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Monomorphic Ventricular Tachycardia in Patients with Brugada Syndrome: A Multicenter Retrospective Study

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Monomorphic Ventricular Tachycardia in Patients with Brugada Syndrome: A multicenter retrospective study.

Running title: Monomorphic ventricular tachycardia in Brugada syndrome.

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Keywords: *Ventricular tachycardia. Ventricular fibrillation. Brugada syndrome. Implantable cardioverter defibrillator.*

ABREVIATIONS

BrS: Brugada syndrome.

ICD: implantable cardioverter defibrillator.

MVT: monomorphic ventricular tachycardia.

RBBB: right bundle-branch block.

RVOT: right ventricular outflow tract tachycardia.

VF: ventricular fibrillation.

ABSTRACT

Background: Isolated cases of monomorphic ventricular tachycardia (MVT) in patients with Brugada syndrome (BrS) have been reported.

Objective: We aimed to describe the incidence and characteristics of MVT in a cohort of BrS patients who had received an implantable cardioverter defibrillator (ICD).

Methods: Data from 834 BrS patients with an ICD in 15 tertiary hospitals between 1993 and 2014 were included.

Results: Mean age was 45.3 ± 13.9 ; 200 patients (24%) were women. During a mean follow-up of 69.4 ± 54.3 months, 114 patients (13.7%) experienced at least one appropriate ICD intervention, with MVT recorded in 35 patients (4.2%) (sensitive to antitachycardia pacing in 15 (42,8%)). Only QRS width was an independent predictor of MVT in the overall population. Specifically, 6 patients presented with right ventricular outflow tract tachycardia (RVOT) (successfully ablated from the endocardium in 4 and epi + endocardial ablation in one), two patients with MVT arising from the left ventricle (LV) (one successfully ablated in the supra lateral mitral annulus) and two patients with bundle branch reentry VT (BBRVt). Significant structural heart disease was ruled out by echocardiography and/or CMR.

Conclusion: In this retrospective study, 4.2% of the patients with BrS implanted with an ICD presented with MVT confirmed as arising from the RVOT in 6, the LV in 2 and BBRVT in 2. Endocardial +/- epicardial ablation was successful in 80% of these cases. These data imply that the occurrence of MVT should not rule out the possibility of BrS. This finding may also be relevant for ICD model selection and programming.

Keywords: *Ventricular tachycardia. Ventricular fibrillation. Brugada syndrome. Implantable cardioverter defibrillator.*

INTRODUCTION

Brugada syndrome (BrS) is an inherited disorder that manifests on ECG with an atypical right bundle-branch block (RBBB) pattern and ST-segment elevation in leads V1 through V3. It is associated with an increased incidence of sudden cardiac death (SCD) as a result of ventricular arrhythmias^{1,2}, mainly polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). However, isolated cases of monomorphic ventricular tachycardia (MVT) have also been described (see *table 1 supplementary material*)³⁻⁴⁴¹⁵. The presence of MVT may be relevant for both the differential diagnosis of patients with MVT as well as the programming and type of implantable cardioverter defibrillator (ICD) employed in this population.

We aimed to describe the incidence of MVT in a large cohort of patients with BrS implanted with an ICD and subsequently followed-up in referral centers.

METHODS

All patients diagnosed with BrS and implanted with an ICD in 15 hospitals between 1993 and 2014 were included. The diagnosis was made after an episode of aborted SCD, during evaluation of syncope in asymptomatic patients with a suggestive ECG pattern recorded during routine examination, or as a consequence of family screening after the diagnosis of BrS in a family member. The registry was approved by the institutional review board, and all subjects gave informed consent.

Patients were included in the study if they had a type 1 Brugada pattern on ECG at baseline on at least one occasion or after provocation with a class I antiarrhythmic drug (determined by availability in each participating hospital; ajmaline, pilsicainide or flecainide) and were implanted with an ICD. The reason for ICD implantation was

based on individual physician discretion. A type 1 ECG was defined as a prominent coved ST-segment elevation displaying J-wave amplitude or ST-segment elevation $\geq$ 0.2 mV at its peak followed by a negative T wave². Echocardiography was performed in all the patients in order to rule out underlying structural heart disease. In borderline echocardiogram cases, cardiac magnetic resonance (CMR) imaging was also performed.

The investigators performed the stimulation protocol reported by Brugada et al¹⁶, consisting of two to three drive cycles (600 - 500 - and 400 ms, S1) and three extrastimuli (S2 to S4). The minimum coupling interval of premature beats was set to 200 ms. Inducible patients were defined as those in whom programmed electrical stimulation induced VF, sustained polymorphic VT (>30 s of duration), or polymorphic syncope VT requiring direct current shock. Ablations were performed in each hospital according to its respective protocol.

In the absence of symptoms or device therapy, patients were seen routinely every 3 to 6 months for clinical review and device interrogation, in accordance with local practice. Alternatively, patients with ICD remote monitoring capabilities reported for follow-up every 6 to 12 months. ICD programming was left to the discretion of the referring electrophysiologist. Following the publication of a multicenter report in 2006¹⁷, programming a single VF zone above 210 to 220 bpm was frequently done. In the event of a shock, the patient was seen at the ICD clinic within 24 hours, and the device was interrogated.

Appropriate therapies were defined as shocks or antitachycardia pacing delivered for VT or VF. Inappropriate shocks were defined as those delivered in the absence of ventricular arrhythmia. Each episode was individually analyzed and the appropriateness of shocks or antitachycardia pacing (ATP) delivered was evaluated by a clinical electrophysiologist in the corresponding center. MVT was defined as a VT

with a stable single cycle length and unchanging QRS morphology (sustained if it lasted more than 30 seconds or if it required termination by ATP or shock; non-sustained when the duration of the MVT was less than 30 seconds). Polymorphic VT was defined as a sustained VT with a multiform QRS or ICD electrogram morphology at a cycle length between 600 and 180 ms¹⁸.

Finally, in those cases where genetic testing was performed, the *SCN5A* gene was routinely screened in all the centers participating in the study. Specifically, all 28 exons of *SCN5A* were amplified by polymerase chain reaction using intronic primers¹⁹. Polymerase chain reaction products were screened for an *SCN5A* mutation by using denaturing high-performance liquid chromatography-DNA sequencing or direct Sanger sequencing according to the laboratory protocols. All the laboratories specified performed a careful analysis in order to classify a nucleotide change as a true mutation or as a variant of unknown significance according to the type of mutation (missense or radical), their presence in highly conserved regions of *SCN5A*, presence in the control databases, results from in silico analysis (prediction software) and data from the literature.

Statistical analysis

Gaussian continuous variables are reported as mean $\pm$ standard deviation and non-Gaussian variables as median [minimum-maximum]. A comparison of baseline characteristics between groups (MVT versus polymorphic VT-VF) was performed with the two-sided t-test (in normally distributed variables) or Mann-Whitney U test (non-normally distributed variables). All tests were two-tailed, and a P-value of 0.05 was considered to indicate statistical significance.

To analyze time duration until the occurrence of MVT, univariate and multivariate Cox proportional hazard regression analysis was utilized. Only variables with a value of

$p < 0.10$ in univariate analysis were included in the multivariate analysis. Sex, age, mean sensed R-wave at implant, previous history of SCD, spontaneous type 1 ECG pattern, asymptomatic status prior to the ICD implantation and SCN5A mutation status were tested in the univariate analysis.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Baseline characteristics

A total of 834 patients were considered eligible for inclusion. The mean age of enrolled patients was 45.3 ± 13.9 y; 200 (24%) of them were women. The patients' baseline characteristics are summarized in table 1.

During a mean follow-up of 69.4 ± 54.3 months, 114 patients (13.7%) experienced at least one appropriate ICD intervention, with MVT recorded in 35 (4.2% of the entire population) (main characteristics are detailed in table 2 while *supplementary figure 1A-F* and *supplementary figure 2A-B* show selected examples of the ICD recordings). Mean tachycardia cycle length of the MVT was 298 ± 44.8 ms (214 - 380 ms). Patients without MVT had longer follow-up duration. Female gender was more common among MVT patients than those presenting with non-MVT tachyarrhythmias (8 females in the MVT group (22.8%) versus 9 females (9.7%) in the group without MVT ($p=0.035$)) (*table 2 supplementary material*). All 35 patients underwent a transthoracic echocardiogram and 9 further underwent CMR imaging to exclude overt structural heart disease).

Three of the 35 patients with MVT were receiving quinidine when the episodes occurred (patient number 9, 14 and 27 from table 2) (in the latter, the MVT was induced

during an exercise stress test (figure 2). In patient number 27 (from table 2) the quinidine therapy was introduced following several episodes of MVT (without any further episodes during 12 months of follow-up).

In the stepwise multivariate models, only QRS width (ms) (hazard ratio, 1.04; 95% confidence interval, 1.01–1.08; $p=0.009$) was an independent predictor of MVT in the overall population (*table 3 supplementary material*).

Electrocardiographic – electrophysiological characteristics

In 15 of 35 patients with MVT, the episodes were terminated by ATP (figure 1, *supplementary figures 1C, 1F and 2*). Electrophysiologic study (EPS) was performed in 22 of these patients (62.8%). In 6 patients, the clinical tachycardia was reproducibly induced (one of them in the second EPS two weeks after an epicardial ablation, shown in figure 3).

Overall, in 10 patients, the VT was documented on a 12 lead ECG: in 2 patients, the electrocardiographic patterns were consistent with typical left or right bundle branch block. In 6 patients, right ventricular outflow tract (RVOT) VT was apparent. One patient exhibited a VT of left lateral mitral annulus origin and another presented with a left inferobasal VT (figure 4).

In the 2 patients with a VT compatible with left or right bundle branch block on ECG, typical (left bundle branch block pattern) or atypical (right bundle branch block pattern) bundle branch reentry ventricular tachycardia (BBRVT) was confirmed during the EPS. In one of the patients, the right bundle branch was successfully ablated without any further inducible VT. In the second patient (number 30), who exhibited atypical BBRVT, the right bundle was not ablated during the initial EPS due to the young age of the patient and concern of inadvertently causing complete AV block. BrS was diagnosed in this patient the day following the procedure during intravenous flecainide treatment for atrial fibrillation with fast ventricular rate (figure 5). The patient received an ICD and

preferred sotalol treatment to a redo procedure with right bundle branch ablation. On sotalol therapy, he experienced no further VT episodes during 12 months of follow-up. Both patients not only carried a SCN5A mutation but also demonstrated a significantly prolonged HV interval (70 ms and 66 ms respectively).

Patients with RVOT-VT also underwent radiofrequency (RF) endocardial ablation and became symptom-free during subsequent follow-up. Remarkably, in patients 22 and 27, the earliest activation site was in the posterior RVOT (figure 2.D and 3.C). In patient 35, the earliest activation was identified in the posteroseptal region, and was also successfully ablated from the endocardium. Patient 25 presented with MVT and frequent ventricular premature beats (VPB) (figure 6) arising from the lateral part of the RVOT, deemed likely from the epicardium. Endocardial ablation failed three times to achieve VT-VPB abolition but achieved a reduction in VPB burden and VT occurrence with subsequent symptomatic improvement. In patients 3 and 12, the RVOT-VT occurred either during or after the epicardial VT ablation (in patient 3, it was spontaneously induced during the procedure and in patient 12, it started 12 months after).

DISCUSSION

This retrospective study examined the incidence and characteristics of MVT in a population of patients with BrS implanted with an ICD. The main finding was that MVT occurred in 4.2% of this select cohort of patients. Of note, QRS width was an independent predictor of MVT in the overall study population. In patients where a VT was captured on 12 lead ECG, the predominant origin of MVT was in the RVOT (n=6), although it was occasionally due to BBRVT (n=2). Accordingly, endocardial ablation (on one occasion combined with epicardial ablation) was effective in controlling the symptoms in almost all patients. These data imply that the occurrence of MVT should

not rule out the diagnosis of BrS. Moreover, this information may be relevant to ICD model selection and programming.

Potential mechanism for MVT in BrS

BrS is an arrhythmogenic disorder with an increased risk of SCD as a result of ventricular arrhythmias, usually polymorphic VT or VF¹. The form of polymorphic VT - VF in BrS is a matter of controversy. The repolarization theory postulates that the VF in BrS is a re-entrant tachycardia initiated by an early-coupled VPB following phase-2 reentry due to a dispersion of repolarization in the right ventricular epicardium²⁰. However, in addition to the repolarization theory, recent studies in humans have also shown evidence of depolarization abnormalities. Areas of low-voltage and fragmented potentials have been described in patients with BrS²¹⁻²⁴. In this setting, the possibility of reentry around these areas is plausible. As a matter of fact, the response to ATP in the vast majority of patients with MVT strongly suggests a re-entrant mechanism. This is further reinforced by the fact that quinidine was unable to reduce the arrhythmia burden in certain cases. Thus, depolarization abnormalities may also be a relevant causative mechanism in this subgroup of patients.

The reason for this epicardial substrate is not completely understood but sodium channel abnormalities have been linked to these structural changes either by inducing fibrosis or apoptosis^{11,25-28}. Subsequently, although we did not identify overt structural heart disease in this series, microscopic structural changes could be diffuse and beyond the resolution of current imaging techniques. Moreover, sodium channel abnormalities have also been shown to be associated with conduction system disease. Interestingly, in the present study, QRS width was found to be an independent predictor of MVT while the same was not true for presence of the SCN5A mutation. Previous existing literature does not provide much information to rule in or rule out an association with the SCN5A mutation, since only two of the aforementioned patients

with MVT and BrS (patients 1 to 12 presented in *table 1 supplementary material*) for whom genetic testing was performed, exhibited this mutation. Hence, further evaluation of this potential association is warranted in future studies.

In our series, we also found that two patients experienced MVT post epicardial VT ablation for RVOT-VT. One case manifested acutely during the procedure and the other presented 12 months subsequent to it. We believe the underlying mechanism of MVT in these patients may be different from that seen in naive patients without epicardial ablation. It could be in part attributable to scar homogenization with the possibility of promoting reentry after RF ablation.

Three patients were receiving quinidine at the time of the observed VT episodes. Quinidine is known to be highly effective in preventing VF induction and spontaneous VF in BrS. It may exert its beneficial effects in BrS by inhibiting I_{to} , thereby restoring electrical homogeneity²⁹. On the other hand, it also prolongs ventricular refractoriness, which may have organized the ventricular arrhythmia, giving rise to the monomorphic configuration. It should be noted however, that in patient 27 shown in table 2, quinidine was very effective in controlling the episodes of MVT, with no further events documented after the introduction of quinidine. Quinidine was also very effective in two previously reported BrS patients presenting with MVT (number 3 and 6, *table 1 supplementary material*). However, due to the limited number of patients receiving quinidine in our series (n=8), these findings need to be viewed with caution and will need further validation in future studies.

Finally, BBRVT is a well-known mechanism of VT in patients with abnormal His-Purkinje conduction. Significant conduction delay within the His-Purkinje system is commonly found in patients with BrS. Mutations in the SCN5A gene encoding the voltage-gated Na⁺ channel α -subunit have been associated with both BrS and isolated progressive cardiac conduction defect (Lenegre-Lev disease) phenotypes^{30,31}. It is

plausible therefore, that the electrophysiological substrates for BBRVT and BrS may share a common genotype. BBRVT may be a potential mechanism of arrhythmia in patients with this syndrome, as it appears to have been the case in at least two patients from our series.

At present, the mechanism underlying the presentation of MVT is not completely understood and merits further consideration. Most likely, the mechanism will prove to be heterogeneous and will not be generalizable to the whole BrS population. It could also be argued that such cases may represent a subclinical cardiomyopathic process akin to arrhythmogenic right ventricular cardiomyopathy (ARVC). These disorders exist on a pathophysiological spectrum initially manifesting as an arrhythmia before structural changes become apparent³². An individual evaluation will then be required when faced with BrS patients with MVT in order to determine the most suitable treatment.

Ventricular tachycardia configuration- Electrophysiological considerations

Ten patients in this series for whom a 12 lead-ECG was obtained during a VT episode were confirmed on EPS to have MVT arising from a focal origin, such as the outflow tracts or mitral annulus, or due to reentry involving both bundle branches.

Regarding the coexistence of outflow tract VT and BrS, it remains to be elucidated whether the electrophysiological heterogeneity within the RVOT³³ could provide a substrate for MVT arising in BrS. In such cases, ventricular arrhythmias in patients with BrS can be prevented by catheter ablation over the anterior aspect of the RVOT²¹. Moreover, in our experience and in previous studies^{9,13}, endocardial ablation has also proven to be effective in this setting. This raises the question of whether thorough endocardial mapping and induction of the VT should be undertaken before contemplating an epicardial approach. This concept was already pointed out by Haïssaguerre et al³⁴ in 2003. They reported 3 highly symptomatic patients in which

endocardial ablation allowed the suppression of recurrences. Interestingly, in the two cases, VPBs exhibited RVOT morphology and long coupling intervals.

Nonetheless, although the RVOT seems to be the predominant origin of the MVT both in our cohort and in some other cases previously reported (see patients number 5, 7 and 11 from *table 1 supplementary material*), various configurations including RBBB morphology have also been described (patient number 33, figure 4; patient number 4, 8 and 12, *table 1 supplementary material*).

Clinical relevance

Young patients with BrS, based on their low risk of bradycardia and MVT, have been considered as a subgroup where the subcutaneous ICD (S-ICD) may be recommended³⁵. Given the finding that a small proportion of patients with BrS as shown in this study may develop MVT, the use of the S-ICD should be carefully evaluated to make sure such patients have no documented MVT prior to implant or a high burden of isolated RVOT ectopy which could trigger MVT.

Although intriguing, the findings of our study do not provide enough evidence to change the current recommendations for ICD programming in patients with BrS and an ICD. Actually, in our opinion, to do so would be imprudent based on the higher rate of inappropriate shocks reported in this population¹⁷. However, we do believe that programming of ATP could be useful in those patients where a MVT has been recorded in order to minimize the occurrence of ICD shocks in BrS transvenous ICD recipients³⁶.

Finally, although MVT should raise the suspicion of a cardiomyopathy like ARVC rather than BrS, it does not exclude the possibility of the latter. Moreover, in those situations where no clear etiology is identified, an ajmaline test should be performed in order to rule out BrS. Our findings could have relevance not only for the diagnostic work-up of patients with MVT but also for their medical treatment. For

instance, some antiarrhythmic drugs, in particular class IC, are often prescribed in patients with RVOT-VT, but maybe contraindicated in the setting of underlying BrS.

Limitations

The main limitation of this study is that a 12-lead ECG and/or electrophysiological evaluation were unable to be obtained in the vast majority of patients with MVT. Consequently, although in our series the most common origin of MVT was due to RVOT and BBRVT, this will have to be reconfirmed in further investigations. Importantly, due to the limited number of patients with MVT, conclusions drawn regarding predictors of MVT should be interpreted with caution.

Additionally, since certain devices were only single chamber, it is possible some events were in fact due to aberrantly conducted supraventricular tachycardia, erroneously interpreted by the device as a ventricular tachycardia and terminated by ATP.

In this retrospective study, a specific patient population was identified across multiple international hospitals by various local electrophysiologists. Although every effort was made to collect data in a uniform and thorough manner, some ascertainment bias may remain. For instance, although care was taken to include BrS patients rather than BrS-like phenotypes, we cannot substantiate this unequivocally. It is conceivable that an included case may have been misinterpreted at a certain center as a BrS-like phenotype³⁷. In addition, SCN5A genetic screening was not performed in all cases.

It has been reported that in patients with RVOT VT and an apparently structurally normal heart, endomyocardial biopsy may be indicative of myocarditis or subclinical ARVC in a significant percentage of cases³⁸. Therefore, one could argue that viral myocarditis may be the cause in some of our cases. We cannot definitely exclude such a possibility since endomyocardial biopsy was not performed. However, this is unlikely because almost all of these patients underwent a transthoracic

echocardiogram and in ambiguous cases, cardiovascular magnetic resonance imaging was also performed prior to ICD implantation in order to rule out myocardial inflammation.

ICD programming was left to the discretion of the referring electrophysiologists. Although programming a single VF zone above 210 to 220 bpm was advocated, less stringent programming parameters may have identified a greater burden of MVT episodes and allowed for a clearer delineation of the response to ATP. Moreover, information concerning ICD programming including zone and therapies had not been taken into account and could have influenced our conclusions in terms of response to ATP and avoidance of shocks.

Finally, we would like to point out that the present study is not a mechanistic study regarding the cause of MVT in BrS; rather it is an observational study documenting the existence of MVT in patients with BrS. Thus, we cannot rule out that some of the VT herein described represents in fact an epiphenomenon unrelated to the underlying channelopathy.

CONCLUSION

We found that the occurrence of MVT in patients with BrS and ICD implantation is not a negligible one. In this multicenter retrospective study, a substantial 4.2% of this population demonstrated MVT, 15 (42.8%) of whom were successfully treated by ATP. As noted earlier, QRS width was an independent predictor of MVT in the overall population. In those patients where a 12-lead ECG captured the VT episode, the predominant origin of MVT was from the RVOT. Consequently, endocardial ablation (on one occasion combined with epicardial ablation) was successful in controlling the symptoms at short-term follow-up. These data suggest that BrS should be part of the differential diagnosis of patients with MVT. Finally, the possibility of BrS in patients with

MVT should be taken into account at the time of ICD model selection and programming.

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LEGENDS TO FIGURES.

Figure 1. Patient 16 (table 2) (A) Typical type 1 ECG Brugada pattern on presentation (B) Absence of structural heart disease in cardiac magnetic resonance imaging (C,D) Several runs of monomorphic ventricular tachycardia correctly identified and treated by ATP.

Figure 2. Patient 27 (table 2): Male BrS patient maintained on quinidine following recurrent atrial fibrillation-induced inappropriate shocks. (A) Baseline ECG performed under quinidine treatment. (B) Exercise testing on quinidine triggers RVOT-MVT, shown in ECG performed to evaluate dyspnea on exertion. (C) Frequent ventricular premature beats (VPB) from RVOT. EPS with isoproterenol infusion triggered only non-sustained MVT similar to the clinical VT. (D, E) Successful endocardial RF ablation documenting earliest activation and a 96% identical pace-map in the posterior RVOT; image D shows in color scale bar the matching percentage between the paced beats and the native extra beats, with a cut-off of 90% (pink color indicates less than 90% concordance, green more than 90% concordance). Post ablation, the patient remains symptom-free (no VT induction in the stress test and absent VPB on Holter monitoring).

Figure 3. Patient 22 (table 2) (A) Normalization of the Brugada ECG pattern following epicardial RVOT ablation for MVT refractory to quinidine. (B, C) Endocardial (B) and epicardial (C) bipolar maps during successful endocardial ablation for subsequently manifest MVT localized to the RVOT (purple indicates electroanatomic normal tissue with a voltage amplitude ≥ 1.5 mV; red indicates electroanatomic scar tissue with a voltage amplitude < 0.5 mV; intermediate colors represent the low-voltage electroanatomic border zone (voltage amplitude > 0.5 and < 1.5 mV)). It is apparent that low voltage zones are found in the anterior free wall - lateral wall of the right ventricle. (D) Late potentials apparent in that region. (F, H) Endocardial bipolar map performed at the time of the second MVT. (E, G) Activation maps. Red color indicates the earliest activation time. (I) 12 lead-ECG morphology and the earliest ventricular activation, which precedes onset of the QRS complex by > 22 ms.

Figure 4. Patient 33 (table 2). (A) Baseline type 1 Brugada ECG pattern. (B) Twelve-lead ECG recording of MVT (C) ICD recorded runs of fast MVTs (with ventriculoatrial dissociation) treated with ICD shocks. LECG: far-field leadless ECG (can to superior vena cava). EGM3: ventricular bipolar near field (right ventricular tip to right ventricular ring). EGM2: auricular bipolar near field (right atrium tip to right atrium ring). ECGM2: ventricular far field (can to right ventricular coil).

Figure 5. Patient 30 (table 2). (A) Baseline ECG. (B) Type 1 Brugada ECG pattern evidenced following intravenous flecainide administration for atrial fibrillation. (D) 12-lead ECG of the MVT induced at the time of the EPS (bundle branch reentry). (E) Presence of VA dissociation during the episode.

Figure 6. Patient 25 (table 2). (A) Baseline ECG pattern. (B) Type 1 Brugada ECG pattern evidenced by ajmaline challenge. (C-D) Several runs of non-sustained MVT (despite beta-blockers, amiodarone and quinidine) recorded in the ICD memory. (E)

Significant prolongation of the fQRSd in the right precordial lead shown in the signal-averaged ECG.

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CLINICAL PERSPECTIVES

To date, little information is available regarding the prevalence, clinical characteristics and management of monomorphic ventricular tachycardia (MVT) in patients with Brugada syndrome (BrS) implanted with an implantable cardioverter desfibrillator (ICD).

We found that the occurrence of MVT in patients with BrS and ICD implantation is not a negligible one. In this multicenter retrospective study, 4.2% of this population presented with MVT, 15 (42.8%) of whom were successfully treated by ATP. Of note, endocardial ablation was shown to be effective in controlling the symptoms at short-term follow-up.

This information may be useful during medical and interventional treatment (thorough endocardial mapping and induction of the VT must be undertaken prior to contemplation of an epicardial approach), ICD programming (consider ATP zones in patients with MVT) and ICD selection (subcutaneous ICD should be carefully evaluated and care must be taken to exclude patients who have documented MVT pre-implant). Finally, findings herein described could be of relevance for the diagnostic work-up of patients with MVT of unknown etiology.

Hence, it is our conviction that due to the particular management protocol of this subgroup of patients, the presence or absence of MVT must be properly evaluated during management of patients with BrS.

TABLES

Table 1. Demographic characteristic of the study population.

	Patients (n=834)
Age (years) (SD)	45.3 (13.9)
Male/Female	634 (76%)/200 (24%)
Spontaneous Type 1 n (%)	391 (46.9%)
PR interval (ms)	176,6 (36.56)
QRS (ms)	104 (19.9)
Aborted SCA n (%)	77 (9.2%)
Genetic positive (n=281)	79 (28.1%)
Syncope n (%)	352 (42.2%)
Asymptomatic n (%)	406 (48.7%)
“R wave” (implantation) (SD) (n=385)	10,8 (4.3)
Remote monitoring	215 (25.8%)
Negative EPS	319 (38.2%)
Positive EPS	301 (36.1%)
EPS not performed	104 (12.5%)

Abbreviations; ICD: implantable cardioverter-defibrillator, SCA: sudden cardiac arrest; SD: standard deviation.

Table 2. Baseline characteristics of those patients with BrS implanted with an ICD and monomorphic ventricular tachycardia included in the present study.

Origin	Gender /Age	Spontaneous Type1 ECG (pharmacological test)	Electrophysiology study	SMVT in the f/u	PVT-VF in the f/u	TTE	MRI	SCN5A screening	VT sensitive to ATP
1. France	M- 64	No (ajmaline, VF during the test)	No EPS performed.	Yes (280 ms)	No	Normal	---	Negative	---
2. France	M- 60	No (ajmaline)	Induction of runs of non-sustained PVT	Yes	No	Normal	---	Negative	Yes
3. France	M- 50	Yes	First EPS: Induction of runs of non-sustained PVT. Second EPS for epicardial VF ablation. One year later runs of SMVT (figure 2.B) treated by ATP.	Yes (RVOT) (260 ms)	No	Normal	---	SCN5A mutation (p.Glu1253Gly) ⁴⁰ .	Yes
4. France	M- 52	Yes	VF induction.	Yes (RVOT provoked in the EST, 286 ms)	Yes	Normal	---	Not performed	---
5. France	F- 29	No (ajmaline)	NSMVT induction in the EPS.	None	No	Normal	---	Negative	---
6. Spain	M- 42	No (flecainide)	No EPS performed.	Yes	No	Normal	---	SCN5A mutation (p.Glu901Lys) ⁴⁰ .	Ineffective
7. Spain	M- 49	No (flecainide)	No ventricular arrhythmias were induced at the time of the EPS.	Yes (300 ms)	No	Normal	---	Negative	Yes

8. Spain	M-22	No (flecainide)	No EPS performed.	Yes (298 ms)	Yes	Normal	---	Not performed	Yes (supplementary fig.2C)
9. Belgium	M-64	Yes	VF induction.	Yes ³⁰ (Under quinidine)	Yes	Normal		SCN5A splice site mutation (c.4813+6_4819+9dupGGGT) ⁴⁰ .	---
10. Belgium	M-25	Yes	No ventricular arrhythmias were induced at the time of the EPS. HV 70 ms.	Yes (BBRV) (330 ms)	Yes			SCN5A splice site mutation (c.4813+6_4819+9dupGGGT) ⁴⁰ .	---
11. Belgium	F-35	No (ajmaline)	VF induction.	Yes (313 ms)	Yes	Normal	Normal	Not performed	Yes
12. Belgium	M-14	Yes	VF induction in the first EPS. Second EPS for RVOT-VT ablation.	Yes (RVOT) (310 ms)	Yes	Normal	Normal.	Not performed	---
13. Belgium	M-8	No (ajmaline)	No ventricular arrhythmias were induced at the time of the EPS.	Yes (320 ms)	Yes	Normal	Normal.	Not performed	---
14. Belgium	M-39	No (ajmaline)	No ventricular arrhythmias were induced at the time of the EPS.	Yes (under quinidine) (380 ms)	No	Normal	---	Not performed	---
15. United Kingdom	M-57	Yes	NSMVT arising from the supra lateral mitral valve annulus.	Yes	No	Normal	Normal	Not performed	---
16. Spain	F-76	Yes (fig.1A)	No EPS performed.	Yes (270 ms)	Yes	Normal	Normal (fig. 1B)	Not performed	Yes (fig. 1A-D)
17. Cuba	M-53	Yes	A SMVT (280 ms) was induced.	Yes (320 ms)	Yes	Normal	---	Not performed	Yes

18. Cuba	M- 36	Yes	No EPS performed.	Yes (340 ms)	Yes	Normal	---	Not performed	Yes (supplementary fig. 2A)
19. Cuba	M- 32	Yes	No ventricular arrhythmias were induced at the time of the EPS.	Yes (290 ms)	No	Normal	---	Not performed	Yes
20. Cuba	M- 27	Yes	No EPS performed.	Yes (310 ms)	Yes	Normal	---	Not performed	Yes
21. Cuba	F- 45	Yes	No EPS performed.	Yes (330 ms)	No	Normal	---	Not performed	Yes
22. United States of America	F- 30	Yes (fig.3)	No EPS pre implantation. VF despite quinidine. EPS without VF induction. Epicardial VT ablation was then performed. Two weeks later presented a SMVT arising from the posterior RVOT region, with reproducible induction and subsequent successful endocardial ablation (fig.3).	Yes (RVOT-VT) (fig.3) (330 ms)	Yes	Normal	---	SCN5A variant (p.Arg27His*) ⁴⁰ .	---
23. Japan	M- 31	No (pilsicainide)	No EPS performed.	Yes (255 ms)	Yes	Normal	---	Negative	Yes (supplementary fig.2.F)
24. Japan	M- 43	No (pilsicainide)	VF induction.	Yes (271 ms)	Yes	Normal	---	Negative	Ineffective
25. France	F- 43	No (fig 6.A) (ajmaline)	No ventricular arrhythmias were induced at the time of	Yes (240-350) (fig.6. C-D)	No	Normal	---	Negative	---

			the EPS.						
26. France	F- 63	No (ajmaline)	No EPS performed.	Yes (210 ms) (supplementary fig 2. E)	No ne	Normal	---	Not performed	---
27. France	M- 31	Yes (fig 2.A)	VF induction.	Yes (RVOT-VT induced in the EST) (fig. 2.C) (360 ms) (under quinidine)	No ne	RV mildly enlarged, RVEF= 45-49%.	---	SCN5A mutation (p.Ala735Val) ⁴¹ .	---
28. France	M-41	Yes	VF induction	Yes (supplementary fig 2.D) (214 ms)	No ne	Normal	---	Not performed	---
29. France	M-38	Yes (flecainide)	VF induction.	Yes (380 ms)	No ne	RV apical akinesia and RV anterior wall hypokinesia	---	Negative	---
30. Belgium	M-36	No (fig 5A) (ajmaline) (fig.5B)	BBRV induced in the EPS. HV 66 ms. (fig 5C and D)	Yes (320 ms)	No ne	Normal	Normal	SCN5A mutation (p.Arg367Cys) ⁴⁰ .	---
31. Belgium	M-47	No (ajmaline)	VF induction	Yes (one single episode of SMVT) (300 ms)	No ne	Normal	---	Negative	---
32. Belgium	F-53	No (ajmaline)	No EPS performed.	Yes (280 ms)	No ne	Normal	---	Negative	---
33. Spain	M-49	Yes (fig 4A)	No EPS performed.	Yes (370 ms, under BB) (fig 4B-C)	No ne	Normal	Normal.	Not performed	Yes
34. Spain	M-53	No (flecainide) (supplementary fig. 2A)	No EPS performed.	Yes (290 ms)	No ne	Normal	Normal	Not performed	Yes (supplementary fig 2B)
35. Spain	M- 63	No (flecainide)	First study negative. After the VT a second	Yes (300 ms)	No ne	Normal	Normal	Not performed	Yes

			EPS was performed where a MVT arising from the RVOT was induced a subsequently ablated (posteroseptal region).						
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Abbreviations; ATP: antitachycardia pacing. BB: beta-blockers. BBRVT: bundle branch reentrant ventricular tachycardia. EPS: electrophysiology study. EST: exercise stress testing. F: female. F/U: follow-up. ICD: implantable cardioverter defibrillator. M: male. MRI: magnetic resonance image. NSVT: non-sustained monomorphic ventricular tachycardia. PVT: polymorphic ventricular tachycardia. RV: right ventricle. RVOT-VT: right ventricular outflow ventricular tachycardia. SMVT: sustained monomorphic ventricular tachycardia. TTE: transthoracic echocardiogram. VF: ventricular fibrillation. VT: ventricular tachycardia.

All *SCN5A* genetic variants classified as “*SCN5A* mutations” are absent or very rare in the EXAC database (0 or 1 occurrence) and have been already published as Brugada disease-causing mutations⁴⁰. *The variant p.Arg27His should be reclassified as genetic variant of unknown significance⁴¹.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5