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Transcatheter ablation in patients with Brugada syndrome

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Since the first description of Brugada syndrome (BrS), several studies were carried out aimed at diagnosis, arrhythmic risk stratification, and available strategies for sudden death prevention. In high-risk patients, the use of an implantable cardiac defibrillator was an evident option since the first description of the syndrome. Nevertheless, this strategy, while proven, as expected, to be effective in sudden death prevention, does not prevent arrhythmias and may not be an adequate or accepted solution for all patients. The need of a non-pharmacological therapy as a potential solution based on the electrophysiological mechanisms underlying the syndrome, led to search for substrate as target for catheter ablation. Advances in the tools, technology, and technical approach enabled to launch studies aimed at mapping the epicardium of patients with BrS in order to identify and ablate the substrate. As described in previous work and in our experience, an anatomically identifiable electrical substrate, which correspond to the typical ECG, is the ablation target. Complete substrate is better identified in a larger area with sodium-channel-blockers. Ablation of all abnormal electrical potentials is able to normalize the ECG and prevent arrhythmias induction. Encouraging preliminary data, if confirmed by longer follow-up and by multicentre randomized study, could change the whole therapeutic management in BrS patients.

Introduction

Since the first description of Brugada syndrome (BrS),[1] several studies were carried out within the Scientific Community particularly aimed at diagnosis, arrhythmic risk stratification, and available strategies for sudden death prevention.

Thirty years later, although several controversies still exist in BrS, various authors reached a clear agreement on many aspects, such as the definition of the electrocardiographic diagnosis (type 1 pattern)[2–4] and the management of high-risk patients symptomatic for arrhythmic syncope or aborted sudden death.[5] In these categories of patients, the use of an implantable cardiac defibrillator (ICD) was an evident option since the first description of the syndrome, confirmed in the last and previous European Society of Cardiology guidelines.[2,3]

Nevertheless, this strategy, while proven, as expected, to be effective in sudden death prevention, does not prevent arrhythmias.

It was, therefore, necessary to find arrhythmia treatment strategies especially for those patients who experienced multiple shocks, which are themselves harmful.

In this category of patient, lead-related complications, infections, inappropriate discharges, and significant psychological sequela, with impaired quality of life, are reported.[6]

Moreover, the percentage of these complications turned out to be significantly higher than those described on populations of patients with ICD implanted for other diseases, probably due to the lower age of BrS patients at diagnosis.[6]

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Finally, ICD implantation may not be an adequate or accepted solution for many patients which pose a therapeutic challenge for physicians. Although the annual incidence of arrhythmic events in asymptomatic subjects with Brugada ECG pattern is low (1%), it cannot be considered as negligible, especially considering that this event may occur in young previously asymptomatic subjects.[7]

The treatment options for asymptomatic patients with spontaneous type I ECG in whom programmed electrical stimulation (PES) induces VF, remain a matter of debate.[8,9] In this category of patient, ICD implant may be considered excessive from a risk/benefit point of view, but leaving those patients untreated is not enough. Quinidine has been reported to be effective in treating patients with BrS,[10,11] but unfortunately the drug is not easy to tolerate over a lifetime because of its side effects and withdrawal is reported in about a one-third of patients.

The need of a non-pharmacological therapy as a potential solution based on the electrophysiological mechanisms underlying the syndrome, led to a search for substrate sites as targets for catheter ablation and this is the latest and most recent chapter in the history of BrS.

Ablation

Advances in the tools, technology, and technical approach (i.e. Sosa technique of gaining access into the pericardium, irrigated-tip ablation catheter, and electroanatomic mapping systems) enabled to launch studies aimed at mapping the epicardium of patients with BrS in order to identify and ablate the BrS substrate.[12]

In 2011, Nademanee *et al.*[13] demonstrated the efficacy of right infundibulum epicardial ablation in reducing the number of appropriate shocks in patients with BrS, ICD, and electrical storm. As a matter of fact, on the basis of previous research it was hypothesized that the outflow tract of the right ventricle (RVOT) was the site where to locate the arrhythmic substrate in patients with BrS: in nine symptomatic patients (recurrent arrhythmias treated with ICD shocks) an endocardial and epicardial mapping of the right ventricular outflow tract was performed. Abnormal electrograms (EGMs) were defined as those with (1) low voltage (1 mV); (2) split EGMs or fractionated EGMs with multiple potentials with two distinct components, with 20 ms isoelectric segments between peaks of individual components; and (3) wide duration (80 ms) or late potentials, with distinct potentials extending beyond the end of the QRS complex. These abnormal low-voltage fractionated EGMs were only present in a wide area of the anterior RVOT epicardium and not elsewhere.[12]

Abnormal EGMs were then targeted for ablation yielding either non-inducible sustained ventricular arrhythmias or disappearance of the Brugada ECG pattern. There were no complications after the ablation except mild pericarditis with quick resolution in 2 patients and a success at follow-up of 90%.

In 2015, Brugada *et al.*[14] described mapping and ablation in 14 BrS patients with ICD and a spontaneous or drug-induced type I ECG pattern, with symptoms attributable to ventricular arrhythmias and high vulnerability for ventricular arrhythmia induction at electrophysiology study. BrS epicardial substrate identification consisted in mapping the entire right ventricle (RV) epicardial surface under baseline conditions and after flecainide infusion. Abnormal EGMs were defined as those with amplitude <1.5 mV or associated wide duration (>80 ms), multiple (>3), or delayed components extending beyond the end of the QRS complex. All abnormal EGMs inside these areas were targeted for RF ablation. Immediate procedural endpoint was the elimination of all the abnormal EGMs identified inside the low-voltage areas during sinus rhythm and the replacement by low-voltage (<0.5 mV) dense scar. In all patients, post-procedure and after a median follow-up of 5 months ECG remained normal despite flecainide testing and ICD did not register any arrhythmic event. Also, in this series the only complication was a mild pericarditis in one patient.

These promising results lead to a prospective study on 135 symptomatic Brugada patients,[15] which provided new insights on pathophysiology, mechanisms, and management of patients with BrS. It was demonstrated that symptomatic BrS patients regardless of the clinical presentation or spontaneous BrS-ECG pattern have a well-defined anatomic and electrophysiological substrate characterized by abnormal fragmented prolonged low-frequency ventricular EGMs. Combined endo-epicardial mapping located the substrate exclusively on the anterior RVOT and RV anterior free wall of the epicardium.

The further strength of this study was not only the high number of patients included, but also the demonstration that, during ajmaline challenge, the target area became wider. This allowed a better identification of the ablation target, which otherwise might be underestimated or missed and explained the improved results.

Substrate ablation of the target area normalized the ECG pattern without complications resulting in ventricular tachycardias/ventricular fibrillation (VT/VF) non-inducibility in all patients.[15]

In 2018, a review of the 11 published studies[16] about epicardial ablation on 180 patients reported at variable follow-up (5–41 months) effectiveness of 96.7% in ventricular arrhythmias prevention.

Despite these studies and the exciting results with low complications, at present only a small fraction of patients with the syndrome still undergo ablation.

Our experience

Patient population

In this retrospective registry, we describe epicardial ablation in selected BrS patients referred from Piedmont to our Institution as high-volume centre for ablative procedures and with extensive experience in ablation of endo-epicardial substrate of ventricular arrhythmias and with heart surgery on site.

Ninety-eight patients, males 75 (76.5%) with an average age of 48.1 ± 10.6 years (median age 48.2 years) were submitted to a total of 104 RV percutaneous endocardial and epicardial mapping and ablation. All patients had a type 1 ECG either spontaneous (80%) or drug-induced.

Of the 53 patients, symptomatic for aborted sudden death or arrhythmic syncope 12 had an already implanted ICD with documented ICD intervention at follow-up (six electrical storm) while 41 patients (none with aborted sudden death) refused ICD implantation.

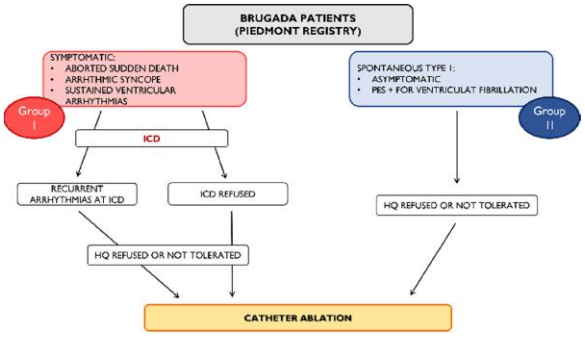

Figure 1 The flowchart describes the patient population of the registry.

In symptomatic patient (*Figure 1*) ablation was proposed if not tolerating or not willing hydroquinidine (HQ) and according to patient and physician preference.

A second group of 45 patients (*Figure 1*) with spontaneous type 1 ECG and VF induced at PES (who presented with symptoms other than syncope/sudden death and a Shangai Score > 3,5)[17] were scheduled for ablation when HQ was refused or not tolerated.

Ablation procedure

Mapping and radiofrequency(RF) ablation procedures were performed following the technique described by Pappone *et al.*[14,15]

Under deep sedation an invasive arterial pressure line was obtained through femoral artery access.

ECG was continuously recorded during the procedure, positioning V5 and V6 electrodes in second intercostal space, right and left parasternal line, respectively.

Through femoral venous access, a multipolar diagnostic catheter was positioned at the right-ventricle apex and then moved to outflow tract. At endocardial mapping no abnormal EGMs were recorded.

All patients were tested with basal PES from two different sites of right ventricle (apex and outflow tract) with up to twoextrastimuli (lowest interval = effective refractory period) and re-tested after ajmaline-type 1 induction if not recorded at basal ECG.

Epicardial access was obtained with subxiphoid puncture using Tuohy needle or with needle-in needle technique.[18]

High-density detailed endocardial and epicardial electro-anatomical RV mapping (*Figure 2*) were performed using 3-dimensional (3D) mapping system (CARTO 3, Biosense Webster, Diamond Bar, CA) using in all patient integration with fluoroscopy (CARTOUnivu module) in association, when available, with pre-acquired heart and vessels imaging (Magnetic Resonance or Computed Tomography, CARTO Merge) during stable sinus rhythm in basal condition and after ajmaline infusion (1 mg/kg in 5 min).

Abnormal EGMs were defined as those with low amplitude (1.5 mV), wide duration (>80 ms), multiple (>3), or delayed components extending beyond the end of the QRS complex and were manually tagged on voltage bipolar and local activation time (LAT) maps (*Figure 2*).

On epicardial surface of the anterior RV (outflow tract and anterior wall) areas with abnormal EGMs were identified: abnormal EGMs areas after ajmaline infusion were

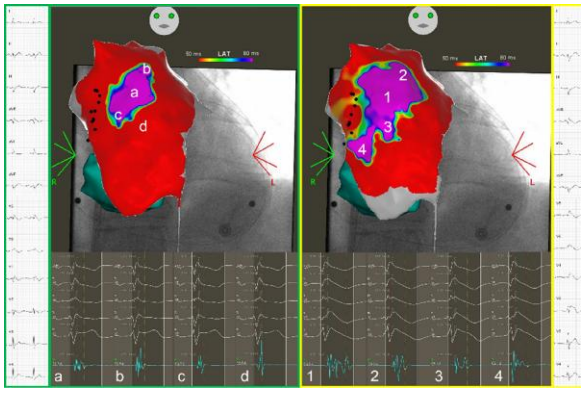

Figure 2 Substrate mapping. The figure is divided in two main panels: left panel describes the mapping phase in basal conditions, right panel describes the substrate mapping after ajmaline infusion. Particularly, in each panel the 12-lead ECG, the local activation time map of the epicardium and the local intracardiac potential are displayed. In all panels, V5 and V6 record V1 and V2 in the II intercostal space. The green maps represent the right ventricle (endocardial mapping) and the red-purple maps are related to the epicardial mapping. In both epicardial maps black dots trace the right coronary and all maps are synchronized with the fluoroscopic image (anteroposterior view with the wire in the pericardial space). Analysing the local activation time map in basal conditions (spontaneous type I ECG on the left), an area of late activation potentials (purple area) can be identified in the epicardial side of the right ventricular outflow tract, as displayed in the IC signals (*A-D*).

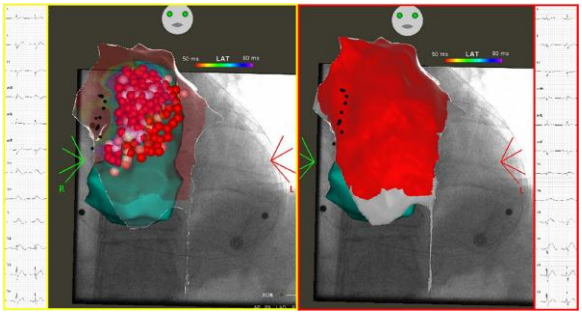

Figure 3 Ablation phase. The picture is divided in two main panels: in the left panel the ablation tags are displayed on the activation map after ajmaline infusion (the target area characterized by late activation potentials is covered by the ablation tags). The right panel describes the activation map after radiofrequency ablation: the epicardial map is red because no more late potentials are detected. The 12-lead ECG after ajmaline infusion and after RF ablation are displayed at the external sides of the figure (left and right, respectively); V5 and V6 records V1 and V2 in II intercostal space. The green maps represent the right ventricle (endocardial mapping), and the other maps are related to the epicardial mapping. In both epicardial maps black dots trace the right coronary and all maps are synchronized with the fluoroscopic image (anteroposterior view with the wire in the pericardial space).

tagged and targeted for ablation (*Figure 2*). Average area was measured as $14 \pm 7\ cm^2$ in basal conditions (with significative difference $P < 0,05$ between patients with no spontaneous type 1 before ajmaline at basal mapping who had an average area of $8 \pm 2\ cm^2$) and $20.1 \pm 8\ cm^2$ after ajmaline.

Radiofrequency was then delivered on abnormal EGMs area (*Figure 3*) recorded in epicardium using an externally irrigated 3.5-mm tip catheter (Thermocool SmartTouch,

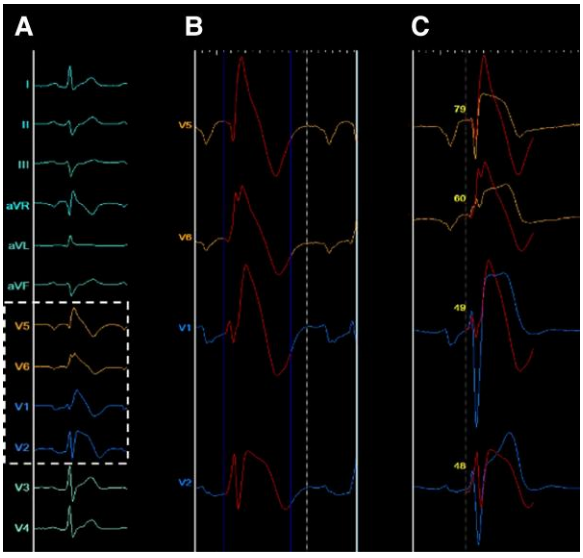

Figure 4 (*A*) 12-lead ECG recorded after ajmaline challenge, V5 and V6 recorded in II intercostal space, right and left parasternal line, respectively as described in text. (*B*) Zoom of V5-V6 (modified V1 and V2) and standard V1-V2 during ajmaline infusion. (*C*) BrS ECG pattern modification during ablation: J wave abolition combined with change of JT segment with complete disappearance of coved pattern: orange ECG recorded in modified V1 and V2 leads in II intercostal space (V5 and V6), blue line records of traditional V1 and V2 during radiofrequency; superimposed red line of ajmaline ECG before ablation. Yellow numbers represent the percentage grade of correlation between basal ECG and ECG recorded during radiofrequency application in each lead.

Figure 5 The picture highlights the differences in the 12-lead ECG during the procedure and after 3-month follow-up. V5 and V6 records V1 and V2 in II intercostal space. (*A*) Ablation procedure: ECGs in basal conditions (spontaneous type I), after ajmaline infusion and at the end of the procedure (after radiofrequency ablation). (*B*) 3-month follow-up: ECGs in basal conditions and after ajmaline infusion.

Biosense Webster) with 35-50 W power control, 45° C temperature limit, and 30 mL/min irrigation.

ECG pattern changes during epicardial ablation were analysed by continuous ECG monitoring (*Figure 4*).

The JT-segment modifications were evaluated using both correlation software integrated in the 3D mapping system (Pattern Matching and PASO module, Biosense Webster) and with the correlation software 'Mapping view' integrated in the EP recording system LabSystem Pro (Boston Scientific).

At the end of the procedure, ajmaline challenge was repeated to ensure abolition of both abnormal ventricular potentials and ECG pattern. In patients for whom the ECG pattern was still inducible, epicardial mapping was repeated to identify any residual abnormal signal for further RF applications until the ECG pattern was definitively abolished.

Programmed electrical stimulation was then repeated with the same protocol used before ablation.

All patients were discharged with preventive anti-inflammatory therapy with colchicine and ibuprofen.

An ajmaline test and a control PES were scheduled for all patients after completion of 1-3 months follow-up.

Results

Acute success

Disappearance of Brugada type 1 ECG pattern was acutely achieved in 100% of patients. Despite this, in 5 patients (5%) PES resulted still positive at the end of the procedure: those without ICD were given a wearable external defibrillator until the next scheduled evaluation.

Follow-up

At 1-3 months the patients were re-evaluated with ajmaline-challenge and PES (*Figure 5*).

Eighty-nine out of 98 (91%) had a complete type 1 ECG elimination both in basal condition and after ajmaline and had a negative PES.

Nine patients (9.1%) had type 1 ECG after ajmaline challenge and 2 of them were still VF-inducible at PES.

In these patients a re-do procedure was proposed, which was performed in 6 patients: all of them had basal and post-ajmaline persistence of abnormal EGMs that were targeted for ablation as above described with complete abolition of abnormal EGMs and BrS type 1 pattern.

The 2 patients with recurrence of VF inducibility after the first procedure where no longer inducible at the end of the second procedure (data confirmed at follow-up).

These results were confirmed at the next evaluation after 1 month.

The three patients who refused the second procedure, received HQ therapy, one was an ICD carrier and the other two had and implanted loop recorder.

At an average follow-up of 2.7 ± 1.5 years (maximum 5 years, minimum 3 months) no ventricular arrhythmic events or deaths from all causes occurred; inappropriate ICD shocks were recorded in 2 patients.

Safety

Our study confirms the low rate of complications and the absence of fatal complications (as already highlighted in

previous work by Nademanee *et al.*,[13] Brugada *et al.*,[14] and Pappone *et al.*[15]

We observed a higher rate of pericarditis in the first phase (9 patients, 8.6% of total procedures), which decreased after we increased preventive therapy (by combining anti-inflammatory drugs and colchicine) and extended the duration up to 3 months for colchicine.

Discussion

As described in previous work,[13-16] we have confirmed the existence of an anatomically identifiable electrical substrate, which correspond to the typical of BrS ECG. This typical pattern has an anatomical correlation. Complete substrate is better identified in a larger area, with pharmacological challenge. Ablation of all abnormal electrical potentials is able to normalize the ECG and prevent arrhythmias induction.

Ablation of BrS substrates appears to be an effective treatment of symptomatic patients, particularly for those with VT/VF and/or ICD shocks after standard therapy has failed. If substrate ablation can truly provide long-term prevention of VT/VF, this could even become an alternative to ICD therapy, which does not prevent VT/VF and only treats episodes when they occur.[16]

Historically, the 'high' and 'low' risk categories were defined, for BrS, in relation to defibrillator implantation, which does not have a favourable risk/benefit ratio for all the patients.

Due to the known problems of long-standing implants, in patients asymptomatic for aborted sudden death or arrhythmic syncope, ICD may have an unfavourable risk/benefit ratio in the long-term and therefore patients are categorized as 'low risk' in absolute terms, which could mislead to under treatment.

Asymptomatic patients run a risk of death, that is ~1% per year in a population with an average age of ~40 years, which is 100–1000 times higher compared with the general population at the same age.[7]

The crucial point is to understand when a risk can be considered acceptable taking into account the risks of the available treatment options. Procedural safety in acute and long-term is then an important issue.

As described by Pappone and Brugada, the arrhythmic substrate is located in the epicardium, implying safety issues for ablation. Similarly, in the last decades the same risks were faced for ablation of VT with epicardial origin, which is now an established technique[18] when performed in experienced high-volume centres.

The extensive epicardial ablation required in patients with Brugada syndrome may lead to pericardial inflammation, which, as demonstrated in the literature and in our experience, does not lead to serious consequences if adequately managed with drug therapy.

In the light of the reported[10-12] and personal experience, ablation is a new promising treatment option for patients affected by BrS.

Ablation procedure revealed to be reproducible and safe when performed in high-volume centres with experience in the treatment of arrhythmias with an epicardial approach.

These preliminary data together with those available so far in the literature[16] are extremely encouraging and, if confirmed by longer follow-up and by multicentre randomized study, could change the whole therapeutic management in BrS patients with intermediate and low risk.

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Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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