TITLE PAGE

a) **Title:** Idiopathic premature ventricular contractions from the outflow tract display an underlying substrate that can be unmasked by a Brugada electrocardiographic pattern at high right precordial leads

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STRUCTURED ABSTRACT

Background and aims: Cardiac magnetic resonance (CMR), has shown conflicting data regarding existence of structural abnormalities in patients with idiopathic premature ventricular contractions (PVCs) from the right ventricular outflow tract (RVOT).

Our aim was to evaluate the prevalence of low voltage areas (LVA) in the RVOT of patients with PVCS from the outflow tract and in a control group. Secondly, assess for the presence of a non-invasive electrocardiographic (ECG) marker.

Methods: 56 consecutive patients, 45 with frequent PVCs (>10000/24h) LBBB, vertical axis, negative in aVL and 11 subjects without PVCs. Arrhythmogenic right ventricular cardiomyopathy was ruled out in all patients. An ECG was performed with V1-V2 at the 2nd intercostal space and the presence of a Brugada ECG pattern (BrP) was assessed. Bipolar voltage map of the RVOT was performed in sinus rhythm (0.5 mV-1.5 mV colour display). Areas with electrograms < 1.5 mV represented the LVA. We tested for the association between high BrP and LVA.

Results: None of the patients in the control group had BrP or LVA. In the PVC group, 29 patients (64%) had type 2 BrP and 28 (62%) had LVAs. LVAs were more frequent in patients with BrP; 93% versus 4%, p<0.0001, which was associated with LVA, OR (95% CI): 202.50 (16.92- 2423), p<0.0001.

Conclusions: LVAs were frequently present in the RVOT of patients with idiopathic PVCs. They were absent in controls and can be unmasked by the presence of BrP in high right precordial leads.

Keywords

Premature ventricular contractions; idiopathic arrhythmias; right ventricular outflow tract; catheter ablation; low voltage areas; remote magnetic navigation; type 2 Brugada ECG pattern; high right precordial leads; second intercostal space

MAIN ARTICLE

1. INTRODUCTION

Idiopathic premature ventricular contractions (PVCs) arise from the outflow tracts in more than 80% of cases, more frequently the right ventricular outflow tract (RVOT)[1]. Cardiac magnetic resonance imaging studies (CMR) have shown conflicting data regarding the existence of structural abnormalities in the RVOT of those patients. Initial studies documented the presence of localized wall bulging, focal wall thinning or fatty replacement in a high percentage of patients[2]. However, most recent studies using ECG gating and imaging with late gadolinium enhancement (LGE) have shown absence of pathological findings in patients with idiopathic RVOT PVCs[3].

Detection of myocardial fibrosis can be assessed noninvasively with CMR using LGE[4] but its detection depends on the type of fibrosis, whether replacement or interstitial fibrosis. In the initial phases of non-ischemic cardiomyopathy for instance, although a certain degree of diffuse fibrosis may be present, it goes undetected by LGE techniques and may be detected by T1 mapping[5].

Previous studies have shown presence of low voltage areas (LVAs) in the RVOT of patients undergoing catheter ablation of frequent PVCs despite normal CMR[6-10]. These findings may suggest the presence of an underlying substrate too subtle to be identified by CMR techniques[11]. The presence of a Brugada electrocardiographic (ECG) pattern (BrP) at the high right ventricular leads has been described in patients with PVCs from the RVOT and was associated with the presence of LVAs[6].

The aim of this study was to evaluate the prevalence of both BrP at high right ventricular leads and that of LVAs in the RVOT, in patients with frequent PVCS from the outflow tracts and in a control group. Secondly, estimate the value of a BrP as a non-invasive electrocardiographic marker of low voltage in the RVOT.

2. METHODS

2.1. Patient population

From 2016 to 2020, we retrospectively studied consecutive patients with symptomatic idiopathic frequent PVCs (>10000/24h) with a LBBB, vertical axis, negative in aVL that were referred for catheter ablation by the same operator. Patients that did not underwent electroanatomical voltage map of the RVOT in sinus rhythm were excluded. The study was carried out in two hospitals. All patients underwent transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler study and standard 12-lead electrocardiogram (ECG). A second ECG was obtained with the right ventricular leads at the level of the second intercostal space (ICS). A treadmill exercise test was performed if symptoms appeared or were aggravated by exercise. All patients with PVCs had a CMR with Gadolinium to exclude the presence of RVOT anomalies.

Arrhythmogenic right ventricular cardiomyopathy was ruled out according to the Task Force Criteria[12] . A 24-Hour Holter recording was performed before ablation and the number of PVCs per 24 hours and the presence of episodes of non-sustained ventricular tachycardia (NSVT), defined as >3 PVCs in a run were assessed. Patients with evidence of conduction delays, electrical diseases or abnormal QRS morphology, as well as patients with previous ablation were excluded.

A control group of consecutive patients without PVCs, that underwent catheter ablation of supraventricular tachycardias since 2019 and agreed to have a voltage map of the RVOT performed in sinus rhythm was also studied.

2.2. Study Design

We retrospectively assessed for the presence of a BrP at the level of the second ICS, in patients with PVCs and in controls. Both groups with and without BrP were compared regarding demographic and clinical characteristics, echocardiographic electrocardiographic and 24 Holter data and electroanatomical

mapping and ablation data. The association between the presence of BrP and presence of LVAs was analysed.

2.3. Standard 12-leads ECG and high right precordial leads ECG

The ECG was performed with standard paper speed and calibration. After a standard 12-lead ECG recording the ECG was repeated, with V1 and V2 leads placed in the 2nd ICS and maintaining the other lead's position. The duration of the QRS in sinus rhythm and the precordial transition of the sinus and ectopic beats, defined as the precordial lead where the QRS changes from predominately negative to predominately positive and the R/S ratio becomes >1 were assessed in the standard ECG both in sinus rhythm and during the PVC. The presence of T wave inversion beyond V1 was evaluated in standard and high right precordial leads ECG.

A BrP, according to the Report of the Second Consensus Conference[13] includes three types: type-1 has a coved ST segment elevation $\geq$ 2 mm, negative T wave and no isoelectric separation of T wave; type-2 has a saddleback appearance with an ST segment elevation of ≥2 mm, trough that is still ≥1 mm ST elevation and then either a positive or biphasic T wave; type 3 has either a saddleback or coved appearance with an ST-segment elevation of < 1 mm. Type 2 and type 3 ECG are not diagnostic of the Brugada syndrome. A consensus report in 2012[14] combined type 2 and 3 of the previous consensus into the new type 2. The BrP in our study was classified in type 1 and type 2 assessed in the standard and in the high right precordial leads position. The ST segment elevation was measured at the take-off point of the QRS-ST. All ECG recordings were evaluated by two independent reviewers blinded to the result of the voltage map.

2.4. Electroanatomic Mapping and Ablation

All patients underwent electroanatomical mapping with CARTO 3 (Biosense-Webster) or EnSite Velocity (Abbott). With the former, all procedures were performed using the Niobe magnetic navigation system

(Stereotaxis) working with the monoplane fluoroscopy system AXIOM Artis (Siemens) as previously described[15]. An irrigated tip Navistar RMT Thermocool catheter (Biosense-Webster) was used with a 3.5-mm distal tip electrode and a 2-5-2 interelectrode distance. With the EnSite Velocity system all procedures were done manually with the monoplane fluoroscopy system BV Pulsera (Philips) and using an irrigated tip Therapy Cool Path or flexibility catheter (Abbott) with a 4-mm distal tip electrode and a 1-4-1 interelectrode distance. The ablation catheter was introduced via the femoral vein, manually advanced to the right atrium and then automatically advanced to the His bundle and RVOT in the magnetic navigation system patients or manually in the EnSite patients, under fluoroscopic guidance. The ablation catheter was then placed at multiple sites on the endocardial surface of the RVOT. The 12-lead surface ECGs and intracardiac electrograms were recorded simultaneously by a digital multichannel system, filtered at 30–300 Hz for bipolar electrograms and at 0.05–525 Hz for unipolar electrograms, displayed at 100 mm/s speed. Two maps were created, a voltage bipolar map in sinus rhythm and an activation map during the PVC. In sinus rhythm the electrograms were analysed in regard of their amplitude and the information was used to generate a 3-dimensional electroanatomical voltage map of the RVOT, with the electrophysiologic information, colour-coded and superimposed on the geometry. The colour display for voltage mapping ranged from purple, representing electroanatomical normal tissue (amplitude $\geq$ 1.5 mV), to red, representing electroanatomical scar tissue (amplitude <0.5 mV). LVAs were defined as areas with bipolar electrograms with an amplitude <1.5 mV. The level of RVOT/pulmonary valve junction was thoroughly determined based on electroanatomical voltage mapping by passing the catheter into the pulmonary artery and slowly withdrawing it to the RVOT. The area immediately below the level of the pulmonary valve displayed intermediate colours corresponding to a bipolar voltage between 0.5 mV a 1.5 mV, defined as the transitional-voltage zone[8]. Presence of LVAs outside the transitional-voltage zone, were assessed.

The activation map was created by mapping several points during each PVCs while using a surface ECG lead as reference. The ablation site was selected based on the earliest endocardial activation time with a QS pattern at the unipolar electrogram and confirmed by the pace mapping that provided at least 11 out of 12 pace matches between paced and spontaneous PVCs. Energy was delivered from an EP Shuttle RF generator (Stockert) between the distal electrode of the ablation catheter and a cutaneous patch, for up to 120 seconds, to a maximum temperature of 43˚C and a power output limit of 50 W. When the application was ineffective, additional applications were delivered to sites adjacent to the earliest activation site. During ablation, light sedation with midazolam (bolus) or remifentanil (continuous perfusion) was administered when needed. Success was defined as abolition of PVCs under isoprenaline infusion until thirty minutes after ablation. All the intracardiac electrograms were reviewed by two senior electrophysiologists blinded to the results of the ECG.

2.5. Statistical analysis

All analyses were performed using SPSS statistical software, version 25.0 (SPSS, Inc, Chicago, Illinois). Data is presented as median and lower and upper quartile (Q_1-Q_3) for continuous variables and as absolute numbers and percentages for categorical variables. Continuous variables were compared with the use of Mann Whitney test for independent samples. Categorical variables were compared with the use of two-side Fischer's exact-test or the chi square test as appropriate for independent samples and with the McNemar test for related samples. Univariable logistic regression analysis and calculation of the respective odds ratios (OR) and 95% confidence intervals (CI) was used to evaluate the discriminative power of BrP as a marker of LVA in the RVOT. The performance of BrP as a diagnostic test including the positive and negative predictive value as well as specificity and sensitivity was based on a 2x2 contingency table and chi square test. For all tests a p value <0.05 was considered as statistically significant.

2.6. Ethics

All patients signed the informed consent form and the study was approved by the Ethical Committee of both hospitals. The study is in compliance with the Helsinki Declaration.

3. RESULTS

3.1. Patient population

56 patients were enrolled, 45 patients with PVCs and 11 patients in the control group of whom eight underwent ablation of atrioventricular nodal reentrant tachycardia, two of accessory pathways and one of typical atrial flutter. Both groups did not differ in relation to age or gender, (Table 1). Patients in the PVC group were more frequently on betablocker therapy, 73% versus 9%, $p<0.0001$.

In the PVC group, all patients were symptomatic, forty-four complained of palpitations, one patient had episodes of dizziness and five patients had a history of fainting, all typically vagal in nature. Two patients had family history of sudden death in one due to a myocarditis and in the other at the age of 64 years and preceded by chest pain. Physical examination, and transthoracic echocardiography, including 2-dimensional, M-mode, and Doppler echocardiography were normal and demonstrated normal right ventricle size and function. The CMR did not show evidence of RVOT abnormalities in any patient.

Twenty patients underwent treadmill exercise test and twelve (60%) had a reduction of PVC frequency with exercise. The 24-hour Holter recording showed a high PVC burden with a median of 20000 (14000-24000)/24 hours and NSVT in 10 patients (22%).

3.2. Standard 12 Lead ECG and high right precordial leads ECG

The mean duration of the QRS was 82 (80-90) ms and three patients in the PVC group displayed T wave inversion beyond V1, not significantly different between the PVC and control group. (Table 1). BrP was absent in the standard ECG.

Eighteen patients displayed T wave inversion beyond V1 in the high ECG, which represents a six-fold increase in comparison with the standard ECG ($p<0.0001$). No patient in the control group showed T wave inversion beyond V1. BrP was present in 29 patients (64%) in the PVC group but absent in the control group, $p<0.0001$. No definite type 1 pattern was observed, all patients displayed a type 2 pattern, the ST elevation was <2mm in 27 patients (example in Figure 2 panel A), and >2mm but without the coved-type morphology in two (example in Figure 2 panel B) . The median ST segment elevation was 1 (1-1.5) mm.

3.3. Comparison between patients with and without BrP in high right precordial leads ECG

The characteristics of patients with and without BrP are depicted in Table 2. There were no significant differences regarding demographic data, clinical variables, PVC burden or presence of NSVT or standard electrocardiographic measurements. However, on the ECG performed in the high position, patients with BrP showed T wave inversion beyond V1 more frequently (45% vs 19%, $p=0.047$).

3.4. Electroanatomical mapping and ablation

3.4.1. PVC group versus control group

The electroanatomical mapping was successfully acquired in all patients, the median number of points per patient used to obtain the RVOT map was 142 (98-300) and the results are displayed in Table 3. The number of points sampled was not significantly different between patients with PVCs and the control group, respectively 141 (102-300) versus 182 (120-317), $p=0.529$. The electroanatomical system used in control group was predominantly Carto (90%), while in the PVC group it was used in approximately 50% of cases, p=0,036. This occurred because Carto is the system used with Stereotaxis, the better choice in terms of safety for mapping the RVOT in the control group.

In forty patients the PVCs originated in the RVOT and in five the origin was in the left aortic cusp. Presence of LVAs outside the transitional-voltage zone were absent in all subjects from the control group (Figure 1) and present in 28 patients (62%) of the PVC group, p<0.0001 (Figure 2).

3.4.2. BrP as risk marker of low voltage areas in patients with PVCs

The number of points sampled for the RVOT map in the PVC group was 141 (102-300) not significantly different between patients with and without BrP respectively, 152 (104-313) versus 118 (99-190), p=0.066 (Table 3). The electroanatomical system used was not significantly different in the two groups neither was the site of origin of the PVCs right versus left. Presence of LVAs outside the transitional-voltage zone were more frequent in the group with BrP, 93% of cases versus 4%, p<0.0001. The site of origin of the PVCs was in the LVA in 18 out of the 45 patients with PVCs (40%) (Figure 3). This percentage was significantly higher in patients with BrP, respectively 59% of cases versus 4%, p=0.001 (Table 3). The success rate was not significantly different in both groups. BrP was a predictor of the presence of LVAs in the RVOT of patients with idiopathic PVCs, OR (95% CI) 202.50 (16.92- 2423), p<0.0001. The positive predictive value was 93%, negative predictive value 94%, sensitivity 96% and specificity 88%.

4. DISCUSSION

The first finding of this study was the presence of a BrP in 64% of patients with PVCs, on the ECG performed at the level of the second ICS. According to the contemporary definition of Brugada syndrome, the diagnostic ECG displays a coved-type ST segment elevation of at least 2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the fourth, third or second ICS[16].The reason for using these higher positioned V1-V2 leads in the diagnosis of Brugada syndrome, is their closer proximity to the RVOT, now known to be the origin of the disease[17]. That is why we used these higher leads in the present study. In our patients, the ST segment elevation had a coved-type or rectilinear descendent morphology but could not be considered a type 1 BrP because it was less than 2 mm except in two patients that had

more than 2 mm but in those the coved-type pattern was absent. Therefore, accordingly to the current guidelines[16] we considered a type 2 BrP. Previous studies have reported the prevalence of BrP in the general population. Holst et al[18] studied 340 healthy subjects and reported an incidence of type 1, 2 and 3 BrP on the second ICS, respectively 0%, 3.3% and 7.1%. Hunuk et al[19] registered similar results in 504 healthy male volunteer subjects. The authors found an incidence of type 1, 2 and 3 BrP on 0.8%, 2% and 7.5% respectively. Chung et al [20] studied a population of 491 collegiate athletes and a type 2 or 3 BrP was seen in 58 (11.8%), no definitive type 1 was observed. The much higher incidence of a type 2 BrP in our PVC patients, and its absence in the control group, raises the hypothesis that the two may be associated. The term Brugada phenocopy was proposed to describe conditions that induce Brugada-like ECG manifestations in patients without true Brugada syndrome[21], and this may be the case. On the other hand, Nademanee et al[22], have demonstrated the presence of fibrosis as well as reduced connexin-43 signal in the RVOT of autopsies of patients with Brugada syndrome. The authors find therefore plausible that Brugada syndrome may reflect a generalized disease of myocardial of the RVOT predisposing it to fibrosis. The role of fibrosis in Brugada syndrome is uncertain, and the clinical phenotype concomitant with cardiac fibrosis remains a matter of ongoing scientific investigation[17].

The second finding in our study was the increase in the percentage of patients with T wave inversion beyond V1 when the ECG was obtained at the level of the second ICS in comparison with the standard ECG position. The diagnosis of ARVC is sometimes difficult, and T wave inversion in V1-V2 is considered a minor criteria[12]. If we accept that the T wave inversion at a higher ICS could have a similar value, then the number of ARVC “possible” cases would increase[12]. However, unlike the ST segment elevation the presence of this T wave inversion was not associated with the presence of LVA.

The third finding in our study was the presence of LVAs outside the transitional-voltage zone, that were absent in subjects without PVCs. The bipolar voltage above the pulmonary valve is typically less than 0.5 mV or even less than 0.1 mV[9] due to the absence or scarcity of myocardium at that level. The voltage

progressively increases as the catheter is withdrawn to the RVOT. The area immediately below the pulmonary valve displays a voltage between 0.5 and 1,5 mV and is described by Yamashina et al[8] as the transitional-voltage zone. The length of this area is variable and according to the authors, longer in patients with malignant arrhythmias than in those with a benign course. In our study the LVAs were outside the transitional-voltage zone, into the RVOT body. Their presence was not significantly different in patients with a RVOT or LVOT origin. Either these results are due to the small number of patients with PVCs from LVOT or the findings are truly independent of the site of origin of PVC in the outflow tract. The presence of LVA in patients with idiopathic PVCs is not a recent finding. In fact, a high number of previous studies have already demonstrated this finding, either with conventional ablation catheters[6-9,22] or recently, with the use of a multipolar catheter to obtain a high-density endocardial voltage mapping[10]. The bipolar voltage depends amongst other things on the recording electrode size and the interelectrode spacing. One may argue that with high density/high resolution mapping the results could be different. We found the presence of LVA outside the transitional-voltage zone in 28 out of 45 patients (62%). Letsas et al[10] mapped the RVOT of patients with idiopathic PVCs using a multipolar catheter with 2 mm electrodes for high density mapping (mean number of sampled points 1096.6 ± 322.3), and identified at least two low bipolar voltage areas less than 1mV in 39 out of 44 patients (88%), a higher percentage than ours. They used an ablation strategy aiming at these LVAs in patients with low PVC burden as previously proposed by Wang at al[23] with good success rates. In our study group in patients with LVAs the site of origin of the arrhythmia was in the LVA in 18 out of 28 patients (64%) of cases. The presence of LVAs did not match the results of the CMR in any of the studies. Detection of fibrosis using LGE has been well validated in ischemic cardiomyopathy and post myocardial infarction, with an excellent agreement between CMR findings and the voltage map[24]. However, that is not true for non-ischemic myocardiopathy. Myocardial fibrosis is a common final pathway in chronic myocardial disease but the type of interstitial fibrosis that occurs in the initial phases of non-ischemic myocardiopathy or ARVC[12] is not reliably detected

with LGE, and other techniques are being investigated[4,5]. On the other hand, we must not forget the true meaning of LVAs. In fact, low bipolar voltage is not synonyms of fibrosis. Bipolar voltage amplitude is influenced by many variables independently of the presence of fibrosis[25]. Boulos et al[26] studied the voltage map in patients with ARVC, normal subjects and idiopathic PVCs. They found a regional difference in the bipolar voltage throughout the right ventricle, and the RVOT displayed the lowest voltage. However, it was well above the 1.5 mV cut-off value (mean 2.6 ± 0.4 mV) in normal subjects and significantly higher than the bipolar voltage in the dysplastic regions of patients with ARVC (0.60±0.06 mV). So, independently of the points discussed above, the presence of LVAs in the middle of normal voltage areas, must be considered an abnormal finding and hopefully a target for ablation.

The last finding was the association of the BrP in the second ICS with the presence of LVAs in patients with apparently normal hearts. We have previously reported this finding with a smaller number of patients, and some limitations namely, the absence of a control group and the fact that CMR was not performed in all patients[6]. The present study confirmed those preliminary results and we were able to demonstrate that the BrP in the second ICS was a predictor of LVAs. The remarkably high odds ratio and wide confidence intervals is due to an extremely low prevalence of LVA in the absence of BrP (1 patient) and extremely low prevalence of absent LVAs in patients with BrP (2 patients).

LVAs may be pointed as a possible target for ablation and BrP may be used as a non-invasive marker.

5. STUDY LIMITATIONS

The study was retrospective. Two different mapping systems were used to obtain the voltage map. Mostly patients in the control group were mapped with Carto and Stereotaxis. We only considered patients that had the map of the RVOT done, so some patients with PVCs that went directly to LVOT mapping were excluded, leaving a small number of patients with the site of origin in the LVOT.

Patients did not repeat the ECG in the second ICS to evaluate if BrP persisted after successful PVC ablation.

6. CONCLUSIONS

Low voltage areas outside the transitional-voltage zone were frequently present in the RVOT of patients with idiopathic PVCs from the outflow tract. Those are absent in controls and can be unmasked by the presence of BrP in high right precordial leads. The site of origin of the PVCs were within the LVA in a high percentage of cases. Low voltage areas are a potential target for PVC ablation and BrP is an accurate non-invasive marker of LVAs.

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TABLES

Table 1. Baseline characteristics and comparison between PVC group and control group

	Overall sample (n=56)	PVC group (n=45)	Control (n=11)	P value
Demographic data				
Age in years, median (Q_1-Q_3)	50 (36-60)	48 (37-61)	50 (33-54)	0.773
Male Gender, n (%)	23 (41)	20 (44)	3 (27)	0.496
Risk factors, history and medications				
Hypertension, n (%)	7 (13)	6 (13)	1 (9)	1.000
Diabetes, n (%)	3 (5)	2 (4)	1 (9)	0.488
Syncope	5 (9)	5 (11)	0 (0)	0.571
Family history of sudden death	2 (4)	2 (5)	0 (0)	1.000
Betablockers, n (%)	34 (61)	33 (73)	1 (9)	**<0.0001**
Standard 12 lead ECG				
QRS duration in ms, median (Q1-Q3)	82 (80-90)	84 (80-90)	80 (79-82)	0.062
T wave inversion beyond V1, n (%)	3 (5)	3 (7)	0 (0)	1.000
BrP, n (%)	0(0)	-	-	-
High right precordial leads ECG				
T wave inversion beyond V1, n (%)	18 (32)	18 (40)	0 (0)	**0.011**
BrP, n (%)	29 (52)	29 (64)	0 (0)	**<0.0001**
24-Hour Holter Monitoring*				
Number of PVCs, median (Q1-Q3) *	-	20000 (14000-24000)	-	-
NSVT, n (%)*	-	10 (22)	-	-
Echocardiogram				
LVEF in %, median (Q_1-Q_3)	57 (56-60)	58 (56-60)	58 (57-59)	0.630

* in the PVC group. BrP: Brugada electrocardiographic pattern; LVEF: left ventricular ejection fraction; NSVT: non sustained ventricular tachycardia; PVC: premature ventricular contractions

Table 2. Baseline characteristics of patients with and BrP in high right precordial leads

	Overall sample (n=56)	With BrP (n=29)	Without BrP (n=27)	P value
Demographic data				
Age in years, median (Q_1-Q_3)	50 (36-60)	45 (35-60)	50 (36-60)	0.896
Male Gender, n (%)	23 (41)	13 (45)	10 (37)	0.596
Patients with frequent PVCs, n (%)	45 (80)	29 (100)	16 (60)	**<0.0001**
Risk factors, history and medications				
Hypertension, n (%)	7 (13)	3 (10)	4 (14)	0.700
Diabetes, n (%)	3 (5)	1 (3)	2 (7)	0.605
Syncope, n (%)	5 (9)	1(3)	4 (14)	0.185
Family history of sudden death, n (%)	3 (5)	0 (0)	3 (11)	0.106
Betablockers, n (%)	34 (61)	21 (72)	13 (48)	0.100
24-Hour Holter Monitoring*				
Number of PVCs, median (Q1-Q3) *	20000 (14000-24000)	17595 (12774-24000)	20112 (15500-28500)	0.325
NSVT, n (%)*	10 (22)	6 (21)	4 (25)	0.726
Standard 12 lead ECG				
QRS duration in ms, median (Q1-Q3)	82 (80-90)	85 (80-90)	80 (80-90)	0.829
PVC precordial transition beyond V3, n (%)*	30 (68)	20 (69)	10 (63)	0.746
PVC transition earlier than SR, n (%)*	14 (31)	7 (24)	7 (44)	0.197
T wave inversion beyond V1, n (%)	3 (5)	3 (10)	0 (0)	0.237
High right precordial leads ECG				
T wave inversion beyond V1, n (%)	18 (32)	13 (45)	5 (19)	**0.047**
Echocardiogram				
LVEF in %, median (Q1-Q3)	57 (56-60)	57 (56-60)	60 (56-64)	0.254

* in the PVC group. BrP: Brugada electrocardiographic pattern; LVEF: left ventricular ejection fraction; NSVT: non sustained ventricular tachycardia; PVC: premature ventricular contractions

Table 3. Electroanatomical mapping and ablation data

	Overall sample (n=56)	PVC group (n=45)	Control (n=11)	P value
Electroanatomical mapping				
Number of points in the map	142 (98-300)	141 (102-300)	182 (120-317)	0.529
Carto/Ensite	34/22	24/21	10/1	**0.036**
LVAs, n (%)	28 (50)	28 (62)	0 (0)	**<0.0001**
	Overall PVC group (n=45)	**With BrP (n=29)**	**Without BrP (n=16)**	**P value**
Electroanatomical mapping and ablation*				
Number of points in the map*	141 (102-300)	152 (104-313)	118 (99-190)	0.066
Carto/Ensite*	24/21	13/16	11/5	0.212
PVCs from RVOT/LVOT*	40/5	26/3	14/2	1.000
LVAs, n (%)*	28 (62)	27 (93)	1 (4)	**<0.0001**
SOO in LVAs, n (%)*	18 (40)	17 (59)	1 (4)	**0.001**
Success, n (%)*	40 (89)	27 (93)	13 (81)	0.330

* in the PVC group. BrP: Brugada electrocardiographic pattern; LVOT: left ventricular outflow tract; LVA: low voltage area; RVOT: right ventricular outflow tract; SOO: site of origin

FIGURES

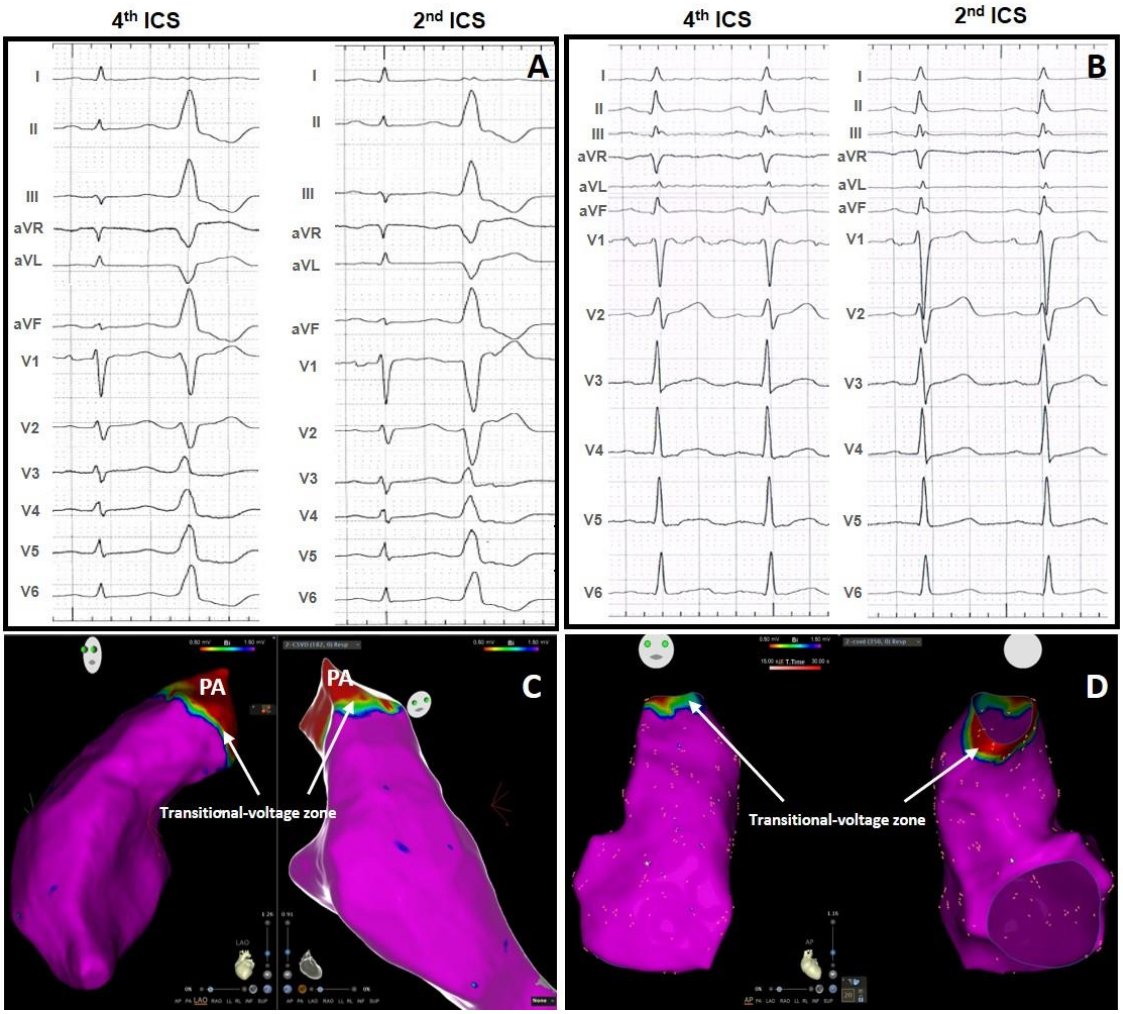

Figure 1. Standard 12-lead ECG and high right ventricular leads ECG without ST elevation in a patient with PVCs (A) and in a control subject without PVCs (B). Normal voltage map without LVAs in the patient with PVCs (C) and in the control subject (D).

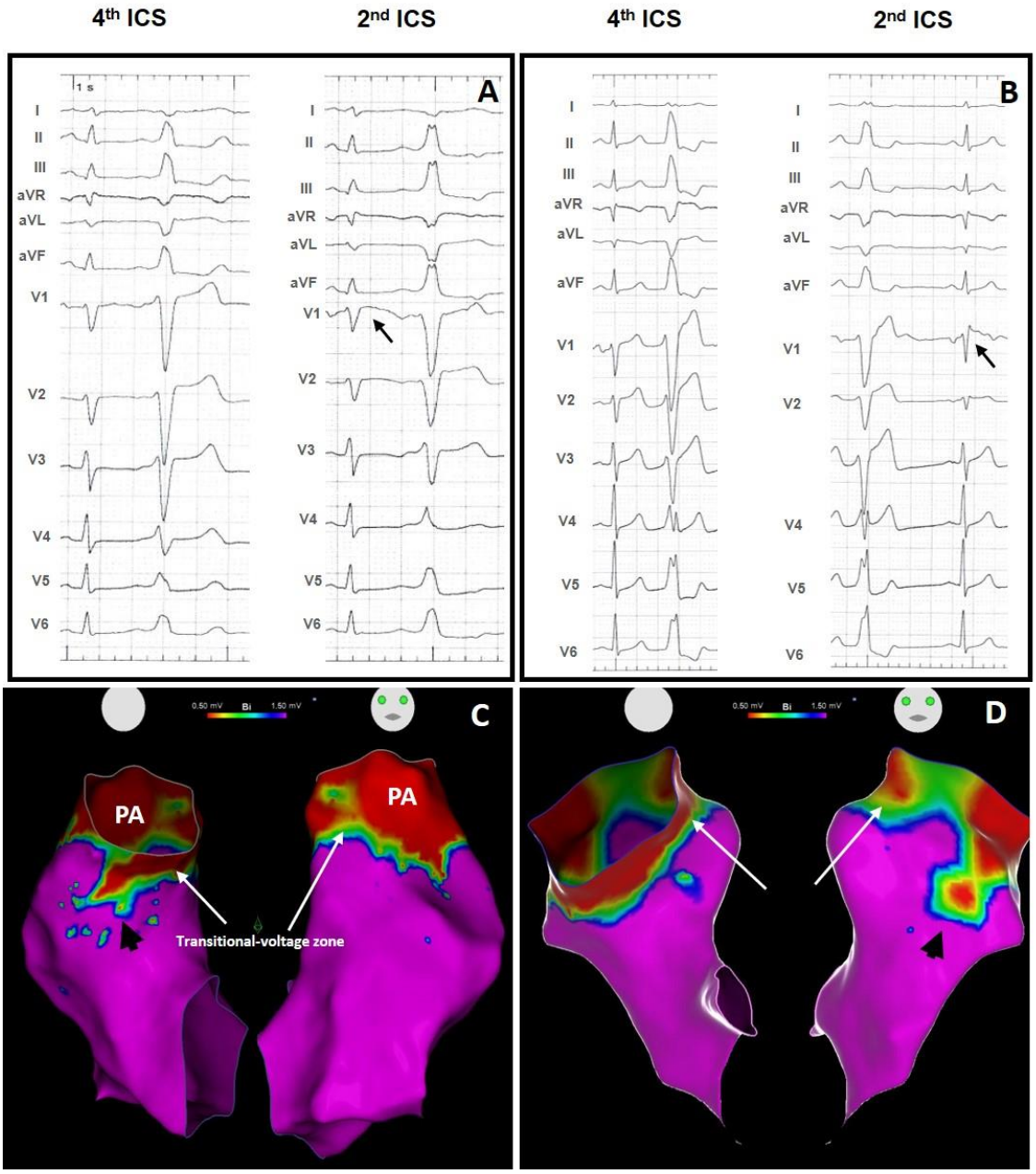

Figure 2. Standard 12-lead ECG and high right ventricular leads ECG with BrP in two patients with PVCs from the RVOT (A and B) and respective voltage map showing an area of low voltage outside the transitional-voltage zone (white arrows), in the septal wall (panel C, black arrow) and in the free wall (panel D, Black arrow)

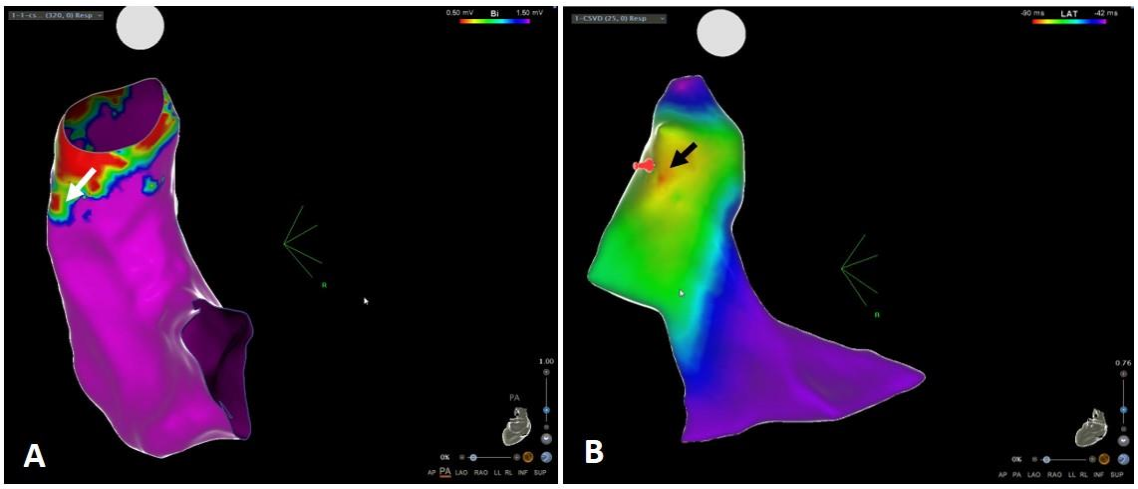

Figure 3. Panel A. Voltage map displaying low voltage area (white arrow). Panel B. Activation map of the same patient showing site of origin of the PVCs (black arrow) in the area of low voltage.