Management of Brugada Syndrome: A 33-Year Experience Using Electrophysiologically-Guided Therapy with Class 1A Antiarrhythmic Drugs

Running title: *Belhassen et al.; EP Guided Drug Management of Brugada Syndrome*

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Abstract:

Background - Information on long-term clinical outcome of patients with Brugada syndrome (BrS) treated with electrophysiologically (EP)-guided class 1A antiarrhythmic drugs (AAD) is limited.

Methods and Results - An aggressive protocol of programmed ventricular stimulation (PVS) was performed in 96 BrS patients (88% males, mean age 39.8 ± 15.9 years). Ten patients were cardiac arrest survivors, 27 had presented with syncope and 59 were asymptomatic. Ventricular fibrillation (VF) was induced in 66 patients, including 100%, 74%, and 61% of patients with cardiac arrest, syncope and no symptoms, respectively. All but 6 of the 66 patients with inducible VF underwent EP testing on quinidine (n=54), disopyramide (n=2) or both (n=4). Fifty four (90%) patients were EP-responders to ≥ 1 AAD with similar efficacy rates ($\approx$90%) in all patients groups. Patients with no inducible VF at baseline were left on no therapy. After a mean follow-up of 113.3 ± 71.5 months 92 patients were alive while 4 died from non cardiac causes. No arrhythmic event occurred during class 1A AAD therapy in any of EP-drug responders and in patients with no baseline inducible VF. Arrhythmic events occurred in only 2 cardiac arrest survivors treated with ICD alone but did not recur on quinidine. All cases of recurrent syncope (n=12) were attributed to a vasovagal (n=10) or non-arrhythmic mechanism (n=2). Class 1A AAD therapy resulted in 38% incidence of side effects that resolved after drug discontinuation.

Conclusions - Our data suggest that EP-guided class 1A AAD treatment has a place in our therapeutic armamentarium for all types of BrS patients.

Implantation of an automatic defibrillator (ICD) has been universally recommended for patients with Brugada syndrome (BrS) who survived a cardiac arrest (class I indication) and is considered useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular tachyarrhythmias (class IIa indication)[1]. In asymptomatic BrS individuals who have inducible sustained ventricular fibrillation (VF) at electrophysiologic study (EPS), ICD implantation is controversial and has a class IIb indication[1].

More than 3 decades ago, we gained experience in the use of class 1A antiarrhythmic drugs (AAD) (mainly quinidine) in patients with idiopathic VF who had spontaneous and inducible sustained VF[2]. We found that these drugs were highly effective in cardiac arrest survivors in preventing the re-induction of VF during EPS and the recurrence of spontaneous VF during long term therapy[3-6]. Following the initial description of the BrS in 1992[7] we realized that some of our patients with idiopathic VF had, in fact, this newly described entity and that their long-term course on quinidine therapy was as good as that of patients with idiopathic VF. Consequently, we extended our experience using EP-guided class 1A AAD therapy in all BrS patients with inducible VF. In the present study, we report our long-term experience in a large cohort of BrS patients with various clinical presentations who underwent EP-guided class 1A AAD therapy.

Methods

Study group

Our study cohort consisted of 96 consecutive patients with BrS who underwent baseline EPS between November 1981 and December 2014. Of these 96 patients, 10 (10.5%) presented with cardiac arrest and 27 (28%) with syncope while 59 (61.5%) were asymptomatic. Three (30%) of the cardiac arrest survivors presented with arrhythmic storm. Also, 3 cardiac arrest patients were

studied before the Brugada et al.'s publication[7] (Fig 1) and were initially reported as suffering

from idiopathic VF.[2] The syncope group included 10 patients with syncope of unknown origin

(SUO) and 17 with presumed vasovagal syncope (VVS). EPS were performed upon presentation

except for one patient who presented to us 12 years after his original cardiac arrest, which was

misdiagnosed as "acute anteroseptal myocardial infarction with normal coronary arteries". Eight

study patients were first-degree family relatives.

All patients had the following characteristics: a) a Brugada-ECG type 1 pattern observed

at patient presentation spontaneously (n=33, 34%) or after administration of a sodium channel

blocker drug (n=63, 66%) [flecainide (2 mg/kg/6min, n=52), ajmaline (1mg/kg/5min, n=8),

procainamide (1000mg/10min, n=1) or oral propafenone therapy (450mg/day, n=2)]; b) no

apparent heart disease as attested by normal echocardiogram as well as normal coronary

angiography in cardiac arrest survivors; c) a minimal follow-up of 3 months following initiation

of therapy. The results dealing with our first 38 BrS patients[4] as well as the cases of 2 cardiac

arrest patients[9, 10] were previously reported.

The study was approved by an institutional review committee and the patients gave

informed consent

EPS at baseline and on class 1A AAD

All patients underwent baseline EPS with programmed ventricular stimulation (PVS). Patients

with inducible sustained VF were invited to undergo a second EPS after receiving several days

of therapy with quinidine (or disopyramide in case of quinidine intolerance). Over the years, two

different formulations of quinidine were used: initially, patients received quinidine bisulfate

(QBS) (Quiniduran®, Teva, Israel). In April 2008, QBS became unavailable in our country and

was replaced with hydroquinidine chlorhydrate (HQC, Serecor®, Sanofi-Aventis, France). The

usual initial daily doses tested at EPS were 1500mg for QBS, 900mg for HQC and 600mg for disopyramide. In 1 patient, the QBS dose tested was 2000mg/day because of low quinidine serum level on 1500mg while in another patient it was decreased to 750 mg because of diarrhea on the 1500mg dose. Three patients who had no VF induced on 1250-1500mg QBS agreed to undergo a third EPS on lower drug dose (1000mg).

EP-drug testing was performed after 3 to 7 days of in-hospital treatment in cardiac arrest survivors. In the other patients it was scheduled after 2-4 weeks of out-of-hospital treatment to ensure good clinical tolerance of the medication before the second EPS.

EP drug testing was usually performed between 2 uptakes of the medication.

During long-term quinidine therapy 9 drug EP-responders consented to undergo 1 (n=8) or 2 (n=1) additional EPS for the following reasons: a) to confirm the long-term efficacy of the same dose (n=4) or that of a lower dose (n=1) of medication; b) to attest that replacement of QBS with HQC did not affect drug response (n=2); c) to assess the mechanism of syncope that occurred during quinidine therapy (n=3). Serum blood levels of quinidine were determined at each EP study.

PVS protocol

In the first study patient our protocol included only the right ventricular apex (RVA), a maximum of 2 extrastimuli and 2 basic cycle lengths (BCL) (Protocol 1). In 1983, we added pacing from the RV outflow tract (RVOT) (Protocol 2; 2 patients). From 1988 the protocol included up to 3 extrastimuli delivered from the RVA and the RVOT (Protocols 3A and 3B). The entire double or triple extrastimulation protocol at the RVA was always performed before moving to the RVOT. A stimulus current of 5 diastolic threshold (DT) (but never >3mA) was initially used (Protocols 1, 2 and 3A) while 2-DT stimulus current was used during the last 7

years (Protocol 3B). From the beginning, our protocol included the repetition (n=10) of double extrastimulation at the shortest coupling intervals that resulted in ventricular capture[11] while in 1988 we added the repetition (n=5) of triple extrastimulation at the shortest coupling intervals (Protocols 3A and 3B).

Definitions

VF is a polymorphic ventricular tachyarrhythmia (cycle length <200 ms) that required cardioversion for termination or resulted in clinical cardiac arrest before spontaneous termination. A patient was considered inducible if VF was induced. Spontaneous arrhythmic event (AE) was defined as sudden death, an episode of documented VF requiring resuscitation or an appropriate ICD shock for VF.

Follow-up

Patients were discharged with the medication regimen that prevented induction of VF and were followed as out-patients every 6 to 12 months. Holter monitoring was yearly performed. Special attention was given to gastrointestinal disorders, platelet count number, liver function tests, serum potassium levels, and QTc values. Quinidine serum levels were checked every 6 months, and the drug dose was modified if necessary to achieve serum levels similar to those found during the last EPS. Patients with inducible VF who did not respond to drugs or were drug intolerant were advised to undergo ICD implantation. In addition, the potential risks and benefits of drug discontinuation with ICD implantation were discussed with each patient at least once yearly**.**

Patient compliance with medications was estimated during each follow-up visit and defined as excellent, moderate or poor as detailed elsewhere[3].

Patients with ICD were followed up at 3-6 months intervals. At each visit, they were

questioned about the presence of syncope or device discharges and their ICD interrogated. Patients with no inducible VF were followed on no therapy on yearly basis. In patients in whom different modes of management were applied during follow-up, all therapy periods were accounted separately. All alive patients were also contacted by telephone in November and December 2014. No patients were lost to follow-up.

Results

Patient clinical characteristics (Table 1)

Our population study included 96 patients [88.5% males, mean age 39.8 ± 15.9 (19-80) years] who underwent a total of 184 EPS. The first 7 patients studied were from the cardiac arrest group while syncopal and asymptomatic patients were studied beginning in April 1999. Both age and gender were similar in all 3 patient groups. A spontaneous Brugada-ECG type 1 was observed in 50%, 26% and 36% in patients presenting with cardiac arrest, syncope or no symptoms, respectively. The proportion of patients with a familial history of BrS or sudden death at age ≤ 60 years was similar in all 3 patient groups (26-31%).

Baseline EPS (Table 2)

Baseline EPS were performed in the absence of antiarrhythmic medications in all but 2 patients, who were receiving amiodarone after their index spontaneous VF. Protocol 3A (n=65) and Protocol 3B (n=31) were the most used. VF was induced in 66 (68.8%) of the 96 study patients (100%, 74%, and 61% in the cardiac arrest, syncope and asymptomatic groups, respectively). (Fig. 2) The inducibility rates were not significantly affected by the PVS protocol used (3A vs. 3B). They were higher in the cardiac arrest group (100%) than in the non cardiac arrest group (65%). The inducibility rate was higher in men than in women (76.5% vs. 9.1%) and in presence (88%) vs. absence (59%) of spontaneous Brugada ECG type 1.

VF induction was achieved with 1, 2 or 3 ventricular extrastimuli in 3, 38 and 25 patients, respectively. Induction of VF with <2 extrastimuli was achieved in 60%, 50% and 69.5% of patients presenting with cardiac arrest, syncope or no symptoms, respectively. In the 3 patient groups, VF was induced during repetition of double or triple extrastimulation in 30%, 45% and 50% of patients, respectively. The RVA was the site of VF induction in 90%, 45% and 50% in the 3 patient groups, respectively. In patients with inducible VF the mean coupling intervals of extrastimuli S3 and S4 that induced VF were usually < 200ms.

Initial EPS on class 1A AAD

Six patients with inducible VF at baseline did not undergo EP drug testing on class 1A AAD due to patients' refusal (n=3), severe conduction disturbances (n=2) or clinical intolerance to QBS (n=1). The remaining 60 patients underwent drug testing on quinidine (n=54) [QBS (n=41), HCQ (n=13)], disopyramide (n=2), or both medications (n=4). Overall 54 (90%) of the 60 patients were EP-responders to at least 1 AAD. These 54 patients included a similar proportion of patients with spontaneous Brugada ECG type 1 (48.5%) than of patients with drug induced Brugada ECG type 1 (52.3%).

Quinidine prevented re-induction of sustained VF in 52 (89.6%) of the 58 patients tested (Fig. 2). The efficacy rates were similar regardless of symptoms at presentation. QBS at a mean dose of 1406±242mg was effective in 40 (89%) of 45 patients while HQC at a mean dose of 900mg was effective in 12 (92.3%) of 13 patients. The mean effective quinidine serum levels were 2.49 + 0.8 mg/l (1.29-5.2) and 1.18 ± 0.44 mg/l (0.8-1.9) for QBS and HCQ, respectively.

In 2 of 3 patients who responded to 1250-1500mg QBS a lower dose (1000mg) was similarly effective in preventing VF induction.

Disopyramide at a mean dose of 500 ± 71mg (300-600) prevented VF induction in 3

(50%) of the 6 patients tested, including 2 patients who did not undergo testing on QBS (due to intolerance) and 1 quinidine-responder who developed drug intolerance. Two of the 3 disopyramide non responders did respond to QBS.

During class 1A AAD therapy in patients not receiving amiodarone, QTc intervals significantly increased by a mean of 9.9 % from 405 ± 30 to 445 ± 36ms (P=0.0001 using paired t test). In the 2 patients under amiodarone, QTc increased from 470 to 560ms and from 460 to 560ms after the addition of quinidine.

Late EP testing on class 1A AAD

Of the 9 patients who underwent repeat EPS on quinidine 1 to 17 (mean 6.8±4.4) years after the initial EPS for reasons listed above, non inducibility of VF was confirmed in 8 patients despite the use of more aggressive PVS protocols at repeat EPS in 2 patients (Figs 3,4). VF was inducible in 1 patient studied on a lower dose of QBS. In 1 patient who developed late (7 years) intolerance to HCQ, repeat EPS on disopyramide showed inducible VF.

Drug tolerance

Quinidine therapy was initially given to 61 patients and resulted in side effects in 23 (38%) patients. During follow-up no patient treated with either quinidine or disopyramide developed any arrhythmia associated with QT prolongation.

Side effects occurred within a few days in 4 patients, within 4 months in 14 patients, and after 1 to 10 years of treatment in 5. In all patients but 4 this resulted in drug discontinuation. Quinidine-related side effects included ≥1 of the following: diarrhea (n=11), thrombocytopenia (n=4), fever (n=2), allergic reaction (n=1), esophagitis (n=1), sinus node dysfunction (n=1), lupus erythematosus-like syndrome (n=1), hepatitis (n=1), hyperpigmentation (n=1) and marked weakness (n=1). In all patients side effects resolved without sequelae upon discontinuation of the

medication. One patient continued suffering diarrhea on 750mg QBS and was given oral cholestyramine (4g BID). This medication suppressed diarrhea without impairing the EP response to the drug.

Treatment with disopyramide was well tolerated in 4 of 6 patients. Of the remaining 2 patients, one agreed to renew QBS (+ cholestyramine).

Drug compliance

Of the 57 patients initially assigned to AAD, only 34 (60%) patients were actually receiving these medications at the completion of follow-up mainly due to drug-induced side effects. At last follow-up, 6 of 9 (67%) cardiac arrest survivors, 8 of 18 (44%) of the patients with syncope and 20 of 30 (67%) of the asymptomatic patients were still treated with class 1A AAD (with or without ICD). However, among the patients still treated an excellent compliance to medications was observed in 89%, 75% and 83% patients presenting with cardiac arrest, syncope or no symptoms, respectively.

ICD therapy

An ICD was implanted in 20 study patients (i.e in 30% of patients with inducible VF): shortly after the initial EP work-up in 8 patients and at a later stage in the remaining 12. Indications for ICD implantation were: 1) intolerance to AAD (n=9) associated with good EP response to medication (n=8); 2) patient's preference despite good EP response to drug (n=4); 3) failure of class 1A AAD to prevent VF induction (n=3); 4) severe cardiac conduction disorders (n=2); 5) failure of disopyramide at EPS after late intolerance to quinidine (n=1); 6) intolerance to AAD precluding EP drug testing (n=1); 7) patient's refusal to undergo EP drug testing (n=1).

Complications (1-3/patient) related to ICD implantation occurred in 11 (55%) patients: inappropriate shocks (n=5) which resulted in severe psychological disturbances in 1 patient,

infections (n=2) requiring device extraction in both patients, lead thrombosis (n=2), lead fracture (n=2), iatrogenic pneumothorax during surgical revision because of oversensing of electrical noise (n=1) and severe brachial plexus injury (n=1). In the latter patient, the brachial plexus injury resolved after months of physiotherapy and the device was removed years thereafter due to patient preference. ICD was not reimplanted in the 3 patients in whom it was removed. In 1 cardiac arrest survivor, the device was not replaced when it reached end-of-life.

Long-term follow-up

Mode of management

Table 1 shows the treatment initiated after the initial EP work-up and the one received at completion of follow-up (up to death in 4 patients) in the study patients who had inducible VF at baseline EPS. The 30 patients with no inducible arrhythmias at baseline EPS were followed on no AAD and none received an ICD.

Follow-up duration

Mean follow-up duration was longer in the cardiac arrest group (219.6±123.2 months) than in the syncope group (112.7±45 months) or the asymptomatic group (97.8±50.5 months). The follow-up duration in non inducible patients and in all subgroups of inducible patients according of their treatment is presented in Table 1.

Medical events

After a mean follow-up of 113.3 ± 71.5 months all but 4 of the study patients were alive. Four patients died from non cardiac causes 1 to 10 years after initial work-up. Of the remaining alive patients, only 1 developed significant heart disease during follow-up. This patient who survived cardiac arrest in 1981 had no significant coronary artery disease at that time but required coronary bypass surgery 18 years later due to severe 3-vessel disease. Of note, our cardiac arrest

survivor of female gender had 2 uneventful pregnancies and normal childbirth during 17 years of quinidine therapy.[4]

Arrhythmic events

Of the 96 study patients, only 2 had documented AE during follow-up. These 2 patients initially presented with cardiac arrest and arrhythmic storm[9,10] and were advised to continue QBS that was effective at EPS in one of them. In both patients arrhythmic storms recurred 30 and 67 months after they discontinued quinidine. The arrhythmias were successfully managed by their ICD although the clinical outcome in one patient was near fatal because of shock-refractory VF.[10] Renewal of quinidine in both cases prevented recurrence of AE during the following 18 years and 13 months, respectively.

Four (40%) of our cardiac arrest survivors (all with inducible VF) did not exhibit recurrent AE during long term follow-up ranging from 7 to 20 years while on no AAD:

- Our first study patient (11/1981) had inducible VF and received EP-guided QBS therapy regularly for 5 years (Figs 1,2); he then decided to discontinue the medication and remained well for the next 6 years. At this point he underwent repeat EPS that showed persistent off-drug inducible VF that was prevented by quinidine therapy (Figs 3,4). The patient renewed QBS but developed thrombocytopenia after 3 years of treatment. For the last 20 years, he has remained arrhythmia-free on no medications and repeatedly refused ICD implantation.

- Our cardiac arrest survivor of female gender was 24 years old at the time of her cardiac arrest. She was uneventfully treated for 17 years (1985-2002) with EP-guided QBS before she decided to get an ICD; no AE has occurred during the following 13 years on no AAD.

- One patient was uneventfully treated with QBS alone for 22 years (1986-2008) when he was recommended by his doctor to discontinue the medication; no AE has occurred during the

subsequent 7 years.

- One patient had cardiac arrest 10 years before EPS showed inducible VF; he has remained

arrhythmia free on ICD without medication for the subsequent 7 years, enjoying an

arrhythmia free period of 17 years after his index cardiac arrest.

Syncopal events

Syncope occurred during follow-up in 12 patients from all groups: cardiac arrest (n=2), SUO

(n=2), SVV (n=5), asymptomatic (n=3). Nine of these 12 patients had inducible VF at baseline

EPS. One cardiac arrest survivor with arrhythmic storms (7/1994) in whom the EP-quinidine

response was confirmed after 5 years, remained asymptomatic for 8 years on 1500mg QBS.

Then he had SUO that prompted a third EPS on QBS. Although only nonsustained polymorphic

ventricular tachycardia (4 sec) could be induced, an ICD was implanted and QBS continued.

Three months and 9 months later, the patient had recurrent syncope without arrhythmia

documentation at ICD interrogation in both instances. After comprehensive discussion with the

patient, it was decided to continue quinidine only and not to replace the ICD upon battery

depletion; no further syncope occurred during follow-up in this patient. In 10 of the remaining 11

patients with recurrent syncope (on quinidine, n=6; on ICD + quinidine, n=2; and on no therapy,

n=3) the clinical story strongly suggested VVS; in 1 patient wearing an implantable ECG

recorder the loss of consciousness episodes was clearly attributed to epilepsy.

Patients with no baseline inducible arrhythmias

All these patients remained asymptomatic during follow-up.

Discussion

Quinidine has been extraordinarily effective in the treatment of VF storms in BrS patients[12], even

at low doses.[13, 14]. In small patient series, the drug also has shown an apparent excellent long-

term efficacy when given to inducible BrS patients who were drug-responders at EP testing.[4, 15]

The experience with disopyramide, another class 1A AAD, is much more limited but its efficacy

seems to be acceptable[16-18]. The present study represents the largest single center experience in

the management of BrS using EP-guided class 1A AAD.

Baseline VF inducibility

In our study the inducibility rates of VF were 100%, 74% and 61% for patients who presented

with cardiac arrest, syncope and the asymptomatic ones, respectively. These figures are higher

than those reported in a meta-analysis (72%, 59% and 40%)[19] or from those recently reported by

Sieira et al. (23.5%, 32.5%, 11.7%)[20] in similar patient cohorts. In the PRELUDE registry of

patients without previous cardiac arrest, VF inducibility rate was 41%.[21]

The higher VF inducibility rate in our study mainly resulted from the aggressiveness of our EPS

protocol that is probably the most aggressive ever used in the EP assessment of BrS patients.

The rationale behind the use of this aggressive protocol was two-fold: a) to maximize the

negative predictive value of EPS; b) to assess the effects of class 1A AAD in a great number of

inducible patients, especially in cardiac arrest survivors for whom we have been looking for an

alternative option to ICD therapy.

Our protocol used: a) high stimulus strength (up to 5 DT) in 71% of our patients; b) no

minimal coupling intervals for extrastimuli; c) use of repetition of double and triple

extrastimulation at the shortest coupling intervals. All these techniques are well known to

increase VF inducibility rate and actually achieved excellent protocol sensitivity (100%) in our

cardiac arrest patients. In contrast, much less aggressive PVS protocols were used in most studies

included in Fauchier et al.'s meta-analysis[19] and in the PRELUDE registry[21] while Sieira et al.[20]

used the least aggressive protocol (single RVA site, limitation of coupling intervals to >200ms,

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no repetition).

Effects of class 1A AAD on VF inducibility at EPS

In our study, class IA AAD therapy was highly and similarly effective in preventing VF induction in all 3 patient groups (≈90% efficacy). We previously found similar success rate in patients with idiopathic VF[3] suggesting that these medications are effective in patients with inducible VF and no obvious heart disease, irrespectively of the pathophysiologic mechanism of the arrhythmia. In a two-center French study[22] involving 44 *asymptomatic* BrS patients with inducible VF who were treated with HQC, the latter was found to effectively prevent VF inducibility in 34 (77.3%) of the patients. In our study, 10 (91%) of 11 asymptomatic patients tested on HQC responded to the medication using a PVS protocol much more aggressive than the one used by Bouzeman et al.[22]. The higher success rate achieved in our patients is probably due to the higher dose of HQC used: in the French study the patients received a fixed dose of 600 mg HCH while we used a dose of 900mg in 9 patients and a dose of 600mg in 2 (including the only 1 non EP responder to HQC).

In our study an excellent long-term reproducibility of EP-guided quinidine therapy[5] was found in 8 of 9 patients while the lack of reproducibility in the remaining patient was attributed to the lower drug dose tested at the repeated study. Such results have a great importance for the long term medical management of BrS patients but require close follow-up in order to detect any change in cardiac status or other abnormalities (such as electrolyte disturbances) that could affect the long-term safety of drug therapy.

Outcome in patients with no inducible arrhythmias

In Fauchier et al.'s meta-analysis of patients with syncope and asymptomatic patients who had no inducible VF[19], an AE occurred during mean follow-up ranging from 20 to 44 months in 4.3%

and 1.1% of patients, respectively. Sieira et al.[20] reported rates of 5.2% and 0.8% in the same

patient population during mean follow-up of 74.3±57.3 months. In PRELUDE[21] an AE occurred

in 4.9% of BrS patients with no history of CA and no inducible VF during a median follow-up of

34 months. Our results in 30 non-cardiac arrest patients who had no inducible arrhythmias at

baseline EPS and were followed without therapy favorably compare with these results by

showing a nil event rate of AE during much longer mean follow-up (129.9±27 months and

86.8±52 months in the syncope and the asymptomatic groups, respectively). This attests of the

high negative predictive value of our PVS protocol likely related to its aggressiveness. However,

our results should be interpreted with caution since they dealt with a relatively small number of

patients having a relatively low arrhythmic risk. In addition, we are aware that BrS is a disease

that may aggravate over the time thus requiring long periods of follow-up before the good long

term prognosis of patients with negative EPS could be ascertained. Therefore we are advising

our patients with no inducible arrhythmias to undergo repeat EPS every 5-10 years.

Arrhythmic events

BrS patients with a history of cardiac arrest are at the highest risk for recurrent AE in the absence

of drug therapy. In their meta-analysis Fauchier et al.[19] reported a 13.5% annual rate of AE or

sudden death in these patients. In the FINGER study[23], an AE occurred at a yearly rate of 7.7%

during follow-up periods of 26 to 68 (mean 44) months. Sacher et al.[24] reported a 48% rate of

appropriate therapy 10 years after ICD implantation in CA survivors. Sieira et al.[20] found that a

history of CA had a hazard ratio of 15.45 (95% CI 5.20 – 45.98, p<0.01) for AE during follow-

up up to 20 years.

In contrast, none of our 10 CA survivors treated with quinidine (9 EP-quinidine

responders and 1 non EP-quinidine responder) experienced an AE during long follow-up periods

(mean 146.4±90.9 months). This included our 3 patients who presented with arrhythmic storms and did not exhibit recurrent AE on quinidine during up to 21.5 years follow-up. These results suggest that quinidine therapy played an important role of in the lack of AE during long-term follow-up in these patients. Furthermore, since 12% of BrS patients presenting with cardiac arrest are prone to develop arrhythmic storm[12] quinidine therapy ought to be discussed in those patients undergoing ICD implantation.

In their meta-analysis of BrS patients with inducible VF who presented with syncope or were asymptomatic Fauchier et al.[19] found that an AE occurred during follow-up in respectively 13.4% and 5.9% of these patients. In PRELUDE[21] a 3.9% incidence of AE was reported in BrS patients without previous cardiac arrest who had inducible VF. Sieira et al.[20] found that an AE occurred in 9.4% of their inducible asymptomatic BrS patients at 1 year and in 21.5% at 5, 10 and 15 years. In contrast we found a nil incidence of AE during long periods of follow-up in our 28 patients without previous cardiac arrest who had inducible VF and were treated with class 1A AAD found effective at EPS. However, comparison of our results with those previously reported should be made with caution since some studies (such PRELUDE[21]) reported a higher proportion of patients with spontaneous type 1-Brugada ECG (56% vs. 32.5% in our study) that is known to be a powerful predictor of AE[21,23].

Syncope

BrS patients presenting with syncope constitute an important diagnostic and therapeutic challenge for several reasons: a) some cases of syncope may actually be related to VF that terminates spontaneously, thus increasing the risk of sudden death in these patients; b) vagal syncope is the most frequent cause of syncope in the general population[25] and probably also in the BrS population.[26]; c) vagal hypertony may facilitate the onset of spontaneous VF in some

BrS patients[27]; d) clinical symptoms suggesting of vagal syncope may also be observed in syncope of cardiac origin[28]. Despite the latter limitation and the relative small number of our patients presenting with syncope, we attempted to clinically classify syncope as SUO or VVS. It was interesting to note, albeit the differences were not statistically significant, that VF inducibility rate was the highest in those patients with syncope of unknown origin (80%), the lowest in asymptomatic patients (61.5%) and intermediate in patients with vasovagal syncope (70.5%). Such findings might suggest a slightly different arrhythmic risk in these 3 groups of patients. More importantly and in agreement with others[29] we found that the mechanism of syncope in our 12 patients who exhibited recurrent syncope was likely vasovagal or non arrhythmic.

Drug tolerance and compliance

The incidence of drug related side effects was similar to that observed in our previous study[4] and played a deleterious role on patient management especially when the medication had to be discontinued after several months or years of treatment. In such cases, we have found it difficult to convince the patients to proceed with ICD therapy so that a non negligible number of patients have finally opted for no therapy at all. However, compliance to medications was satisfactory in patients who well tolerated drug therapy and might even be improved by increasing the frequency of the patients' visits at our consultation.

Comparison with ICD therapy

The initial objective of our study was not to compare the efficacy and complications of EP-guided AAD therapy vs. ICD, already discussed elsewhere[30], which should deserve a randomized study. However, we observed two interesting findings: a) the incidence and the severity of ICD related complications were higher than those related to drug therapy and are

expected to increase over the time due to multiple ICD replacements needed during patient's life, especially in the younger; b) our management policy using EP-guided class 1A AAD therapy enabled us to implant ICD in only 20 (21%) of our study patients, that is lower than the implantation rate in other studies involving similar patient populations.

Study limitations

Assessing the EP efficacy of AAD therapy after a few days of treatment in our patients is reasonable, however establishing its long-term clinical efficacy is a more difficult task due to: a) the small number of control patients with inducible VF initially assigned to no drug therapy; b) the low incidence rate of AE rate in these patients including 40% of our cardiac arrest survivors who have remained arrhythmia-free during very long follow-up periods; c) the fact that a substantial number of patients have discontinued their medications during the course of the study mainly due to drug-related side effects. Therefore we have been careful in ascribing the long-term beneficial results observed with class 1A AAD as an *"excellent clinical outcome in drug-treated patients"* rather than as an excellent long term efficacy of the medications used.

Conclusions

The results of our single center study in a large cohort of BrS patients with various clinical presentations and who have inducible VF using an aggressive PVS protocol show an excellent protective effect of class 1 AAD (mainly quinidine) during EP testing and an excellent clinical outcome in drug-treated patients. This result was achieved despite the fact that a substantial number of inducible patients were found to be on no treatment at the completion of follow-up. We believe that EP specialists should discuss the EP-class 1A AAD guided option with their patients before choosing ICD providing: a) the patients are committed to a life-long drug therapy and b) they exhibit a good tolerance to the medication. Patients who refuse the ICD option

(including cardiac arrest survivors) may be good candidates for such type of management.

Finally, patients with non inducible VF may be confident about the AE risk although longer

follow-up is necessary before we can be conclusive on this point.

Conflict of Interest Disclosure: None.

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Table 1: Main study results

Patient presentation	Aborted CA (n=10)	Syncope (n=27)			Asymptomatic (n=59)
		All (n=27)	SUO (n=10)	VVS (n=17)	
Male sex	9 (90%)	25 (93%)	10 (100%)	15 (88%)	51 (86%)
Age, mean±SD (years)	21-57 (34±13)	19-80 (42±16)	19-80 (45±22)	23-61 (38±10)	18-79 (40±14)
ECG BrS type 1					
- spontaneous	5 (50%)	7 (26%)	2 (20%)	5 (29%)	21 (36%)
- during pharmacologic testing	5 (50%)	20 (74%)	8 (80%)	12 (71%)	38 (64%)
Familial history of BrS/SCD	3 (30%)	7 (26%)	3 (30%)	4 (24%)	18 (31%)
Inducible VF at EPS	10 (100%)	20 (74%)	8 (80%)	12 (70.5%)	36 (61%)
EP-guided class 1A AAD	10 (100%)	19 (95%)	8 (100%)	11 (92%)	31 (86%)
- responders	9 (90%)	17 (89.5)	8 (100%)	9 (82%)	28 (90%)
- non-responders	1 (10%)	2 (10.5%)	0	2 (18%)	3 (10%)
Initial treatment assigned in inducible patients (n=66)					
- only class 1A AAD	8	18	8	10	30
- only ICD	1	1	0	1	5
- both class 1A AAD + ICD	1	0	0	0	0
- no treatment	0	1	0	1	1
Treatment at last follow-up (n=62) or at death (n=4) in inducible patients*					
- only class 1A AAD	2	8	4	4	19
- only ICD	2	3	1	2	6
- class 1A AAD + ICD	4	0	0	0	1
- no treatment	2	9	3	6	10
Mean follow-up duration (months) in inducible patients (n=66)					
- of all patients	219.6±123.2	112.7±45	117.4±44.4	109.6±45.2	97.8±50.5
- on class 1A AAD (with or without ICD)	146.4±90.9	60.3±69.2	78.4±70.9	47.2±64.8	65.6±52.5
- on ICD only	88.8±34.4	64.8±37.1	95±0	54.7±37.7	90.1±56
- on no treatment	188.5±116.5	92.8±28.4	72.3±34.6	103.1±17.2	92.1±36
Mean follow-up duration (months) in non inducible patients	-	129.9±27	142±5	125±30.5	86.8±52

AAD = antiarrhythmic drug; BrS = Brugada syndrome; CA = cardiac arrest; EPS = electrophysiologic study; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; SUO = syncope of unknown origin; VF = ventricular fibrillation; VVS= vasovagal syncope.

*ICD was not accounted if the device has been extracted or reached end-of life (n=4)

Table 2: Results of baseline programmed ventricular stimulation in the study patients

Patient presentation	Aborted CA (n=10)	Syncope (n=27)			Asymptomatic (n=59)
		All	**SUO (n=10)**	**VVS (n=17)**	
Induction of VF	10	20	8	12	36
INDUCIBLE GROUP (n=66)					
PVS protocol					
#1	1				
#2	2				
#3A/ #3B	5/2	16/4	7/1	9/3	23/13
Number extrastimuli at VF induction					
1 ES	1	0	0	0	2
2 ES	5	10	4	6	23
3 ES	4	10	4	6	11
Site of VF induction					
RVA	9	13	7	6	22
RVOT	1	7	1	6	14
VF induction with repetition	3	9	4	5	18
Mean S2/S3/S4 CI at VF induction (CL 600)	248/210/190		218/183/175	229/196/194	230/193/196
Mean S2/S3/S4 CI at VF induction (CL 400)	220/173/170			210/175/180	213/177/180
NON-INDUCIBLE GROUP (n=30)					
PVS protocol					
#1	0	0	0	0	0
#2	0	0	0	0	0
#3A/#3B	0	7/0	2/0	5/0	14/9
Mean shortest S2/S3/S4 CI at CL 400ms from RVOT			NA	210/175/175	218/189/190

CL= basic cycle length; CI = coupling intervals; PVS = programmed ventricular stimulation; RVA = right ventricular apex; RVOT=right ventricular outflow tract; other abbreviations as in Table 1.
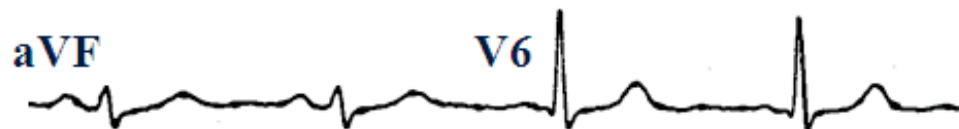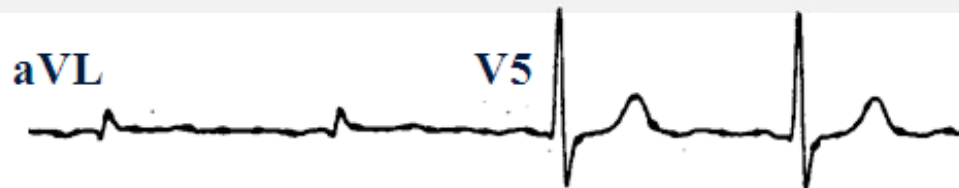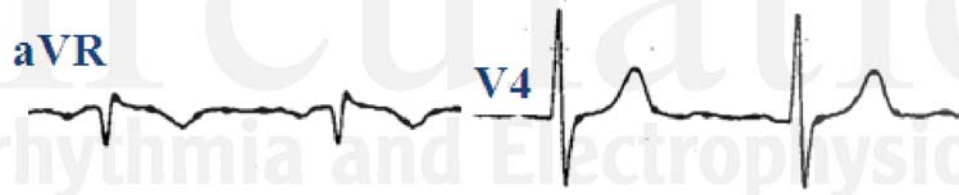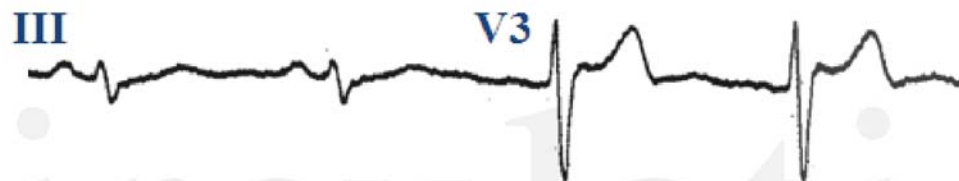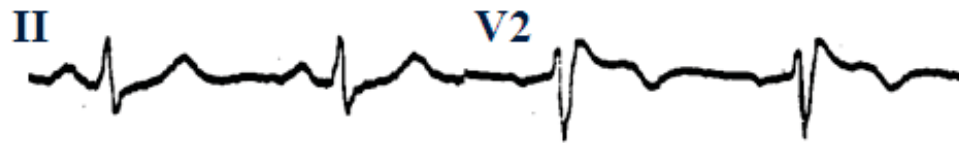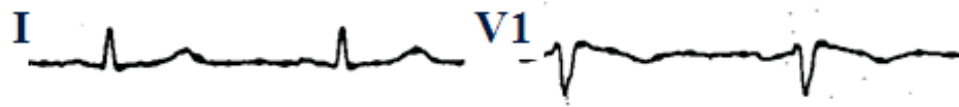
Figure Legends:

Figure 1: Twelve lead ECG of a 52-year-old man after cardiac arrest showing typical type 1 Brugada pattern[8] (on no antiarrhythmic medication). (*with permission from Ref#3).*
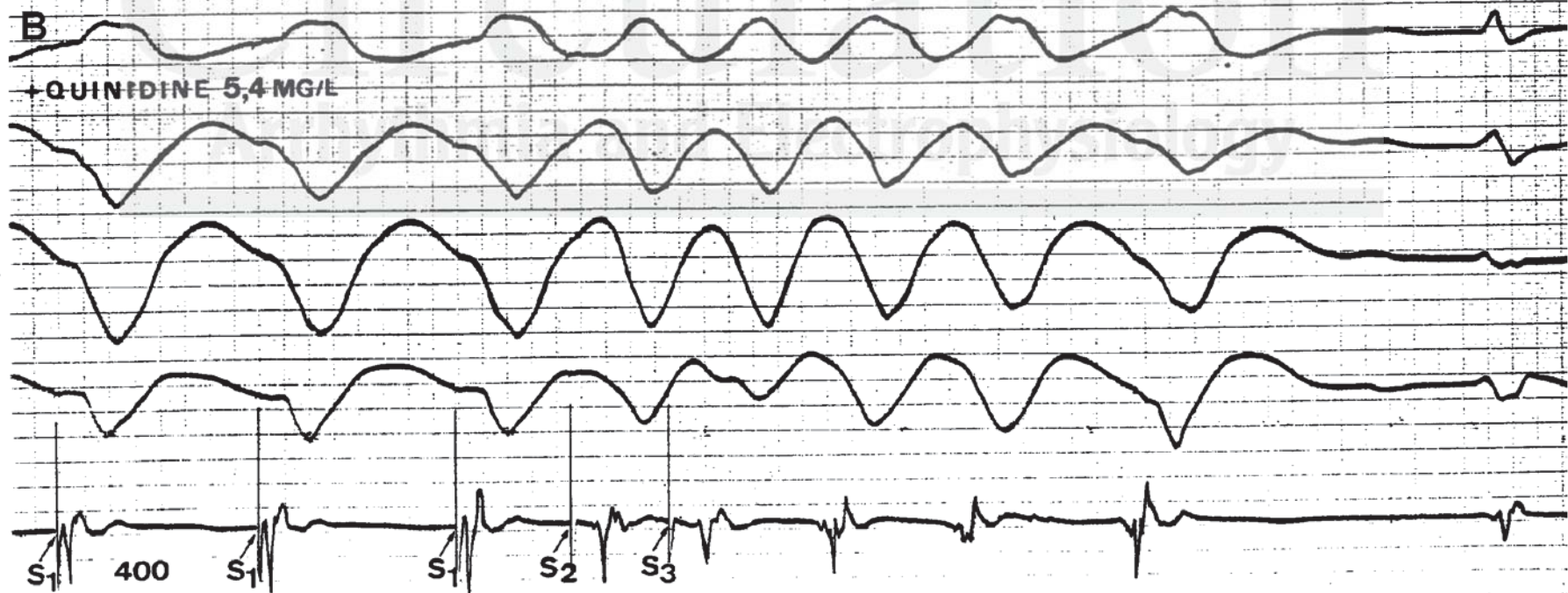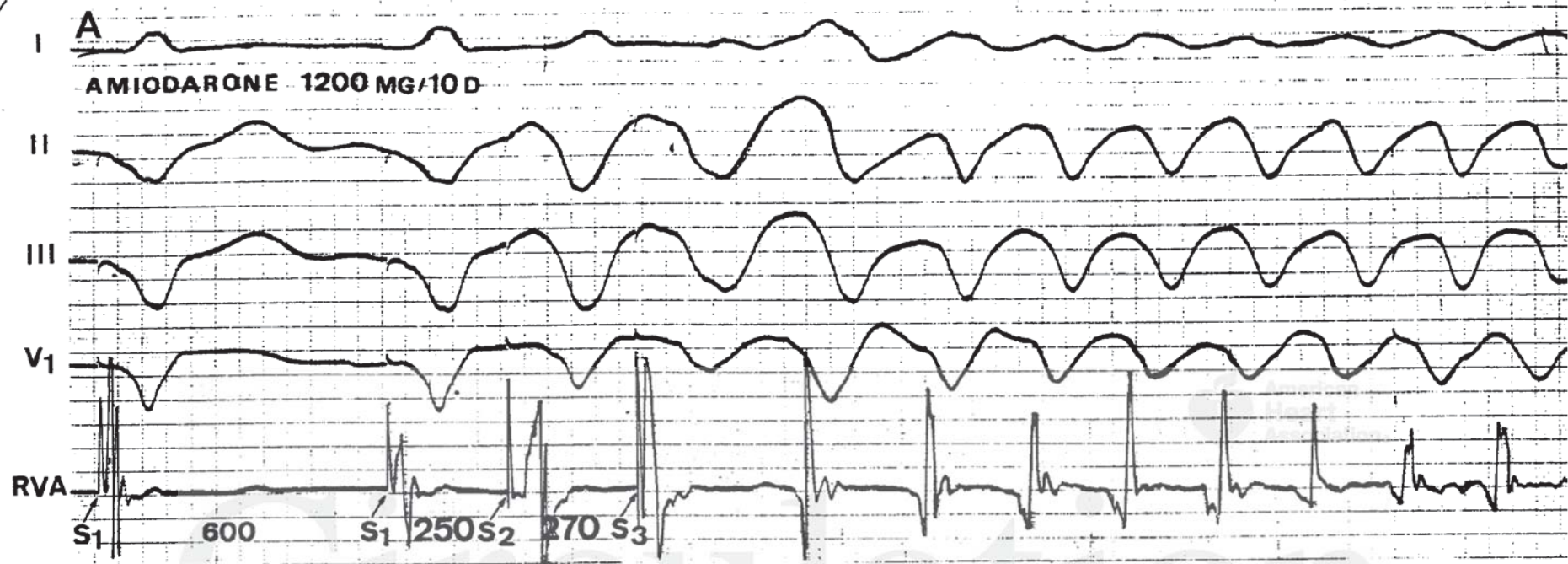
Figure 2: Data from the initial EPS (November 18, 1981) performed after 10 days of amiodarone therapy (1200mg daily). (A) During baseline VF was induced at an "immediate trial" of double extrastimulation delivered from the right ventricular apex (RVA); (B) After addition of quinidine, only a few repetitive ventricular complexes were Induced using a protocol that included up to two extrastimuli and repetition (n = 10) of double RVA extrastimulation. (*with permission from Ref#3).*

Figure 3: Data from the EPS performed 11 years later (July 7, 1992) while on no antiarrhythmic medication. (A) Single ventricular complexes were induced during repetition (n = 5) of double RVA extrastimulation at the same coupling intervals (600/250/200).
(B) VF was induced at the 6th trial of double extrastimulation using the same coupling interval. (*with permission from Ref#3).*
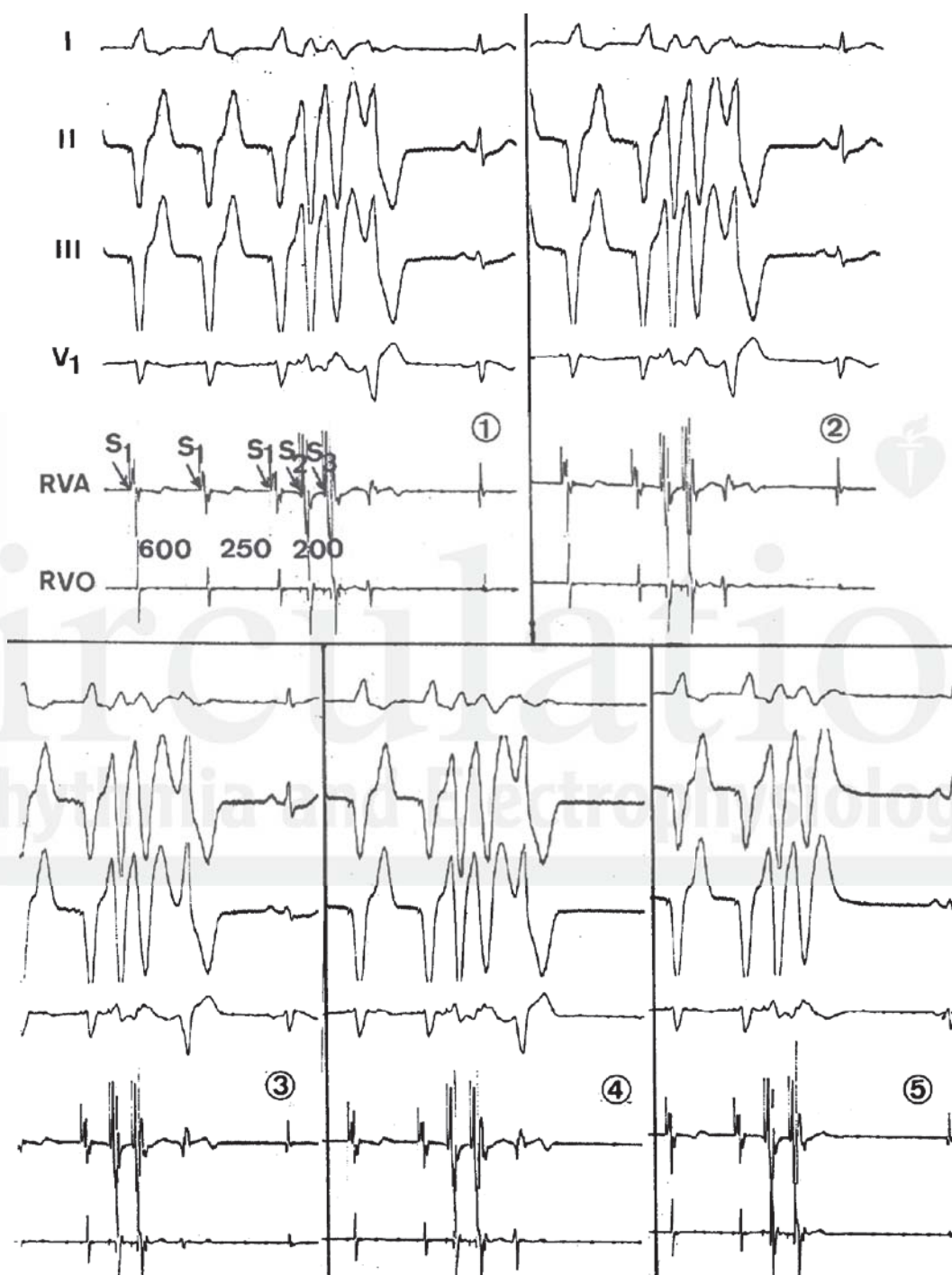
Figure 4: A few days after administration of quinidine (1500 mg/day), VF could no longer be induced using repetition (n=10) of double extrastimulation and repetition (n=5) of triple extrastimulation at the shortest coupling intervals delivered from the RVA and the RV outflow tract. Note a persistent Brugada sign in lead V1. (*with permission from Ref#3)*

A

I

AMIODARONE 1200 MG/10 D

II

III

V1

RVA

S1   600   S1 250 S2 270 S3

B

+QUINIDINE 5,4 MG/L

S1   400   S1   S1   S2   S3

B