CLINICAL REVIEW

# Ablation of atrial fibrillation in patients with Brugada syndrome: A systematic review of the literature

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## Abstract

Supraventricular arrhythmias are common in Brugada syndrome (BS), and notoriously difficult to manage with medical therapy secondary to associated risks. Pulmonary vein isolation (PVI) is often utilized instead, but its outcomes in this population are not well-known. We aim to provide a holistic evaluation of interventional treatment for Atrial fibrillation (AF) in the BS population. Electronic databases Medline, Embase, Cinahl, Cochrane, and Scopus were systematically searched for publications between 01/01/1995 and 12/31/2017. Studies were screened based on predefined inclusion and exclusion criteria. A total of 49 patients with BS and AF were included. Age range from 28.8 to 64 years, and 77.5% were male. 38 patients were implanted with implantable cardioverter-defibrillators (ICD) at baseline, and of them, 39% suffered inappropriate shocks for rapid AF. 34/49 (69%) of patients achieved remission following a single PVI procedure. Of the remaining, 13 patients underwent one or more repeat ablation procedures. Overall, 45/49 (91.8%) of patients remained in remission during long-term follow-up after one or more PVI procedures in the absence of antiarrhythmic drug (AAD) therapy. Postablation, no patients suffered inappropriate ICD shock. Furthermore, no major complications secondary to PVI occurred in any patient. AF ablation achieves acute and long-term success in the vast majority of patients. It is effective in preventing inappropriate ICD therapy secondary to rapid AF. Complication rates of PVI in BS are low. Thus, in light of the risks of AADs and risk of inappropriate ICD shocks in the BS population, catheter ablation could represent an appropriate first-line therapy for paroxysmal atrial fibrillation in BS patients.

## 1 | INTRODUCTION

Approximately 20% of patients with Brugada syndrome (BS) develop supraventricular arrhythmias.[1] Atrial fibrillation (AF) in particular comprises 10%–20%.[2–4] Medical antiarrhythmic therapy in those patients is particularly challenging because some drugs may increase the risk of sudden cardiac death in BS. Moreover, the presence of AF concomitantly with BS and an implantable cardioverter-defibrillator (ICD) often leads to inappropriate shock.[5]

Pulmonary vein isolation (PVI) is an effective method for controlling paroxysmal AF[6] by electrically isolating the pulmonary veins (PVs) from the left atrium (LA). PV isolation often eliminates the need for antiarrhythmic drugs, and may therefore provide a uniquely attractive treatment modality for AF in patients with BS. However, the efficacy of PV isolation is unknown in this patient population. Only small series of patients have been published so far, and as such, the utility of the technique in BS remains undetermined.

The present study sought to provide a holistic evaluation of interventional treatment for AF in the BS population by: (i) consolidation of the existent literature in order to draw conclusions from a sufficient population size, (ii) assessment of demographic and clinical indications for procedural intervention, (iii) evaluation of the hazards and complications of intervention.

## 2 | METHODS

A systematic review and best-evidence synthesis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

### 2.1 | Literature search

Electronic databases Medline, Embase, Cinahl, Cochrane, and Scopus were systematically searched for publications between 01/01/1995 and 12/31/2017. The following search terms were used: "atrial fibrillation ablation in Brugada syndrome"; "pulmonary vein isolation in Brugada syndrome"; "atrial fibrillation in patients with Brugada syndrome"; "catheter ablation of atrial tachyarrhythmias". Each article's references were screened for additional relevant papers that may have been missed by the initial search.

### 2.2 | Eligibility criteria

Titles and abstracts were screened for eligibility via the following criteria.

### 2.2.1 | Inclusion

- Languages: English, French, Swedish, Arabic, Norwegian, Danish, and Spanish.
- Publication type: Original manuscripts in peer-reviewed journals.
- Study design: Systematic reviews, meta-analyses, randomized-controlled trials (RCTs), case-control and cohort studies. Studies reporting adequate follow-up information were included.
- Study population: Human participants of all ages who have BS, AF and have undergone pulmonary vein isolation.
- Study outcomes: Acute success, complication rates, and long-term follow-up.

### 2.2.2 | Exclusion

- Study design: Nonsystematic reviews, cadaveric, biomechanical, and laboratory studies. Patient overlap between two included studies; aka efforts were made to ensure that no patient's data was included twice.
- Study population: Animals.

### 2.3 | Screening

Initially, one reviewer read all titles retrieved from the database search and removed citations clearly unrelated to AF ablation in BS. Subsequently, an abstract review was carried out. Full-text articles were obtained for all abstracts except those that clearly did not meet the eligibility criteria. If after analysing the full text, the eligibility of an article remained uncertain, a second reviewer conducted a full-text analysis of the article to determine eligibility. A third reviewer was consulted in the event of disagreement. Level of agreement on study eligibility was tested using the kappa statistic and 95% confidence interval.

### 2.4 | Critical appraisal

Two reviewers appraised eligible papers using the modified Scottish Intercollegiate Guidelines Network (SIGN) criteria. [8] Reviewers were international scientists and/or had experience in systematic review methodology.

### 2.5 | Data extraction

Extracted data: (i) study name, authors and publication date; (ii) publication language; (iii) publication type; (iv) geographic origin; (v) study design; (vi) BS definition; (vii) Population size; (viii) participant

characteristics; (ix) preprocedural work-up; (x) electrophysiological details of the PV isolation; (xi) prognostic factors/outcomes; (xii) complications; (xiii) follow-up periods, and (xiv) key findings. These endpoints were summarized in two tables (Tables 1 and 2).

## 2.6 | Statistical analysis

Categorical data are presented as numbers (n) and percentages, as well as a range from minimal up to maximal reported values, with a corresponding grouped median. Continuous data are expressed as mean and standard deviation.

## 3 | RESULTS

### 3.1 | Demographic characteristics

A total of 49 patients from four different studies were included in the analysis[9–13] (Table 1). All patients had a concomitant diagnosis of BS and AF, and all were referred for AF ablation. Mean age range from 28.8 to 64 years. The vast majority of patients were male (77.5%). All patients had paroxysmal AF. Only 12 (24.4%) patients had a baseline type 1 BS pattern, whereas all others had drug-induced type 1 BS. 38 patients (77.5%) underwent ICD implantation prior to AF ablation. Of them, 39% suffered inappropriate shock therapy (for AF). Seven patients (14%) were resuscitated from ventricular fibrillation.

Pharmacologic Therapy: Out of the four series, only three of them reported on the use of antiarrhythmic drugs (AADs) prior to ablation. In the series by Sairaku et al[9], no patients were prescribed AADs. A patient described by Mugnai et al[10] was maintained on a combination of sotalol and bisoprolol. In all reported patients, medical treatment was ineffective for AF control.

Cardiac comorbidities: None of the patients included in the cohort had signs of structural heart disease. One patient described by Mugnai et al[10], as well as all patients reported by Yamada et al[11], had typical cavotricuspid isthmus (CTI)-dependent atrial flutter.

### 3.2 | Follow-up and endpoint definition

In all studies, clinical follow-up consisted of physical examination, ECG and a minimum duration of 24 hours of holter recording. These parameters were assessed at 3, 6, and 12 months post-op, as well as every 6 months after the first year. Follow-up of ICD data was performed every 6 months in the outpatient clinic in all studies. None of the studies mentioned the use of remote device monitoring. Recurrence of an atrial arrhythmia was defined as an episode of an atrial arrhythmia lasting >30 s.[10,12]

### 3.3 | Electrophysiological strategy

Little variation in ablation protocol was observed. Consistently, all groups performed circumferential PV antrum isolation or an encircling ipsilateral pulmonary vein isolation using an electroanatomic mapping

**TABLE 1** Demographic characteristics

| Authors (year) | Population (n) | Age | Male (n,%) | ICD | Previous SCD | Inappropriate shock | Type 1 BrS | PAF | AF duration | SCN5A | AFI | LA (mm) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yamada (2008)[9] | 6 | 42–61 | 5 (83.3%) | 3 (50%) | 0 (0%) | 3 (50%) | 1 (16.6%) | 5 (83.3%) | 3 week–8 years | 4/5 (80%) | 6 (100%) | 32-38 |
| Sairaku (2013)[10] | 6 | 53 (28.8–64) | 6 (100%) | 6 (100%) | 2 (33.3%) | 5 (83.3%) | 3 (50%) | 6 (100%) | 0.5–6 years | 1/3 (33.3%) | N/A | N/A |
| Kitamura (2016)[12] | 14 | 51.9 | 14 (100%) | 14 (100%) | 4 (28.6%) | 8 (57.1%) | 4 (28.6) | 14 (100%) | N/A | 0/2 (0%) | N/A | 32.6 + 5.4 |
| Mugnai (2017)[13] | 23 | 47 ± 18 | 13 (56.2%) | 15 (65%) | 1 (4%) | 4 (27%) | 4 (17%) | 23 (100%) | N/A | 2/11 (18%) | 1 (4.4%) | 38 ± 6.9 |
| Total | 49 | 42–64 | 38 (77.5%) | 38 (77.5%) | 7 (14.2%) | 20 (40.8%) | 13 (24.5%) | 48 (98.0%) | 3 weeks–6 years | 7/21 (33.3%) | 7 (14.2%) | 32-44.9 |

Abbreviations: AF: atrial fibrillation; AFl: atrial flutter; BrS: Brugada syndrome; ICD: implantable cardioverter defibrillator; LA: left atrium; NA: nonapplicable; PAF: paroxysmal atrial fibrillation; SCD: sudden cardiac death.

**TABLE 2** Outcomes during long-term follow-up

| Author | Initial Strategy | Drugs in the f/u | Success | Number of patients requiring redo procedures | Days of f/u | Complications | Inappropriate shocks |
|---|---|---|---|---|---|---|---|
| Yamada (2008) | PV+CTI (RF) | 0 | 6/6 (100%) | Redo in 1 patients for focal AT from the mitral isthmus. | 11 ± 6 5-20 months | None | 0 |
| Sairaku (2013) | N/A (RF) | 0 | 5/6 (83.3%) | 2 (33.3%) | 43.2 (19.9–74.4) | None | 0 |
| Kitamura (2016) | PVI (RF) | N/A | 14 (100%) | Scheduled follow-up EPS was performed in all 14 patients. Two patients, we performed ablation for non-PV trigger AF. The lone patient with recurrence of PAF underwent their third and fourth sessions of catheter ablation and had neither further recurrence of PAF | 3.3 ± 1.4 years | None | 0 |
| Mugnai (2017) | PVI (6RF-17CB) PVI+ICT in 1 (RF) | None in the success group. Among 6 patients with recurrence, two (33%) did not undergo a repeat procedure because an alternative strategy with medical therapy was decided | 20 (86.7%) | 4 (reisolation of reconnected PV except one patient who presented with a roof dependent atrial fluter) | 35.0 ± 25.4 months | One patient (20%) experienced transient phrenic nerve palsy Another patient experienced an acute pericarditis that resolved in 2 weeks | 0 |

Abbreviations: CB: cryoballoon; F/u: follow-up; ICD: implantable cardioverter desfibrillator; PAF: paroxysmal atrial fibrillation; PV: pulmonary veins; RF: radiofrequency.

system. The endpoint of the PV isolation was either the elimination or dissociation of the PV potentials recorded from the circular catheters placed within the PVs and exit block from the PVs. In all included series, after the map was completed, radiofrequency (RF) energy was applied through a 3.5 mm irrigated tip ablation catheter in a power-controlled mode with a power limit of 35 W and a maximum temperature of 48°C. Power was decreased to 20–25 W when ablating on the posterior wall in order to avoid esophageal injury. None of the studies reported complex fractionated atrial electrogram mapping/ablation or systematic RF lines during the first attempt.

In the study by Mugnai et al[10], while some patients underwent RF ablation, others had cryoballoon (CB) ablation instead. CB ablation utilized either the first-generation CB (Arctic Front, Medtronic©) or the second-generation CB (Arctic Front Advance, Medtronic©).

In the event of previous history of cavotricuspid isthmus (CTI) dependent atrial flutter, a CTI line was created with an endpoint of bidirectional conduction block; this was the case in all of the patients from Yamada et al's study.[11]

## 3.4 | Procedural outcomes

Yamada et al[11] reported on six patients undergoing PVI with a follow-up period of 11 ± 6 months. 5/6 (83%) patients were free of symptomatic AF without use of AADs after the first procedure. The last patient suffered early recurrence of AF and a newly developed atrial tachycardia (AT). A second procedure was promptly performed. The tachycardia was a focal AT originating from the mitral isthmus. After the AT was eliminated by a few RF applications, neither AF nor AT could be induced despite burst atrial pacing with isoproterenol infusion. Ultimately, during the remainder of the follow-up period, 6/6 (100%) patients were free of any symptomatic atrial arrhythmias without use of AADs.

Sairaku et al[9] reported AF recurrence in two patients, 32 and 60 months after the first ablation session. They both underwent a second ablation session. The ICD recorded asymptomatic episodes of paroxysmal AF with a short duration even after the blanking period of the second session in one of them. However, he did not experience any further inappropriate ICD shocks after ablation. The remaining five patients remained free of AF without any AADs during a median follow-up period of 43.2 [19.9, 74.4] months after ablation.

Kitamura et al[12] reported no AF recurrence between the 3-month blanking period and 6-month follow-up. Scheduled follow-up electrophysiologic study (EPS) was performed in all 14 patients, during which 45 of 56 PVs remained isolated (80.4%). Subsequently, 11/11 reconnected PVs underwent successful isolation. In two patients, non-PV trigger was recorded reproducibly during isoproterenol infusion (1 due to the coronary sinus ostium and 1 due to the septal superior vena cava–right atrium junction). Ablation targeted at these triggers was thus performed. However, 57.1% of patients (8/14) did not require repeat ablation therapy during follow-up EPS. After follow-up EPS, 13/14 patients (92.9%) had no recurrence of atrial tachyarrhythmia during a mean period of 3.3 ± 1.4 years. The only patient with recurrence of PAF underwent third and fourth sessions of catheter ablation.

Subsequently, he had neither recurrence of PAF nor inappropriate ICD therapy during a follow-up period of 3.1 ± 1.2 years. Thus ultimately, all 14 patients could be maintained in sinus rhythm after 1-4 ablation procedures, without the need for AADs.

In the study by Mugnai et al[10], 17 patients (73.9%) were free of AF without AAD therapy at a mean follow-up time of 35.0 ± 25.4 months (median 36 months). Among five patients who underwent first-generation CB ablation, two (40%) experienced AT/AF recurrence during a mean follow-up period of 38.4 ± 24.4 months. Among 12 patients who underwent second-generation CB ablation, two (17%) had AF recurrence in a mean follow-up period of 29.4 ± 13.1 months. In those who underwent RFA, two patients (33%) experienced AT/AF recurrence after a mean follow-up of 37.5 ± 35.3 months. Overall, 6/23 patients (26%) exhibited recurrence of atrial tachyarrhythmias. Of those, five (83%) had atrial fibrillation and one (17%) had a left atrial flutter. The latter developed symptomatic left atrial flutter 2 months following RFA PVI. Repeat RFA showed persistent PVI isolation, and ablated the roof-dependent left flutter. Among six patients with AT/AF recurrence, two (33%) did not undergo a repeat procedure because an alternative strategy with medical therapy was chosen. Four redo procedures were performed using RFA. Overall, persistent PV isolation could be documented in 11 of 16 PVs (69%). After a mean follow up of 25.7 ± 13.2 months (median 18 months) from the redo procedures, three of four patients (75%) were still free from AT/AF recurrence. The last patient experienced recurrence of AF 15 months after the redo procedure and was treated with anticoagulant therapy only. Ultimately, a total of 20/23 patients (86.7%) were free of AF relapse at the last follow-up assessment.

Of a total of 49 BS patients herein included, 45 (91.8%) patients' AF was successfully controlled with PVI. Moreover, two of the remaining four did not attempt repeat ablation, and may have been able to achieve remission had alternate strategies not been instated. Of 20 patients who had experienced inappropriate ICD interventions for AF (40.8%), none presented further ICD shocks following their last ablation. Common to all studies, no major complications were described.

# 4 | DISCUSSION

The main findings of the study are: (i) freedom from AF recurrence in patients with BS and paroxysmal AF after PV isolation (by means of RFA or CB technology) is high; (ii) PVI often obviates the need for AADs after intervention; (iii) ablation decreases the incidence of inappropriate ICD intervention for AF; (iv) major intervention-related complications are rare.

## 4.1 | Background

Previous studies have demonstrated that the index of atrial conduction abnormalities and atrial arrhythmogenesis are substantiated in BS.[13-15] A shorter action potential duration and steeper restitution curve in the setting of a shorter diastolic interval are observed.

These disparities are thought to relate to the smaller late sodium current[13] or greater transient outward potassium current[16] as compared to the normal heart.

The incidence of AF in patients with BS is high.[2-4] Both shortening of refractoriness and conduction delay may be critical in AF induction. Results from previous studies and the present findings suggest that triggers coming from PVs play an important role in the genesis of AF in these patients.[17] Phase 2 re-entry may also be contributing to its development. Of note, the onset of AF in patients with BS is often preceded by fluctuations in autonomic tone, commonly during the night.[15] An increased vagal tone may reduce atrial conduction velocities and shorten the effective refractory period, leading to the induction of AF.

It is well known that the clinical management of AF in patients with BS is challenging. The use of sodium channel blockers confers risk owing to their potential proarrhythmic effects, including fatal ventricular arrhythmia. In addition, the safety of drug use, other than quinidine[18,19] and bepridil[20] in BrS has not been clearly investigated, especially when used for treatment of AF. In fact, the vast majority of patients herein included were not previously maintained on AADs, underlining physicians' reluctance to prescribe AADs in this setting.

## 4.2 | Procedural success

PVI is commonly utilized for treatment of refractory AF. The literature indicates that in the normal AF population, a 79.8% long-term success rate is observed.[21] There is wide variability, however, and success for PAF may be higher. Our data point to high success rates of PVI in BS as well. Through multiple PVI procedures instituted as clinically indicated, the combined BS population successfully achieved a 91.8% remission rate during long-term follow-up. As such, and in light of the substantial risks of AADs in this population, PVI provides a reliable and appealing alternative.

## 4.3 | Temporal trends

Studies included within this analysis span from 2008[11] through 2017.[10] During this time, a shift in available technology and insight into AF ablation has occurred. As such, advancements during this time period could have baring on procedural results. Moreover, we have seen an evolution of the preferred procedural protocol to include nonfluorscopic 3-dimensional mapping or CB. However, although based on a limited number of patients, there does not appear to be significant differences in outcomes between the first study published in 2008[11] and the last in 2017.[10] Nevertheless, quantitative data must be contextualized to the available technology with which it was derived before clinically relevant conclusions can be drawn regarding variations of success over time.

## 4.4 | Adjunctive effects

Many patients with BS are implanted with ICDs. Programming a single VF zone above 210 to 220 bpm is sometimes suggested.[22]

Inappropriate shocks resulting from atrial tachyarrhythmias remain common, and can be highly problematic for these patients. In fact, more than 40% of the patients included in this study suffered inappropriate shocks for rapid AF. Remarkably, none presented shocks after ablation, irrespective of whether remission had been successfully achieved. As such, AF ablation offers a useful approach to prevent inappropriate shocks.

## 4.5 | Complications

As is demonstrated in our patient population, the rate of major complications secondary to PVI in experienced centers has become minimal. As the BS population is subject to higher than normal complication rates from AADs, and as this population is relatively younger than the average AF population, procedural risks may prove lower than those of medical therapy. An individual assessment of each BS patient's risks from PVI must be undertaken in light of these data, and utilized to guide clinical decision-making.

## 4.6 | Limitations

The present study has several limitations that must be acknowledged. The total number of patients included is relatively small secondary to limited published data on the topic. Studies on AF ablation in BS patients are rare, and the temporal variability in published data makes it difficult to aggregate results reliably. The use of different ablation techniques and mapping systems, as well as variable follow-up and outcome measures further impedes accurate comparison and aggregation of results across studies. No attempt was made to locate and incorporate unpublished data, which introduces the potential for publication bias. These sources are often difficult to identify and acquire when not indexed in databases such as Medline. Lack of indexing is a significant barrier to successfully incorporating unpublished data into the search methodology. For this reason, unpublished data were not included in this review. Importantly, almost the entire patient sample had paroxysmal AF. As such, results cannot reliably be generalized to patients with the nonparoxysmal forms.

## 5 | CONCLUSION

The results of the present study indicate that AF ablation achieves acute and long-term success in the vast majority of patients. Moreover, it is effective in preventing inappropriate ICD therapy secondary to rapid AF. Complication rates of PVI in BS are low. These results suggest that, in light of the risks of AADs and risk of inappropriate ICD shocks in the BS population, catheter ablation could represent an appropriate first-line therapy for PAF in BS patients.

### CONFLICT OF INTEREST

Authors declare no Conflict of Interests for this article.

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