Characterization of the Electrophysiological Substrate in Patients with Barlow's Disease

[Authors]

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ABSTRACT

BACKGROUND. Myxomatous mitral valve prolapse (MVP) and mitral-annular disjunction (Barlow disease) are at-risk for ventricular arrhythmias (VA). Fibrosis involving the papillary muscles and/or the infero-basal left ventricular (LV) wall was reported at autopsy in sudden cardiac death (SCD) patients with MVP.

METHODS AND RESULTS: Twenty-three patients with VA were enrolled, including five with syncope and four with a history of SCD. Electrophysiological parameters were correlated with VA patterns, ECG inferior negative T wave (nTW), and late gadolinium enhancement (LGE) assessed by cardiac magnetic resonance. Premature ventricular complex (PVC) burden was 12061.9±12994.6 /24 hours with a papillary-muscle type (PM-PVC) in 18 patients (68%). Twelve-lead ECG showed nTW in 12 patients (43.5%). A large Uni<8.3mV area (62.4+/- 45.5 cm2) was detected in the basal infero-lateral LV region in 12 (73%) patients, and in the papillary muscles (2.2+/- 2.9 cm2) in 5 (30%) of 15 patients undergoing EAM. A concomitant Bi<1.5 mV area (5.0±1.0 cm2) was identified in 2 patients. A history of SCD, and the presence of nTW, and LGE were associated with a greater Uni<8.3mV extension: (32.8+/-3.1 cm2 vs. 9.2+/-8.7 cm2), nTW (20.1+/-11.0vs.4.1+/-3.8cm2), and LGE (19.2 ± 11.7 cm2 vs. 1.0 ± 2.0 cm2, p=0.013), respectively. All patients with PM-PVC had a Uni<8.3mV area.

CONCLUSIONS: Low unipolar low voltage areas can be identified with EAM in the basal infero-lateral LV region and in the papillary muscles as a potential electrophysiological substrate for VA and SCD in patients with MVP and Barlow disease phenotype.

Keywords

Mitral valve prolapse, sudden death, ventricular tachycardia, ventricular fibrillation, risk stratification, premature ventricular complexes, papillary muscles

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INTRODUCTION

Mitral valve prolapse (MVP) is the most common valvular heart disease, affecting 2% to 3% of the general population[1]. The cornerstone of the disease is a myxomatous degeneration in the mitral leaflet tissue, with the displacement of one or both leaflets into the left atrium above the annular coaptation plane [2, 3]. Although MVP is generally considered a benign condition, several studies report ventricular arrhythmias (VA) and sudden cardiac death[4-7]. Left ventricular (LV) fibrosis at the post-mortem examination of the papillary muscles and/or infero-basal wall is considered as a potential substrate for arrhythmia development in sudden death MVP patients[8]. Consistently, late gadolinium enhancement was identified by cardiac magnetic resonance (CMR) in the same regions in patients with MVP and VA. Patients with myxomatous MVP and mitral annular disjunction (MAD) (Barlow disease phenotype) with related infero-basal stretching are regarded as high-risk subsets for VA. However, electrophysiological studies focusing on the substrate of VA in MVP with Barlow disease phenotype are scarce.

In this study, we investigated the role of programmed electrical stimulation (PES) and electro-anatomical mapping (EAM) in the risk stratification of MPV patients with Barlow disease phenotype and documented VA.

METHODS

Study population

A consecutive series of patients with MVP due to Barlow disease, referred to our institute between 2013 and 2017 for complex ventricular arrhythmia work-up, including invasive electrophysiological study was enrolled and retrospectively analyzed. The patients with MVP were categorized as Barlow disease using the following clinical and echocardiographic phenotype: non-ejectional mid-systolic click and late systolic murmur at cardiac auscultation; extensive myxomatous degeneration of mitral leaflet with MAD and late tissue Doppler peak velocity signal of the infero-basal wall at the echocardiographic examination. Exclusion criteria were: absence of complex ventricular arrhythmias, atrial fibrillation at the time of echocardiographic studies, concomitant significant valvular heart disease, previous myocardial infarction or angiographically significant coronary artery disease, severe arterial hypertension, unstable critically ill condition, left ventricular dysfunction, concomitant primary or iatrogenic long QT interval. Our institute's ethics committee approved the study and the patients provided written informed consent.

Echocardiographic study

All patients underwent transthoracic echocardiography (TTE) and subsequent transesophageal echocardiography (TEE) using an EPIQ echocardiograph (Philips Ultrasound, Andover) equipped with a 5S and 7X-t probes. We performed two-dimensional (2D), three-dimensional (3D), and color Doppler imaging using the standard approach. In every patient, MV segments were classified as normal or prolapsing (displacement >2mm of MV segment above the antero-posterior annular plane along the inter-commissural coaptation surface. Myxomatous degeneration was defined as a relevant redundance of the mitral valve leaflet during the diastole with a clear thinning during the systole. MAD was recognized and measured using a TTE parasternal long-axis view or TEE 3 chamber view, as a systolic separation between atrial insertion of the posterior leaflet and the atrial site of the infero-basal wall of the left ventricle. Pattern velocity of the infero-basal wall of the left ventricle was assessed with tissue Doppler, and late peak velocity was annotated. We based MR severity on conventional parameters. In addition, Color Doppler was carefully addressed to map the site and the number of regurgitant jets. Final MV imaging was acquired and digitally stored.

Electrocardiography

All patients underwent a standard 12-lead electrocardiogram. Analyzing T wave polarity, we categorized the following patterns:

- “inferior nTW pattern”: the presence of negative T-waves (nTW) in at least 2 of the II, III, aVF leads;

- “lateral nTW pattern”: the presence of nTW in at least 2 of the V4, V5 and V6 leads;

- “infero-lateral nTW pattern”: the presence of nTw in at least 2 of the II, III, aVF leads and 2 of the V4, V5 and V6 leads.

The QTc interval was measured according to the conventional method. Premature ventricular beats (PVC) were categorized according to the following ECG characteristics: bundle branch block morphology (right or left), axis (right or left, inferior or superior), QRS duration morphology of the QRS complex in V1 (R, Rr', rR', qR, QR, qRr' qrR', Rs, rS, RSr', Rsr',rSR', rsR', and variable[9]. Papillary-muscle type PVC (PM-PVC) was defined following the algorithm from A'Aref et al.[9].

VA diagnosis was obtained by 12-lead ECG, Holter recordings, and ICD interrogations. The presence of non-sustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (VT), and ventricular fibrillation (VF) episodes were annotated. Pre-procedural PVC burden was assessed with 24-hour Holter monitoring. PVCs were defined as “frequent” in presence of >10000 PVCs / 24 hours. All patients underwent preprocedural clinical assessment, including symptoms, VA, and previous resuscitated sudden cardiac death (SCD) documentation.

Cardiac Magnetic Resonance

CMR was performed in 15 patients. Images were obtained with Philips Ingenia 1.5T MR system (Koninklijke Philips N.V. Netherlands) and post-processed with Philips Intellispace by two independent physicians. Steady-state free precession short-axis sequences were used for LV and RV volumes and LVEF. LV and RV end-diastolic volumes were indexed by body surface area (CMR-LVEDVi and CMR-RVEDVi, respectively). T2-weighted short tau inversion recovery (STIR) images were obtained. Proton density-weighted images with fat suppression were used. Cine 3D short and long-axis sequences were visually analyzed for LV and RV morphological or wall motion abnormalities. Early gadolinium perfusion was performed with Gd-D03A-butrol with Perf-BTFE sequences. After 10 minutes, late gadolinium enhancement (LGE) was assessed with inversion recovery sequences. Inversion times were adjusted to null normal myocardium, and areas of LGE were localized following the American Heart Association 17-segment model for the LV12.

Invasive electrophysiological evaluation

Programmed electrical stimulation (PES) and electro-anatomical mapping (EAM) were performed under conscious sedation. A quadripolar catheter was introduced into the right ventricle (RV) via the femoral vein. PES was carried out using two drive trains and triple extrastimuli. PES was considered as positive when VF or sustained VT was induced.

A 3.5-mm irrigated-tip mapping/ablation catheter (Thermocool SmartTouch or Thermocool ST/SF^{TM}, Biosense Webster, Diamond Bar, CA, USA) was advanced in the LV with a retrograde transaortic and/or trans-septal approach. When the trans-septal approach was used, the ablation catheter was advanced in the left atrium through a steerable introducer (Agilis, Abbott, Illinois, USA). Systemic anticoagulation with unfractionated heparin was instituted before introducing any catheter in left cardiac chambers, targeting an activated clotting time of > 250 seconds. All procedures were performed with the CARTO® 3 mapping system (Biosense Webster, Johnson & Johnson Medical S.p.A., CA, USA). Two- and Three-Dimensional TTE or TEE were used to visualize the LV papillary muscles and infero-basal LV wall, and the contact between catheters and myocardial tissue. Valvular sites were identified by echocardiographic monitoring during the procedure, and intracavitary points with poor contact were excluded. The collection of points for ventricular substrate mapping was allowed only in presence of a contact force > 9 grams[10]. Areas with Unipolar endocardial voltage <8.3 mV (Uni<8.3) were considered as "low-voltage", based on previous reports[11, 12]. Bipolar endocardial voltages <1.5 mV (Bi<1.5) were defined as "low-voltage"; areas with bipolar endocardial voltages <0.5mV (Bi<0.5) were defined as "scar"[13]. Both bipolar and unipolar endocardial abnormal voltage areas were measured offline using the CARTO surface area measurement tool; tagged valvular structures were excluded from the analysis. Late potentials (LPs) were defined as any bipolar low voltage electrogram (<1.5 mV) with a single component or multiple continuous delayed electrical components, occurring after the local ventricular EGM[14, 15].

Statistical analysis

Continuous variables were reported as median (interquartile range); binary or categorical variables as percentages. Comparisons between group patients were performed with the Mann-Whitney U-test for continuous variables, with Pearson-χ^2 or Fisher's exact tests for binary or categorical variables. Linear correlation was evaluated with the Kendall method. Statistical significance was set at p=0.05, adjusted with Bonferroni's correction in presence of multiple comparisons. Analyses were performed using R statistical software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' characteristics

Twenty-three patients (5 male and 18 female; 41.7±13.7 years) were enrolled in the study. The clinical and echocardiographic characteristics of the study population are summarized in Table 1. Clinical presentation at the first electrophysiological evaluation was palpitations in 14 patients, syncope in 5 patients, and resuscitated SCD due to ventricular fibrillation (VF) in 4 patients. Nine patients had mild mitral regurgitation, 7 patients had moderate mitral regurgitation and 5 patients had severe mitral regurgitation.

Electrocardiography

Twelve-lead ECG showed inferior nTW in 12 of the 23 patients, associated with lateral nTW in 6 patients. The presence of NSVT and history of resuscitated SCD did not differ among patients with (6 and 2 patients, respectively) or without nTW (8 and 3 patients, respectively; p=1.0 for both).

ECG Holter monitoring revealed a high PVC burden, including 12061.9±12994.6 PVC/24 hours (502.6±541.4 PVC/hour). Ten out of 23 patients showed ≥ 10.000 PVC/24 hours. PM-PVC were found in 18 patients (68%) and they were associated with a significantly higher prevalence of nTW (11/18, 61%), compared with other PVC patterns (none of the 5 patients with other PVCs morphologies had nTWs; p=0.03). There was no significant difference regarding PVC burden among patients with or without nTW (14798±13119 vs 10320± 13353 PVC/ 24 hours, p=0.27). All 4 patients with SCD had PM-PVC, and none of the 5 patients without PM-PVC had SCD; however, 14 patients with PM-PVC had no previous SCD episode (p=0.5).

Non-sustained ventricular tachycardia (NSVT) was documented with ECG Holter monitoring in 14 patients, including 6 patients (42.9%) with nTW and 8 patients (66.7%) without nTW (p=0.7). LVEF was 60.7±5.7% in patients with previous SCD and 60.6±6.6% in patients without SCD (p=0.97).

Programmed electrical stimulation and electro-anatomical mapping

Among the 21 patients undergoing PES, 4 patients showed inducible VA, including sustained VT and VF (inducibility rate 19%). Patients with PES positive for VA induction showed more frequent PVC than patients with negative PES (27000± 10816 PVC /24 hours vs 8707±11244 PVC /24 hours, p=0.019, respectively). One Patient with resuscitated SCD (25%) and 3 patients without SCD (15.8%, p=0.35) had PES positive for VA inducibility; sensitivity, specificity, positive predictive value, and negative predictive value of PES for VA in patients with previous SCD were respectively 0.25, 0.94, 0.5, 0.84. Even though NSVT was documented in all 4 patients with positive PES, 10 patients with NSVT showed negative PES (p=0.1). Three patients with VA induced by PES showed nTW (inferior in 2 patients and lateral in 1 patient), with no significant differences compared with patients without induced VA (3/4 vs 6/17, respectively, p=0.27). No differences regarding LVEF were found among patients with positive and negative PES (56.2±2.6%, vs 61.4±6.5%, p=0.08) (Table 2).

Fifteen patients underwent EAM (457.6±201.1 acquired points) (Table 3). Eleven patients (73%) showed Uni<8.3 areas in the sub-mitral-annular region (extension: 62.4±45.5 cm^2), including the basal infero-lateral segments of the LV; a concomitant Bi<1.5 area (extension 5.0±1.0 cm^2) was present in only two patients. LPs were identified in the sub-mitral-annular region in 2 patients. EAM of papillary muscles showed the presence of Uni<8.3 areas in 5 patients (extension 2.2±2.9 cm^2), without significant (>1 cm^2) low-voltage bipolar areas; LPs were identified in the same region in 8 patients. Patients with nTW had greater Uni<8.3 areas in the submitral annular region, than patients without nTW (20.1 ±11.0 cm^2 vs. 4.1±3.8 cm^2, respectively p=0.002). No significant differences regarding the extension of Bi and Uni low voltage areas were found in papillary muscles among patients with or without nTW. No significant differences were found in the extension of Bi and Uni low voltage areas among patients with NSVT (1.5±2.0 cm^2 and 13.8±11.7 cm^2, respectively), or without NSVT (1.1±2.2 cm^2, p=0.7 and 9.3±11.6 cm^2, p=0.5, respectively). Patients with previous SCD had larger Bi<1.5 (4.5±0.7 cm^2) and Uni<8.3 areas (32.8±3.1 cm^2), compared to patients without SCD (0.8±1.6 cm^2, p=0.008 and 9.2±8.7 cm^2, p=0.002, respectively). PM-PVC pattern was more frequent in patients with Uni<8.3 areas in the LV infero-basal segment (11 patients, 100%) than patients without Uni<8.3 areas (1 patient, 25%; p=0.008). Uni<8.3 area was 10.1±8.7 in patients with PM-PVC.

The 3 patients without any Bi or Uni low voltage areas had ≤ 5000 PVCs /24; only 1 of them had NSVT; none had SCD. None of the 3 patients without Bi or Uni low voltage areas had VA induction by PES.

Cardiac Magnetic Resonance and electrophysiological findings

Fifteen of the 23 patients underwent CMR; we found LGE in any LV segment in 11 of them (73.3%). LGE was localized in the basal-lateral LV in 5 patients (45.4%); in 4 patients (36.4%) LGE was found both in the basal-lateral LV and papillary muscles. Patients with nTW more frequently showed LGE (8 patients, 100%), than those without nTW (3 patients, 42.9%, p=0.026). Of the 4 patients without LGE, one had NSVT, none had >10000 PVC/24 hours, or resuscitated SCD. Uni<8.3 area was larger in patients with LGE (19.2 ± 11.7 cm^2 vs 1.0 ± 2.0 cm^2, p=0.013) without significant differences regarding Bi<1.5 areas.

DISCUSSION

The main finding of this clinical series analysis is that electrophysiological evaluation may identify the substrate of ventricular arrhythmias in patients with MVP and Barlow phenotype. Low unipolar voltage areas (<8.3 mV) were frequently found in the sub-mitral-annular region of the LV inferior or lateral wall and papillary muscles, with a greater extension in patients with nTW or LGE. Even though the inducibility rate of VA is low, the LV submitral-annular inferolateral wall should be considered as an arrhythmogenic zone targeting electrophysiological studies in MVP with Barlow disease.

Arrhythmogenesis in patients with mitral valve prolapse

In the MVP population, some patients may develop life-threatening arrhythmias, which may be the result of the complex interplay between the substrate, the mechanical stretching, and electrical triggers. Animal models demonstrate that PM mechanical traction may trigger local premature ventricular activation[9], transient after-potentials, and propagated action potentials [10][11]. Stretch-induced depolarization may induce PVC that can be the main clinical finding triggering malignant arrhythmias [12][13]. Furthermore, mechanical traction has been associated with a prolongation of the ventricular functional refractory period and action potential heterogeneities, which can serve both as the substrate for polymorphic VT and as the trigger for short-coupled PVC ("R from T mechanism")[14]. The shape variation of the wavefront activation arising from the abrupt change in muscle fiber orientation, together with the additional sink due to electrical PM mass, may create a "source-sink mismatch" condition in the PM region[20]. During VF, reentrant wavefronts transiently anchored to the papillary muscles; PM disconnection led to the non-inducibility of sustained VT[21]. In the series by Santoro et al., the main mechanism of VF originating from the PM was short coupled PVC [22].

An arrhythmic MVP substrate has been identified by histopathology and CMR. Basso et al.[8] detected in all cardiac sudden-death patients endo-perivasal and patchy replacement-type fibrosis at the level of PM, and, in the majority of cases, sub-endocardial/mid-mural fibrosis in the infero-basal LV wall under the posterior mitral valve leaflet. In vivo CMR demonstrated LV LGE in 93% of arrhythmic MVP vs. 14% of control subjects, with a regional distribution overlapping the histopathological findings. Furthermore, in a large primary mitral regurgitation cohort, the highest arrhythmic event rate was recorded in MVP patients with replacement fibrosis (7.7%), followed by MVP patients without replacement fibrosis (2.7%) and non-MVP patients (0.6%)[24]. Besides LGE, MAD and myocardial deformation abnormalities detected by CMR were associated with VA[16].

The present study identified low voltage areas in the sub-mitral-annulus region of the LV and papillary muscles of our patients with MVP. Eleven patients showed Uni<8.3 areas in the sub-mitral-annulus region concomitant with Bi<1.5 areas in 2 patients. Five patients presented an additional Uni<8.3 area in the papillary muscles region. Low voltage unipolar signals in the presence of normal bipolar voltage are a marker of deep intra-myocardial or epicardial scar, while low voltage bipolar signals are present in areas with endocardial scar[17]. The present electro-anatomical findings are consistent with LGE mid-wall striae, or patchy patterns reported in patients with MVP[18, 19], and the sub-endocardial/mid-mural fibrosis identified by histopathology[8]. A previous study by Syed et al. [25] did not identify any low voltage areas in 14 patients with MVP and a history of cardiac sudden death. However, this is in contrast with their own finding of fractionated, delayed, or mid-diastolic LV electrograms in all patients with MVP and previous cardiac arrest, and in all cases of sustained VA induced during the PES[25]; those electrograms are usually the expression of myocardial scar. The high-density mapping (457.6±201.1 mapping points) used in our study, with ≤10 mm distance between acquired points in regions of interest, and confirmed good contact between tissue and catheter[10] may have allowed the correct identification of myocardial substrate; on the contrary, the study by Syed et al. [25] used a lower resolution mapping (100 mapping points).

In our experience, patients with LGE at CMR had a larger Uni<8.3 area (19.2 ± 11.7 cm^2), compared with patients without LGE (1.0 ± 2.0 cm^2, p=0.013). The presence and the extent of replacement fibrosis by LGE have already been associated with adverse clinical outcomes and ventricular arrhythmias both in patients with coronary artery disease (CAD) and nonischemic cardiomyopathies [20-22]. In our cohort of patients, the presence of large Uni<8.3 areas appeared as a marker of SCD.

Risk stratification in patients with mitral valve prolapse

MVP is an underrecognized cause of SCD in young adults, accounting for 7% of total events and 13% of female victims [8]. The estimated rate of sudden cardiac death in patients with MVP is 0.2% to 0.4% per year, with the cause of death being attributed to malignant VAs[4]. Several small cohort studies attempted to identify the patient characteristics associated with major cardiac events; however, results are still contradictory, and comprehensive risk stratification is not available. Female gender, young age, bileaflet MVP have been associated with an increased risk of death[26] [27]. Inverted or isodiphasic T waves in the inferior leads were found in >80% of the cases of MVP-related SCD[8]. Electrocardiographic abnormalities such as nTW are frequent findings in patients with VA, even though specificity is low. In our experience, the 11 patients with nTW (47.8%) showed larger Bi<1.5 and Uni<8.3 areas in the sub-mitral-annular LV region, compared with those patients without nTW. Therefore, the presence of nTW might be the 12-lead electrocardiographic expression of local voltage abnormalities in the sub-mitral annular region, requiring a substantial amount of fibrosis before becoming evident. Although the cohort was small, we did not find any significant difference between patients with or without nTW regarding PVC burden, NSVT, and history of resuscitated SCD.

Wei et al. showed that a large PVC burden was associated with a higher rate of non-sustained and sustained VT [28]. In a large cohort of 595 consecutive patients, 9% had severe VA (VT ≥180 beats/min and/or history of proven VT/VF), 27% had moderate VA (VT 120 to 179 beats/min), 8% had mild VA (≥5% PVC and/or VT <120 beats/min), and 57% had no/trivial ectopy (<5% PVC). Arrhythmia severity was strongly associated with adverse outcomes, with mortality rates at 8 years after diagnosis ranging from 10±2% in patients with no/trivial VA to 15±3% for mild and/or moderate, and 24±7% for severe arrhythmia ($p = 0.02$). Severe VA was independently associated with mortality after adjustment for clinical covariates (adjusted HR: 2.94; 95% CI: 1.36 to 6.36; $p=0.006$)[30]. LVEF is a major predictor of arrhythmic events in several clinical settings, including patients with coronary heart disease, heart failure, and catheter ablation of ventricular arrhythmias[23-25]. In the present cohort, we did not find significant LVEF differences among patients with or without a history of resuscitated SCD. MVP patients might be exposed to the risk of sudden cardiac death even before systolic dysfunction becomes evident. It is, therefore, mandatory to identify more sensitive risk factors.

PES has an established value in the stratification of patients with re-entry-related cardiac arrhythmias. In patients with ischemic cardiomyopathy and mildly reduced LVEF, VA induction by PES is an indication for ICD implantation[26]. In the present study, PES sensitivity for SCD was low, with only one SCD patient (25%) presenting positive PES; therefore, the usefulness of PES alone for risk stratification in patients with Barlow disease is limited. We might speculate that this might be related to the ability of PES to induce macro-reentry-related arrhythmias, not those associated with other electrophysiological mechanisms.

Electroanatomical mapping might provide novel findings for risk stratification. In particular, large Uni<8.3 and Bi<1.5 areas were frequent findings in patients with SCD; on the opposite side of the risk spectrum there are patients without Uni and Bi low voltage areas, who did not present with SCD episodes in our cohort.

Limitations

The small size of our cohort is the most important limitation of the study, thus allowing us only hypothesis-generating observations. The study model, being focused only on Barlow disease with overt VA phenotype, allowed us to identify the arrhythmogenic substrate, but it did not allow us to provide a risk stratification model for all Barlow phenotype patients. Further prospective studies, with larger cohorts and a wider spectrum of the disease are needed to enhance the arrhythmogenic stratification risk in the general population with Barlow disease.

Conclusions

In the settings of MVP with Barlow disease phenotype, EAM showed the presence of unipolar low voltage areas in the basal LV infero-lateral wall, or papillary muscle, in patients with documented ventricular arrhythmias. The presence of large Uni<8.3 areas was associated with SCD. The greater extension of low voltage areas, together with papillary muscle PVC type, may identify the arrhythmogenic substrate targeting electrophysiological studies in Barlow disease. Further prospective studies are needed to enhance the arrhythmogenic stratification risk in the general population with Barlow disease.

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TABLES

Table 1. Patient characteristics. Clinical characteristics of full study cohort and patients stratified by history of sudden cardiac death. LVEF: left ventricular ejection fraction. NSVT: non-sustained ventricular tachycardia. nTW: negative T wave. PES: programmed electrical stimulation. PVC: premature ventricular complexes. SCD: sudden cardiac death.

	Overall (N=23)	No history of SCD (N=19)	History of SCD (N=4)	p-value
Age (Years)	41.5 (33.2, 49.3)	40.7 (33.2, 49.3)	44.6 (40.1, 53.3)	0.50
Gender (F)	17 (77.3%)	15 (83.3%)	2 (50.0%)	0.21
nTW	10 (43.5%)	7 (36.8%)	3 (75.0%)	0.28
PVC>10000	10 (52.6%)	9 (47.3%)	1 (25.0%)	0.60
NSVT	14 (63.6%)	13 (68.4%)	1 (33.3%)	0.53
ICD	5 (21.7%)	3 (15.8%)	2 (50.0%)	0.19
Palpitations	14 (60.9%)	14 (73.7%)	0 (0.0%)	0.01
Syncope	5 (21.7%)	5 (26.3%)	0 (0.0%)	0.54
SCD	1 (4.5%)	0 (0.0%)	1 (33.3%)	0.14
LVEF (%)	60.0 (58.5, 65.0)	60.0 (58.5, 64.0)	62.5 (58.2, 65.0)	0.839

Table 2. Patients' characteristics stratified by the result of programmed electrical stimulation. LGE: presence of late gadolinium enhancement at cardiac magnetic resonance. LVEF: left ventricular ejection fraction. NSVT: non sustained ventricular tachycardia. nTW: negative T wave. PES: programmed electrical stimulation. PVC: premature ventricular complexes. SCD: sudden cardiac death.

	Overall (N=21)	No VA inducible at PES (N=17)	VA inducible at PES (N=4)	p-value
Age (years)	41.5 (35.0, 49.8)	40.7 (31.2, 50.7)	43.7 (40.5, 46.7)	0.70
Gender (F)	16 (80.0%)	13 (81.2%)	3 (75.0%)	1.00
NSVT	14 (66.7%)	10 (58.8%)	4 (100.0%)	0.25
Palpitations	14 (66.7%)	13 (76.5%)	1 (25.0%)	0.09
Syncope	5 (23.8%)	3 (17.6%)	2 (50.0%)	0.23
SCD	2 (9.5%)	3 (15.8%)	1 (25.0%)	0.02
PVC>10000	10 (47.6%)	7 (41.1%)	3 (75.0%)	0.31
Papillary PVC	16 (76.2%)	12 (70.6%)	4 (100%)	0.55
nTW	9 (42.8%)	6 (35.3%)	3 (75.0%)	0.27
LVEF (%)	60.0 (58.0, 63.0)	60.0 (60.0, 65.0)	54.5 (53.8, 56.0)	0.01
LGE	10 (47.6%)	8 (66.7)	2 (100.0%)	0.90

Table 3. Patients' characteristics stratified by the presence of unipolar areas <8.3 mv in the sub annular region. LGE: presence of late gadolinium enhancement at cardiac magnetic resonance. LVEF: left ventricular ejection fraction. NSVT: non-sustained ventricular tachycardia. nTW: negative T wave. PES: programmed electrical stimulation. PVC: premature ventricular complexes. SCD: sudden cardiac death.

	Overall (N=15)	No sub annular scar (N=4)	Sub annular scar (N=11)	p-value
Age (years)	40.7 (33.2, 49.3)	40.3 (36.3, 40.7)	46.6 (31.9, 50.2)	0.59
Gender (F)	12 (80%)	4 (100.0%)	8 (72.7%)	1.00
NSVT	9 (60.0%)	1 (25.0%)	8 (72.7%)	0.28
Palpitations	11 (73.3%)	4 (100%)	7 (63.6%)	0.45
Syncope	3 (20.0%)	0 (0.0%)	3 (27.3%)	0.66
SCD	1 (6.7%)	0 (0.0%)	1 (9.1%)	1.00
PVC>10000	6 (40.0%)	0 (0.0%)	6 (54.5%)	0.19
Papillary PVC	12 (80%)	1 (25.0%)	11 (100.0%)	0.01
nTW	6 (40.0%)	0 (0.0%)	6 (54.5%)	0.19
LVEF (%)	60.0 (58.5, 65.0)	66.0 (63.8, 67.8)	60.0 (56.5, 61.5)	0.06

FIGURES

Figure 1

Electroanatomical mapping by transeptal approach in a patient with Barlow disease. Left lateral view. Panel A: the map shows the presence of a large area of low unipolar voltages (<8.3 mV; gradient of colors including red, yellow, green and blue) in the sub mitral annulus region of the left ventricle; other regions of the left ventricle present normal unipolar voltages (pink). Panel B: presence of a small area of low bipolar voltages (<1.5mV; gradient of colors including red, yellow, green, and blue).