

Repolarization abnormalities unmasked with a 252-lead BSM system in patients with ARVC and healthy gene carriers

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Abstract

Background: Diagnosing arrhythmogenic right ventricular cardiomyopathy (ARVC) at an early stage can be challenging even after ECG recording and a combination of several imaging techniques. The purpose of this study was to explore if a body surface mapping (BSM) system with 252-leads could identify repolarization abnormalities and thereby diagnose early stages of ARVC.

Methods: ARVC patients, gene carriers without signs of ARVC and controls underwent a 12-lead resting ECG, signal-averaged ECG, echocardiography, 24-hours Holter monitoring, and BSM with electrocardiographic imaging (ECGI). All 252-leads, divided into four quadrants of the vest, were analyzed regarding concordances between T wave polarity and QRS main vector.

Results: Of 40 patients included there were 12 ARVC patients, 20 gene carriers, and 8 controls. The ARVC patients had two different repolarization patterns, one with more pronounced negative T waves at the lower left panel and another with mixed changes that clearly differed from the controls, all of whom had a normal 12 lead ECGs and consistent repolarization patterns on their BSM recordings. The patterns observed in ARVC patients were also present in 5/20 (25%) gene carriers, three of whom had normal resting ECG. A novel repolarization index successfully detected all ARVC patients and 88% of gene carriers with pathologic repolarization pattern.

Conclusions: The finding that abnormal repolarization patterns could be unmasked by BSM in 25% of healthy gene carriers, suggests that it may potentially be a useful tool for identifying early manifestations of ARVC. Further and larger studies are warranted to assess its diagnostic accuracy.

KEYWORDS

arrhythmogenic, body surface mapping, cardiomyopathy, repolarization, right ventricular

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1 | INTRODUCTION

The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is complex, particularly at the earlier stages of the disease, requiring extensive work-ups including resting electrocardiogram (ECG), signal-averaged ECG (SAECG), cardiac imaging, histology, and genetic tests according to 2010 Task Force Criteria (TFC).^{1,2}

Genetic diagnostic testing has enabled screening of family members to identify ARVC gene carriers potentially predisposed to develop the disease. In a serial evaluation of at-risk family members almost 30% had signs of an electrical progress indicated by the development of a new electrical TFC criterion, which was either repolarization or depolarization abnormalities or ventricular arrhythmias, during follow-up preceding the development of structural changes observed by magnetic resonance imaging (MRI).³ The timing of the first manifestation of the disease is difficult to predict and is still a challenge both in gene carriers and in family members with mutation-negative probands.

The 12-lead ECG has a central role in the diagnosis of ARVC revealing both depolarization and repolarization abnormalities, of which T wave inversions in V1-V3 and beyond is a pathognomonic feature in ARVC.^{2,4,5} The initial ECG can be normal and T wave inversion may evolve with time as part of a disease progression.^{6,7} A normal ECG does thus not exclude an ARVC diagnosis.⁸ It has recently been demonstrated that new vectorcardiographic right-precordial-directed parameters can distinguish ARVC patients with normal ECG from controls with a relatively high specificity, indicating that a subset of ARVC subjects have subtle repolarization and depolarization abnormalities undetectable with conventional ECG.⁹

Electrocardiographic imaging (ECGI) is a noninvasive body surface mapping (BSM) technique recording multiple electrocardiograms from a vest to reconstruct epicardial electrograms enabling isochrones of cardiac conduction.¹⁰ Epicardial potentials are reconstructed using a mathematical algorithm and geometrical information from a Computer Tomography (CT)-scan.¹⁰ Electrophysiological abnormalities in ARVC patients has been shown to correlate with areas of scar tissue as depicted by ECGI and late gadolinium enhancement.¹¹

The purpose of the present study was to investigate whether BSM could identify subtle repolarization abnormalities undetected by conventional techniques, thus unmasking an early clinical manifestation of ARVC in gene carriers.

2 | METHODS

2.1 | Patient selection

A cross-sectional study of ARVC patients, healthy gene carriers and controls from an ARVC cohort at Uppsala University Hospital was performed between December 2018 and April 2019. Patients with a definite ARVC diagnosis² and family members who had tested positive for any ARVC family mutation but without structural abnormalities on imaging or history of ventricular arrhythmias, were prospectively included in the study. Repolarization changes (T wave inversion in V1-

V3 or beyond) or depolarization changes (Terminal Activation Duration > 55ms on ECG or presence of late potentials on SAECG) were permitted in gene carrier group in order to compare consistencies with the BSM system. Family members who had tested negative for the family desmosomal mutation served as controls.

Patients with pacemaker dependency, 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 body mass index (BMI) > 31 were excluded with respect to the radiation exposure from the chest computer tomography (CT).

The study was approved by the Regional Ethical Review Board (Dnr2018/369) and complied with the Declaration of Helsinki.

2.2 | Study design

All patients underwent a detailed conventional diagnostic evaluation for ARVC consisting of resting 12-leads ECG, SAECG, 24-hour Holter monitoring, and two-dimensional (D)-echocardiography with standardized right ventricular projections and measurements.² The right precordial ECG lead (V4R) was also used, in order to evaluate it as a diagnostic tool for ARVC.

2.3 | Electrocardiographic imaging using body surface mapping and signal analysis

A 252-unipolar lead BSM vest (CardiInsight, Medtronic, MN, USA) was used for the recording of body surface potentials at a sampling rate of 1000 Hz during a 10-minute recording.¹⁰ Non-ECG triggered CT scan with a low radiation protocol (approximately 1 mSv) was used in order to provide geometrical information needed for analysis of the epicardial signals, to be presented elsewhere. The analysis of surface ECG depolarization changes has been reported in previous study.¹² An analysis of epicardial signals was beyond the scope of this study and will be reported elsewhere.

All recordings were evaluated qualitatively regarding T-wave polarity and its concordance with the QRS complex main polarity. Leads with no signals or too noisy signals which precluded an evaluation of the polarity of the T wave and QRS complex were excluded from the analyses. A T-wave was defined as positive if the deflection was above the baseline (> 1 mm), negative if it was below the baseline (> 1 mm), and isoelectric if close to baseline (< 1 mm). T-waves with both positive and negative deflection were defined as biphasic. The QRS complex was defined as positive if the R wave amplitude was higher than the S wave amplitude and negative if the S wave amplitude was higher than the R wave. When the R and S wave amplitudes were equal the QRS complex was characterized as balanced. A T wave was defined concordant with the QRS when it had the same polarity as the QRS complex (i.e., both T wave and QRS complex were either positive or negative) and discordant when not (i.e., when the T wave was negative the QRS wave was positive and vice versa). When the T wave was isoelectric or

Color code	Definition	ECG pattern
	negative concordant T waves	
	positive discordant T waves	
	positive concordant T waves	
	negative discordant T waves	
	isoelectric or biphasic T waves, or inconclusive concordance	
	none or too noisy signals	

FIGURE 1 Explanation of color codes used for repolarization vectors in relation to QRS vector [Color figure can be viewed at wileyonlinelibrary.com]

biphasic or when the QRS complex was balanced, the concordance was defined as inconclusive.

The T - QRS concordance and its polarity were graphically illustrated in separate repolarization maps. Each individual lead of the vest was assigned a specific color code (Figure 1) related to the outcome of the T - QRS concordance analysis. Each body surface map was divided into four panels related to its' position on the chest: right front (rightF), right back (rightB), left front (leftF), and left back (leftB) panels (Figure 2). All repolarization maps were then analyzed both visually and mathematically.

In an explorative attempt to better discriminate a normal repolarization pattern from a pathologic one, a quantitative analysis of the repolarization patterns was performed to create a repolarization index. The number of leads with negative, positive, isoelectric, and biphasic T waves, respectively, were calculated in the whole vest. The number and positions of leads with negative concordant, positive discordant, positive concordant, and positive discordant T waves were also analyzed. All 250 recordings in the 40 patients were manually analyzed by the first author blindly. In order to assess inter-observer variability, 20% of randomly selected recordings (approximately 250 recordings in eight randomly chosen subjects = 2 016 recordings) were analyzed blindly by a physician trained in interpreting ECG signals (ES). Moreover, all repolarization maps were visually analyzed and explored unblindly for categorization into one of three repolarization patterns by the first author. The analysis was repeated blindly by the first author and one co-author (ES) for the assessment of inter-observer variability. Consensus was made for two disparate interpretations.

2.4 | Statistical analysis

Continuous variables were reported as mean \pm SD and categorical variables summarized as percentages. 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 .05 was defined

as statistically significant. In order to develop a repolarization index that differentiated the normal repolarization pattern from the pathologic ones, a logistic regression analysis was used. The data analysis was performed with SPSS statistical software (IBM SPSS statistics, version 27).

3 | RESULTS

3.1 | Patients

The demography, clinical findings, and results of conventional diagnostic tests in the three study groups are presented in Table 1. The sex and age distribution did not differ statistically in the three study groups.

ARVC patients: All 12 patients fulfilled definite ARVC criteria according to modified task force criteria 2010.² All patients were in sinus rhythm during the study except for one patient who had atrial fibrillation. Four patients were on antiarrhythmic drugs, including flecainide in two cases and sotalol in two other cases.

Gene carriers: A total of twenty gene carriers were included in the study. All individuals were in sinus rhythm during the study. The SAECG demonstrated late potential in five cases, of whom three fulfilled 3/3 criteria and two had 1/3 criteria for late potentials.

Controls: All eight controls, had a normal 12-lead ECG. The SAECG showed a filtered QRS duration > 114 ms as the only positive criteria for late potentials in two controls (Table 1).

3.2 | BSM repolarization maps and patterns

Based on the analysis of repolarization maps in ARVC patients and controls, three repolarization patterns could be identified and classified as repolarization pattern 1, pattern 2, and repolarization pattern 3.

Repolarization pattern 1 showed a consistently negative T - QRS concordance in the rightF and rightB panels (Figure 2). The leftF panel

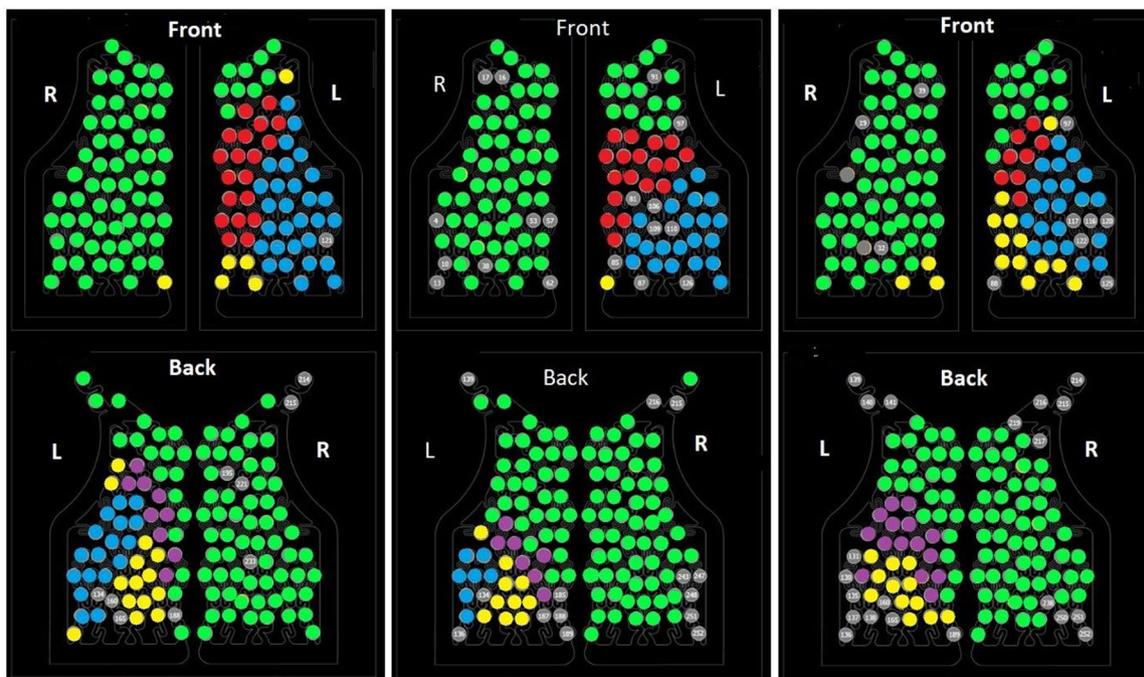


FIGURE 2 Examples of normal repolarisation (pattern 1) as recorded by the Body Surface Mapping system in two controls and in one healthy gene carrier. The repolarisation pattern 1 on the front and back of the chest recorded from the 252-leads BSM vest in two healthy controls (A and B) and in one healthy gene carrier (C). Note that the repolarisation patterns seen in normals and also in this gene carrier, were similar with negative concordant T waves (green dots) both at the right Front and right Back panels, while the T waves change successively from negative concordant (green dots) at the upper half of the left Front panel, to positive discordant (red dots) in the middle and finally positive concordant (blue dots) at the bottom. R = right, L = left (green = negative concordant T waves; red = positive discordant; blue = positive concordant; purple = negative discordant T waves; yellow = isoelectric or biphasic T waves, or inconclusive concordance; grey = none or too noisy signals) [Color figure can be viewed at wileyonlinelibrary.com]

showed a gradual change from negative concordant T waves in the upper half, to positive discordant T waves in the middle and finally to positive concordant T waves at the bottom. The leftB panel showed a greater non-consistent variation in the polarity and concordance of the T waves (Figure 2). This pattern was found in all eight controls and none of the ARVC patients and was defined as a normal pattern.

Repolarization pattern 2 was characterized by the same pattern in RightF and RightB panels, with negative, concordant T waves, whereas the transition of T waves from negative concordant to positive concordant observed in the leftF panel in Repolarization pattern 1 was absent (Figure 3). *Repolarization pattern 3* varied widely and showed no consistent changes of T wave and QRS concordances, which were totally different from patterns 1 and 2 both in the right and left panels (Figure 4). The repolarization patterns 2 and 3 appeared in all ARVC patients and were considered as pathologic. Repolarization pattern 2 was present in three ARVC patients and repolarization pattern 3 in nine patients. The two ARVC patients without T wave inversion in V1-V3 on the resting ECG showed repolarization pattern 3 on their BSM recordings.

Based on these defined patterns of repolarization, gene carriers were classified as having either normal or pathological repolarization patterns: Fifteen gene carriers had a normal repolarization pattern (type 1) and none of them had abnormal T wave inversions on the surface ECG. The other five gene carriers had pathological patterns, four

of whom had repolarization pattern 2 and one repolarization pattern 3. T wave inversion on surface ECG in V1-V3 was seen in one individual with type 2 pattern and in another with type 3 pattern. The three remaining gene carriers with abnormal BSM patterns had normal ECGs. No correlation was noted between older age and abnormal repolarization patterns.

The visual analysis of the repolarization patterns was performed by the first author and repeated in a blinded manner by the second author with 95% interobserver agreement. The interobserver agreement in the evaluation of T-QRS polarity and concordance was estimated approximately 90%. The number of leads with missing or too noisy signals were comparable in the three study groups.

3.3 | Repolarization index

The statistical analysis exploring predictor variables that best could discriminate pathological from normal repolarization patterns is shown in Table 2. The best predictor variables were the negative concordant T waves in the right panel (NegConcordant rightF +rightB) and the positive discordant T waves in the leftF panel (PosDiscordant leftF). Using logistic regression, we could define a repolarization index according to the following equation:

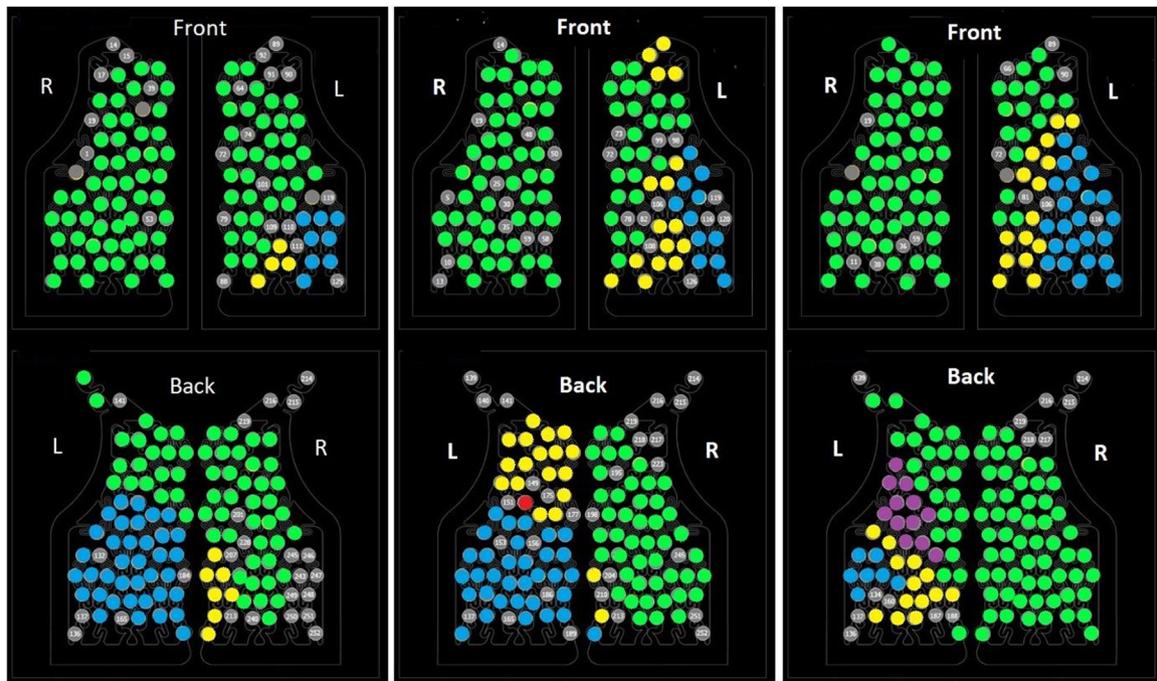


FIGURE 3 Examples of abnormal repolarization (pattern 2) recorded in two ARVC patients and one healthy gene carrier. Repolarisation pattern 2 on the front and back of the chest recorded in two ARVC patients (A and B) and one healthy gene carrier (C). Note that despite the interindividual variations in the leftB panels, all three patients had similar patterns in the rightF and rightB panels with mainly negative concordant T waves (green dots). The characteristic pattern seen in the leftF pattern in normal individuals (repolarisation pattern 1) has disappeared. Same abbreviations as in figure 2 [Color figure can be viewed at wileyonlinelibrary.com]

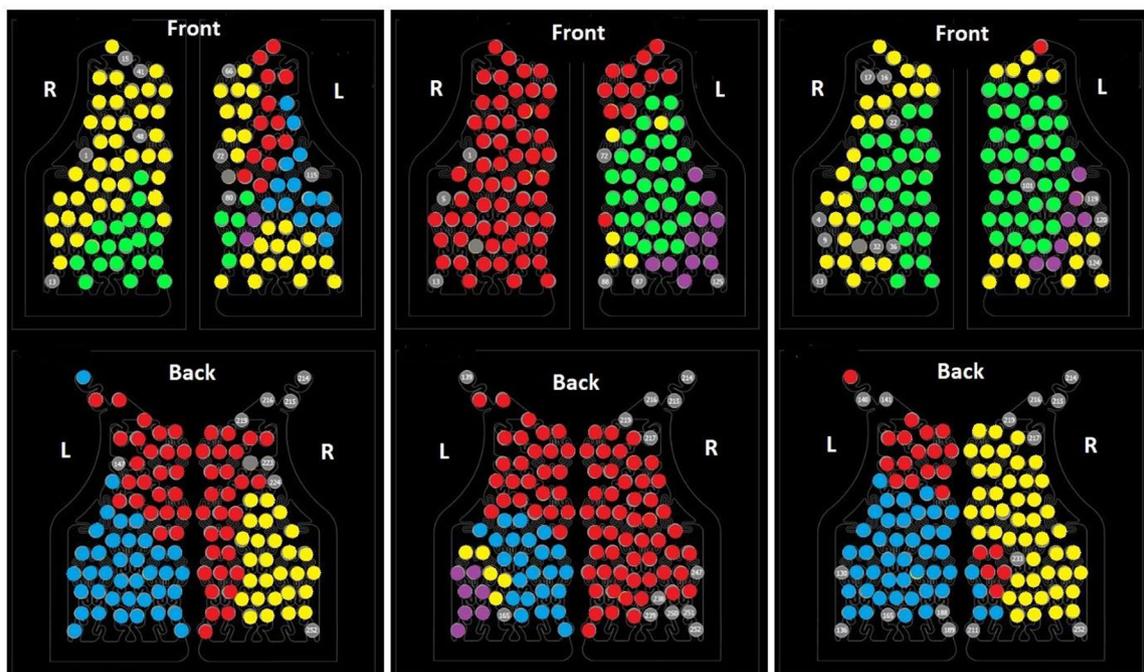


FIGURE 4 Examples of abnormal repolarization (pattern 3) recorded in two ARVC patients and one healthy gene carrier. Repolarization pattern 3 on the front and back of the chest recorded in two ARVC patients (A and B) and one healthy gene carrier (C). Note the variable repolarisation in all four panels. Same abbreviations as in figure 2 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline clinical characteristics of the study populations

	Controls (n = 8)	ARVC patients (n = 12)	Healthy gene carriers (n = 20)
Sex, males	5 (62.5)	8 (66.7)	8 (40)
Age, years, mean (SD)	39 (18)	50 (16)	44 (14)
Height	174	176	174
Weight	74	76	77
<u>Gene mutations</u>	0 (0)	10 (83)	20 (100)
PKP-2		7 (58)	10 (50)
DSP		1 (8)	4 (20)
DSG-2		2 (16)	3 (15)
DSC-2		0	3 (15)
<u>Clinical events / Arrhythmias</u>			
Cardiac syncope	0	3 (25)	0
Aborted SCD	0	1 (8)	0
Non-sustained VT	0	4 (33)	0
Sustained VT	0	6 (50)	0
≥500 VES/ 24 hours	0	8 (67)	0
ICD	0	10 (83)	0
Antiarrhythmic drugs	0	4 (33)	0
Prior VT ablation	0	1 (8)	0
<u>Echocardiographic examination</u>			
RV WMA	0	8 (67)	0
RVOT - PLAX (mm/m ²), mean ±SD	1.6 (0.2)	1.9 (0.3)	1.5 (0.2)
- PSAX (mm/m ²), mean ±SD	1.7 (0.2)	2.0 (0.2)	1.6 (0.3)
RV-FAC < 40%	0	11 (92)	0
LV-EF % (mean±SD)	62 (4)	63 (4)	61 (4)
<u>12-lead ECG</u>			
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
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
<u>SAECG</u> : late potentials (1-3 criteria)	2 (25)	11 (92)	5 (25)

Figures are numbers with percentages in brackets unless otherwise stated. DSC-2: desmocollin-2; DSG-2: desmoglein-2; DSP: desmoplakin; ICD, Implantable Cardioverter Defibrillator; LVEF, left ventricular ejection fraction; n, number of study subjects; PKP-2: plakophilin-2; PLAX /PSAX, parasternal long/short axis; RV, right ventricle; RV-FAC: right ventricular-fractional area change; RVOT, right ventricular outflow tract; SAECG, Signal Averaged-ECG; SCD, Sudden Cardiac Death; SD, standard deviation; TAD, Terminal Activation Duration; VES, Ventricular Extrasystoles; VT, Ventricular Tachycardias; WMA, wall motion abnormalities; .

Figures denote any of respective ECG abnormalities.

Repolarization index = $28 - 0.2 \times (\text{NegConcordant rightF} + \text{rightB}) - 0.6 \times (\text{PosDisconcordant leftF})$

The repolarization index in the equation represents the logarithm of the odds (probability of a pathologic repolarization pattern/ probability of a normal repolarization pattern). As shown in Figure 5 the

cut-off for the repolarization index was zero, with positive values indicating a pathologic repolarization pattern and negative values indicating a normal repolarization pattern. When applied in all three study groups, 23/23 subjects with normal repolarization pattern and 15/17 with pathologic repolarization patterns were classified correctly using

TABLE 2 Quantitative analysis of the three repolarization patterns using the body surface mapping system in ARVC patients, gene carriers, and normal controls

	RP1 (n = 23)	RP2 (n = 7)	RP3 (n = 10)	Overall P-value	RP1 vs. RP2 P-value	RP1 vs. RP3 P-value
T-wave Polarity						
Negative	159 (12)	153 (17)	59 (26)	<.05	1.000	<.05
Positive	46 (12)	34 (9)	103 (50)	<.05	.223	<.05
Isoelectric	18 (14)	24 (9)	40 (50)	.143	-	-
Biphasic	5 (6)	2 (4)	31 (27)	<.05	.622	<.05
Negative rightF+rightB	109 (8)	98 (13)	28 (28)	<.05	.214	<.05
Positive leftF	36 (7)	13 (8)	11 (10)	<.05	<.05	<.05
T-wave Polarity + QRS concordance						
NegConcordant	149 (13)	140 (15)	34 (33)	<.05	.877	<.05
PosDisconcordant	14 (7)	1 (1)	56 (51)	<.05	<.05	.164
PosConcordant	28 (11)	32 (8)	36 (26)	.865	-	-
NegDisconcordant	7 (8)	6 (8)	18 (15)	.061	-	-
Inconclusive	30 (16)	35 (12)	88 (43)	<.05	1.000	<.05
NegConcordant rightF +rightB	109 (8)	96 (13)	24 (26)	<.05	.141	<.05
PosDisconcordant leftF	13 (6)	0 (0)	6 (7)	<.05	<.05	<.05
PosConcordant leftF	20 (7)	12 (7)	5 (6)	<.05	.121	<.05

The figures are mean number of leads with one standard deviation in brackets for a specific T wave polarity and T wave polarity + QRS concordance, respectively, for each repolarization pattern in all study subjects. Independent-samples Kruskal-Wallis test (multiple groups) and Mann-Whitney U-test (two groups) were performed with the Bonferroni post hoc correction for multiple comparisons.

(rightF = right front panel; rightB = right back panel, leftF = left front panel, RP1 = repolarization pattern 1, RP2 = repolarization pattern 2, RP3 = repolarization pattern 3; vs = versus.).

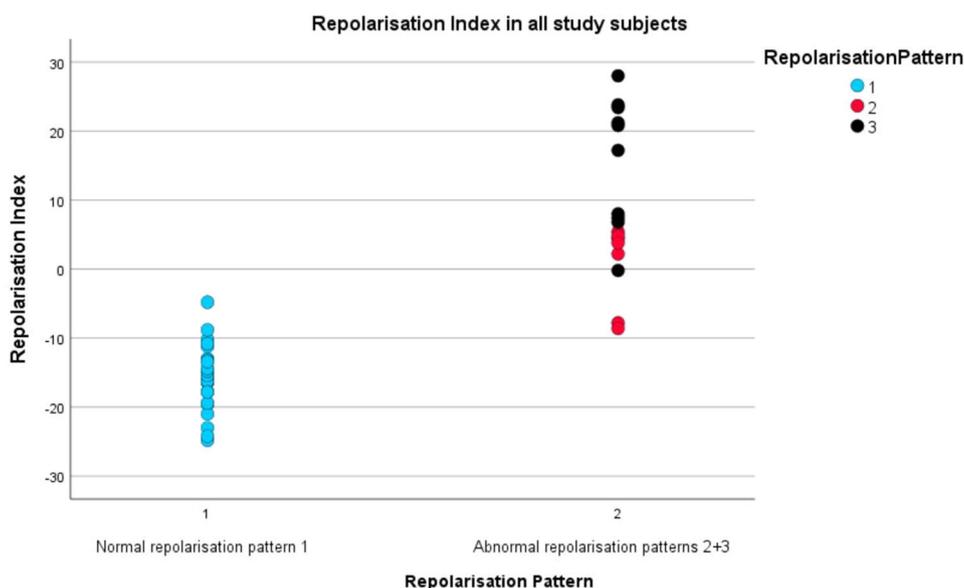


FIGURE 5 The repolarization index in all study subjects. Note that positive index values indicate an abnormal repolarization pattern 2 or 3 and that negative ones mainly indicate a normal repolarization pattern 1. The repolarization index successfully identified all patients with normal repolarization pattern 1 and the majority (88%) of patients with an abnormal repolarization pattern. Two patients with repolarization patterns that visually were defined as abnormal were evaluated as normal according to the repolarization index [Color figure can be viewed at wileyonlinelibrary.com]

the repolarization index. Both subjects who were incorrectly classified as normal were gene carriers, had a repolarization pattern 2 in visual evaluation of the repolarization map and had neither repolarization nor depolarization abnormalities on resting ECG.

4 | DISCUSSION

To our best knowledge, this is the first study analyzing repolarization patterns using a 252-lead BSM system in patients with ARVC and gene carriers. The present results suggest that BSM recordings can unmask repolarization abnormalities in ARVC patients, as well as in genetically predisposed family members even in the absence of signs of the disease.

By performing a detailed analysis of various repolarization patterns recorded by a BSM system in ARVC patients, we could identify differences that set apart these patterns from those found in controls, thereby defining them as pathologic. All controls had consistent patterns in both right panels with negative concordant T waves at the upper half and positive T waves at the lower part of the left front panel reflecting the T wave morphology in precordial leads on the 12 lead ECG. The ARVC patients on the contrary, demonstrated more negative T waves at the lower part of the leftF panel, reflecting anterior precordial T wave inversions. Further, the abnormal repolarization pattern detected by the BSM in the 2/12 ARVC cases who lacked T wave abnormalities on resting ECG, may indicate that BSM is a more sensitive tool in detecting repolarization abnormalities compared to conventional 12 lead ECG.

The BSM vest displays the polarity and concordance of T waves with a higher resolution compared to the conventional 12 lead ECG, due to the large number of electrodes. Because of their anatomical proximity to the right ventricle, the right, middle plus lower parts of the left front panel of the BSM vest reflect the electrical activity of most parts of the right ventricle. Changes in T wave polarity and concordance detected by these BSM recordings are thus a reflection of disturbed repolarization of the right ventricle. The conventional precordial ECG leads cover only a limited part of the lower left front panel of the BSM vest, which means that changes in T wave polarity and concordance (i.e. negative or isoelectric T waves) limited to that particular location will not be detectable by the conventional ECG. Similarly, changes in T wave polarity that are limited to the right panels of the BSM will also not be covered by the conventional 12 lead ECG, unless a right precordial ECG lead, V4R or aVR, is used. In theory, the V4R lead could also detect right ventricular repolarization abnormalities more accurately because of its closer anatomical proximity to the right ventricle compared to other precordial ECG leads. The usefulness of lead V4R as an additional diagnostic tool seemed limited, however, since even though T wave inversion in V4R was present in 83% of ARVC patients, it was also observed in half of the controls.

A delayed repolarization of the right ventricle, probably due to structural abnormalities, has previously been reported.^{13–15} Comparing QRST integral maps, recorded by a 62 leads BSM system, abnor-

mal patterns with negative QRST integrals have been observed on the right frontal part of the thorax in ARVC patients, but not in controls or in patients with idiopathic RVOT tachycardia.^{13,14} Another study using T wave integral maps, obtained by a 120-channel BSM system, revealed lower T-wave integrals in the right lower front region of the torso in ARVC patients compared to controls and patients with idiopathic RVOT tachycardia, indicating the presence of local disturbances in refractoriness and conduction velocity.¹⁵ These findings are consistent with our observations that repolarization abnormalities can be detected in right panels and in frontal parts of the left panel in ARVC patients.

In the present study, the BSM system also detected a divergent repolarization pattern in 5/20 gene carriers, three of whom had no precordial T wave inversion on the surface ECG. Thus, the additive diagnostic yield of BSM system regarding repolarization abnormalities was 3/20 (15%). Abnormal repolarization patterns unmasked by BSM in ARVC patients and gene carriers without corresponding changes in their 12 lead ECG recordings, may reflect early changes in the electrical phase of the disease that are more easily detected by BSM. The observed repolarization abnormalities detected by BSM in healthy gene carriers, suggest that early abnormal repolarization changes in the right ventricle may reflect minimal changes even at the cellular level, not detectable with conventional techniques.

MRI was not included in the study protocol for the healthy gene carrier population since electrical abnormalities seem to precede detectable structural changes.³ Screening for electrical abnormalities, including 12-lead ECG, signal-averaged ECG, and Holter monitoring, has been reported to be more sensitive than imaging modalities.¹⁶

The clinical impact of the repolarization abnormalities detected by the BSM recordings among the ARVC patients in our study is yet unknown. Previous studies have shown that extensive ECG repolarization abnormalities are associated with right ventricular dilatation and dysfunction,^{17–19} and may even reflect the extent of right ventricular scarring, indirectly evaluated by electroanatomic voltage mapping in ARVC patients.^{20,21}

The finding of a novel repolarization index, as explored in the present study, distinguishing controls from ARVC patients, suggests that BSM may potentially be a useful tool for identifying early manifestations of the disease. It should be emphasized though, that the cohorts in this explorative study were small and an evaluation of such repolarization index in larger study groups is warranted.

The repolarization abnormalities detected in gene carriers without obvious structural changes or arrhythmias may, however, well imply early changes at the cellular level in individuals susceptible to disease progression at an early stage. As arrhythmias and sudden death can occur even at earlier stages of the disease, before the development of structural abnormalities, the findings may have significant implications regarding time schedules of regular follow-ups and extent of rhythm monitoring.²² Further developments aiming at a more user-friendly vest with lower number of electrodes and at lower costs are, however, warranted.

4.1 | Limitations

Our observations were based on a rather small population and even if our study groups were quite homogenous, the value of BSM for the detection of early manifestations of ARVC needs to be confirmed in larger studies. Since MRI was not included in the study protocol for the healthy gene carrier population, the presence of minor structural abnormalities only detectable by MRI cannot be excluded, even though previous studies have shown that electrical abnormalities precede detectable structural changes.

5 | CONCLUSIONS

The 252-lead BSM system was capable of revealing repolarization abnormalities not detected by conventional ECG in ARVC gene carriers, which may have important implications in early diagnosis of the disease. Further and larger studies are warranted aiming to assess its accuracy as an early diagnostic tool and improving technology lowering costs.

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CONFLICTS OF INTEREST

Varvara Kommata and Elena Sciaraffia 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 Merck Sharp & Dohme outside the submitted work.

AUTHOR CONTRIBUTIONS

The conceptualization and design of the study was performed by Varvara Kommata and Carina Blomström-Lundqvist. Data collection, analysis and interpretation were performed by Varvara Kommata and Elena Sciaraffia. The manuscript was drafted by Varvara Kommata and reviewed – reworked by co-authors for final approval.

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