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Original Article

Catheter ablation for electrical storm in Brugada syndrome: Results of substrate based ablation

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ABSTRACT

Background: Brugada syndrome (BrS) is known to cause malignant ventricular arrhythmia (VA) and sudden cardiac death (SCD). Patients with implantable cardioverter defibrillator (ICD) may experience recurrent shocks from ICD. Recent reports indicate that radiofrequency ablation (RFA) in BrS is feasible, and effective. Catheter ablation of premature ventricular complexes (PVCs) triggering VA and substrate modification of right ventricular outflow tract (RVOT) has been described.

Methods and results: Five patients (4 males, age-23 to 32 years) with BrS and electrical storm (ES) despite being on isoprenaline infusion and cilostazol (phosphodiestrase-3 inhibitor) underwent 3 dimensional electroanatomic mapping and RFA. Ventricular fibrillation was easily inducible in two patients. Voltage map of right ventricle was created in sinus rhythm in all patients. Substrate modification of RVOT was performed endocardially in one patient, both endocardial and epicardial in three and only epicardially in one patient. Brugada pattern gradually resolved over one week in all patients post procedure. These patients completed follow up of median 40 months (1.5–70). One patient had inappropriate shock due to atrial fibrillation, one had an episode of VF and appropriate shock 24 months after the RFA. The remaining four patients had no device therapy or VA in device log on follow up.

Conclusion: Abnormal myocardial substrate is observed in RVOT among patients with BrS. Substrate modification in these patients may abolish Brugada pattern on the ECG and prevents spontaneous VAs on long term follow up.

1. Introduction

Brugada syndrome (BrS) is a genetic disease that accounts for approximately 20% of sudden cardiac death (SCD) in patients with structurally normal hearts.[1] This syndrome is characterized by an ST-segment elevation in right precordial leads (V1–V3) unrelated to ischemia, electrolyte disturbances or obvious structural heart disease. It is accompanied by right bundle branch block (RBBB) like morphology of the QRS.

This condition can cause recurrent malignant ventricular tachycardia (VT), polymorphic VT and ventricular fibrillation (VF).[2] Implantable cardioverter defibrillator (ICD) is the standard of care for symptomatic patients with BrS. Patients with BrS continue to experience frequent ICD shocks, and electrical storm (ES) in them is associated with high mortality and morbidity. Electrical storm is defined as three or more sustained episodes of VT/VF or appropriate shocks from an ICD within 24 h. We report five patients with BrS who underwent successful catheter ablation for frequent ICD shocks and/or ES.

2. Methods

2.1. Patients

Five patients with BrS (4 males; age-23 to 32 years) presented with recurrent ICD shocks for VT/VF between August 2010 and January 2017. Three of them had undergone ICD implantation for

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spontaneous Type I Brugada pattern and resuscitated cardiac arrest, and the other two for arrhythmic syncope with spontaneous type I Brugada pattern.

Electrophysiology study (EPS) and radiofrequency catheter ablation (RFA) was performed under three dimensional (3D) electroanatomic mapping system (EAMS) in all.

2.2. Electrophysiology study and radiofrequency ablation

After an informed consent EPS and RFA was performed under local anesthesia and conscious sedation. Endocardial and epicardial aspects of the right ventricle (RV) including the right ventricular outflow tract (RVOT) were accessed via the transfemoral and percutaneous subxiphoid approaches respectively. A 3D electroanatomical shell of the right ventricular endocardium and epicardium was created using a 3D EAMS (CARTO 3 Navigation System (Biosense Webster Inc., Diamond Bar, CA, USA), or Ensite Velocity Navigation system (NavX; St. Jude Medical Inc., St. Paul, MN, USA)). Abnormal electrograms (EGMs) defined as: fractionated potentials (FP; defined as a continuous multi component EGM with amplitude <1 mV and duration >50 msec), split EGMs (two discrete EGMs separated by an isoelectric interval of >50 msec), isolated late potentials (ILP; defined as EGMs inscribed entirely after the QRS complex) and low voltage EGMs (bipolar voltage <1.5 mv, filtered at 30–300 Hz with a notch filter at 50 Hz) were tagged in sinus rhythm (Fig. 1). Induction of sustained VT or VF was then attempted using the following stimulation protocols: Programmed extrastimulation (PES) was performed in all patients, and up to three extrastimuli were delivered from the RV apex and the RVOT. Programmed extrastimulation using short-long-short (SLS) sequence protocols upto ventricular effective refractory period was performed. When these protocols did not induce VT/VF, a protocol of burst pacing upto 300 ms from the RV apex and the RVOT was used. In case of non-inducibility of VT/VF, these protocols were then repeated from the left ventricle (LV). In case of non-inducibility of sustained ventricular arrhythmia from the RV and LV at baseline, induction was attempted during an infusion of Phenylephrine (0.1–0.5 mg bolus over 1 min followed by an infusion of 0.5–1 μg/kg/min, the end points for dose escalation being achievement of any of the following: 1. Systolic BP $\geq$200 mmHg, 2. increase in mean arterial pressure by $\geq$50 mmHg, and 3. Increase in sinus cycle length by $\geq$ 25%). Finally an infusion of Propofol (20 mg bolus followed by an infusion of 20–60 mg/ h, was titrated to achieve maximum possible deep conscious sedation without compromising spontaneous respiration). After the initial patient, the mapping strategy was modified to include remapping of the endocardium and epicardium during intravenous infusion of procainamide (10 mg/kg over 30 min), regardless of the findings observed during mapping in the baseline state. This was performed for patients no. 2, 3 and 4, but not for patient no 5. Patient 5 had just recovered from a VF storm and was on inotropes and pharmacological provocation was considered unsafe. Stimulation protocols were avoided during infusion of procainamide. Irrigated RFA was performed using an 8F deflectable CELSIUS Thermocool D curve catheter (Biosense Webster, Diamond Bar, CA, USA), or a 7F deflectable Therapy Coolpath medium curve catheter (St. Jude Medical Inc., St. Paul, MN, USA) to deliver 30 W energy at 43 °C catheter tip temperature at an irrigation rate of 2 ml/ min in the epicardium and up to 30 ml/min in the endocardium. Areas of fractionated electrograms and late electrograms(whether observed at baseline or during Procainamide infusion) were ablated during sinus rhythm. Similar stimulation protocols were repeated after completion of ablation. The procedure was defined as successful only if no tachycardia (neither nonsustained/sustained VT/VF or premature ventricular contractions (PVCs)) was induced post ablation.

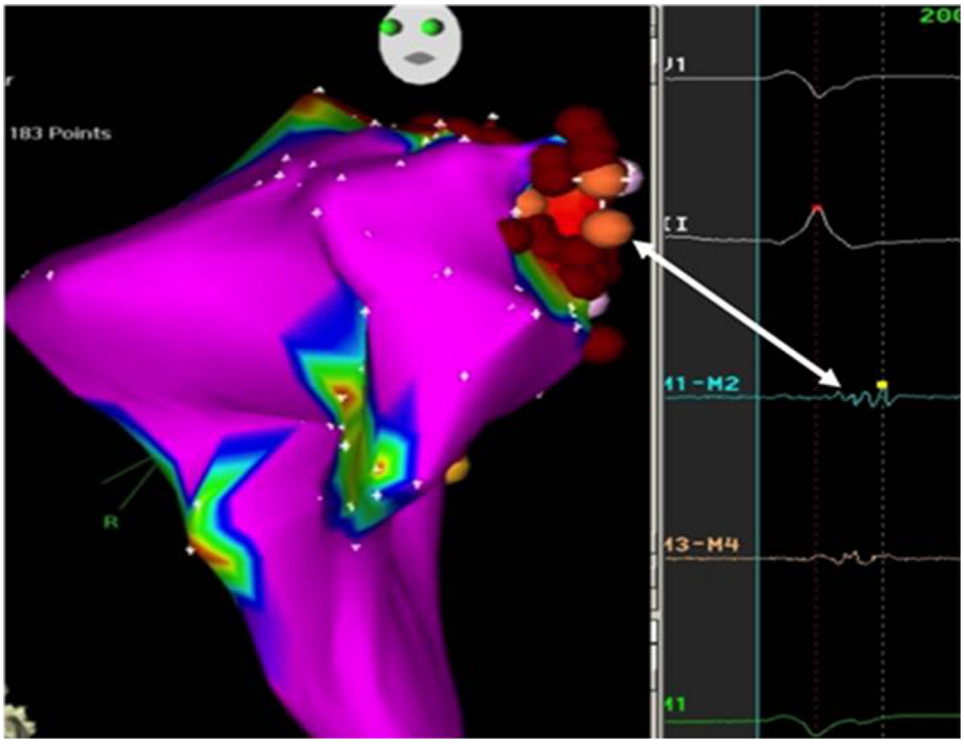

Fig. 1. Voltage guided 3D EAM of RV in LAO view showing: Isolated late potential (white arrow, orange tag) recorded after the QRS from a discrete area of the RVOT septal endocardium in patient no.1; red tag- site of ablation.
3D EAM- three dimensional electroanatomical map; LAO: left anterior oblique view; RVOT: right ventricular outflow tract.

Table 1
Baseline characteristics and follow up.

Patient no.	Age (years)	Sex	AADs pre RFA	Duration from ICD implant to RFA (months)	No. of ICD shocks[a] before RFA	Timing of RFA	Duration of follow up after RFA (months)	No. of ICD shocks post RFA
1	23	M	I,[b]C[c]	14	32	August 2010	81	0
2	27	M	I,C,Q[d]	4	6	October 2011	67	1[e]
3	32	F	I,C	8	3	December 2013	41	0
4	31	M	I,C,Q	59	21	July 2013	46	1[f]
5	32	M	I,C	37	35	January 2017	4	0

AADs: Anti-arrhythmic drugs; RFA: radiofrequency ablation; ICD: Implantable cardioverter defibrillator.
[a] All shocks were appropriate shocks for VT/VF(ventricular tachycardia/ventricular fibrillation).
[b] I = Isoprenaline infusion for electrical storm.
[c] C = Oral Cilostazol.
[d] Q = Oral Quinidine; used in only two patients due to non-availability.
[e] One inappropriate shock for atrial fibrillation.
[f] One appropriate shock for VF, 24 months post RFA.

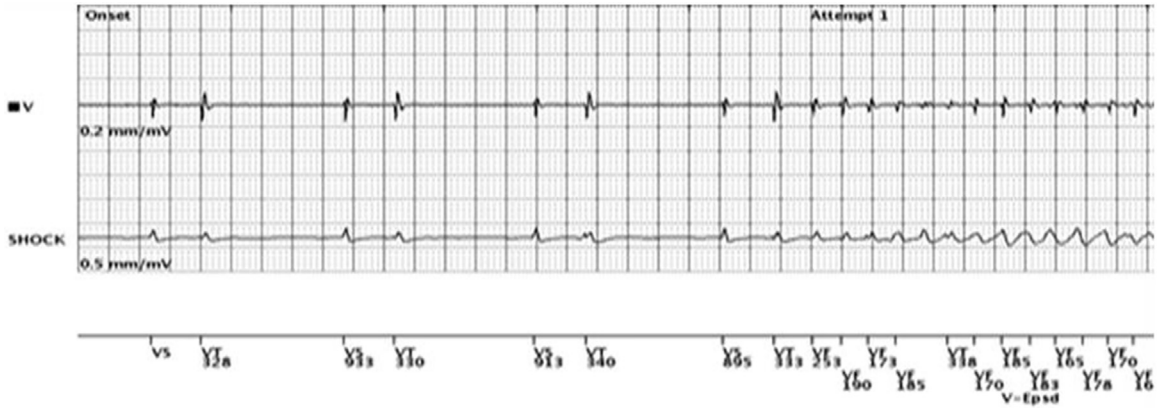

Fig. 2. ICD recording from patient no.3, showing a period of ventricular bigeminy followed by initiation of ventricular fibrillation (VF) by a PVC of fixed coupling interval. ICD: Implantable cardioverter defibrillator; PVC: premature ventricular contraction; VT: ventricular tachycardia.

3. Results

Table 1 describes the baseline characteristics of the patients. All patients experienced recurrent ICD shocks despite drug therapy (Table 1). ICD interrogation revealed single PVCs of fixed coupling interval triggering VF in three out of five patients (Fig. 2). But, none had spontaneous or inducible PVCs during EP Study. Hence a strategy of ablating triggering PVCs was not pursued.

Table 2 summarizes the EP findings and RFA strategies employed. All but one patient (Patient No. 3) had Type I Brugada pattern during EPS;. In patient no. 3 baseline ECG was normal when taken up for procedure, but after injection procainamide ECG changed to type III Brugada pattern (Fig. 3A). Right ventricular endocardial substrate map was created in all patients. The epicardial substrate map of RV was created in all except the first patient, in whom ablation of abnormal endocardial substrate had abolished the Brugada pattern (Fig. 4); besides, at that point, we

Table 2
Electrophysiology study findings and radiofrequency ablation strategies in individual patients.

Patient no.	VA induced in the EP lab	Area of RVOT showing abnormal signals (low voltage, ILP, fractionated)	Area of RVOT ablated
1	VF	Anterior free wall and high septum in the endocardium	Endocardial
2	VT	Endocardium- Septum and posterior wall. Epicardium-Anterior wall	Endocaridal + Epicardial
3	VF	Endocardium- Anterior free wall Epicardium- Anterior wall	Endocaridal + Epicardial
4	NSVT	Endocardium- None Epicardium- Anterior wall	Epicardial
5	None	Endocardium- Anterior free wall Epicardium- Anterior wall	Endocaridal + Epicardial

VA- ventricular arrhythmia; EP lab- electrophysiology laboratory; VF- Ventricular fibrillation; VT- Ventricular tachycardia; NSVT- Nonsustained ventricular tachycardia; RVOT- Right ventricular outflow tract; ILP- isolated low potentials.

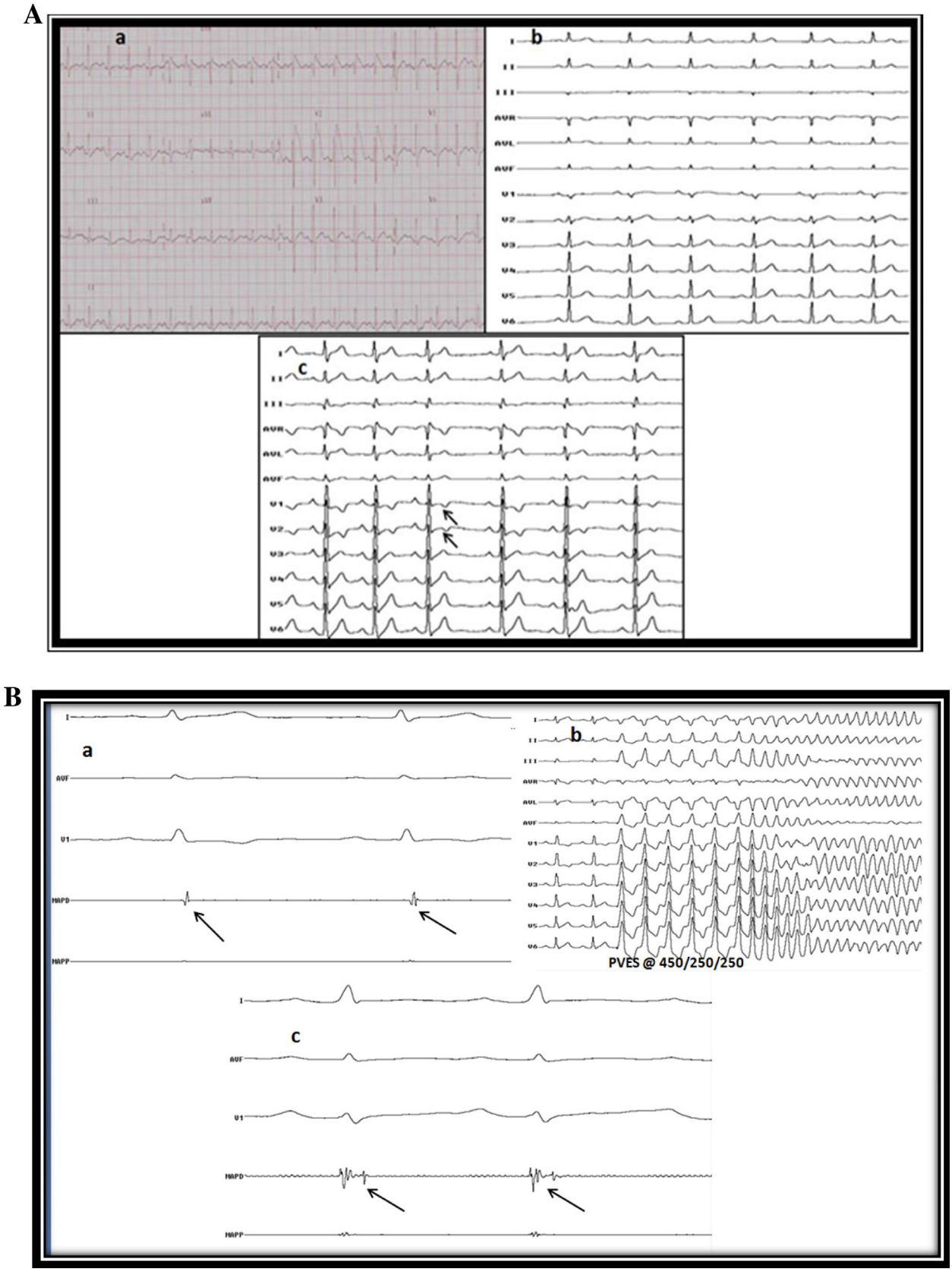

Fig. 3. A: (a) Baseline clinical ECG of patient no.3 at the time of presentation, showing type I Brugada pattern. (b) Baseline ECG in the EP lab. (c) ECG after injection procainamide showing Brugada type III pattern. Black arrows showing tall R wave, ST depression and T wave inversion in V1, V2. EP lab: electrophysiology laboratory. B: Patient number 3: (a) Surface ECG and intracardiacs: MAPD showing low voltage but no abnormal signals in the RVOT free wall (black arrows). (b) Surface ECG showing: PVES inducing ventricular fibrillation. (c) Surface ECG and intracardiacs: MAPD showing fractionated and late potential (black arrows) at the same site as (a) after injection procainamide. MAPD: mapping catheter distal; MAPP: mapping catheter proximal; RVOT: right ventricular outflow tract; PVES: Programmed ventricular extrastimulation.

were still exploring the optimal mapping and ablation strategies. Among the four patients who underwent combined endocardial and epicardial substrate mapping, the epicardial substrate was abnormal in all, and was limited to the epicardial aspect in one. Electrical abnormalities were present in the RVOT and spared the rest of the RV in all patients. Electrical abnormalities were in the form of low voltage areas and ILPs in all; four patients had FPs in addition to low voltage areas and ILPs. The substrate map was repeated during procainamide infusion in patients no. 2, 3 and 4. Procainamide infusion did not change the map in patients 2 and 4. Intravenous procainamide converted the normal ECG to a Type III Brugada pattern in patient no. 3, as well as extended the area of FPs and ILPs in both endocardial and epicardial aspects (Fig. 3B). Brugada pattern normalized in their ECGs after RFA in all patients. A reduction in precordial ST elevation, was noted in all patients immediately after RFA. Two out of five patients (Patients no.2 and 4), developed post ablation pericarditis and resolution of precordial ST elevation occurred 3 to 5 days after RFA (due to concomitant ECG changes of ablation-induced pericarditis).

3.1. Follow up

All patients were followed up initially on a weekly basis for three weeks, and then at three months post ablation. Thereafter, they were followed at six monthly intervals. The median duration of follow up after RFA was 46 months (range 4–81 months). Table 1 shows the pre and post RFA follow up periods, and number of VT/VF episodes before and after RFA. During follow up, one patient had a single episode of VF at 24 months after RFA. Inappropriate shock due to atrial fibrillation occurred in one patient. The other three patients were free of VT and VF on follow up.

4. Discussion

4.1. Pathophysiology of the ECG pattern and ventricular arrhythmias in Brugada syndrome

Mechanism of VT/VF among patients with BrS are not well understood. Available data suggests that electrophysiological (EP) abnormalities in the RVOT are responsible for VT/VF in patients with BrS.[3–5] Kakishita et al.[6] studied ICD logs in patients with BrS and recurrent VT/VF. They observed that, in two third of patients with BrS, VF is preceded by isolated premature beats, mostly single and with long coupling interval. Brugada syndrome causes mainly polymorphic VT or VF; monomorphic VT is uncommon.[7–9] One patient in our series (Patient No. 2) had monomorphic hypotensive VT during EPS (Fig. 5).

4.2. Treatment options for recurrent VT/VF in Brugada syndrome

Implantable cardioverter defibrillator is the standard of care in patients with BrS for secondary prevention of SCD. However they may develop recurrent VT/VF and ICD shocks with significant morbidity. Pharmacological therapy with quinidine bisulphate (not widely available) and cilostazol (phosphodiesterase type III inhibitor) may be tried to prevent ICD shock in these patients, but may not be always effective. Intravenous infusion of isoproterenol may be useful in BrS with ES. There are few reports of successful RF ablation by to prevent recurrence of VT/VF.[4,10–13,15]

4.3. Ablation strategies in Brugada syndrome

4.3.1. Ablation of triggering PVCs

Two third of patients with BrS and VT/VF have PVCs triggering VT/VF. Few studies have shown that PVCs were seen to arise from RVOT area and focal RF ablation of PVCs prevented recurrence of VT/VF.[4,12] In our series, three of our patients had trigger PVCs noticed in device log, however none had spontaneous or inducible trigger PVC during EPS. This approach of targeting the PVCs was not possible in such patients.

4.3.2. Substrate modification

Many non-invasive and invasive studies have shown that EP abnormalities responsible for cardiac arrhythmias in BrS are located in RVOT and anterior right ventricular area.[4,10–14] Electrophysiological abnormalities in the form of late potentials, fractionated potentials, split potentials and low voltage areas were noticed in our patients in endocardial as well as epicardial surface of RVOT/right ventricular area as reported by some authors.[10,11,13,15] Substrate modification, either endocardial or epicardial has shown to prevent recurrent VT/VF and ICD shocks in these patients.[10,11,13,15]

4.3.3. Epicardial versus endocardial substrate

There is no consensus about the site of electrophysiological abnormality in BrS, whether it involves epicardial or endocardial aspect or RVOT. Postema et al.[14] reported EP abnormality in RVOT endocardium. In contrast, Nademanee et al.[11] observed abnormal epicardial substrate with no abnormality in the endocardium. Substrate modification of endocardial or epicardial area prevented

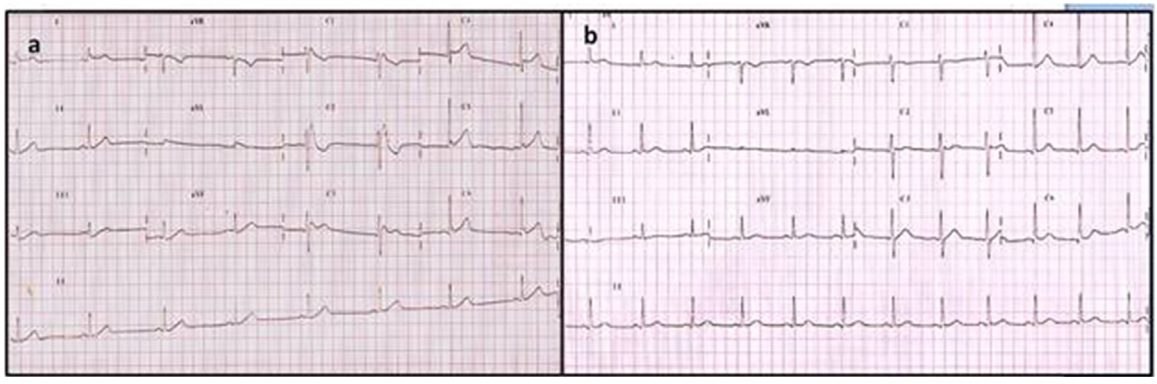

Fig. 4. a) Pre RFA ECG from patient no.1 showing type 1 Brugada pattern; b) Post RFA ECG from the same patient showing complete resolution of ECG abnormalities following RFA in the RVOT septal endocardium.
RFA = radiofrequency ablation; RVOT = right ventricular outflow tract.

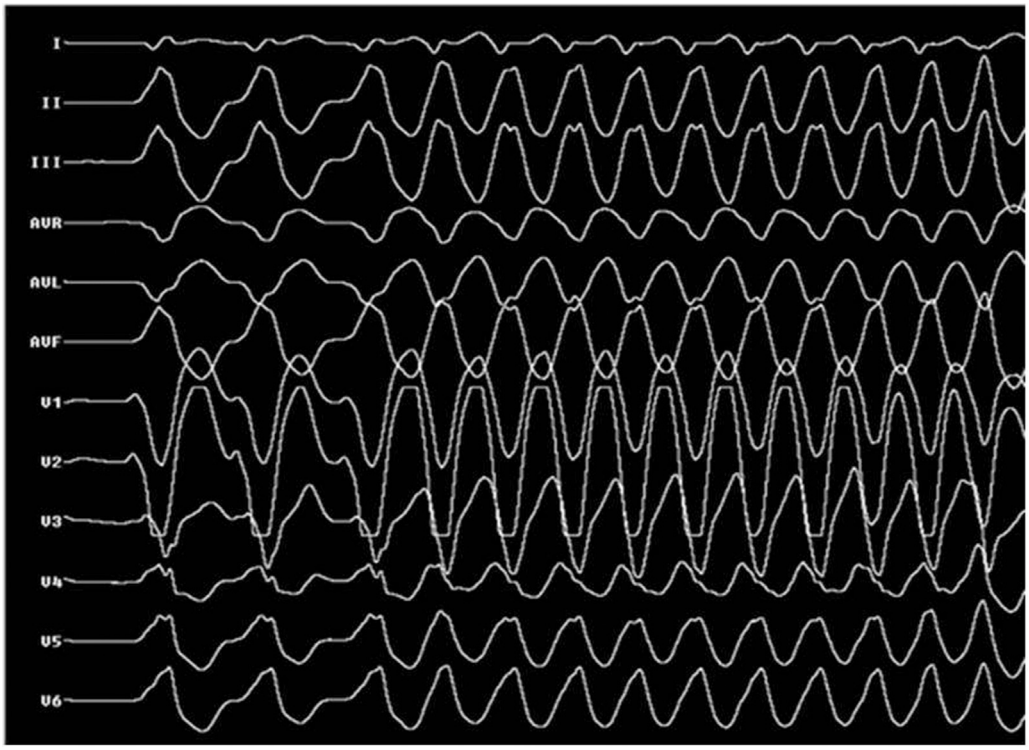

Fig. 5. Rapid monomorphic VT of left bundle, right inferior axis morphology induced in patient no. 2.

recurrence of VT/VF off medications.[10,11,13] We observed abnormalities in the form of late potentials, fractionated EGMs, and low voltage EGMs endocardially (septal as well as free wall of RVOT/RV) as well as epicardial surface of RVOT and RV. The first patient underwent endocardial ablation only. The second patient underwent epicardial ablation however; the Brugada pattern disappeared only transiently. Additional ablation of RVOT endocardium resulted in persistent resolution of Brugada pattern. Our results indicate that these patients has heterogenous substrate, as abnormal electrograms can be present in either RVOT epicardial region, endocardial region or both (Table 2). Administration of intravenous procainamide helps to unmask some of these potential targets. All patients are free of ES, however one patient had one VF shock 24 months post ablation. Saha et al.[15] reported a case of BrS with electrical storm with both endo and epicardial substrate. They performed combined ablation of both the surfaces of RVOT and reported long term freedom from VT/VF.

4.4. Procainamide for mapping

Sodium channel blocker like procainamide causes reduction in INa current and unmasks Brugada type I pattern. Abnormal potentials seen during RV mapping seen in our series may be due to functional abnormality and it correlated with Brugada pattern on surface ECG. A recent study by Brugada et al.[10] used flecainide as sodium blockage, however they studied only changes in epicardial map with flecanide. Intravenous (IV) procainamide has a shorter half life of three to four hours compared to flecanide which has the elimination half life of 7–19 h. Because of its longer half life, flecainide may have delayed side effects.[16,17] We believe, procainamide may be safer and can be used to unmask abnormal electrical substrate in patients of BrS during an ablation procedure. More studies are required to validate the use of sodium channel blockage in RFA of BrS.

4.4.1. End point of ablation in substrate modification

Nademanee et al.[11] and Sunsaneewitayakul et al.[13] suggest that resolution of Brugada pattern on surface ECG should be taken as an end point of ablation. Brugada pattern resolved in all our patients post ablation. Patient No. 3 had inducible VT/VF despite resolution of Brugada pattern. However, the patient is free of VT/VF post RFA. This report and others,[4,11] suggests that re-inducibility of VT/VF should not be taken as an end point of ablation.

4.5. Complications

Radiofrequency ablation in BrS appears safe. There are few reported complications of RFA in BrS like RBBB,[13] and pericarditis.[10,11] One patient in our series (Patient No.2) who underwent epicardial ablation had pericarditis and pericardial effusion which recovered uneventfully; Patient No.4 had pericarditis without significant effusion.

4.6. Limitations

The study group consists of only five patients and a larger study may be required to elucidate the heterogeneous substrate in BrS. Longer follow up may be required to understand the long term results of catheter ablation.

5. Conclusion

Catheter ablation is feasible in patients with BrS who have recurrent ICD shocks. Substrate based ablation of RVOT area is effective in preventing recurrence of VT/VF in patients with drug refractory BrS. Electrical substrate can be heterogeneous involving either endocardial orepicardial or both surface of RVOT. A short acting sodium channel blockade may be safe and useful in unmasking areas of abnormal potentials and help in guiding

catheter ablation. Our limited experience indicates that RFA can be useful for patients with BrS and recurrent ventricular arrhythmias with ICD shocks.

Conflict of interest

None to declare.

Financial assistance

None.

Key messages

What is known?

- Catheter ablation in Brugada Syndrome on epicardial surface of right ventricular outflow tract can eliminate drug refractory electrical storm.
- In patients presenting with premature ventricular contractions (PVCs) triggering malignant ventricular arrhythmias (VAs), these PVCs can be targeted for ablation.

What this manuscript adds?

- Substrate in patients with Brugada syndrome appears to be variable.
- Abnormal intracardiac signals can be observed in endocardial and or epicardial aspect of RVOT.
- Sodium channel blockade helps to unmask abnormal areas in some patients.
- Triggering PVCs may not be induced in the EP laboratory and hence cannot be targeted for ablation.

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