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Hydroquinidine Therapy in Brugada Syndrome

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OBJECTIVES We sought to assess hydroquinidine (HQ) efficacy in selected patients with Brugada syndrome (BrS).

BACKGROUND Management of asymptomatic patients with BrS and inducible arrhythmias remains a key issue. Effectiveness of class Ia antiarrhythmic drugs, which inhibit the potassium transient outward current of the action potential, has been suggested in BrS.

METHODS From a cohort of 106 BrS patients, we studied 35 who received HQ (32 men; mean age 48 ± 11 years). Patients had asymptomatic BrS and inducible arrhythmia (n = 31) or multiple appropriate shocks from an implantable cardioverter-defibrillator (ICD) (n = 4). Asymptomatic patients with inducible arrhythmia underwent electrophysiologic (EP)-guided therapy. When ventricular tachycardia (VT)/ventricular fibrillation (VF) inducibility was not prevented, or in case of HQ intolerance, an ICD was placed.

RESULTS Hydroquinidine prevented VT/VF inducibility in 76% of asymptomatic patients who underwent EP-guided therapy. Syncope occurred in two of the 21 patients who received long-term (17 ± 13 months) HQ therapy (1 syncope associated with QT interval prolongation and 1 unexplained syncope associated with probable noncompliance). In asymptomatic patients who received an ICD (n = 10), one appropriate shock occurred during a follow-up period of 13 ± 8 months. In patients with multiple ICD shocks, HQ prevented VT/VF recurrence in all cases during a mean follow-up of 14 ± 8 months.

CONCLUSIONS Hydroquinidine therapy prevented VT/VF inducibility in 76% of asymptomatic patients with BrS and inducible arrhythmia, as well as VT/VF recurrence in all BrS patients with multiple ICD shocks. These preliminary data suggest that preventive treatment by HQ may be an alternative strategy to ICD placement in asymptomatic patients with BrS and inducible arrhythmia. (J Am Coll Cardiol 2004;43:1853–60) © 2004 by the American College of Cardiology Foundation

The Brugada syndrome (BrS) is an inherited arrhythmogenic disease associated with a risk of sudden cardiac death due to ventricular fibrillation (VF) (1). The proposed mechanism of the arrhythmia and ST-segment elevation involves imbalance between the inward (I_{Na} and I_{Ca}) and outward currents, mainly the transient outward current (I_{to}), at the end of phase 1 of the epicardial action potential (2,3). Because of the high rate of recurrence of the arrhythmic events and because no drug was found to be effective, patients rescued from sudden cardiac death or those who experienced syncope are candidates for an implantable cardioverter-defibrillator (ICD) (4,5). In asymptomatic patients diagnosed at random or after a family inquiry, risk stratification is not clearly established. According to Brugada, a spontaneous coved-type electrocardiographic (ECG) pattern and ventricular tachycardia (VT) or VF inducibility during electrophysiologic (EP) study are predictive of a poor outcome (5). Patients will experience an arrhythmic event in 17% of the cases during a mean follow-up of 27 months. Updated results showed that asymptomatic patients with inducible arrhythmia will have an arrhythmic event in 12% of the cases during a follow-up of 31 months, regardless of the presence of a spontaneous coved-type ECG (6). The predictive value of other markers is not established. The presence of familial sudden cardiac death is not associated with an increased risk, and there was only a trend toward a worse prognosis in males than in females (p = 0.07) (5). Consequently, in the absence of another recognized option, prophylactic placement of an ICD in asymptomatic subjects with inducible arrhythmia and spontaneous coved-type ECG of BrS was proposed (5,7). Nevertheless, VT/VF inducibility has been found to be a poor predictor of the recurrence of arrhythmic events in symptomatic patients in two reports (8,9). A recent international consensus emphasized the lack of conclusive evidence to guide risk stratification in asymptomatic patients with BrS (10). The management of asymptomatic patients with BrS remains a key issue. The therapeutic options are either a prophylactic ICD, with the issue of long-term management of the ICD, or no treatment at all, with the risk of sudden cardiac death as a first symptom.

In 1999, Belhassen et al. (11) observed that class I antiarrhythmic agents, which inhibit I_{to} (mainly quinidine), prevented arrhythmia induction, as well as arrhythmia recurrences, in a long-term follow-up in four of five cardiac arrest survivors with BrS. At the same time, quinidine efficacy was mentioned in isolated cases, including pediatric patients with incessant polymorphic VT (12,13). Also, normalization of the ST-segment was described with quinidine (14). As quinidine appeared to be a valuable drug in

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Abbreviations and Acronyms

BrS = Brugada syndrome
ECG = electrocardiogram
EP = electrophysiologic
HQ = hydroquinidine
ICD = implantable cardioverter-defibrillator
I_{to} = transient outward current
VF = ventricular fibrillation
VT = ventricular tachycardia

symptomatic patients, we assumed that it may also represent a pharmacologic option in asymptomatic patients.

The aim of this study was to report our experience with hydroquinidine (HQ) in selected patients with BrS, especially in asymptomatic patients with inducible arrhythmia.

METHODS

Study population. The entire BrS population followed in our institutions (University Hospital of Amiens-Picardie, Amiens, and Lariboisière University Hospital, Paris) includes 106 patients. These patients had documented symptomatic VT/VF in 13 cases, unexplained syncope in 13 cases, and no symptoms in the 80 remaining cases (Fig. 1).

In this population, HQ therapy has been systematically and prospectively used since 1999 in asymptomatic patients with BrS and inducible arrhythmia (n = 31) and in symptomatic patients with BrS who experienced multiple appropriate ICD discharges (n = 4). The study population (Table 1) includes 35 consecutive patients (32 men; mean age 48 ± 11 years [range 18 to 76 years]).

Brugada syndrome was diagnosed in accordance with current diagnosis criteria (10). In symptomatic patients or subjects with a familial history of BrS, diagnosis was based on a coved-type pattern of ST-segment elevation in more than one right precordial ECG lead (V_1 to V_3) in the presence or absence of a sodium channel blocker. For asymptomatic patients with a saddle-type ECG, a >0.2-mV drug-induced coved ST-segment elevation in the right precordial leads was required. The absence of structural heart disease was verified by noninvasive and invasive investigations, including two-dimensional echocardiography, magnetic resonance imaging, and coronary angiography with right and left ventricular angiography, as appropriate. Sodium channel blockade challenge was carried out by ajmaline intravenous infusion (1 mg/kg/s). Ajmaline challenge was classified as positive if a >0.2-mV downsloping ST-segment elevation measured 20 ms after the end of

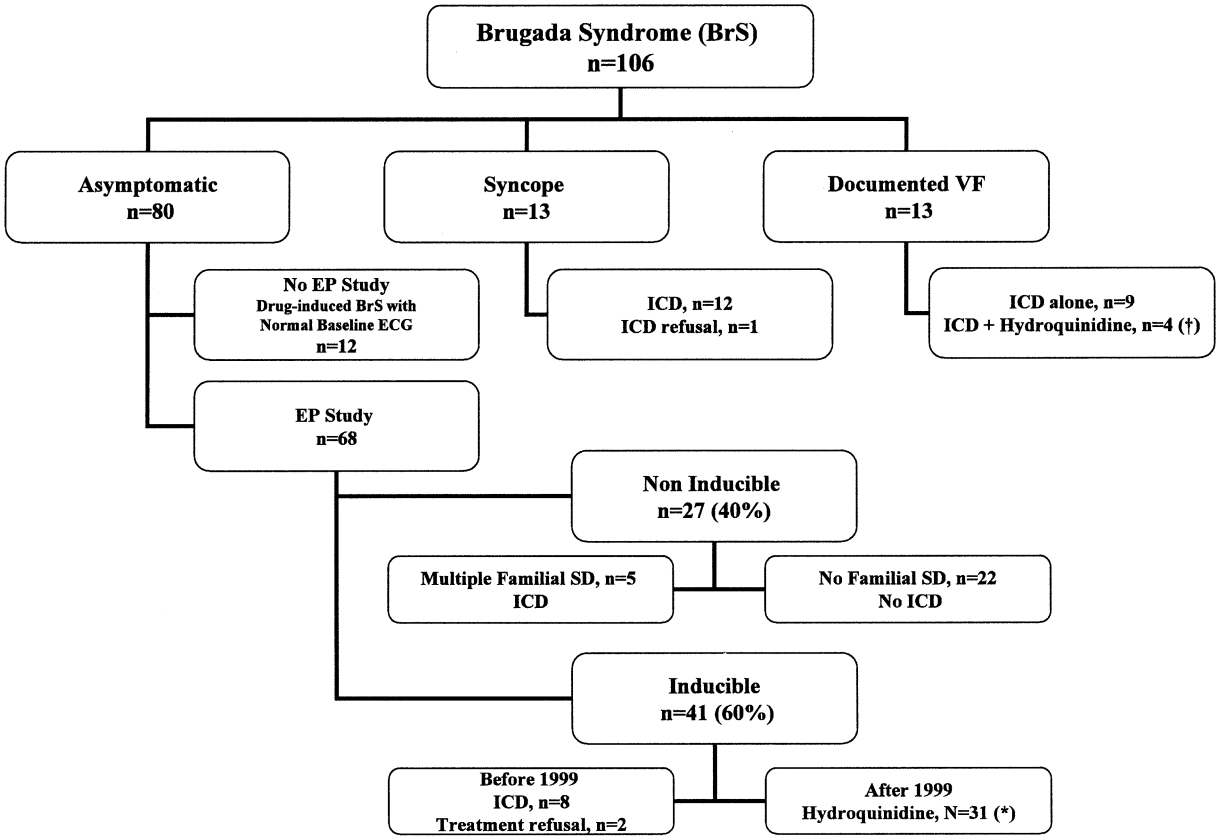

Figure 1. Brugada syndrome (BrS) population. Among the BrS cohort followed in both institutions, 80 patients were asymptomatic. From 1999, hydroquinidine therapy was prescribed to asymptomatic patients with BrS and inducible arrhythmia **(*)** (n = 31). In case of noninducibility, patients were not treated, except in case of multiple familial sudden deaths. In case of drug-induced BrS with a normal baseline electrocardiogram (n = 12), the electrophysiologic (EP) study was not performed. The study population also includes four BrS patients **(†)** who had multiple implantable cardioverter-defibrillator (ICD) shocks. SD = sudden death; VF = ventricular fibrillation.

Table 1. Study Population

	BrS Patients (n = 35)
Age (yrs)	48 ± 11 (18–76)
Male	32 (91%)
Asymptomatic BrS and inducible arrhythmia	31 (89%)
BrS and multiple ICD shocks	4 (11%)
Familial form	
None	22 (63%)
Familial BrS	7 (20%)
Familial SD	4 (11%)
Familial BrS and SD	2 (6%)
ECG pattern	
Coved	23 (66%)
Drug-induced	12 (34%)
QRS duration (ms)	102 ± 15
HV interval (ms)	49 ± 10
QTc interval (ms)	402 ± 20
RVERP (ms)	233 ± 18
Induced VT cycle length (ms)	186 ± 18

Data are presented as the mean value ± SD (range) or number (%) of patients.
BrS = Brugada syndrome; ECG = electrocardiographic; ICD = implantable cardioverter-defibrillator; RVERP = right ventricular effective refractory period; SD = sudden death; VT = ventricular tachycardia.

the QRS complex was observed in the right precordial lead, including V_1 and V_2 recorded in the second intercostal space (2,15). *SCN5A* mutations were present in five (28%) of the 18 patients who were genotyped.

A "slow-release" HQ preparation (HQ chlorhydrate; Serecor, Sanofi-Synthelabo Laboratory, Paris, France) was given at the standard dose of 300 mg twice a day. Modifications of the ECGs were compared immediately before HQ and after the beginning of the treatment in an attempt to minimize the influence of spontaneous variation. The EP studies were repeated after a trial period of at least two weeks. Hydroquinidine intake was increased to 900 mg/day when the patients were still inducible and had a plasma level <3 μmol/l (the usual concentration by fluorimetry is 3 to 6 μmol/l). A second EP study on HQ was proposed after dose adjustment. In case of noninducibility at HQ 600 mg/day, the dose was maintained no matter what the HQ plasma level was.

Electrophysiologic study. Electrophysiologic study was performed (once written, informed consent was obtained) at baseline and under HQ with a standardized protocol, including a driving cycle length at 600 and 400 ms, with up to three extrastimuli and a coupling interval until the refractory period but without repetition of extrastimulation. The right ventricular apex and right ventricular outflow tract were paced at twice the right ventricular diastolic threshold. Nonsustained VT was defined as VT of more than six complexes. Inducibility of VT/VF was defined as the induction of monomorphic or polymorphic VT lasting >20 s or degenerating into VF. Because of the usual irregularity of polymorphic VT, we chose to define the VT cycle length as the mean cycle length of the beats occurring during the first second of tachycardia. The right ventricular effective refractory period was measured at the right ventricular apex and was defined as the longest S_1S_2 interval that failed to evoke a ventricular response at a pacing cycle length of 600 ms.

Statistics. Variables are expressed as the mean ± SD. Correlations between categorical variables were assessed by the phi coefficient. This measure is similar to the correlation coefficient in its interpretation. Phi compares the product of the diagonal cells (a · d) to the product of the off-diagonal cells (b · c) in a four-fold table. Two binary variables are considered positively associated if most of the data fall along the diagonal cells. In contrast, two binary variables are considered negatively associated if most of the data fall off the diagonal. The effects of HQ on the ECG and EP continuous variables were assessed with the paired Student *t* tests. A value $p < 0.05$ was considered as significant.

RESULTS

Trial period with HQ (Fig. 2 and Table 2). The EP study was repeated under HQ in 29 of the 31 asymptomatic patients with BrS and inducible arrhythmia. A total of 20 of the 29 asymptomatic patients were not inducible with 600 mg/day HQ. Plasma levels were below the therapeutic value in three of the nine patients who were still inducible. Hydroquinidine was increased to 900 mg/day, and VT/VF became noninducible in two of these three cases. The third patient refused an EP study at 900 mg/day. At last, HQ prevented VT/VF inducibility in 22 (76%) of 29 of the asymptomatic patients with BrS. The mean HQ plasma level was comparable in both groups: 2.7 ± 1.3 μmol/l in noninducible patients and 2.8 ± 1.6 μmol/l in patients with persistent VT/VF inducibility.

Decreased or disappearance of ST-segment elevation on the ECG occurred in 12 (34%) of 35 patients. There was no correlation between ST-segment modification and VT/VF inducibility (phi coefficient = 0.18, p = 0.32). The corrected QT (QTc) interval and QRS duration were slightly but significantly prolonged (Table 2).

During the first month of HQ therapy, drug intolerance (diarrhea) occurred in seven (20%) patients, leading to HQ withdrawal in two patients. A rise in hepatic enzymes (three-fold upper normal value of transaminase) associated with nausea and asthenia occurred after a week of treatment in one patient. Hydroquinidine-induced hepatitis was reversible after withdrawal of the treatment. These three patients received an ICD.

Long-term treatment with HQ. Patients who were not inducible with HQ and had a good tolerance, together with the patient who refused the EP study (n = 21) and the four patients with BrS and multiple ICD shocks, received long-term treatment (Fig. 2).

In the 21 asymptomatic patients with BrS and inducible arrhythmia, 17 (81%) were asymptomatic after 17 ± 13 months of follow-up. Two patients had to stop HQ at the second and fifth month, respectively, for troublesome diarrhea and received an ICD. Two other patients experienced syncope during follow-up (Table 3). The first patient was 51

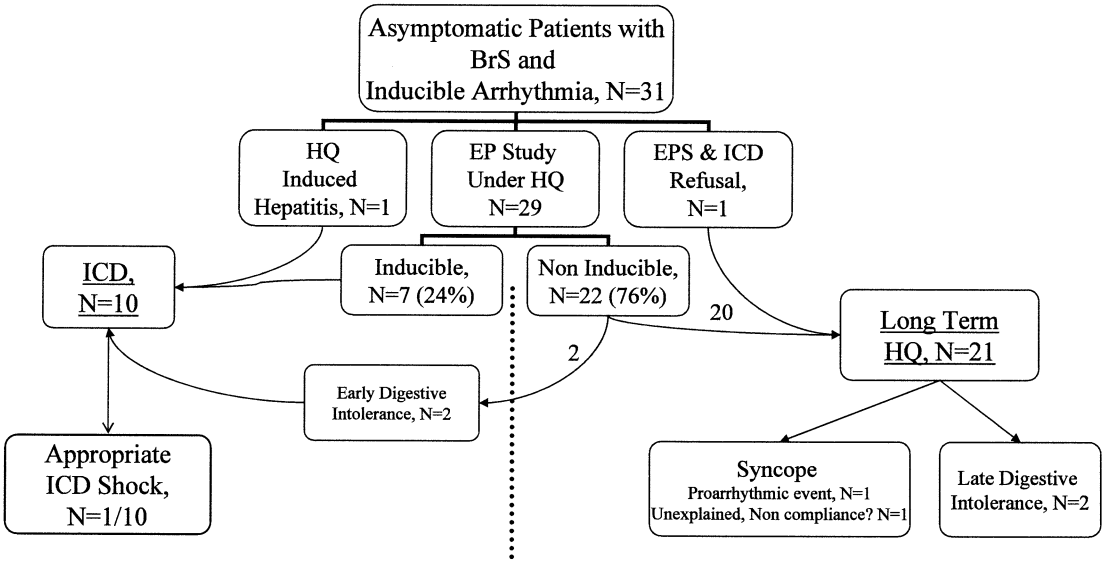

Figure 2. Electrophysiologically guided therapy. After a trial period with hydroquinidine (HQ), BrS patients underwent EP study (EPS). Of 31 asymptomatic patients with BrS and inducible arrhythmia, 29 underwent an EP study with HQ. The rate of ventricular tachycardia (VT)/ventricular fibrillation (VF) noninducibility was 76% (22 of 29). Abbreviations as in Figure 1.

years old and experienced two short syncopal episodes at work, 12 months after the beginning of HQ at the dose of 600 mg/day. The plasma HQ level was not measured on arrival, and the QTc interval was 409 ms. The plasma HQ level, measured after five days of hospitalization, was 4.65 μmol/l, and simultaneously, the QTc interval was 447 ms. No spontaneous ventricular arrhythmia could be documented during a 48-h period of ECG monitoring. Noncompliance was suspected due to a normal QTc interval on arrival. Hydroquinidine was stopped, and an ICD was inserted. No ICD discharge occurred during the one-year follow-up. The second patient was also 51 years old and had a diurnal sensation of tachycardia, dizziness, and then syncope only one month after HQ was started. During ECG monitoring, runs of VT were recorded (Fig. 3). The ECG showed persistent downsloping ST-segment elevation and a negative T-wave in leads V_1, V_2, and V_3. The QTc interval was prolonged to 530 ms, whereas it was only 425 ms before treatment. This was the longest QTc interval recorded in all of the BrS patients treated with HQ. A QTc >500 ms was observed only in this patient. Kalemia was 3.6

Table 2. Hydroquinidine in Patients With Brugada Syndrome

	HQ Therapy Patients (n = 35)	p Value*
Mean dose (mg/day)	609 ± 89	
Plasma level (μmol/l)	2.7 ± 3.3	
Side effects		
Diarrhea	7 (20%)	
Treatment withdrawal	2 (5.7%)†	
Adverse drug reaction		
Reversible hepatitis	1 (3%)	
Effects on ECG and electrophysiologic intervals		
Delta QRS duration	13 ± 12	<0.001
Delta QTc interval	10 ± 7	<0.001
Delta HV interval	8 ± 11	0.003
Delta RVERP	17 ± 19	<0.001
Effects on ECG pattern of BrS		
Unchanged ECGs	23 (66%)	
Normalization or reduction of ST-SE	12 (34%)	
Programmed ventricular stimulation with HQ	29	
Noninducible	22 (76%)	
<3 Repetitive beats	16	
Nonsustained pVT (up to 20 s)	5	
Nonsustained mVT (up to 20 s)	1	
Sustained VF or pVT	7 (24%)	
Delta VTCL (%)	17 ± 17	0.006

*By the paired *t* test. †Two other hydroquinidine withdrawals (second and fifth months) were necessary during the long-term period. Data are presented as the mean value ± SD or number (%) of patients.

Delta = ECG variation under hydroquinidine; HQ = hydroquinidine; mVT = monomorphic ventricular tachycardia; pVT = polymorphic VT; ST-SE = ST-segment elevation; VF = ventricular fibrillation; VTCL = ventricular tachycardia cycle length; other abbreviations as in Table 1.

Table 3. Follow-Up

Follow-Up of Asymptomatic Patients With BrS and Inducible Arrhythmia Receiving Long-Term Treatment With Hydroquinidine	
Number of patients	21
Follow-up in months (range)	17 ± 13 (1–42)
Events during follow-up	4
Digestive intolerance	2
Syncope associated with prolonged QTc interval	1
Unexplained syncope	1
ICD placement	4

Follow-Up of Asymptomatic Patients With BrS and Inducible Arrhythmia Who Received an ICD	
Number of patients	10
Follow-up in months (range)	13 ± 8 (3–28)
Events during follow-up	
Appropriate shock	1

Abbreviations as in Table 1.

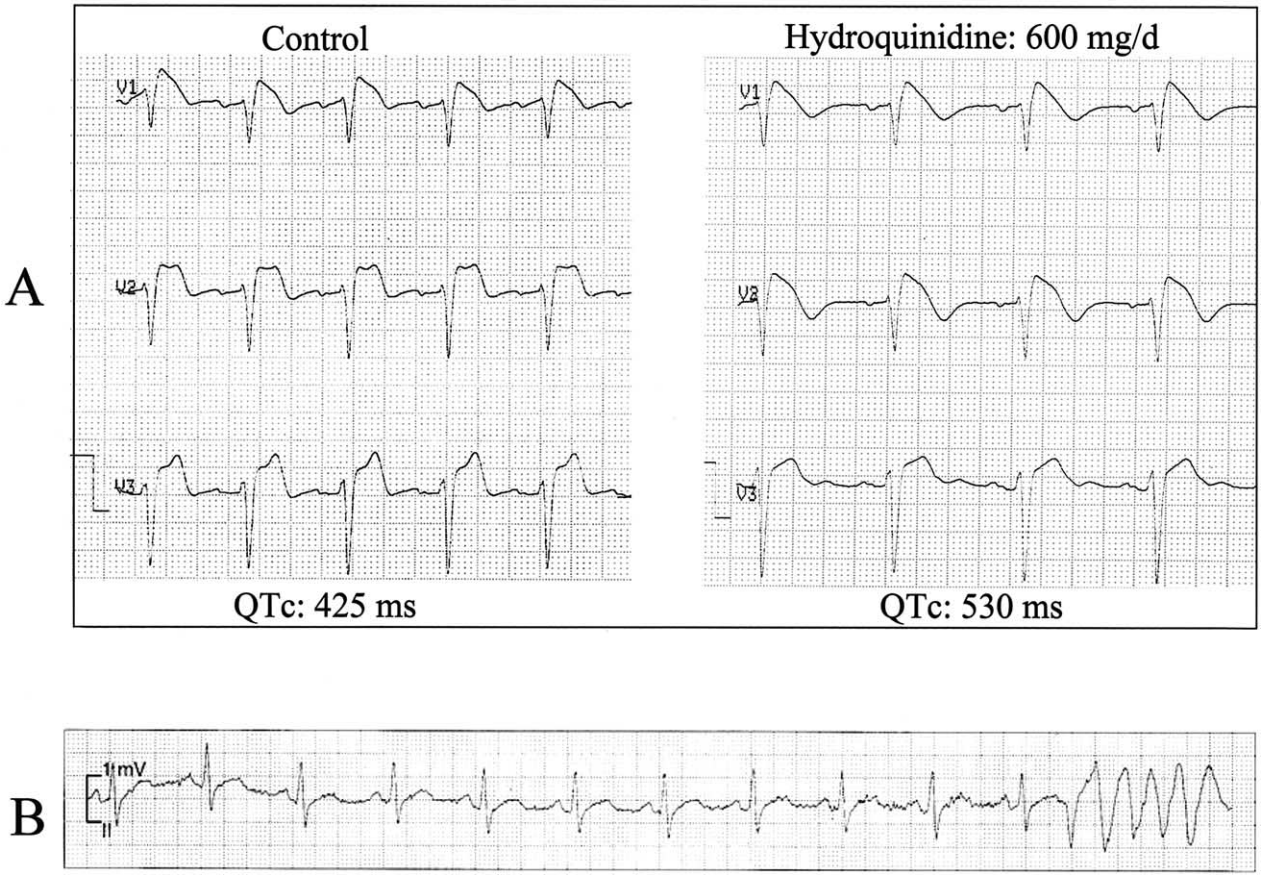

Figure 3. **(A)** Major QTc interval prolongation observed in a patient who had syncope only one month after the beginning of HQ. The *SCN5A* mutation was not found in this patient. Measurement of the QT interval includes the inverted T wave observed after the downsloping ST-segment elevation in lead V_2. **(B)** Monomorphic runs of VT were recorded in the emergency room, but in only one lead. No recurrence of syncope was observed after withdrawal of HQ during a follow-up of one year. Syncope may be attributed to a drug inefficacy or to a proarrhythmic effect of HQ. The argument for drug failure is the absence of typical pause-dependent torsade de pointes and of a long coupling interval. The argument for a proarrhythmic event is major QTc interval prolongation. Abbreviations as in Figure 1.

mEq/l, and the plasma HQ level was 4.6 μmol/l. No mutation in *SCN5A* was identified. Hydroquinidine was withdrawn and an ICD was placed without any events during one-year follow-up. Two hypotheses could explain the syncope in this patient: 1) a drug inefficacy resulting in runs of VT; and 2) a possible proarrhythmic effect with HQ treatment.

In the 10 asymptomatic patients with BrS and inducible arrhythmia who received an ICD for persistent VT/VF inducibility under HQ or for early drug intolerance, we observed one appropriate shock (polymorphic VT/VF) during a follow-up of 13 ± 8 months. The shock occurred during nocturnal sleep, four months after ICD placement in a 45-year-old man who previously had digestive intolerance with HQ. Brugada syndrome had been recognized 17 months earlier on a systematic 12-lead ECG. In another patient, we also observed multiple inappropriate shocks due to oversensing of the T-wave six months after implantation. Lead repositioning had to be performed.

The main clinical characteristics of the patients with BrS and multiple ICD shocks are summarized Table 4. In this group, no recurrences of shocks or VT/VF with HQ were evidenced when the ICD memories were checked. A striking effect on runs of VT was documented in one patient (Fig. 4). None of these patients underwent programmed ventricular stimulation with HQ therapy.

DISCUSSION

The main results of this preliminary study are the following: 1) HQ prevented VT/VF inducibility in 22 (76%) of the 29 asymptomatic patients with BrS and inducible arrhythmia. 2) During long-term HQ therapy (17 ± 13 months), a documented nonsustained VT associated with QTc prolongation (QTc interval 530 ms) occurred in one (3.7%) of the 21 asymptomatic patients with BrS and inducible arrhythmia. Also, an unexplained syncope was observed in a patient in whom HQ compliance was uncertain. Improvement of outcome with HQ therapy might be expected with careful QT interval surveillance. 3) During a follow-up of 13 ± 8 months, an appropriate shock was noted in one (10%) of the 10 patients who received an ICD. 4) In a patient with BrS and multiple ICD shocks, HQ prevented shocks and the VT/VF episodes.

Table 4. Clinical Characteristics of Patients With Multiple Implantable Cardioverter-Defibrillator Discharges

Patient Number	Age (yrs)	Gender	Symptoms	ECG Type	Familial Form	Baseline EP Study	ICD Shocks Before HQ	HQ Dose (mg/day)	ICD Shocks After HQ
1	18	M	Nocturnal SD	Permanent, coved-type	No	Inducible	16 in 37 months	600	0 in 26 months
2	40	M	Nocturnal SD	Permanent, coved-type	Familial SD	Not performed	>30 in 7 years and electrical storm	600	0 in 12 months
3	71	M	Nocturnal SD	Transient, coved-type	Familial BrS	Inducible	12 in 6 months	600	0 in 10 months
4	42	M	Nocturnal syncope	Permanent, coved-type	Familial SD	Inducible	6 in 4 months	600* then 900	0 in 10 months

*One shock with 600 mg/day.
EP = electrophysiological; M = male; other abbreviations as in Tables 1 and 2.

Effects of HQ on VT/VF inducibility. In previous reports, VT/VF inducibility in asymptomatic BrS patients varied from 12% to 64% (5,16–18). We have, in our BrS population, a rate at the upper limit (60%), which may be explained by two factors. First, according to recent recommendations (5,10), we have not investigated 12 patients with asymptomatic BrS and normal baseline ECGs. Inducibility is known to be low (18%) in this subpopulation of BrS (5). Then, it has been reported that VT/VF inducibility is high when, as in our series, two pacing sites are used and when the shortest coupling interval reaches the refractory periods (18).

Prevention of VT/VF inducibility with quinidine in BrS patients was first reported in 1999 by Belhassen et al. (11). These authors found after reassessment of a series of 34 patients with idiopathic VF treated with a class I antiarrhythmic, mainly quinidine, that five patients had BrS. They pointed out that VT/VF inducibility had been prevented in four (80%) of the five patients, a rate very close to the rate found here (76%). This seems a meaningful result, as these patients have a high reproducibility (85%) of their baseline inducibility (19). Identically, it is important to note that, even if the clinical relevance of drug-induced suppression of VT/VF inducibility has been recently questioned in predicting efficacy, especially in patients who have ischemic reentry, the physiopathologic situation is different here. In fact, in patients with BrS, the purported arrhythmia mechanism is different (phase 2 re-entry) (2,3). Also, the left ventricular function, which is the main predictor of outcome in patients with ischemic heart disease, is normal in BrS.

Effect of HQ on recurrence of arrhythmic events. The results obtained by Belhassen et al. (20) with quinidine were

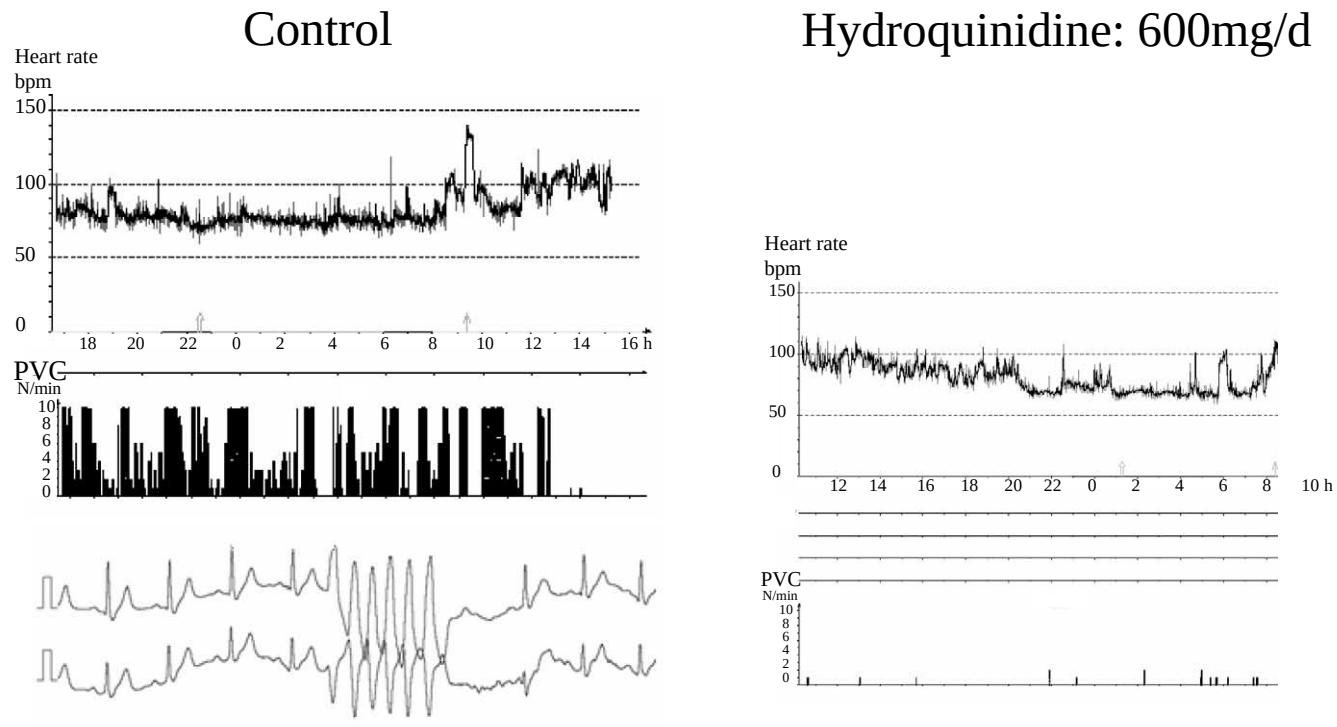

Figure 4. Effect of HQ in one of the four patients with BrS and multiple ICD shocks. Control = numerous salvoes of VT; HQ = dramatic reduction of ventricular arrhythmia after two days of treatment. Abbreviations as in Figure 1.

recently updated. Their experience included seven cardiac arrest survivors with a mean follow-up of 125 months. They did not observe the recurrence of arrhythmic events in the six symptomatic patients treated with quinidine. The seventh patient received an ICD because of extracardiac drug intolerance. High efficacy of quinidine has been also mentioned in isolated symptomatic cases (12,13). These observations are similar to the results observed here in the BrS patients with multiple ICD shocks.

In contrast, no other drug has been found to be effective in the clinical recurrence of the arrhythmic event, except a beta-agonist (12) and cilostazol (21) in isolated cases of electrical storms. The Brugada brothers related their experience in patients treated with amiodarone and/or beta-blockers in a study published in 1998 (4). The rates of an arrhythmic event during a follow-up of 34 months were similar (30%) in patients treated with antiarrhythmic drugs or with an ICD. Recently, the Defibrillator versus Beta-blockers for Unexplained death in Thailand (DEBUT) trial showed, in the sudden unexpected death syndrome, which includes a majority of BrS, that ICD was superior to beta-blockers in preventing sudden death (22). No mortality was observed in the ICD group, as compared with a sudden death rate of 18% in the beta-blocker group.

Effects of HQ in asymptomatic patients with BrS and inducible arrhythmia. Syncope occurred in 2 (9.5%) of the 21 asymptomatic patients with BrS and inducible arrhythmia who received HQ during a follow-up of 17 months. These events were associated with a major QTc prolongation in one case and related to possible noncompliance in another patient. Based on an intention-to-treat analysis, they represent a failure of the treatment. Monitoring of the QTc interval appears to be a useful tool to assess HQ cardiac tolerance and compliance—both crucial determinants. Syncope was observed in the only asymptomatic patient with BrS and inducible arrhythmia who had QTc interval prolongation >500 ms. Major QTc interval prolongation with HQ can occur in a subset of patients with BrS. QT interval prolongation and a BrS ECG pattern have been reported in a family with the *SCN5A* mutation (23). Any other genetic defect-producing action potential duration prolongation could also lead to the same phenotype with HQ treatment. We believe that in case of a major QTc interval prolongation, it is preferable to withdraw HQ. Conversely, when the QTc interval remains normal, noncompliance may be suspected and eventually confirmed by the plasma level. Of note, quinidine bisulfate was used in the Belhassen et al. (11) study and HQ chlorhydrate here. As these two drugs are two different active forms with different active metabolites, their plasma values, as well as their mean doses, are not comparable. Careful control of the QTc interval must be instituted in BrS patient receiving HQ and might improve the outcome of HQ therapy.

The rate of 10% (1 of 10 patients) of arrhythmic events during a period of 13 months in asymptomatic patients with BrS and inducible arrhythmia treated with a prophylactic ICD is similar to the 12% rate of arrhythmic events observed in asymptomatic patients followed for 31 months in the study from Brugada et al. (6), but our series had a shorter follow-up. Importantly, it is not appropriate to consider this group as a control group to assess the result of HQ therapy. First, treatment was not allocated after randomization. Then, HQ prevented VT/VF inducibility in patients receiving HQ, but not in patients treated with an ICD. This characteristic may be the consequence of different forms of channel disease.

HQ intolerance. In the work of Belhassen et al. (11), quinidine was stopped in one case (14%) because of extracardiac drug intolerance. Our experience is similar, with a rate of 14% (5 of 35) of HQ interruptions for extracardiac side effects (gastrointestinal intolerance).

Electrocardiographic changes with quinidine. Normalization of ST-segment elevation in BrS patients receiving quinidine was first described in two patients by Alings et al. (14). In the 35 BrS patients treated with HQ, we observed a reduction or normalization of the ECGs in 34% of cases. The reduction or normalization of the ST segment with HQ treatment was not correlated to prevention of VT/VF inducibility. This has been already described with one BrS patient treated with disopyramide (24). Spontaneous variations of ST-segment elevation cannot be ruled out and possibility accounts, in part, for ST-segment modifications.

Study limitations. The small number of patients, the short follow-up, and the absence of a control group and of ECG documentation of clinical events in patients receiving HQ (ECG loop recorder) are the main limitations of this preliminary study. Consequently, it is not adequate to recommend HQ therapy to all asymptomatic patients with BrS and inducible arrhythmia. A large, prospective, randomized, controlled trial employing the protection of ICDs is necessary to validate the true role of HQ in such a population.

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