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QRS dispersion detected in ARVC patients and healthy gene carriers using 252-leads body surface mapping: an explorative study of a potential diagnostic tool for arrhythmogenic right ventricular cardiomyopathy

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Abstract

Background: The diagnosis of ARVC remains complex requiring both imaging and electrocardiographic (ECG) techniques. The purpose was therefore to investigate whether QRS dispersion assessed by body surface mapping (BSM) could be used to detect early signs of ARVC, particularly in gene carriers.

Methods: ARVC patients, gene carriers without a history of arrhythmias or structural cardiac changes and healthy controls underwent 12-lead resting ECG, signal-averaged ECG, echocardiographic examination, 24-hours Holter monitoring, and BSM with electrocardiographic imaging. All 252-leads BSM recordings and 12-leads ECG recordings were manually analyzed for QRS durations and QRS dispersion.

Results: Eight controls, 12 ARVC patients with definite ARVC and 20 healthy gene carriers were included. The ECG-QRS dispersion was significantly greater in ARVC patients (42 vs. 25 ms, $p < .05$), but failed to fully differentiate them from controls. The BSM-derived QRS dispersion was also significantly greater in ARVC patients versus controls (65 vs. 29 ms, $p < .05$) and distinguished 11/12 cases from controls using the cut-off 40msec. The BSM derived QRS dispersion was abnormal (> 40 ms) in 4/20 healthy gene carriers without signs of ARVC, which may indicate early depolarization changes.

Conclusions: QRS dispersion, when assessed by BSM versus 12-lead ECG, seem to better distinguish ARVC patients from controls, and could potentially be used to detect early ARVC in gene carriers. Further studies are required to confirm the value of BSM-QRS dispersion in this respect.

KEYWORDS
arrhythmogenic, cardiomyopathy, QRS dispersion, right ventricular

1 | INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by ventricular arrhythmias, sudden cardiac death (SCD), and fibrofatty replacement of predominately the right ventricle (RV), even though the left ventricle (LV) may be involved at later stages of the disease.[1] The diagnosis of ARVC, particularly at early stages of the disease such as in gene carriers, is complex

and requires extensive work-ups, including electrocardiogram (ECG), cardiac imaging, signal average ECG (SAECG), histology, and genetic tests.[2]

Resting ECG has a central role for the diagnosis, evaluating repolarization, and depolarization changes during sinus rhythm, as well as morphologic changes of the QRS complex during ventricular arrhythmias.[2] The depolarization abnormalities considered as criteria for the ARVC diagnosis are the presence of epsilon waves on surface ECG, late potentials on SAECG and prolonged terminal activation duration (TAD).[2] Although the presence of epsilon waves is a major diagnostic criterion, the high interobserver variability and their manifestation at later stages of the disease makes them less useful in that respect.[2,3] A TAD > 55ms in leads V1-V3 and the presence of late potentials on SAECG are minor diagnostic criteria.[2,4,5] Late potentials are not specific for ARVC and their value for the detection of a mild disease has not yet been evaluated.[6] Other variables reflecting depolarization abnormalities, such as QRS fragmentation and low voltage are seen in patients with advanced disease and are not included in the Task Force Criteria (TFC) of ARVC.[2,7–11]

In previous studies, QRS dispersion on resting ECG has been suggested as an independent predictor for SCD in ARVC and has been associated with RV dilatation and ventricular arrhythmias.[12,13] The value of QRS dispersion as a diagnostic criterion for ARVC has, however, not yet been established, although it may mechanistically be justified, as a higher QRS dispersion could reflect a more extensive tissue scarring and delayed conduction.

The novel noninvasive Body Surface Mapping (BSM) technique, using a 252-unipolar leads vest, enables the recording of multiple electrograms from the whole thorax and further a reconstruction of epicardial potentials for mapping during tachycardia.[14] Other applications using the epicardial signals has been reported in ARVC patients.[15]

The purpose of the present study was to investigate whether QRS dispersion of the surface ECG signals recorded by the 252-lead BSM vest, could provide further diagnostic information in gene carriers or in patients with early stages of ARVC.

2 | METHODS

2.1 | Patient selection

A cross-sectional study of ARVC patients, healthy gene carriers, and controls was performed at the Uppsala University Hospital during the period December 2018 and April 2019. ARVC patients with a definite diagnosis according to 2010 TFC were prospectively included in the study. Healthy gene carriers who had tested positive for the family mutation, but who had no arrhythmias or structural changes on two-dimensional echocardiography focusing on the right ventricle were also prospectively included. The presence of repolarization changes (precordial T wave inversion) or depolarization changes (TAD > 55ms or presence of late potentials on SAECG as defined by having at least 1/3 late potential criteria) were, however, allowed in order to study consistencies with the BSM system. Healthy family members who had tested negative for the known family mutation and showed no echocardiographic or electrocardiographic abnormalities served as controls. Pacemaker-depended patients, or those with complete bundle branch block, other cardiomyopathy, channelopathy, coronary artery disease, heart failure unrelated to ARVC, or history of cardiac surgery were excluded from the study. Pregnant women and patients with BMI > 31 were excluded because of the radiation exposure from chest computer tomography (CT).

The study was approved by the Regional Ethical Review Board (Dnr2018/369) and complied with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 | Study design

All patients, gene carriers and healthy controls underwent a diagnostic evaluation for ARVC including resting 12-leads ECG (including V4R), SAECG, 24-h Holter monitoring and two-dimensional (D)-echocardiography with special focus on the right ventricle. A 252-unipolar leads BSM system (CardioInsight, Medtronic, MN, USA) recorded unipolar body surface potentials at a sampling rate of 1000 Hz during a ten minutes recording followed by a low radiation dose thoracic CT scan for later analysis of epicardial signals.[14] In the present study, the QRS dispersion, calculated by the 252 recorded signals using the BSM vest, was analyzed. The analysis of surface ECG repolarization changes and epicardial signals was outside the scope of this study and will be reported elsewhere.

2.3 | Analysis of QRS dispersion from 12 lead ECG

A standard 12-lead ECG was recorded (10 mm/mV, paper speed 50 mm/s) in all patients. The right precordial lead V4R was obtained by moving the V4 lead at the right midclavicular line on the fifth intercostal space.

The overall mean QRS duration of all QRS complexes was automatically calculated. The QRS-complex duration in each lead was manually measured using digital calipers starting from the beginning of the QRS complex to its end and calculated as the mean value of three consecutive QRS complexes by one cardiologist blinded to the diagnosis (VK). Whenever the onset or offset of the QRS complex could not be identified, the lead was excluded. The standard deviation of all measured QRS durations in each lead was also calculated.

The ECG leads were grouped in four different anatomical groups: right precordial leads (V1-V3), left precordial leads (V4-V6), lateral leads (I, aVL, aVR), and inferior leads (II, III, aVF). The V4R was reported separately, as it is not part of a conventional surface ECG.

For the assessment of intraobserver variability, 20% of randomly selected samples were analyzed twice by the same cardiologist.

The QRS dispersion from the 12-lead ECG (ECG-QRS dispersion) was defined as the difference between the minimum and maximum mean QRS duration from all 12 ECG leads. The QRS durations selected for the assessment of the ECG-QRS dispersion were not corrected for the heart rate.
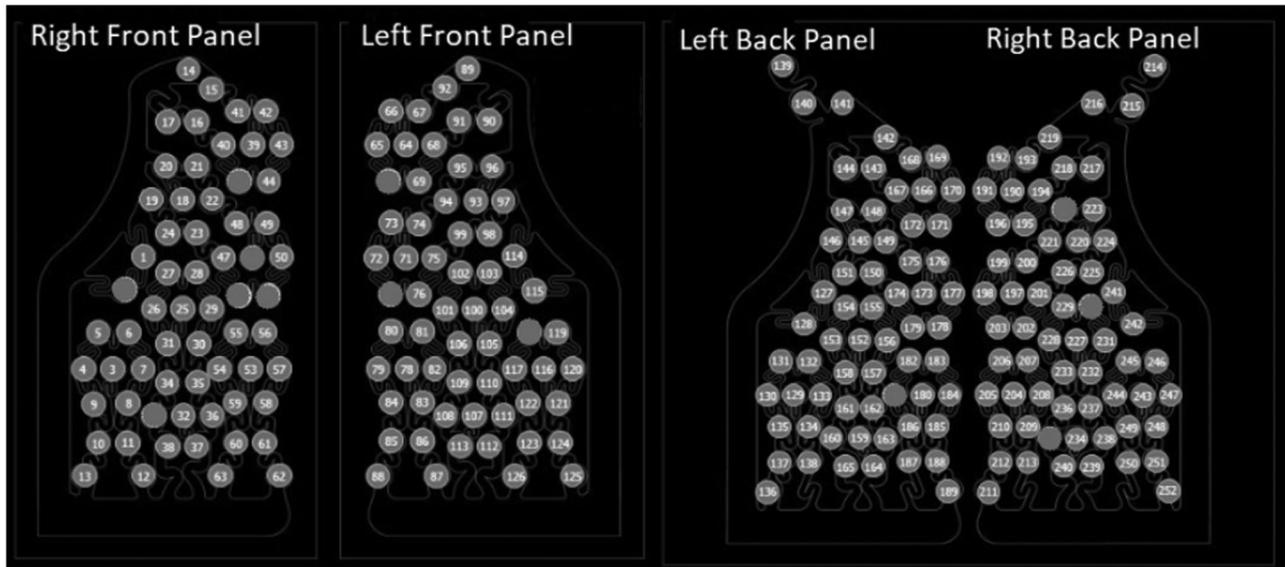
FIGURE 1 The 252-leads BSM vest divided in panels. The 252-leads BSM vest divided in four panels for the purpose of the study. Note that the front panels are seen from the front of the patient, while the back panels are seen from the back of the patient. As seen in this figure the right front panel includes leads 1—63, the left front panel leads 64—126, the left back panel leads 127—189, and the right back panel the leads 190—252

2.4 | Analysis of QRS dispersion from body surface mapping

Three beats from each patient with minimum possible noise were exported from the BSM system to the MATLAB software (MATLAB version R2019b, MathWorks, Natick, MA, USA) for a manual analysis of QRS-complex durations. For each lead, the QRS duration was measured, starting from the beginning of the QRS complex to its end, using electronic calipers and calculated as the mean QRS duration of the three beats. Measurements were performed by two authors (VK, ME) after consensus agreement, both blinded to the clinical data. The standard deviation of all measured mean QRS durations in each patient was also calculated. An overall mean QRS duration was calculated as the mean value of all mean QRS durations.

The BSM-QRS dispersion was defined as the difference between the longest and the shortest mean QRS duration among all 252 leads of the BSM system in each patient. When the minimum or maximum mean QRS duration differed more than 5 ms from the numerically closest value the lead was excluded in order to avoid outliers that would result in an overestimation of the BSM-QRS dispersion. The mean QRS duration was not corrected for the heart rate. In accordance with previous studies on ECG-QRS dispersion, a value > 40ms was used as cut off or defined as pathologic.[12,16]

Although minimal and maximal values are generally weak markers of the true dispersion in ensemble distributions, it was analyzed for a comparison with the previously reported ECG-QRS dispersion. BSM-QRS dispersion based on the difference between the 5% and 95% of all QRS durations are expected to be more reliable, and was therefore also analyzed. The BSM-QRS dispersion 5—95% was defined as the difference between these two values.

Apart from calculating an overall BSM-QRS dispersion of all 252 leads, a "panel-QRS dispersion," defined as the difference between the

minimum and maximum QRS duration of each panel separately was also calculated. The 252-leads BSM vest was thus divided into four panels related to its' position on the chest; right front, right back, left front, and left back panels (Figure 1).

2.5 | Comparison of ECG-QRS dispersion with BSM-QRS dispersion

The ECG-QRS dispersion and BSM-QRS dispersion were compared with regard to their ability to discriminate ARVC patients and gene carriers from controls. The localization of the greatest QRS prolongation detected with both methods were also compared in order to assess the most important site for QRS dispersion that can detect early depolarization changes.

2.6 | Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) and categorical variables summarized as percentages. The normal distribution of the data was tested with the Shapiro-Wilk test. Continuous variables were compared using Mann-Whitney U test or Kruskal-Wallis test and categorical variables with Pearson chi-square test. A p-value of < 0.05 was defined as statistically significant. Intra-class correlation coefficient was used to determine intra-observer variability of the measurements of QRS duration at 12-lead ECG. A receiver operating characteristic (ROC) analysis based on the ARVC patients and the controls was performed in order to assess the sensitivity and specificity of ECG-QRS dispersion and BSM-QRS dispersion using both minimal and maximal values and the 5% and 95% of all QRS durations. The data analysis was performed with SPSS statistical software (IBM SPSS statistics, version 27).

TABLE 1 Baseline characteristics of the study populations

	Controls (n = 8)	ARVC patients (n = 12)	Healthy gene carriers (n = 20)
Sex, males	5 (62.5)	8 (67)	8 (40)
Age, years, mean (SD)	39 (18)	50 (16)	44 (14)
Desmosomal gene mutations	0 (0)	10 (83)	20 (100)
Heart failure	0	4 (33)	0
≥500 VES/ 24 hours	0	8 (67)	0
Sustained VT	0	6 (50)	0
Non-sustained VT	0	4 (33)	0
Sustained VT and Aborted SCD	0	1 (8)	0
Heart rate, bpm, mean (SD)	61 (9)	56 (9)	64 (9)
12 lead ECG repolarization abnormalities*;	0	12 (100)	2 (10)
T wave inversion V1-V3 or beyond	0	10 (83)	2 (10)
T wave inversion III and aVF	0	7 (58)	0
T wave inversion V5-V6	0	4 (33)	0
12 lead ECG depolarization abnormalities*:	0	9 (75)	2 (10)
Prolonged TAD in V1, V2 or V3	0	8 (67)	2 (10)
Epsilon waves	0	6 (50)	0
Late potentials on SAECG	2 (25)	11 (92)	5 (25)
FQRSd, ms, mean (SD)	107 (8)	153 (27)	110 (16)

Figures are numbers with percentages in brackets unless otherwise stated.

Bpm, beats per minute; *n*, number of study subjects; ms, milliseconds; SCD, Sudden Cardiac Death; SD, standard deviation; VT, Ventricular Tachycardias; VES, Ventricular Extrasystoles; ICD, Implantable Cardioverter Defibrillator; TAD, Terminal Activation Duration; SAECG, Signal Averaged-ECG; FQRSd, filtered QRS duration.

*Figures denote any of respective ECG abnormalities.

3 | RESULTS

3.1 | Patients

The demography and clinical findings in the three study groups are presented in Table 1.

Controls: All eight controls had a normal 12-lead ECG. The SAECG revealed a filtered QRS duration > 114 ms in two cases, which per definition fulfils criteria for late potentials (≥114 ms) according to the 2010 TFC.[2]

ARVC patients: Twelve patients with definite ARVC according to modified TFC 2010 were included in the study.[2] A desmosomal mutation was found in 10 patients, seven of whom had a mutation in the PKP-2 gene, two in the DSG-2 gene, and one in DSP gene. Two patients had no mutations in an ARVC panel. All patients were in sinus rhythm during the study except for one patient who had atrial fibrillation. Four patients were on antiarrhythmic drugs (flecainide in two cases and sotalol in two cases).

Gene Carriers: Of the twenty healthy gene carriers included, ten had a mutation in the PKP-2 gene, three in the DSG-2 gene, three in the DSC-2 gene, and four in the DSP gene. All individuals were in sinus rhythm during the study. No patient had a history of ventricular arrhythmias or cardiac-related syncope and no patient was on medication with antiarrhythmic drugs.

3.2 | QRS duration and dispersion from resting 12-leads ECG

The mean QRS duration, QRS duration in each lead group, and standard deviation (SD) of QRS durations in each group are presented in Table 2. The widest QRS complexes were located to V1-V3 in 7/8 controls and in 11/12 ARVC patients (Table 3). The widest and most narrow QRS complexes had the same location in gene carriers. Intra-class correlation coefficient for the intra–observer variability of the QRS durations was 0.92. The ECG-QRS dispersion was significantly greater in the ARVC group compared to both controls and healthy gene carriers (Table 2).

3.3 | QRS duration and dispersion from BSM recordings

The minimum and maximum QRS duration, the QRS d 5% and QRS d 95%, the mean QRS duration and the SD in each patient are presented in Table 2. The longest QRS duration was found in ECG leads located to the left front panel of the vest in 7/12 ARVC patients and 3/8 controls, to the right front panel in 5/12 ARVC patients, and 3/8 controls and to the left back panel in two cases in each of the groups (Table 3). The BSM-QRS dispersion was significantly greater in the ARVC group as

TABLE 2 QRS durations from 12-lead ECG and BSM recordings

	Controls (n = 8)	ARVC patients (n = 12)	Healthy gene carriers (n = 20)	p-values
12-leads ECG				
QRS d mean	89 (12)	98 (18)	89 (9)	.376
QRS d min	71 (7)	82 (15)	67 (6)	<.05
QRS d max	97 (7)	123 (18)	97 (10)	<.05
QRS d SD	8 (3)	13 (5)	9 (2)	<.05
QRS d V4R	80 (6)	105 (16)	79 (11)	<.05
QRS d V1-V3	91 (8)	111 (19)	90 (10)	.050
QRS d V4-V6	86 (10)	100 (22)	80 (8)	<.05
QRS d I, aVL, aVR	78 (7)	91 (18)	75 (6)	<.05
QRS d II, III, aVF	84 (11)	99 (16)	77 (7)	<.05
ECG-QRS dispersion	25 (8)	42 (15)	29 (7)	<.05
BSM recordings				
QRS d mean	84 (10)	104 (15)	84 (8)	<.05
QRS d min	69 (9)	67 (8)	64 (10)	.504
QRS d max	98 (11)	132 (19)	99 (9)	<.05
QRS d SD	6 (1)	14 (4)	8 (2)	<.05
QRS d 95%	94 (11)	124 (17)	85 (9)	<.05
QRS d 5%	74 (9)	79 (11)	71 (9)	.136
BSM-QRS dispersion	29 (7)	65 (17)	35 (6)	<.05
BSM-QRS disp LF panel	26 (7)	57 (21)	31 (7)	<.05
BSM-QRS disp RF panel	20 (8)	44 (21)	25 (8)	<.05
BSM-QRS disp LB panel	19 (4)	34 (20)	23 (7)	<.05
BSM-QRS disp RB panel	13 (4)	25 (22)	14 (6)	.741
BSM-QRS dispersion 5−95%	21 (5)	45 (13)	24 (6)	<.05
Missing leads	30 (8)	33 (14)	40 (11)	.109

The figures are mean QRS duration in milliseconds with one standard deviation in brackets unless otherwise stated.

disp , dispersion; d = duration; n , number of study subjects; SD, standard deviation, min, minimum value, max, maximum value, LF, front left panel, RF, front right panel, LB, back left panel, RB, back right panel.

compared to controls and gene carriers (Table 2). The BSM-QRS dispersion 5−95% was comparable to the one based on minimum and maximum QRS duration (Table 2).

3.4 | Correlation between ECG-QRS dispersion and BSM-QRS dispersion

The ECG-QRS dispersion was abnormal, i.e. > 40 ms, in 5/12 ARVC patients as compared to controls who all had normal ECG-QRS dispersions, as shown in figure 2. Thus, the ECG-QRS dispersion with the cut-off 40msec could only distinguish a minority of ARVC patients from controls (figure 2). A ROC analysis showed that a cut-off 40 msec had a 60% sensitivity and a 100% specificity (Figure 3).

The BSM-QRS dispersion was abnormal, i.e., > 40 ms, in all except one ARVC patients whereas it was normal (≤40ms) in all except one of the controls. The ARVC patient with a normal BSM-QRS dispersion (< 40ms) had no ECG depolarization abnormalities but fulfilled four

major ARVC criteria (echocardiographic abnormalities, T wave inversion in V1-V3, typical LBBB morphology ventricular tachycardia, and positive gene mutation).[2] The control with abnormal BSM-QRS dispersion (41ms) revealed no ARVC criteria apart from a total filtered QRS duration of 116ms on SAECG. A cut-off at 40ms could thus successfully distinguish ARVC patients from controls in 11/12 ARVC cases (Figure 2). A ROC analysis of BSM-QRS dispersion revealed a 92% sensitivity and over 90% specificity for the cut-off 40msec (Figure 3).

The BSM-QRS dispersion 5−95% revealed comparable findings; all ARVC patients but one had a dispersion > 30ms, and all controls except for one < 30ms. A cut-off 30 ms could thus successfully distinguish 11/12 ARVC cases. A ROC analysis of BSM-QRS dispersion 5−95%, revealed comparable findings with a 92% sensitivity and over 90% specificity for the cut-off 30ms (Figure 3), although the area under the curve (AUC) was highest for the BSM-QRS dispersion 5−95% (Figure 3).

Six of the seven ARVC patients with normal ECG-QRS dispersion (≤40ms) had abnormal BSM-QRS dispersion (i.e., > 40ms) (Table 3). The

TABLE 3 The location of longest and shortest QRS duration in individual controls and ARVC patients assessed by 12-leads ECG and 252-leads BSM recordings

ID	Longest and shortest QRS in BSM recordings				Longest and shortest QRS in 12-leads ECG			
	RFpanel	LFpanel	LBpanel	RBpanel	V1-V3	V4-V6	aVL, I, aVR	II, III, aVF
Controls								
C1	+	+			+		+	
C2	+	+			+	+		
C3		+	+		+			+
C4		+			+		+	
C5		+		+	+			+
C6	+		+		+		+	
C7	+		+		+		+	
C8	+		+				+	+
ARVC patients								
P1	+	+			+			
P2	+	+		+	+	+	+	
P3	+	+			+		+	
P4			+		+	+		
P5		+		+	+			+
P6	+	+			+		+	+
P7	+						+	+
P8		+			+		+	
P9		+			+		+	
P10	+		+		+	+		
P11	+		+	+	+		+	
P12		+			+		+	

The table shows the location of the longest and shortest QRS duration in all ARVC patients and controls assessed by both 252-leads BSM and 12-leads ECG. The location of the longest and shortest QRS duration at the BSM recordings were considered the panels where the leads with the ten maximum, respectively minimum values were located. When more than one location is marked, the highest or shortest values were spread equally at more than one panel. The location of the longest and shortest QRS duration at ECG were considered the leads with the maximum and minimum values. When more than one leads are marked, the maximum or minimum values were similar in more than one leads. Note that the longest QRS durations were located in the anterior leads of ECG (V1-V3) in almost all the controls and patients, whereas the shortest were most commonly located in the lateral leads, followed by the inferior leads in both groups. The locations of both longest and shortest QRS duration recorded by BSM were more variable.
The location with the longest QRS duration is marked with blue and the location with shortest QRS duration with grey.
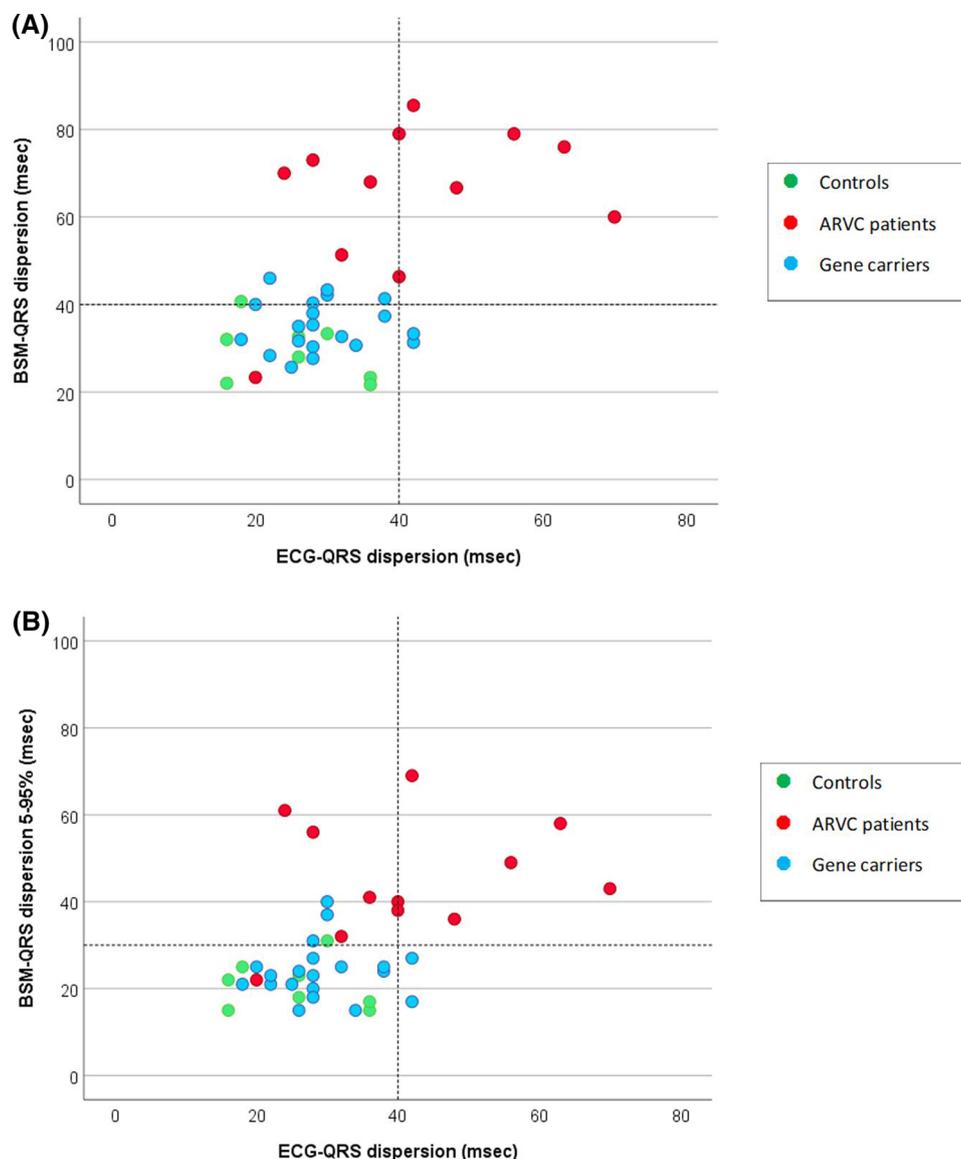
FIGURE 2 The BSM-QRS dispersion and ECG-QRS dispersion in all study groups. (A) BSM-QRS dispersion and ECG-QRS dispersion in all study groups. Note that a BSM-QRS dispersion > 40ms could successfully detect 11/12 ARVC patients, whereas only 5/12 ARVC patients could be detected by the ECG-QRS dispersion. Note also that four gene carriers had a slightly greater BSM-QRS dispersion as compared with two having slightly greater ECG QRS dispersion. (B) BSM-QRS dispersion5-95% and ECG-QRS dispersion in all study groups. The BSM-QRS dispersion 5−95% > 30ms could also successfully detect 11/12 ARVC patients. The ARVC patient with BSM-QRS dispersion 5−95% < 30ms was the same as the one in the BSM-QRS dispersion analysis (A). Three gene carriers had a BSM-QRS dispersion 5−95% > 30ms, all of whom had a BSM-QRS dispersion > 40ms

longest QRS duration in these patients were located to the front right panel in four cases, back left panel in one case and upper part of the front left panel in one case, i.e., locations that do not correspond to any of the 12 leads of the surface ECG. In the remaining ARVC patients, the longest QRS durations were found in parts of the BSM panels that were represented by conventional leads of the 12-leads ECG (Table 3).

Most healthy gene carriers (18/20) had a normal ECG-QRS dispersion (i.e., ≤40 ms). The two gene carriers with an abnormal ECG-QRS dispersion of 42ms (Figure 2), also had a TAD > 55ms and late potentials on the SAECG but normal BSM-QRS dispersions. Moreover, four gene carriers had slightly prolonged BSM-QRS dispersions, ranging between 41 and 46ms (Figure 2), although none of them fulfilled any

depolarization or repolarisation criteria on the 12-leads ECG or any criteria for late potentials on SAECG. The remaining 16 gene carriers had a normal BSM-QRS dispersion (≤40 ms). Using BSM-QRS dispersion 5−95% three gene carriers with values > 30ms were identified, all of whom had a pathologic BSM-QRS dispersion.

4 | DISCUSSION

To our best knowledge, this is the first study exploring the potential diagnostic value of QRS dispersion using a 252-lead BSM system in ARVC patients and healthy gene carriers. A BSM-QRS
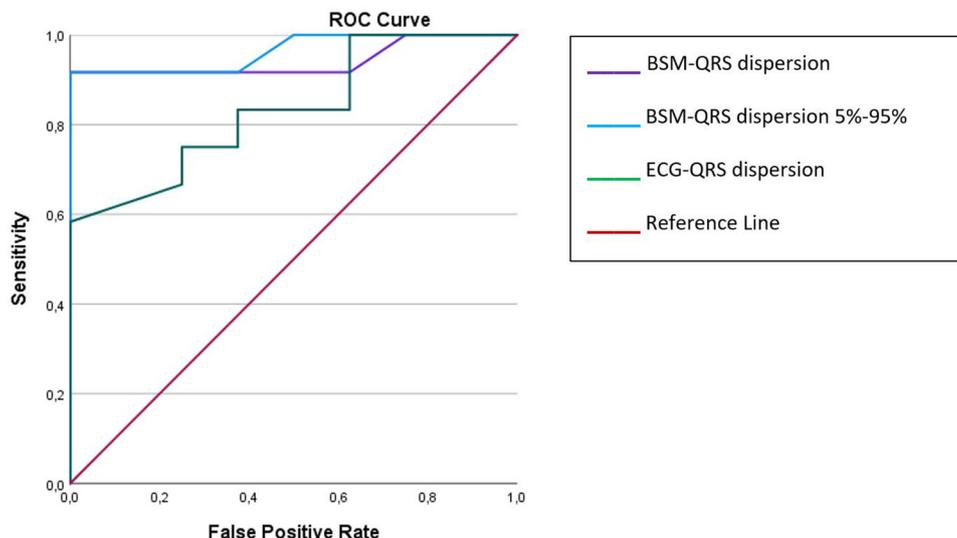
FIGURE 3 ROC curves for BSM-QRS dispersion and ECG-QRS dispersion. The ROC curves for BSM-QRS dispersion (purple), BSM-QRS dispersion 5–95% (blue), and ECG-QRS dispersion (green). The area under the curve (AUC) is 0.943 for the BSM-QRS dispersion, 0.964 for the BSM-QRS dispersion 5–95%, and 0.833 for the ECG-QRS dispersion

dispersion > 40 ms could differentiate nearly all ARVC patients from controls as opposed to the corresponding ECG-QRS dispersion. All patients who were detected by an ECG-QRS dispersion > 40ms, were also detected by a BSM-QRS detection > 40ms, but not all patients with a BSM-QRS detection > 40ms, had a high ECG-QRS dispersion. ROC analysis confirmed a higher sensitivity and specificity for BSM-QRS dispersion compared to ECG-QRS dispersion. These findings indicate that the BSM-QRS detection is more sensitive in detecting ARVC and may potentially prove useful as diagnostic tool for early manifestations of the disease.

The apparently higher detection capacity of BSM recordings was likely related to the large number of leads as it enabled the detection of QRS prolongation in areas on the chest not covered by the conventional 12-lead ECG. This was confirmed by the observations that in six ARVC patients, an abnormal QRS dispersion (> 40ms) was only detected by the BSM-system and not by the surface ECG recoding, and by the finding that the longest QRS durations were found in locations that did not correspond to any ECG lead. The greater QRS dispersion in the ARVC group is likely related to the local prolongation of the QRS in affected areas, since the maximum QRS duration was significantly longer in ARVC patients, while the minimum QRS duration in the BSM recordings did not differ between the study groups. It should be noted, that the cut-off 40ms used in this study, was based on previous studies on ECG derived QRS dispersion, based on minimum and maximum QRS dispersion. Comparable results were obtained when analyzing the BSM-QRS dispersion 5–95% showing that all but one ARVC patients was detected with a cut-off 30ms. The ROC analysis, however, revealed that the AUC was highest for the BSM-QRS dispersion 5–95%, which may indicate that it may be superior to QRS dispersion based on minimum and maximal values.

It was previously shown that the extent of ECG depolarization abnormalities correlates to the extent of endocardial conduction delay and scarring, as assessed by endocardial mapping in ARVC patients.[17]

Thus, the location of the BSM leads with prolonged QRS could reflect areas of delayed conduction of the affected myocardium, a known and common feature in ARVC.[18,19] These findings are further supported by the reported correlation between the extent of QRS dispersion ($\geq$40 ms) and right ventricular outflow tract area, right ventricular end-diastolic and end-systolic volume assessed by cardiac magnetic resonance in ARVC patients.[16] The study was small but the findings indicate that localized right ventricular dilatation may affect QRS dispersion. Given the high BSM-QRS dispersion in the present study, the BSM system may well prove to identify the location of areas with abnormal conduction reflecting both electrophysiological and structural abnormalities representing changes on either the structural or cellular level in ARVC.

The abnormal QRS dispersion observed among healthy gene carriers in the present study were all just above the 40ms cut-off level, irrespective of the method used. The two gene carriers with abnormal ECG-QRS dispersion and the four with abnormal BSM-ECG dispersion did not overlap. Even if the BSM-QRS dispersion changes were small and only slightly above the detection limit of 40msec it might be an early expression of the ARVC disease. It has previously been demonstrated that marked conduction delays may be present in patients with early stages of ARVC in the absence of structural changes, particularly when paced at short coupling intervals.[20] The degree of conduction delay correlated with the degree of ARVC progression.[20] Thus, even small changes of BSM-QRS dispersion, as detected in some of the gene carriers in the present study, could indicate early cellular changes or an initial less extensive myocardial scarring causing local conduction delays and QRS prolongation. Related to the limited number of subjects in the present cohort, further studies are warranted to better clarify the correlation between localized BSM-QRS dispersions with cellular or structural myocardial changes in ARVC patients and gene carriers.

The analysis of the BSM-QRS dispersion 5–95% revealed comparable findings. The three gene carriers with BSM-QRS dispersion

5−95% > 30ms were all detected by the BSM-QRS dispersion based on minimum and maximum values. Gene carriers with marginal BSM-QRS dispersion values were not defined as pathologic with the BSM-QRS dispersion 5−95%. The findings warrant further analysis in larger studies.

As this was an explorative study evaluating for the first time the potential value of BSM-ECG dispersion for ARVC diagnosis, only patients with typical ARVC disease with predominantly right ventricular involvement were included. The value of QRS dispersion in diagnosing ARVC patients with left ventricular involvement was beyond the scope of the present study and warrants further studies. Even though the ROC analysis revealed a high sensitivity and specificity, the results warrant confirmation in larger studies.

Given the large number of electrodes in the BSM system, a more user friendly, less time-consuming, and more cost-effective methodology is warranted, as all analyses of the BSM recordings were performed manually. An automatization of the signal analysis and a selection of a smaller number of crucial electrodes is imperative in order to facilitate the implementation of this method in clinical practice.

5 | LIMITATIONS

Vaughan Williams Class IC antiarrhythmic drugs may affect conduction and was used in four ARVC patients during the study. However, no differences could be seen between these patients and those without antiarrhythmic drugs in terms of QRS durations on conventional ECG, nor in the BSM recordings. Since the population of the present study was rather small an evaluation of the BSM-QRS dispersion as a diagnostic tool in a larger cohort is warranted.

6 | CONCLUSIONS

In the present study, the BSM-QRS dispersion versus the 12-lead ECG dispersion seemed to better distinguish ARVC patients from controls and detected gene carriers with slightly greater BSM-QRS dispersion, which hypothetically could express an early stage of the disease. Larger studies are required to confirm these results and to further explore the value of BSM-QRS dispersion in various ARVC cohorts.

AUTHOR CONTRIBUTIONS
Varvara Kommata: Concept/ design, Data collection, Data analysis/ interpretation, Statistics, Drafting

Marwa Elshafie: Data collection, Data analysis/ interpretation, Approval of article

Elena Sciaraffia: Critical revision of article, Approval of article

Mauricio Perez: Critical revision of article, Approval of article

Robin Augustine: Critical revision of article, Approval of article, Funding secured

Carina Blomström-Lundquist: Concept/ design, Data interpretation, Critical revision of article, Approval of article, Funding secured

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CONFLICTS OF INTEREST

Varvara Kommata, Marwa Elshafie, Elena Sciaraffia, Mauricio Perez, Robin Augustine have no conflict of interest to disclose. Carina Blomström-Lundqvist reports receiving grants from Medtronic during the conduct of the study; and personal fees from Bayer, Sanofi, Boston Scientific, and Cathprint outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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