Outcome after Implantation of Cardioverter Defibrillator in Patients with Brugada Syndrome: a Multicenter Israeli Study (ISRABRU)

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Abstract

Background: Many electrophysiologists recommend implantable cardioverter defibrillators for patients with Brugada syndrome who are cardiac arrest survivors or presumed at high risk of sudden death (patients with syncope or a familial history of sudden death or those with inducible ventricular fibrillation at electrophysiologic study).

Objectives: To assess the efficacy and complications of ICD therapy in patients with Brugada syndrome.

Methods: The indications, efficacy and complications of ICD therapy in all patients with Brugada syndrome who underwent ICD implantation in 12 Israeli centers between 1994 and 2007 were analyzed.

Results: There were 59 patients (53 males, 89.8%) with a mean age of 44.1 years. At diagnosis 42 patients (71.2%) were symptomatic while 17 (28.8%) were asymptomatic. The indications for ICD implantation were: a history of cardiac arrest (n=11, 18.6%), syncope (n=31, 52.5%), inducible VF in asymptomatic patients (n=14, 23.7%), and a family history of sudden death (n=3, 0.5%). The overall inducibility rates of VF were 89.2% and 93.3% among the symptomatic and asymptomatic patients, respectively (P = NS). During a follow-up of 4–160 (45 ± 35) months, all patients (except one who died from cancer) are alive. Five patients (8.4%), all with a history of cardiac arrest, had appropriate ICD discharge. Conversely, none of the patients without prior cardiac arrest had appropriate device therapy during a 39 ± 30 month follow-up. Complications were encountered in 19 patients (32%). Inappropriate shocks occurred in 16 (27.1%) due to lead failure/dislodgment (n=5), T wave oversensing (n=2), device failure (n=1), sinus tachycardia (n=4), and supraventricular tachycardia (n=4). One patient suffered a pneumothorax and another a brachial plexus injury during the implant procedure. One patient suffered a late (2 months) perforation of the right ventricle by the implanted lead. Eleven patients (18.6%) required a reintervention either for infection (n=1) or lead problems (n=10). Eight patients (13.5%) required psychiatric assistance due to complications related to the ICD (mostly inappropriate shocks in 7 patients).

Conclusions: In this Israeli population with Brugada syndrome treated with ICD, appropriate device therapy was limited to cardiac arrest survivors while none of the other patients including those with syncope and/or inducible VF suffered an arrhythmic event. The overall complication rate was high.

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The Brugada syndrome is an inherited disorder associating syncope or sudden cardiac death due to ventricular fibrillation in patients with no structural heart disease who have right bundle branch block and ST-segment elevation in the right

ICD = implantable cardioverter defibrillator
VF = ventricular fibrillation

precordial leads V1 to V3 [1,2]. Based on the Brugada data [3-5] many electrophysiologists worldwide have recommended the implantable cardioverter defibrillator for symptomatic patients (survivors of cardiac arrest or syncope) and for asymptomatic patients with the Brugada electrocardiogram considered to be at risk of sudden cardiac death (mainly those who have inducible VF at electrophysiological study) [2,6]. The efficacy of this approach in preventing sudden cardiac death in symptomatic patients has been confirmed in several studies [7,8], but the beneficial role of ICD in asymptomatic presumably "high risk" patients is controversial [7,8]. On the other hand, several studies have shown a high incidence rate of ICD-related complications, especially inappropriate shocks [5,8]. We conducted a retrospective, multicenter study in Israel to evaluate the benefits and the complication rate among patients with Brugada syndrome who were treated with an ICD for primary or secondary prevention of sudden cardiac death.

Patients and Methods

We collected data on the entire population of patients with Brugada syndrome who received an ICD in 12 medical centers in Israel between 1994 and 2007. Only patients with at least 3 months follow-up after ICD implantation were included in the study. The diagnosis of Brugada syndrome was made as the result of a workup following an episode of cardiac arrest, syncope, palpitations or in asymptomatic patients due to a suspicious ECG or a family history of sudden cardiac death or Brugada syndrome.

ECG definition

A type 1 Brugada-ECG was defined as a prominent coved-type ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave in more than one right precordial lead (V1 to V3) occurring either spontaneously or after the administration of a sodium channel blocker (flecainide or procainamide) [2]. A type 2 ECG was defined as saddle-back appearance with ST-segment elevation ≥ 2 mm (0.2 mV), a trough displaying ≥ 1 mm ST elevation, and then either a positive or biphasic T wave. A type 3 ECG was defined as either a saddle-back or coved-appearance ST elevation of < 1 mm (0.1 mV). The baseline ECG was classified as normal if the abovementioned ST abnormalities were absent.

Sodium channel blocker challenge

Patients with a type 2 or 3 ECG pattern underwent a challenge with a sodium channel blocker agent [2] to unmask the diagnostic ECG pattern. The agent chosen was flecainide (i.v. flecainide 2 mg/kg body weight for 6–10 minutes with a maximum of 150 mg) owing to its availability in Israel. The test was considered to be positive if a type 1 Brugada-ECG pattern was obtained following the medication.

Electrophysiological study

An electrophysiological study was performed at the investigators' discretion. The protocol of programmed ventricular stimulation used in most laboratories (9 of 12) included delivery of up to three extrastimuli from two right ventricular sites (apex and outflow tract), using two basic cycle lengths with stimulus current at double diastolic threshold, with no systematic repetition of extrastimulation and keeping the minimal coupling intervals of 200 msec. In two laboratories (Shaare Zedek Medical Center in Jerusalem and Sourasky Medical Center in Tel Aviv), the protocol was more aggressive, including higher stimulus current (up to fivefold the diastolic threshold but always ≤ 3 mA), as well as repetition of double (n=10) and triple (n=5) extrastimuli at the shortest coupling intervals that allowed ventricular capture [9]. At Kaplan Hospital (Rehovot), a protocol similar to the one just described was followed using double diastolic threshold stimulus current.

The result of the study was considered positive if a single episode of sustained ventricular tachyarrhythmia (lasting > 30 sec or requiring earlier termination because of hemodynamic intolerance) was induced.

ICD implantation

Single or dual-chamber ICDs were implanted depending on the operator's preference. Implantation was performed with a non-thoracotomy transvenous lead system in all patients. All patients received an ICD capable of electrocardiogram storage at the time of ventricular arrhythmia episodes and shocks.

Following the ICD implant the patients were routinely examined at 3 to 6 month intervals for clinical review and device interrogation. In the event of an ICD discharge patients were seen at the ICD clinic and the device memory was interrogated. Appropriate ICD discharges were defined as shocks delivered for ventricular tachycardia or VF, and inappropriate shocks were defined as those delivered in the absence of documented ventricular arrhythmia.

Results

Patient characteristics

Twelve Israeli centers participated in the study with more than half the patients collected from three hospitals (see Appendix). There were 59 patients (53 males, 89.8%), aged 17–84 years (44.1 ± 14).

Thirty-seven patients (62.7%) had a type 1 Brugada-ECG spontaneously observed at baseline on at least one occasion. Thirteen patients (22%) had a type 2 Brugada-ECG at baseline who converted to type 1 upon administration of flecainide. Six patients (10.2%) with a baseline type 2 ECG did not undergo a flecainide test. Of these six patients, three had a history of syncope, two were survivors of cardiac arrest, and one was asymptomatic with a family history of cardiac arrest. One patient (1.7%) had a baseline type 3 ECG that converted to a type 1 pattern after the administration of flecainide. Two patients (3.4%) had a normal baseline ECG. One was referred due to syncope and a family history of sudden cardiac death; the second was asymptomatic but with a familial history of sudden cardiac death. In both patients the ECG converted to a type 1 pattern after administration of flecainide.

At diagnosis 42 patients (71.2%) were symptomatic while

17 patients (28.8%) were asymptomatic (in fact 3 patients were included in the asymptomatic group although they complained of palpitations). A spontaneous type 1 Brugada-ECG pattern was observed in 26 (61.9%) of 42 symptomatic patients and in 11 (64.7%) of 17 asymptomatic patients (P = NS).

In symptomatic patients (n=42), the indication for ICD implantation was syncope (31 patients, 73.8%) and a history of aborted cardiac arrest (11 patients, 26.2%). Among the asymptomatic patients (n=17) the indication for ICD implantation was inducible VF (n=14, 82.4%) including 3 patients with a history of sudden cardiac death and 1 with a family history of lethal Brugada syndrome. In 3 patients (17.6%) the indication for ICD implant was a family history of sudden cardiac death: in two of these patients an EPS was not performed while the remaining patient had a negative EPS.

An EPS was performed in 28 of the 42 symptomatic patients (66.7%) and in 15 of the 17 asymptomatic patients (88.2%) ($P < 0.05$). VF was induced in 4 of 5 patients (80%) who presented with cardiac arrest (n=11), 20 of 22 (90.9%) who presented with syncope (n=31) and 14 of 15 asymptomatic patients (93.3%). The overall inducibility rates of VF were 89.2% and 93.3% among the symptomatic and asymptomatic patients (P = NS).

In 11 patients (7 symptomatic and 4 asymptomatic) with inducible VF at baseline, we assessed the effects of oral quinidine on VF inducibility [10]. Quinidine therapy was effective in preventing reinduction of VF in 7 patients (64%) (5 symptomatic and 2 asymptomatic); however, the medication had to be discontinued due to side effects in 5 patients. In the other 2 patients (both quinidine EPS responders with prior cardiac arrest) an ICD was implanted due to patient preference after 17 years of uneventful quinidine therapy (n=1), and syncope of unknown cause with inducible non-sustained polymorphic ventricular tachycardia on quinidine at EPS after 8 years of therapy (n=1). In four patients quinidine therapy failed to prevent VF induction. Finally, in two patients quinidine led to adverse side effects and could not be tested at EPS.

Follow-up

The mean follow up period for the study group was 45 ± 35 months (range 4–160 months). The follow-up duration was > 70 months in 12 patients (20%). One patient died from cancer 6 months after ICD implantation. All other patients are alive. Five patients (8.4%), all with a prior history of cardiac arrest, had appropriate device therapy. In this patient population the appropriate device therapy rate was 45.4% (5 of 11). Four of these five patients received quinidine without further arrhythmic events. Among the 48 patients who did not have a previous cardiac arrest none had appropriate device therapy during a mean 39 ± 30 month follow-up period. Complications were encountered in 19 patients (32%). Inappropriate shocks occurred in 16 patients (27.1%). This was caused by lead failure/dislodgement (5 patients), T wave oversensing (2 patients), device failure (1 patient), sinus tachycardia (4 patients) and supraventricular tachycardia (4 patients). One patient had a pneumothorax during the implant procedure. Another patient was severely invalidated by brachial plexus injury following the procedure. One patient suffered a late (2 months) right ventricle perforation by the implanted lead (Fidelis 6949-65, Medtronic Inc) that manifested with severe chest pain and shock associated with pericardial effusion. This patient underwent the emergency extraction of the device and the right ventricle lead. He subsequently underwent EPS on quinidine that showed no inducible arrhythmias and the medication was given on a long-term basis. Eleven patients (18.6%) required a reintervention either for a lead or device problem (10 patients) or infection (1 patient). Eight patients (13.5%) required psychiatric assistance during follow-up, either because of concerns related to the diagnosis of Brugada syndrome or to complications related to the ICD implant, mostly inappropriate shocks (7 patients). In two of them the psychological disturbance resulted in the loss of employment.

There were no differences between low and high volume centers regarding the complication rates. Also, there were no differences in complication rates between patients who had a positive EPS and those who had a negative one and between patients who presented with cardiac arrest and those who did not.

Discussion

The aim of our study was to evaluate the long-term outcome in a series of patients with Brugada syndrome who received an ICD for primary or secondary prevention in 12 Israeli medical centers between 1994 and 2007. Seventy percent of the Israeli centers (including all high volume centers) using ICDs participated in this study. The vast majority of patients were symptomatic at diagnosis, with syncope as the major complaint followed by cardiac arrest. A quarter of the patients included in this study were asymptomatic at diagnosis and the main indication for ICD therapy was inducibility of VF at EPS followed by a family history of sudden cardiac death.

The major finding of our study was that during a mean follow-up of almost 4 years after ICD implantation, appropriate device therapy was limited only to roughly half of the cardiac arrest survivors while none of the other patients, including those with a history of syncope and/or inducible VF at EPS, suffered an arrhythmic event. In addition, the overall ICD-related complication rate was especially high, including a single potentially lethal event.

Efficacy of ICD

A meta-analysis of prognostic studies of patients with a Brugada-ECG to assess predictors of events has shown the high risk of arrhythmic events associated with a history of aborted sudden cardiac death or syncope [11]. In addition, a low predictive accuracy of EPS was found so that there is presently a consensus in the EPS community that such patients should receive an ICD without undergoing EPS. Data from the few studies of patients with Brugada syndrome who have received an ICD have confirmed these results. In the largest multicenter study, by Sacher et al.

EPS = electrophysiological study

[8], in 220 patients with Brugada syndrome and ICD including 18 patients (8%) with a history of cardiac arrest and 88 (40%) with a history of syncope, the rates of appropriate ICD shocks were 22% and 10%, respectively, during a mean follow-up period of 38 ± 27 months. In a smaller retrospective study from Dr. Pedro Brugada's laboratory in 47 patients who underwent prophylactic ICD implantation, Sarkozy et al. (5) could not confirm the previously well-established finding of syncope as a predictor of future arrhythmic events [4,7,11]. Sarkozy and team attributed this to the inclusion of vasovagal syncope in the "syncope" group, which may falsely suggest an increased risk of sudden death. The results of our study showing a high rate (45.4%) of appropriate ICD shocks in the patients with a history of aborted cardiac arrest are consistent with the results of previous studies [3,5,7,8]. However, the fact that syncope did not predict future arrhythmic events in our patients, despite inducibility of VF in most of them (90.9%), is striking and more consistent with Sarkozy's findings. The difficulty to differentiate between a benign vasovagal syncope and a potentially fatal syncopal arrhythmia suggests that patients with "benign syncope" comprised most of our syncopal patient population. However, the inclusion of such patients should not be avoided since increased vagal tone has been shown to increase the occurrence of a Brugada-ECG pattern [12,13] as well as the propensity to facilitate VF induction [14]. In addition, typical vasovagal episodes may mimic arrhythmic events (Swissa and Belhassen, unpublished data).

The role of ICD therapy in asymptomatic patients considered to be at risk for arrhythmic events is less defined and even more controversial than in symptomatic patients. In an editorial referring to a meta-analysis conducted by Paul et al. [15] on the role of programmed ventricular stimulation in patients with Brugada syndrome, Viskin and Rogowski [16] systematically analyzed the reasons for the major differences between the results published by the Brugada brothers with the data published in 15 other studies. The Brugadas found high inducibility rates during EPS and a high rate of spontaneous arrhythmic events in their patients, suggesting a high positive predictive value of EPS. Opposite results were found in the other studies. Our results are in congruence with the results of these other studies.

Complications

The complication rate in our study was particularly high, occurring in one-third of the patients who underwent implantation. These data are similar to those reported in other studies [5,8]. The main complication was inappropriate shocks, mainly due to lead problems and ineffective discrimination between sinus tachycardia and supraventricular arrhythmias. Moreover, almost one-fifth of the patients required a reintervention due to lead or device problems. The most potentially disastrous complication, observed in one asymptomatic patient, was represented by cardiac perforation with an ICD lead. Cardiac perforation by implanted pacemaker or defibrillator lead occurs at a complication rate of 0.4–2.0% [17,18] and may be lethal [19]. However, some recent data suggest that the frequency of lead-related cardiac perforations may be even higher, especially for ICD leads manufactured by St. Jude Medical Inc. [19, 20]. Our findings show that this complication is not specific to the leads from this company.

Eight patients required psychiatric assistance either due to concerns related to the diagnosis of Brugada syndrome or complications related to the ICD implant. This particular problem has been addressed in previous studies conducted on different populations of patients implanted with an ICD in which a device shock resulted in a deterioration in the quality of life and in mental health concerns [21-24]. The number of patients suffering a psychiatric disturbance in our study was particularly high in comparison to a previous report [8]. This problem may have an important personal and social impact, particularly in Brugada patients who are young and therefore expected to undergo multiple device replacements and lead extractions during their life [25].

Study limitations

The protocol of programmed ventricular stimulation used in this multicenter study was not uniform. In about a quarter of the patients a very aggressive protocol was used. Applying a more aggressive protocol may lead to a false positive EPS, resulting in patients receiving an ICD without a clear indication. On the other hand, it should be noted that the sensitivity of standard protocols in cardiac arrest survivors is far from satisfactory. In the meta-analysis by Paul et al. [15], VF inducibility rates ranging from 81% (Brugada series) to 57% (collected from 15 other series) were found with standard protocols in patients with prior cardiac arrest.

The follow-up duration in our study was similar to that of previous studies but may be considered relatively short for a genetic disease in which lethal cases have been reported to occur at all ages, from childhood to the elderly (range 2 days–84 years) [2]. Therefore, conclusions regarding the actual role of ICD therapy especially for primary prevention of sudden cardiac death should be made with caution.

Conclusion and clinical implications

In this Israeli population of patients with the Brugada syndrome implanted with an ICD and followed during a mean 45 month period the appropriate device therapy rate was limited to cardiac arrest survivors, while none of the other patients including those with syncope or positive EPS suffered an arrhythmic event. The overall complication rate was particularly high, especially inappropriate shocks, need for reintervention, and psychological disturbances. The high rate of ICD-related complications as well as the apparent lack of benefit of ICD in patients with no prior cardiac arrest should prompt physicians to look for alternative strategies of treatment. One involving quinidine therapy in electrophysiologic-drug responder patients has been developed during the last three decades at the Sourasky Tel Aviv Medical Center [10,25]. Selected patient populations with the Brugada syndrome such as young patients or those with device-related complications are the most suitable. Absolute requirements for this medical option include an excellent patient tolerance to medication and commitment to long-term pharmacological therapy. To date, none of the 50 symptomatic or asymptomatic

patients with the Brugada syndrome treated with quinidine at the Sourasky Tel Aviv Medical Center has suffered an arrhythmic event during follow-up (unpublished data).

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Appendix. Number of patients per medical center

Tel Aviv Sourasky Medical Center, Tel Aviv (n=14); Sheba Medical Center, Tel Hashomer (n=9); Soroka Medical Center, Beer Sheva (n=9); Kaplan Hospital, Rehovot (n=6); Hadassah-Hebrew University Medical Center, Jerusalem (n=4); Meir Hospital, Kfar Saba (n=3); Barzilai Hospital, Ashkelon (n=3); Assaf Harofeh Hospital, Zerifin (n=3); Rambam Medical Center, Haifa (n=3); Wolfson Medical Center, Holon (n=2); Rabin Medical Center (Beilinson Campus), Petah Tikva (n=2); Shaare Zedek Medical Center (n=1), Jerusalem.

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