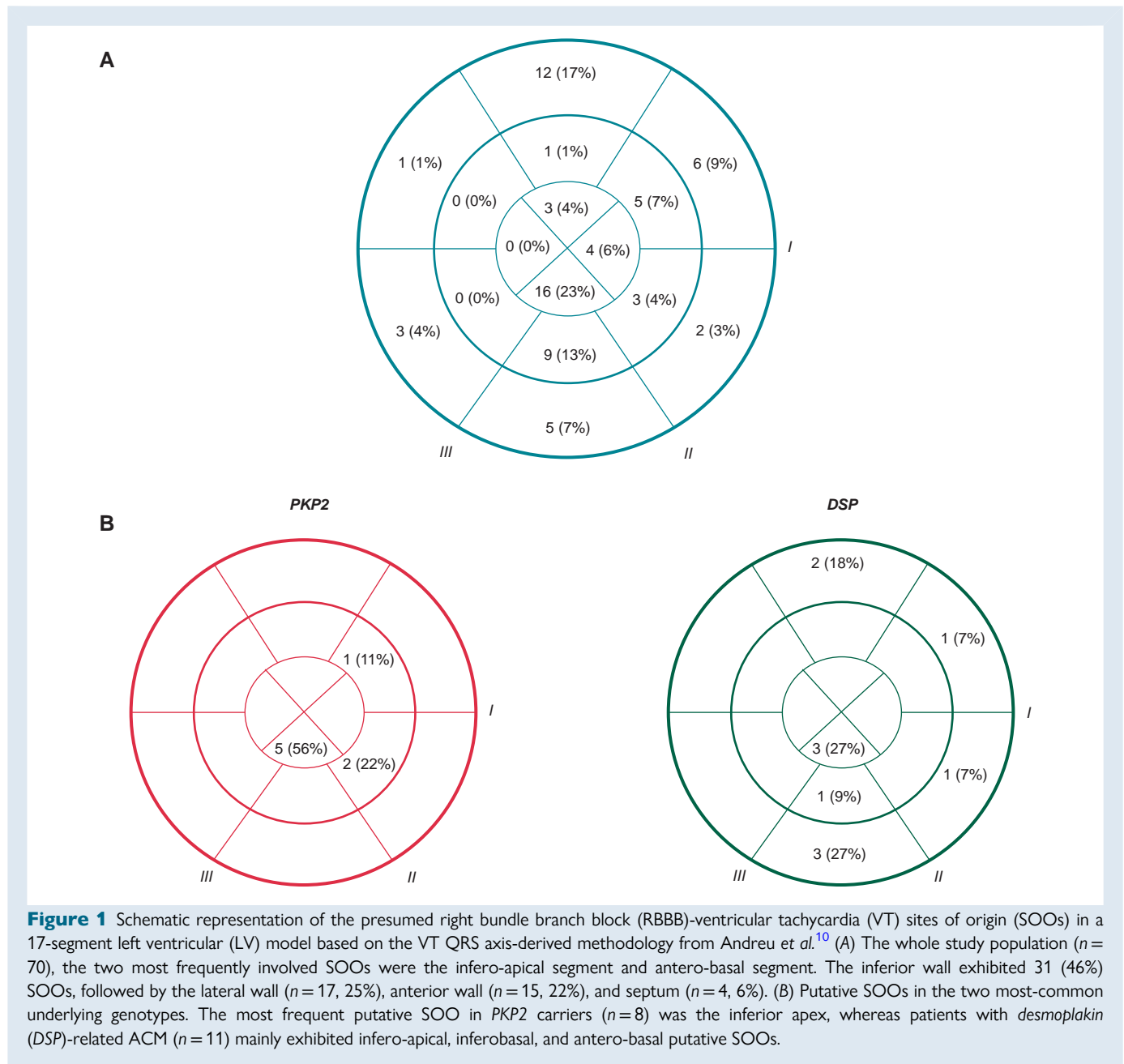
Data are *n* (%), median (interquartile range), or mean  $\pm$  SD. ECG, electrocardiogram.

<sup>a</sup>Data available for 69 patients.

<sup>b</sup>Data available for 61 patients.

### Baseline electrocardiogram

Main baseline ECG characteristics are in *Table 2*. Four patients with a ventricular paced QRS were excluded from the QRS analysis. Most patients (*n* = 34, 52%) exhibited a left-axis. Mean QRS amplitude was comparable in inferior and lateral leads (*P* = 0.22). Low QRS voltage predominated in lateral leads, but QRS fragmentation was more frequent in inferior leads. T-wave inversion (TWI) was equally

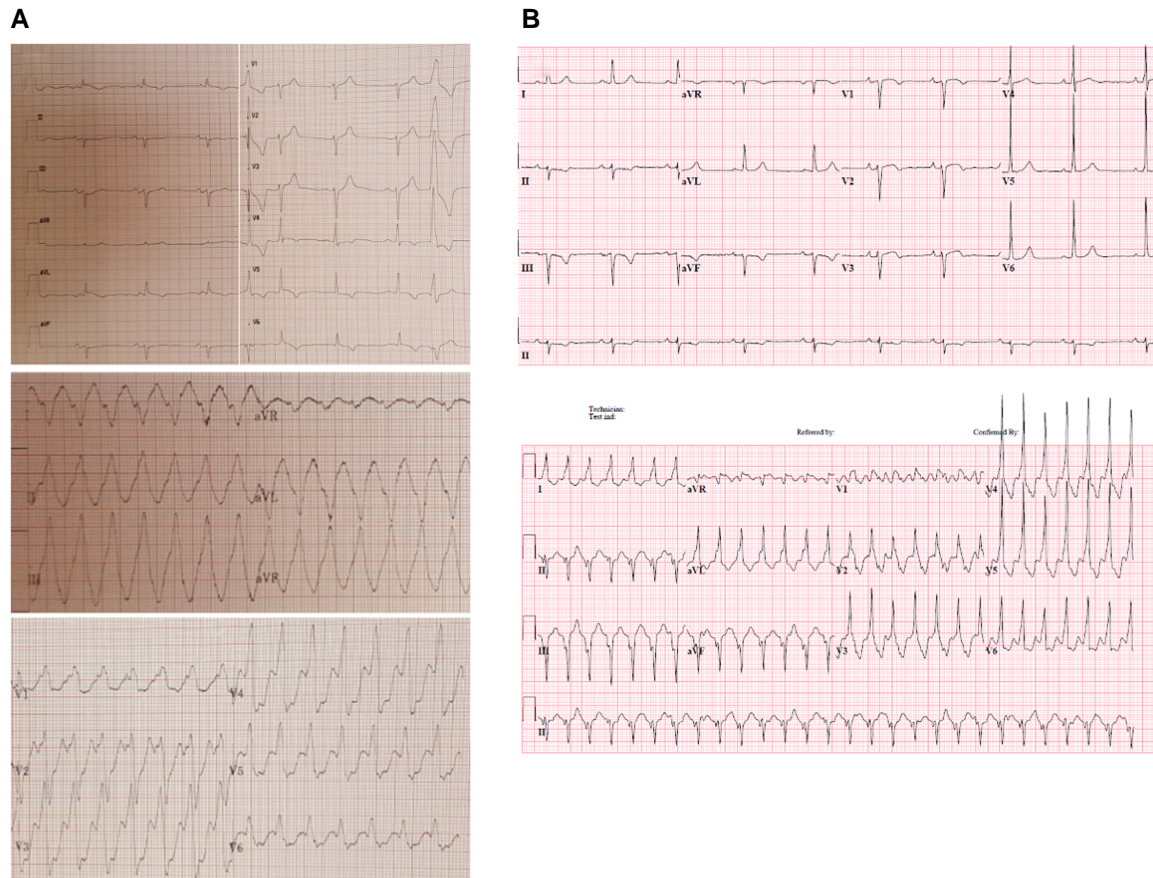


**Figure 1** Schematic representation of the presumed right bundle branch block (RBBB)-ventricular tachycardia (VT) sites of origin (SOOs) in a 17-segment left ventricular (LV) model based on the VT QRS axis-derived methodology from Andreu *et al.*<sup>10</sup> (A) The whole study population ( $n = 70$ ), the two most frequently involved SOOs were the infero-apical segment and antero-basal segment. The inferior wall exhibited 31 (46%) SOOs, followed by the lateral wall ( $n = 17$ , 25%), anterior wall ( $n = 15$ , 22%), and septum ( $n = 4$ , 6%). (B) Putative SOOs in the two most-common underlying genotypes. The most frequent putative SOO in *PKP2* carriers ( $n = 8$ ) was the inferior apex, whereas patients with *desmoplakin* (*DSP*)-related ACM ( $n = 11$ ) mainly exhibited infero-apical, inferobasal, and antero-basal putative SOOs.

frequent in inferior ( $n = 28$ , 42%) and lateral ( $n = 27$ , 40%) leads. TWI in inferior leads was associated with reduced LV ejection fraction (LVEF;  $46 \pm 10$  vs.  $53 \pm 8$ ,  $P = 0.02$ ). QRS duration was inversely correlated with LVEF (Pearson  $Rho -0.39$ ,  $P = 0.008$ ). A *phospholamban* (*PLN*) mutation was significantly associated with low QRS voltage in all limb leads ( $n = 4/5$ , 80%, vs.  $n = 15/61$ , 25%, for other genes,  $P = 0.02$ ). A *desmoplakin* (*DSP*) mutation was significantly associated with QRS fragmentation in inferior leads ( $n = 6/11$ , 55%, vs.  $n = 9/55$ , 16%,  $P = 0.02$ ) and with low QRS voltage in lateral limb leads ( $n = 10/11$ , 91% vs.  $n = 34/56$ , 61%,  $P = 0.01$ ). As compared with patients with RBBB-VT alone, those with both RBBB-VT and LBBB-VT documented clinically more frequently exhibited an epsilon-wave in V1-V3 (7, 27%, vs. 3, 8%,  $P = 0.03$ ) and TWI in inferior leads (15, 58%, vs. 13, 33%,  $P = 0.04$ ) (see [Supplementary material online, Table S2](#)).

### Right bundle branch block-ventricular tachycardia: electrocardiogram sites of origin in the left ventricle

ECG characteristics of RBBB-VT ECGs are in [Table 3](#). The putative RBBB-VT SOOs were estimated with the QRS axis-derived methodology from Andreu *et al.* and are reported in [Figure 1A](#). The two most frequently involved SOOs were the infero-apical segment ( $n = 16$ , 23%) and the antero-basal segment ( $n = 12$ , 17%). Overall, the inferior wall harboured 31 (46%) SOOs, followed by the lateral wall ( $n = 17$ , 25%), anterior wall ( $n = 15$ , 22%), and septum ( $n = 4$ , 6%). The most frequent putative SOO in *PKP2* carriers was the inferior apex, whereas *DSP*-ACM patients ( $n = 11$ ) mainly exhibited infero-apical, infero-basal and antero-basal putative SOOs ([Figure 1B](#)). The proportion of inferior SOOs was more frequent in patients with than without TWI in inferior



**Figure 2** Representative examples of right bundle branch block (RBBB)-ventricular tachycardias (VTs) and their corresponding sinus rhythm (SR) electrocardiography (ECG) graphs. (A) Top: SR ECG showing T-wave inversion (TWI) in lateral leads and low QRS voltage in lateral limb leads. Bottom: RBBB-VT with a left QRS axis-positive concordance in the precordial leads, corresponding to an LV latero-basal exit. (B) Top: SR ECG showing TWI and low QRS voltage in inferior leads. Bottom: RBBB-VT with superior QRS-axis and positive concordance in the precordial lead, suggesting an LV infero-basal exit.

limb leads (16/28, 57%, vs. 15/38, 39%), yet not reaching statistical significance ( $P = 0.2$ ) (see example in Figure 2A). Conversely, a lateral SOO predominated in patients with TWI in lateral leads (9/27, 33%), whereas a lateral SOO was involved in a few patients without TWI in lateral leads (8/40, 20%) ( $P = 0.3$ ) (see example in Figure 2B).

### Assessment of putative sites of origin by electro-anatomical data

Overall, 19 patients underwent catheter ablation and among them, the clinical RBBB-VT exit site could be identified by the mean of activation mapping or pacemapping in 16. In these patients, the VT exit site showed good concordance with the putative SOOs estimated by 12-lead ECG (Table 4). The VT exit was localized by activation mapping in the epicardial LV in 12/13 (92%) patients with endo-epicardial mapping, with further successful ablation. The VT exit was localized in the LV endocardium in a single patient (1/13) with endo-epicardial mapping. Among the three patients with LV endocardial access only, the VT was successfully mapped and ablated in the endocardial LV in two patients. Although the inferior wall was the predominant putative SOO, many VTs (9/16, 56%) were mapped in the lateral epicardial LV but still remained in the vicinity of the putative SOO  $\pm 1$  segment (15/16, 94%), with the exception of 1 patient (Table 4, Patient 26).

### Origin of right bundle branch block-ventricular tachycardias with a superior axis

Superior-axis RBBB-VTs ( $n = 30$ , 43%) were the predominant RBBB-VT category (Figure 1A). Among these cases, only 10 (32%) were compatible with the ECG description from Marchlinski et al.<sup>5</sup> that suggests an inferior RV origin, and 12 patients underwent a catheter ablation procedure with EAM. Endocardial LV and epicardial mapping were performed in 9/12 patients with superior-axis RBBB-VT who underwent ablation. All of these patients exhibited a LV epicardial low-voltage area. The clinical superior-axis RBBB-VT could be mapped in 7/12 patients and the VT critical isthmus was located in the epicardial infero-lateral LV in 3 patients, in the epicardial inferior LV in 3 patients, and in the endocardial infero-septal LV in 1 patient. Among the seven mapped VTs, four were compatible with the ECG description from Marchlinski et al.<sup>5</sup> and were found to exit at the epicardial inferior LV (2 patients), in the epicardial infero-lateral LV (1), and in the endocardial infero-septal LV (1). Figures 3 and 4 show examples of two patients with a clinical superior-axis RBBB-VT compatible with the description from Marchlinski et al. that suggests an inferior RV origin that was in fact ablated in the LV. Of note, in one patient, a LV epicardial infero-lateral critical isthmus responsible for a clinical superior-axis RBBB-VT

coexisted with an epicardial lateral isthmus responsible for an inferior-axis RBBB-VT (Figure 3).

## Discussion

This multicentre study is the first to assess RBBB-VT morphology and its correlations with baseline ECG, genetic and electro-anatomical data in 70 patients with ACM and documented RBBB-VT. Our main findings are that (i) depolarization and repolarization abnormalities suggesting LV involvement such as low QRS voltage and TWI in inferior/lateral leads were frequent; (ii) the most frequent SOOs were the inferior and lateral LV walls; and (iii) RBBB-VTs with a superior axis originated from the inferior LV on EAM.

### Study population and inclusion criteria

The study population is a subset of patients from the European Survey on ACM, which reported the relative prevalence of LBBB- and RBBB-VT in 954 patients with ACM and documented VT.<sup>4</sup> We included patients with a possible and borderline diagnosis according to the 2010 TFC criteria. The phenotypical landscape of ACM, including biventricular and left-dominant ACM, is wide and not adequately portrayed by current TFC criteria.<sup>6,11,12</sup> In our study, 30% of patients did not fulfill definite TFC criteria, which is an expected finding, considering that RBBB-VT and LV involvement detected by cardiac MRI does not count as diagnostic criteria in the 2010 TFC.

Other studies focusing on biventricular or left-dominant ACM also included patients with borderline/possible diagnoses.<sup>11,13,14</sup> In the largest cohort of 107 patients with DSP-related ACM, only 34% fulfilled definite TFC criteria, a proportion similar to ours.<sup>14</sup> Also, several points of our population suggest ACM rather than dilated cardiomyopathy: (i) pathogenic variants belonged to the ACM spectrum; (ii) most of our patients had RV dysfunction, which is rare in DCM<sup>12</sup>; and (iii) we found a high proportion of inverted T-waves in infero-lateral leads and low QRS voltage in limb leads are comparable to a recent ECG description of patients with LV-dominant ACM.<sup>15</sup> Last, most of our patients retrospectively fulfilled the Padua criteria,<sup>7</sup> except those without genetic results mandatory for criteria fulfillment. Excluding patients with borderline/possible diagnosis would likely have resulted in excluding patients with LV-dominant ACM.

### Sinus rhythm electrocardiogram abnormalities

Although ECG abnormalities in ACM with LV involvement have been previously described,<sup>16</sup> we established associations between SR abnormalities, underlying genotype and RBBB-VT morphology. Overall, 46% of our patients had left-axis deviation; 42% and 41% had TWI in the inferior and lateral leads; and 51% had low QRS voltage in limb leads. TWI in inferior leads was associated with low LVEF. These findings are comparable to those reported previously.<sup>13,15,16</sup> However in a recent study, TWI beyond V3 was not correlated with LV involvement but rather with severe RV dilatation in a recent study.<sup>17</sup> Also, repolarization abnormalities have been associated with the extent of RV remodelling as quantified by EAM.<sup>18</sup> The underlying genotype was not disclosed and many patients had severe RV systolic dysfunction. A difference should be made between advanced 'RV-dominant' disease in which LV involvement is a late feature and a marker of disease severity and biventricular or LV-dominant disease. In our study, only 17% of patients had V1-3 TWI, which suggests low to moderate RV involvement.

A *PLN* mutation was significantly associated with low QRS voltage in limb leads, in line with a previous study on *PLN*-associated ACM.<sup>19</sup> Low QRS voltage has been associated with diffuse LV fibrosis, and severe and diffuse LV fibrosis is a hallmark of *PLN*-related ACM.

We report for the first time an association between a DSP pathogenic variant and QRS fragmentation in inferior leads. DSP pathogenic variants

were particularly represented in our study including patients with sustained VT, a finding possibly related to the highly arrhythmogenic nature of this ACM subform. DSP-related ACM is associated with circumferential subepicardial LV fibrosis, predominating in the LV infero-lateral wall.<sup>14</sup> DSP-related ACM is also associated with LV wall thinning and inflammation and is particularly prone to the occurrence of malignant arrhythmia.<sup>14</sup> QRS fragmentation has been proposed as an alternative to high-amplification ECG-detected epsilon waves as a marker of depolarization abnormalities in 'RV-dominant' ACM.<sup>8</sup> QRS fragmentation may be useful in LV-dominant ACM, particularly in DSP-related ACM, in which it could be a marker of arrhythmogenic fibrosis involving the LV.<sup>20</sup>

### Sites of origin of right bundle branch block-ventricular tachycardia in arrhythmogenic cardiomyopathy

We used a simple method to assess the LV putative SOOs based on the VT QRS axis, created by Andreu et al.<sup>10</sup> The putative SOO correlated well with the VT exit as defined by VT activation mapping during ablation procedures in 17 patients. Most putative SOOs remained within 1 segment of the VT exit. The two most frequently involved SOOs were the infero-apical and antero-basal segments, both mainly corresponding to a lateral VT exit in patients who underwent VT ablation.

### Superior-axis right bundle branch block-ventricular tachycardias

In our study, superior axis RBBB-VTs were the predominant RBBB-VT type. In a recent work from Marchlinski et al.<sup>5</sup> including 110 ARVC

**Table 4** Comparison of presumed RBBB-VT sites of origin to VT mapping

Pt. N.	Presumed LV RBBB-VT site of origin <sup>a</sup>	VT exit determined by EAM
2	Infero-apical*	Epicardial LV, mid infero-lateral
10	Infero-apical*	Epicardial LV, mid inferior
12	Antero-basal	Endocardial LV, mid antero-lateral <sup>b</sup>
17	Infero-apical*	Epicardial LV, mid inferior
18	Infero-apical	Endocardial LV, mid infero-septal <sup>b,c</sup>
19	Mid inferior	Endocardial LV, infero-basal <sup>b,c</sup>
20	Basal antero-lateral	Epicardial LV, basal-lateral
21	Mid anterior	Epicardial LV, basal-lateral
22	Basal antero-lateral	Epicardial LV, basal-lateral
23	Infero-apical*	Endocardial LV, mid infero-septal
25	Basal antero-lateral	Epicardial LV, basal antero-lateral
26	Infero-septo-basal	Epicardial LV, basal anterior
28	Mid infero-lateral	Epicardial LV, mid inferior
44	Antero-basal	Epicardial LV, basal lateral
45	Infero-basal	Epicardial LV, basal lateral
46	Infero-basal	Epicardial LV, basal lateral

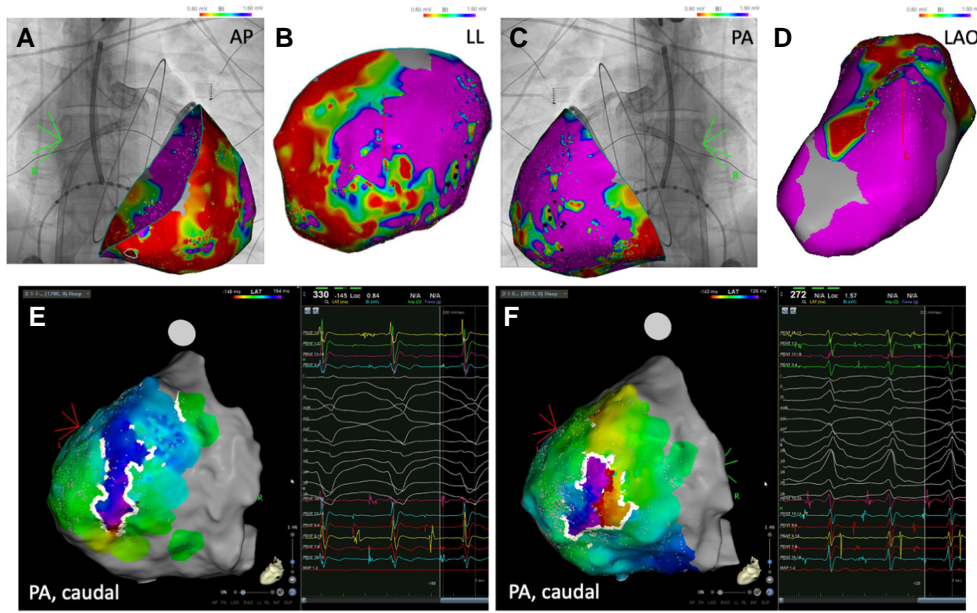
EAM, electro-anatomic mapping; ECG, electrocardiogram; LV, left ventricle; RBBB, right bundle branch block; VT, ventricular tachycardia.

\*VT morphology compatible with the ECG description from Marchlinski et al.<sup>5</sup> for an inferior RV origin.

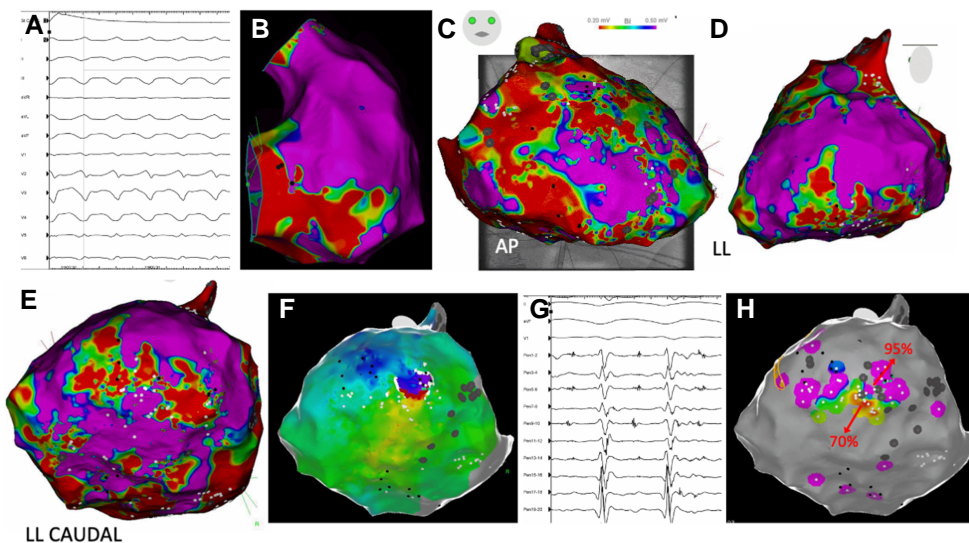
<sup>a</sup>Using the methodology from Andreu et al.<sup>10</sup>

<sup>b</sup>No epicardial mapping.

<sup>c</sup>Identified by pacemapping.



**Figure 3** Right bundle branch block (RBBB)-ventricular tachycardia (VT) mapping in a 32-year-old woman with *desmoplakin* (DSP) biventricular arrhythmogenic cardiomyopathy and a subcutaneous implantable cardioverter-defibrillator. (A–C) Epicardial bipolar voltage mapping (0.5–1.5 mV) performed with a Pentaray multipolar catheter (Biosense Webster, Irvine, CA) showing extensive RV epicardial scar and patchy LV scar at the inferior and lateral walls. (A) antero-posterior (AP) view, (B) left lateral (LL) view, (C) postero-anterior (PA) view. (D) Endocardial LV mapping showing limited anterior and latero-basal scar. (E) Activation mapping of the superior axis clinical RBBB-VT showing an epicardial infero-lateral LV critical isthmus. (F) During the same procedure, an inferior axis RBBB-VT was induced and used an epicardial lateral isthmus located in the vicinity of the clinical VT.



**Figure 4** A case-based illustration of a 48-year-old man with biventricular mutation-negative arrhythmogenic cardiomyopathy [definite Task Force Criteria (TFC) diagnosis with major depolarization, repolarization and structural criteria]. (A) The clinical right bundle branch block (RBBB)-ventricular tachycardia (VT) with an early precordial transition and QRS is compatible with the Marchlinki et al. description suggesting an infero-apical right ventricular (RV) origin. (B) Endocardial RV bipolar voltage mapping (Pentaray) showing a typical sub-tricuspid scar area. (C–E) Epicardial bipolar voltage mapping showing extensive RV and inferolateral left ventricular (LV) scar. (F) Activation mapping showing the macro-reentrant clinical VT with a critical isthmus located in the epicardial infero-apical LV. (G) Mid-diastolic potentials recorded within the critical isthmus. (H) Pace-mapping shows a transition from high (95%) to low (70%) concordance with the clinical VT, a finding compatible with a critical isthmus site.



patients, 17% had RBBB-VT, and surprisingly, 58% of the RBBB-VTs had a RV origin from the inferior RV wall. RV origin was assessed by activation or pace-mapping at the RV endo- or epicardium. The proposed mechanism was that VT originating from a dilated RV inferior wall can produce RBBB-VT in the precordial leads. The VT QRS morphology indicating an RV origin had an early precordial transition in V2–V3 and a left-superior VT QRS axis. In our study, among VTs with a superior axis, only 10 (32%) were compatible with this description. Among patients who underwent VT mapping and ablation, all superior-axis VTs were mapped in the inferior LV, mostly epicardially, including those compatible with the description from Marchlinski *et al.* These findings are not incompatible. Their study population was composed of 'RV-dominant' forms fulfilling definite TFC criteria, with mainly RV structural dysfunction and arrhythmogenic substrate, which was also emphasized by all patients with RBBB-VT also demonstrating LBBB-VT.

## Study limitations

The retrospective nature of our study conveys an inherent risk of selection bias. Second, our analysis of the putative SOOs is mainly based on a methodology using 12-lead ECG VT QRS axis analysis, in a population not including ACM patients. Although the putative SOOs showed good concordance with VT exits mapped during VT ablation, caution should be applied. An ongoing study derived from the European Study on ACM will address VT mapping and ablation in this patient population. Fourth, SR ECGs were performed at different centres with different filters, which were not disclosed for most patients and which could alter visualization of complex abnormalities such as QRS fragmentation, QRS notching or epsilon-waves. This prevented us to assess QRS fragmentation by quantitative methods which are more robust. Fifth, published criteria for ECG identification of epicardial exits were not included in VT tracings analyses, and we found high inter-observer variability when assessing these criteria. Re-entrant circuits are mostly subepicardial in ACM, and this feature should remain true for VTs originating from the thicker LV.

## Conclusions

In a multicentre study including 70 patients with ACM and clinically documented RBBB-VT, we found frequent SR depolarization and repolarization abnormalities suggesting LV involvement, including low QRS voltage and TWI in inferior/lateral leads. VT seemed to originate mainly from the inferior and lateral LV walls, whereas RBBB-VTs with a superior axis originated from the inferior LV rather than the RV.

## Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

Data will be provided upon reasonable request to the corresponding author.

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