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CLINICAL RESEARCH

New-onset atrial fibrillation as first clinical manifestation of latent Brugada syndrome: prevalence and clinical significance

Carlo Pappone[1]*, Andrea Radinovic[1], Francesco Manguso[1], Gabriele Vicedomini[1], Simone Sala[1], Francesco Maria Sacco[1], Giuseppe Ciconte[1], Massimo Saviano[1], Maurizio Ferrari[2], Elena Sommariva[2], Stefania Sacchi[1], Cristiano Ciaccio[1], Eleftherios M. Kallergis[1], and Vincenzo Santinelli[1]*

[1]Division of Electrophysiology and Cardiac Pacing, Department of Cardiology, San Raffaele University Hospital, Via Olgettina 60, 20132 Milan, Italy; and [2]Laboratory of Clinical Molecular Biology DIBIT 2, San Raffaele University Hospital, Milan, Italy

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Aims To evaluate the prevalence, clinical significance, and prognosis of latent Brugada syndrome (BrS) in patients with new-onset atrial fibrillation (AF) unmasked by class 1C antiarrhythmic drugs.

Methods and results Between January 2000 and June 2008, all consecutive patients with new-onset AF, who after flecainide exhibited typical Brugada ECG pattern, underwent electrophysiologic, pharmacologic, and genetic testing. Among 346 patients [median age 53 years; interquartile range (IQR), 15], 11 (3.2%; median age 51 years; IQR, 19) diagnosed as lone AF exhibited typical Brugada ECG pattern. Genetic testing was negative. Ventricular tachycardia/ventricular fibrillation (VT/VF) was induced by electrophysiologic testing (five patients) or during flecainide infusion (one patient). Six patients with type 1 ECG pattern and inducible VT/VF underwent ICD implantation. During a median follow-up of 31.5 months (range: 10–85) after ICD implantation, three patients developed BrS and one of them experienced VF. Patients without ICD (five patients) remained asymptomatic during a median follow-up of 74 months. Persistent type 1 pattern occurred only in the three patients who developed BrS.

Conclusion This study, for the first time, reveals the prevalence of latent BrS in patients with new-onset lone AF, which may precede VT/VF. Persistence of type 1 and ventricular tachyarrhythmias inducibility represents a marker of electrical instability leading to sudden death.

Keywords Brugada syndrome • Sudden cardiac death • Atrial fibrillation

Introduction

Electrocardiographically characterized by a distinct ST-segment elevation in the right precordial leads (V1–V3), the Brugada syndrome (BrS) is associated with a high risk of sudden cardiac death in young and otherwise healthy adults.[1–7] Recent studies have reported a close relationship between atrial fibrillation (AF) and BrS at risk,[8–18] but whether new-onset AF may be the first clinical manifestation of electrical instability preceding ventricular tachyarrhythmias in patients with latent BrS remains unknown. Concealed BrS may be unmasked by class 1C antiarrhythmic drugs (AADs),[19,20] which are frequently used worldwide in the growing AF population. Accordingly, the purpose of this prospective long-term study was to assess the prevalence, clinical significance, and prognosis of latent BrS unmasked by class 1C AADs in patients with new-onset AF.

Methods

All consecutive patients admitted to the Emergency Department who received intravenous administration of flecainide for termination of new-onset paroxysmal AF were recruited and those who exhibited

* Corresponding author. Tel: +39 02 26437310, Fax: +39 02 26437326, Email: carlo.pappone@hsr.it (C.P.); vincenzo.santinelli@hsr.it

typical Brugada ECG changes were selected for this prospective study. Patients with other causes of ST-segment elevation according to the BrS second consensus report were excluded from the study.[6] Patients who received other AADs and/or electrical cardioversion or those with ejection fraction <50% were also excluded. Clinical data such as age, gender, and family history of sudden cardiac death were collected and prospectively evaluated. Once identified, patients with latent Brugada ECG pattern underwent pharmacologic and electrophysiologic testing (EPT). The study design was approved by the hospital Ethics Committee after informed consent was obtained.

Pharmacologic testing

To assess a potential conversion to typical type 1 Brugada ECG pattern, patients with type 2 Brugada ECG pattern underwent pharmacologic testing with intravenous flecainide at a dose of 2 mg/kg body weight over 10 min with a maximum of 150 mg. The drug was administered during continuous electrocardiographic recording and, after administration of the last dose, the ECG was continuously recorded for another 10 min. The test was considered positive if type 2 ECG pattern converted to a coved-type ECG with an ST-segment elevation of more than 0.2 mV in more than one right precordial lead.

Electrophysiological testing

Electrophysiologic testing was performed in a fasting, drug-free, and non-sedated state in patients with typical type 1 ECG pattern. Programmed atrial and ventricular stimulation was performed up to three extrastimuli from the coronary sinus and the right ventricular apex or out-flow tract at two basic cycle lengths of 500 and 400 ms. S2 was shortened to the effective refractory period (ERP) of both the atrium and the ventricle, but the shortest coupling intervals of S3 and S4 were limited to 200 ms in the right ventricle.

Genetic testing

Potential SCN5A mutations (after written informed consent), which have been linked to BrS, were evaluated in all patients. Genomic DNA was extracted from peripheral blood with EZ1 Bio-Robot extractor (Qiagen). Molecular analysis was conducted on every exon of the SCN5A gene with intronic flanking regions (with exception of part of the 5′ non-translated region from −187 to −45, exon 1, and of the 3′ non-translated region from 6341 to 8313, exon 28) by polymerase chain reaction amplification. SCN5A reference sequences: NCBI NM_000335 (mRNA: nucleotides are numbered starting from the ATG) and NCBI NP_000326 (protein). Mutational screening was performed using Denaturing High Performance Liquid Chromatography (DHPLC, Transgenomic) and/or automated DNA sequencing (ABI 3130, Applied Biosystems).

Study endpoints

The primary endpoint was to evaluate the prevalence of latent typical Brugada ECG pattern and its clinical, electrophysiologic, and genetic characteristics among patients with new-onset AF. Brugada ECG pattern fluctuations on all available ECGs and follow-up data were also analysed.

Definitions

New-onset AF was defined as a first documented episode of symptomatic paroxysmal AF without prior history of the arrhythmia. Lone AF was defined as AF occurring in the absence of structural heart disease including a history of hypertension and left ventricular hypertrophy, as determined by the physical examination, electrocardiography, chest radiography, and echocardiography. Typical type 1 ECG Brugada pattern was considered a coved-type ST elevation >2 mm with descending terminal portion of the ST-segment in at least one right precordial lead[6,7] at the sternal margin of the third and fourth intercostal spaces. Typical type 2 ECG pattern was defined as a saddleback-shaped ST-segment elevation >1 mm.[6,7] Patients with typical Brugada ECG pattern who became symptomatic or experienced spontaneous life-threatening tachyarrhythmias were defined as BrS patients. Electrophysiologic testing was defined as positive if induction of ventricular tachycardia/ventricular fibrillation (VT/VF) required direct cardioversion and/or polymorphic VT lasted >30 s.[6,7] Sustained inducible AF was defined as AF induced by atrial extrastimuli lasting >30 s. An atrial extra-stimulus was delivered after eight beats of drive pacing at a basic cycle length of 500–600 ms. The S1–S2 interval was decreased in 10 ms steps until the ERP of the right atrial appendage was reached.

Follow-up

Patients underwent serial visits, including a 12-lead ECG, a 24 h ambulatory ECG recording regularly at 1, 3, and 6 months, and thereafter every 6 months or whenever clinical circumstances required unscheduled visits. The 12-lead ECG in the absence of drugs was analysed and PQ, QRS, and QTc intervals were measured. The QT interval was corrected using Bazett's formula ($QTc = QT/\sqrt{RR}$). The maximum P-wave duration was calculated in all 12-lead ECGs of the surface electrocardiogram simultaneously recorded. The measurements of the P-wave duration were performed manually by two of the investigators by using callipers and a magnifying lens (10-fold magnification). The onset of the P-wave was defined as the junction between the isoelectric line and the beginning of P-wave deflection, and the offset of the P-wave as the junction between the end of the P-wave deflection and the isoelectric line. To control for potential fluctuations and short-term changes, all available ECGs which were performed during in-hospital stay and at each unscheduled or regular follow-up visit were included into the analysis. ECGs were performed in the absence of AADs or any drug which affects cardiac repolarization and at normal electrolyte serum levels. The right precordial leads V1 and V2 were placed in the same position at each follow-up (at the sternal margin of the third and fourth intercostal space) and recorded by the same operator. In patients who underwent ICD implantation, the device was interrogated at each follow-up visit. ICD interventions were classified as appropriate or inappropriate on the basis of stored electrogram analysis. Atrial and ventricular tachyarrhythmias were documented by ECG, 24 h Holter recording, or by ICD data memory. All ICD interventions were reviewed by two experienced investigators.

Statistical analysis

The Fisher's exact test was used to measure the association for categorical variables. Mann–Whitney *U* test was used to compare differences for continuous variables between lone AF patients who did or did not exhibit typical Brugada ECG pattern. The General Linear Model Repeated Measures procedure was used to analyse the variance when the same measurements were made several times on each subject. All tests of significance were two-sided. A probability of ≤0.05 was considered significant. SPSS software for Windows release 17.0.0 (SPSS Inc.) was used for the statistical analysis.

Results

Between January 2000 and June 2008, among 1523 consecutive screened patients with new-onset AF, 346 [median age 53 years; interquartile range, 15; 59.8% male] were enrolled and successfully

treated with flecainide at a dose of 2 mg/kg for a first documented episode of paroxysmal AF. We excluded patients with acute myocardial infarction (353 patients) or congestive heart failure (235 patients) and those with chronic respiratory disease and right ventricular hypertrophy or systemic hypertension and left ventricular hypertrophy (141 patients). Many patients (448 patients) had other reasons to be excluded (AADs, cardioversions, psychotropic drugs, alcohol intoxication, thyroid dysfunction, etc.). No patient had prior ECG abnormalities consistent with Brugada ECG pattern and all of them had a normal ejection fraction. *Figure 1* shows enrolment and outcomes of the study population. Of the 346 patients, 190 had lone AF (60% male), 99 had hypertension without hypertensive cardiomyopathy, 35 had diabetes mellitus associated with hypertension, and 22 had stable coronary artery disease with prior myocardial infarction. Of the study population, 7 patients with hypertension (5 patients) and coronary artery disease (2 patients) showed transient atypical saddle-back ECG pattern, which did not convert to typical Brugada ECG pattern after flecainide challenge, while 11 patients (11/346, 3.2%), all diagnosed as having lone AF (11/190, 5.8%; median age 51 years, *Table 1*), exhibited typical type 1 ECG pattern (3 patients) or typical type 2 (8 patients) after or immediately before conversion to sinus rhythm (*Figure 1*). The characteristics of patients with lone AF who exhibited Brugada ECG pattern were not different from that of the remaining 179 patients who did not (*Table 1*). The clinical, electrophysiologic, and genetic characteristics of patients with typical Brugada ECG pattern are summarized in *Table 2*. A predominance of male patients was observed (9/11, 82%) (*Table 2*). All patients had no previous syncope or cardiac arrest (*Table 2*). Their medical history was unremarkable, while family history was positive for sudden cardiac death only in one patient (patient 11) (*Table 2*), and there was no family history of AF. Previous ECGs did not reveal any abnormalities including P-wave duration and morphology, QRS duration and ST-segment morphology. At admission, liver function, renal function, thyroid profile, serum electrolytes, and troponins were within the normal range. No evidence of other causes of ST-segment elevation was found. Flecainide challenge was able to convert type 2 into typical type 1 ECG pattern and in one patient transition was associated with VF development preceded by VT originating from the RVOT (*Table 2*; *Figure 2*). Data on results of programmed atrial and ventricular stimulation are presented in *Table 2*. Sustained inducible AF was observed in 4 patients and VT/VF was inducible in 5 out of 10 patients by two or three extrastimuli in the right ventricle apex or out-flow tract (*Figures 3* and *4*); AF and VT/VF were both inducible in 4 patients (*Table 2*). Genetic testing did not identify SCN5A mutations. Patients with positive EPT and the patient who had VF during flecainide infusion underwent ICD implantation (*Figure 1*).

Follow-up

The median follow-up period for the entire study population was 66 (range: 10–90) months and the follow-up duration for each patient is reported in *Table 2*. Patients with ICD had a median follow-up of 31.5 (range: 10–85) months, whereas those without

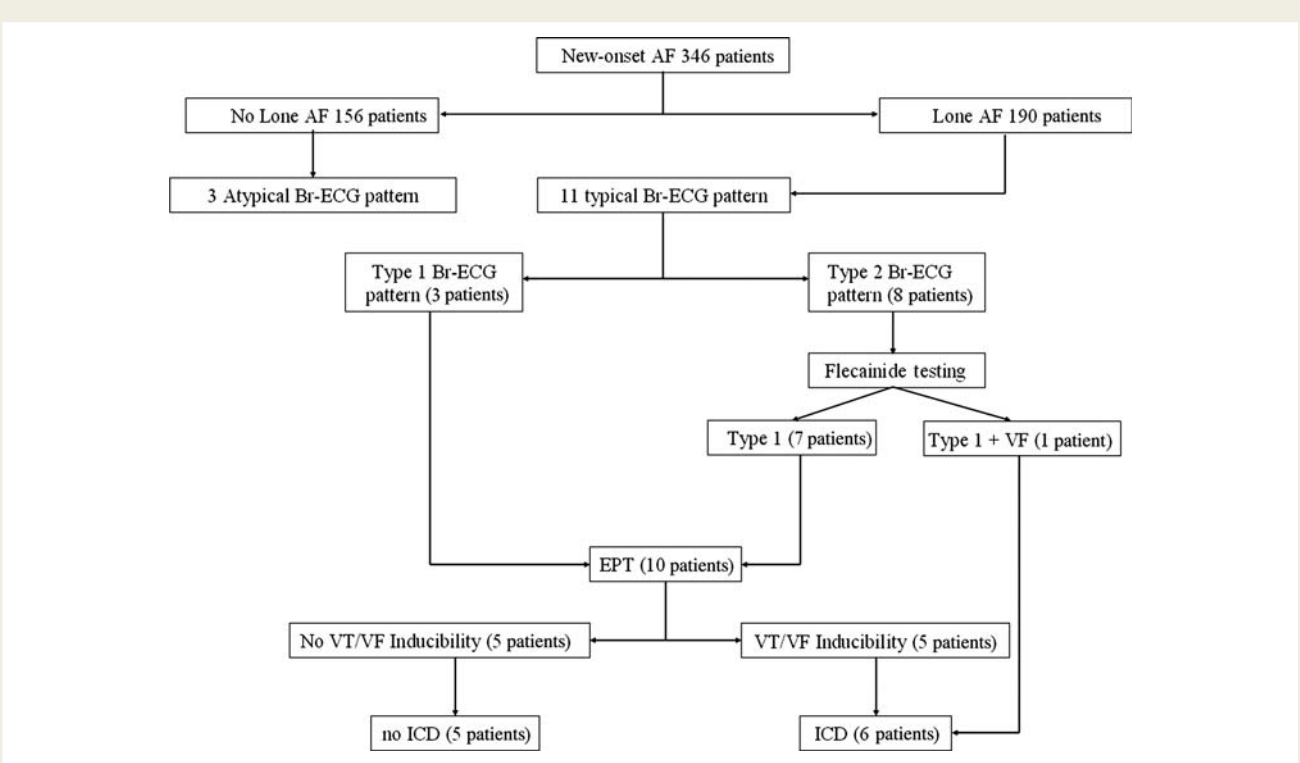

Figure 1 Enrolment and outcome of 346 patients with new-onset atrial fibrillation. Among 190 patients classified as having lone atrial fibrillation, 11 exhibited Brugada ECG pattern after flecainide. Six patients underwent ICD implantation and three of them developed Brugada syndrome.

Table 1 Characteristics of lone atrial fibrillation patients who did or did not exhibit typical Brugada ECG pattern

	No Br-ECG pattern, $n = 179$	Br-ECG pattern, $n = 11$	*P*-value
Age (years)	49 (44–53)	51 (39–58)	0.63
Male (%)	105 (58.7)	9 (81.8)	0.21
Ejection fraction	59 (58–65)	60 (56–65)	0.82
PQ duration (ms)	160 (155–170)	155 (151–170)	0.37
QRS duration (ms)	100 (90–110)	100 (95–108)	0.96
QTc interval (ms)	408 (400–415)	410 (398–410)	0.84
Max P-wave duration (ms)	120 (115–130)	120 (115–125)	0.54

Data are expressed as medians (25th percentile and 75th percentile) except when indicated.

had a median follow-up of 74 (range: 66–90) months. A total of 213 scheduled and unscheduled 12-lead surface ECGs were collected with a median number of ECGs per patient of 20, ranging from 13 to 35. The ECG intervals, including PR, QRS, and QTc intervals, remained unchanged in patients with and without ICD.

ICD patients

After ICD implantation (6 patients), a total of 58/83 ECGs (70%) were classified as typical coved type 1 pattern. During follow-up, three patients (patients 3, 7, and 9) experienced spontaneous episodes of VT/VF (*Table 2*). The time of the first episode occurred 13, 15, and 7 months after ICD implantation, respectively. Of them, two had dizziness due to self-terminating episodes of rapid ventricular tachyarrhythmias (>250 b.p.m.) not requiring ICD intervention and one patient had VF appropriately treated by ICD shock. ICD data analysis showed that before the onset of ventricular tachyarrhythmias, silent episodes of AF lasting 2, 5, and 7 h occurred. Also, only in these three patients, a type 1 Brugada ECG pattern was constantly documented in all available ECGs with maximal ST-segment elevation of 0.45 ± 0.21 mV. Among the remaining three patients with ICD, two (patients 8 and 10, *Table 2*) experienced silent episodes of AF lasting from 1 to 9 h, which in one occasion caused an inappropriate ICD intervention (patient 10) which did not require long-term therapy (*Table 2*). Overall, inducible, both atrial and ventricular, tachyarrhythmias were observed in four patients (patients 3, 7, 8, and 10) (*Table 2*). The PQ ($P = 0.19$), QRS ($P = 0.92$), QTc duration ($P = 0.38$), and maximum P-wave duration ($P = 0.09$) of patients with spontaneous AF and/or VF episodes were not different from the patients without recurrences.

No ICD patients

Among patients without ICD (5 patients), type 1 and/or type 2 patterns were documented in about 20% of all available ECGs (26/130 ECGs). Serial Holter monitoring did not document ventricular tachyarrhythmias or AF recurrence. A brief self-terminating silent episode of atrial flutter lasting about 10 min was recorded occasionally in one patient during Holter monitoring (patient 1) (*Table 2*). No patient exhibited permanent type 1 BrS.

Table 2 Characteristics of patients with lone atrial fibrillation and latent Brugada syndrome

Patient No.	Age	Gender	Family history	SCN5A mutation	Initial Br-ECG pattern	ECG pattern after flecainide	AF inducibility	VT/VF inducibility	ICD	Persistence of type 1 ECG pattern	Follow-up (months)	Arrhythmic events
1	64	F	–	–	CO	–	–	–	None	–	90	AFL
2	45	M		–	SB	CO	–	–	None	–	88	
3	58	M	–	–	SB	CO	+	+	ICD	+	85	VT+AF
4	39	M	–	–	SB	CO	–	–	None	–	74	
5	36	M	–	–	SB	CO	–	–	None	–	69	
6	44	M	–	–	SB	CO	–	–	None	–	66	
7	51	M	–	–	CO	–	+	+	ICD	+	45	VT+AF
8	74	F	–	–	SB	CO	+	+	ICD	–	35	AF
9	31	M	–	–	SB	CO+VF	0	0	ICD	+	28	VF+AF
10	58	M	–	–	CO	–	+	+	ICD	–	18	AF
11	55	M	+	–	SB	CO	–	+	ICD	–	10	

AF, atrial fibrillation; AFL, atrial flutter; BrS, Brugada syndrome; CO, coved-type ECG pattern; SB, saddle-back type ECG pattern; VF, ventricular fibrillation; VT, ventricular tachycardia.

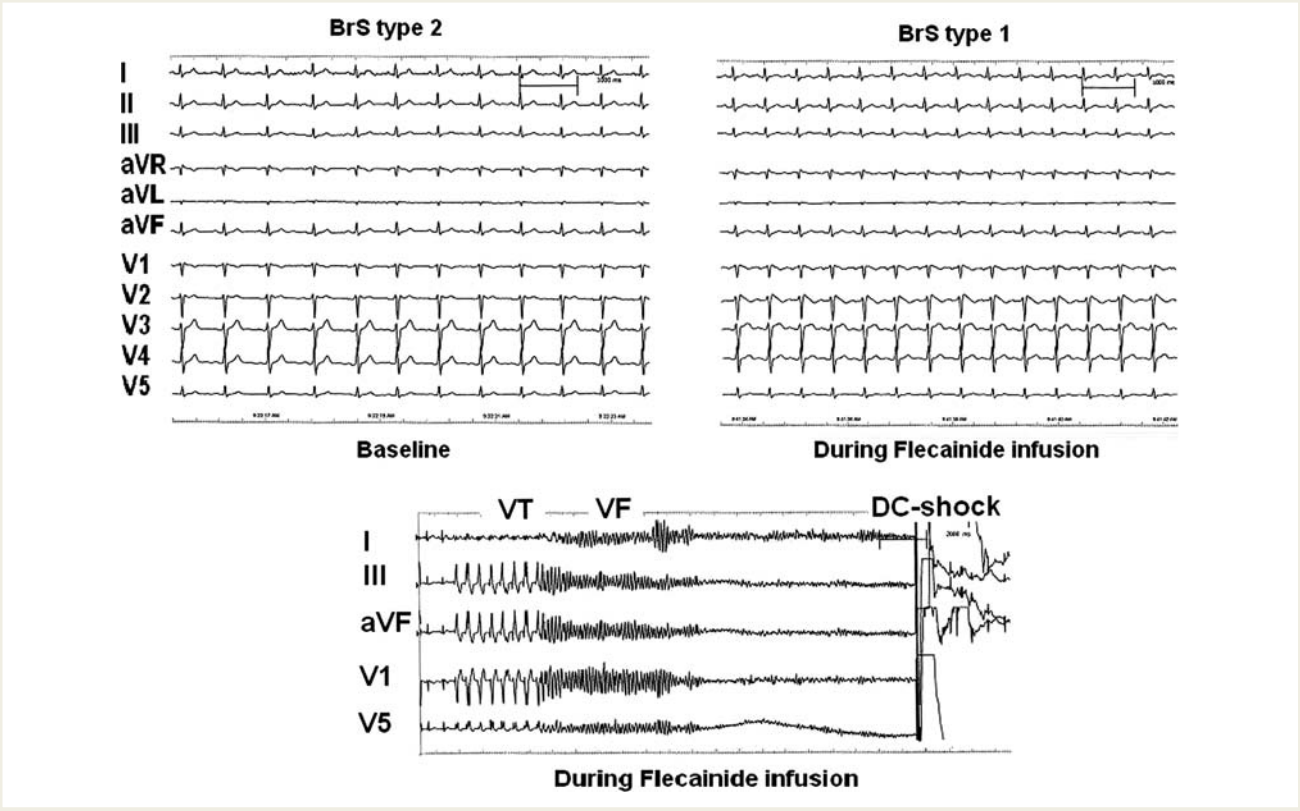

Figure 2 Patient 9. The figure shows conversion from type 2 ECG pattern to typical type 1 Brugada syndrome ECG pattern during drug challenge with flecainide (top two panels). Ventricular fibrillation developed at the end of drug administration and required DC shock for termination (bottom panel).

Discussion

Main findings

This study, for the first time, reveals the prevalence of latent BrS in patients with new-onset AF treated with class 1C antiarrhythmic agents, which is 3.2% (11/346) and 5.8% (11/190) in the subgroup of lone AF patients. Among the 11 patients with new-onset AF and newly unmasked Brugada ECG pattern, 3 developed BrS (3/11, 27.3%) and 1 developed VF (1/11, 9.1%), appropriately treated by an ICD shock. None of the patients had SCN5A mutation. Six patients received ICD implantation because of inducible VT/VF and flecainide-induced VF. Self-terminating VT was documented in two patients and VF in one patient, appropriately treated by ICD shock. Persistence of typical type 1 ECG pattern and inducibility of VT/VF characterize subjects with new-onset AF and newly unmasked Brugada ECG pattern at risk of developing life-threatening tachyarrhythmias.

Latent Brugada syndrome in patients with lone atrial fibrillation

Patients with BrS can display a variety of symptoms ranging from totally asymptomatic subjects to patients who die suddenly. Syncope, seizures, palpitations, and nocturnal agonal respiration have all been reported as the first symptom at presentation. Up to 20% of the patients have concomitant supraventricular tachyarrhythmias,[16,17] frequently AF. However, whether AF may be the first clinical manifestation of a latent BrS preceding ventricular tachyarrhythmias and sudden cardiac death is unknown. In the present study, among 346 patients with new-onset AF, 190 were diagnosed as having lone AF, 11 of them exhibited typical Brugada ECG patterns, 3 developed BrS (3/11, 27.3%), and 1 patient (1/11, 9.1%) experienced VF. It is well known that patients with lone AF represent a minority of the entire AF population with a prevalence ranging from 2 to 11%, which indicates that after applying strict criteria this form may be even much more rare than previously considered. In our series of patients with latent Brugada ECG pattern, VF occurred in one patient, but two other patients experienced self-terminating life-threatening tachyarrhythmias which suggest that the risk of sudden death could be higher. Our observations while supporting recent studies on the close relationship between AF and life-threatening events,[13] for the first time, document that new-onset AF may precede life-threatening events and VF, representing a marker of both atrial and ventricular electrical instability of latent BrS. Identification of such population is necessary, since, unlike lone AF patients who have a normal life expectancy,[21] BrS patients may be at risk of sudden cardiac death.[5,6] Of note, in the initial report by Brugada *et al.*,[1] two out of the eight affected subjects had paroxysmal AF and one patient was suffering from episodes of AF soon after birth, preceding syncopal episodes in childhood, suggesting that

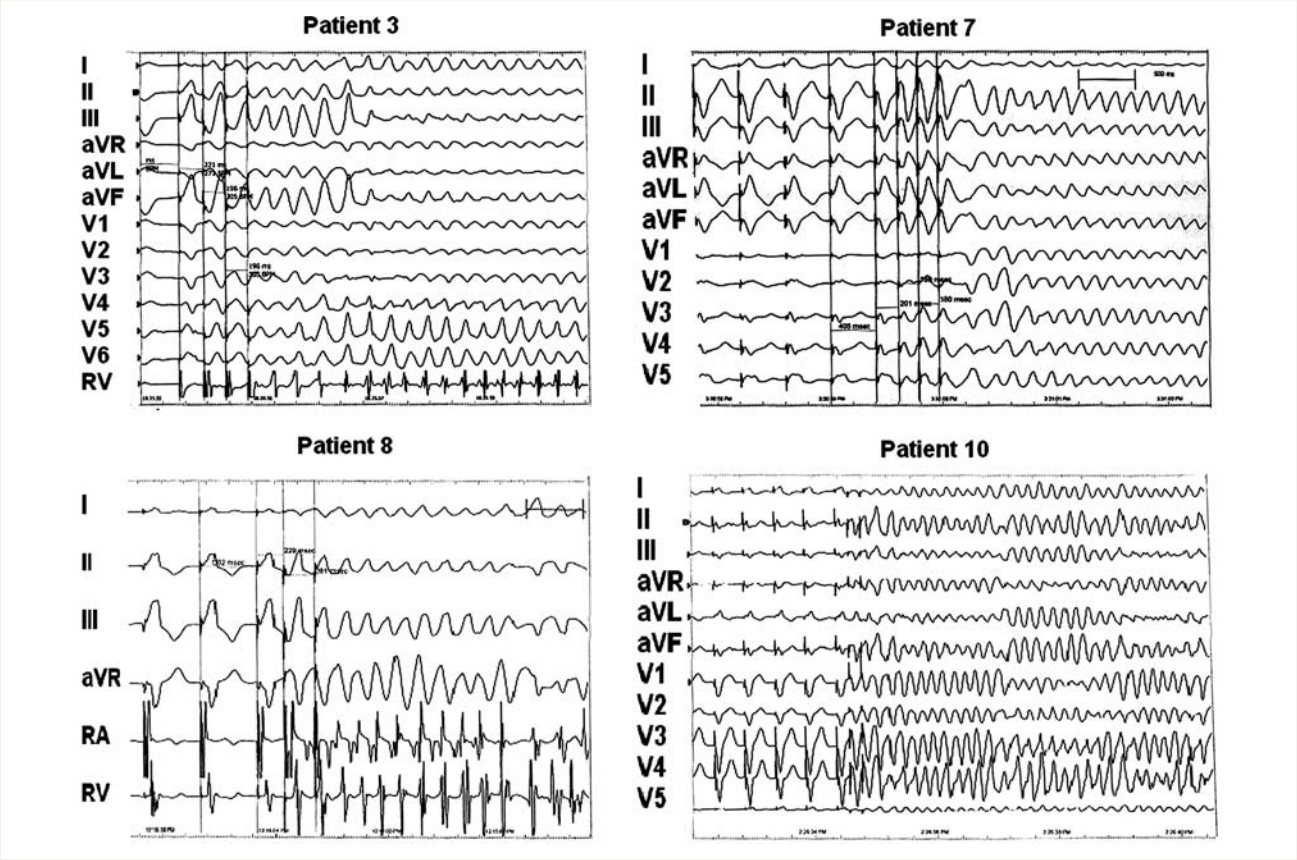

Figure 3 Induction of ventricular tachycardia/ventricular fibrillation by programmed ventricular stimulation with triple (patients 3 and 7) or double (patients 8 and 10) extrastimuli applied in the right ventricle.

paroxysmal AF may be considered a marker of both atrial and ventricular electrical instability which in some cases may precede the onset of ventricular tachyarrhythmias. Recently, Kusano *et al.*[8] stated that in patients with diagnosed BrS, spontaneous AF and VF are closely linked clinically and electrophysiologically. Also, a higher incidence of atrial arrhythmias including AF has been reported in BrS patients with an ICD than in those without.[16]

Electrophysiologic profile of patients with lone atrial fibrillation and latent Brugada syndrome at risk of sudden death

Risk stratification in BrS is complex and in the asymptomatic population it is still controversial.[3–6] At present, the most important risk factors include previous cardiac arrest, the presence of spontaneous or induced typical diagnostic ECG pattern, and ventricular inducibility, but in asymptomatic patients, usefulness of EPT is debated.[3–5] Recently, Eckardt *et al.*[4] demonstrated that a spontaneous-coved type 1 ECG was predictive of worse outcome, which suggests that persistence of this pattern may increase the probability to develop life-threatening ventricular tachyarrhythmias. In the present study, persistence over time of the typical type 1 Brugada ECG pattern characterized BrS patients who developed life-threatening ventricular tachyarrhythmias and VF. Inducibility was also important since one-half of patients with inducible VT/VF became symptomatic for life-threatening tachyarrhythmias. Of note, frequent symptomatic episodes of AF after the first one were recorded in patients who experienced tachyarrhythmias, but asymptomatic AF episodes were also recorded in patients who did not. Patients without ICD had a lower incidence of AF episodes during the follow-up, but this may be due to latent episodes not being detected despite serial Holter ECGs. Patients with inducible VT/VF who remained asymptomatic did not show type 1 persistence but transient fluctuations of Brugada ECG pattern with frequent ECG normalization in all available ECGs were recorded suggesting that risk may be lower in patients with transient ECG normalization or fluctuation. Veltmann *et al.*[22] emphasized that over a total of 310 ECGs of BrS patients, the rate of inducible VF was significantly higher in patients with more than 50% type 1 ECGs than in those with less than 50% diagnostic ECGs. More recently, Richter *et al.*[23] have reported that type 1 ECG pattern was associated with a higher incidence of appropriate ICD shocks. The results of our study while confirming these findings underline the need to accurately analyse the persistence of coved-type ECG pattern with potential amplitude changes in a large number of ECGs to determine persistence of electrical instability over time. In the present study, no mutations in the SCN5A gene were found, which is in agreement with previous

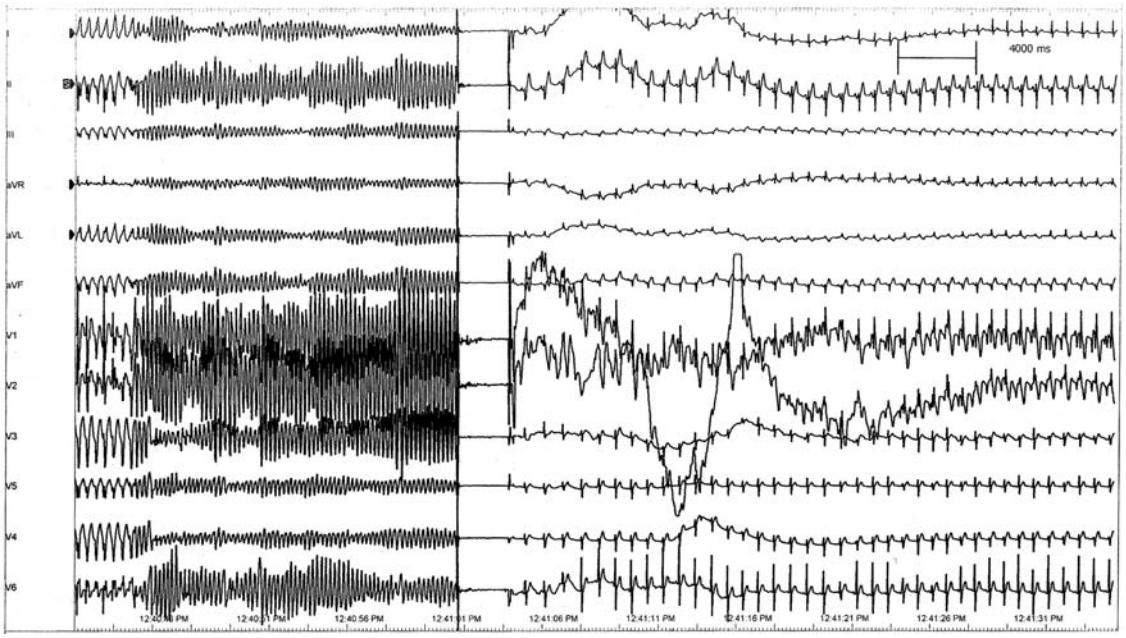

Figure 4 Patient 11. Continuous 12-lead ECG recording showing induction by two extrastimuli delivered in the right ventricle of atypical ventricular tachycardia degenerating into ventricular fibrillation, which was terminated by DC shock. The paper speed is 5 mm/s.

studies reporting SCN5A mutations in only 18 to 30% of patients with BrS.[6] In addition, the incidence of SCN5A mutations can vary widely according to whether the patients were familial or sporadic cases of BrS.[24] The authors did not identify any SCN5A mutation among the 27 sporadic cases of BrS, suggesting a genetic heterogeneity of the disease. Finally, our experience suggests that the self-administered 'pill-in-the pocket' approach with class 1C AADs, which has been recently suggested as a therapeutic strategy in patients with new-onset AF and structurally normal hearts,[25] may be unsafe and perhaps should be avoided unless administered previously in the hospital.

Study limitations

Although many regions of SCN5A gene for mutations were analysed in this study, the possibility of SCN5A polymorphism or mutations occurring in other regions of the gene cannot be completely excluded. Patients with new-onset AF and ejection fraction $<50\%$ or those with contraindication to flecainide were excluded from the study; therefore, our results do not apply to this patient population. Future studies with larger numbers of patients are needed to define the risk of sudden death in patients with lone AF and newly unmasked Brugada ECG pattern.

Conclusions

This study, for the first time, reveals the prevalence of latent Brugada ECG pattern in new-onset lone AF population. Among newly unmasked Brugada ECG pattern patients, about one-third may develop a BrS, which may lead to sudden cardiac death. In these patients, persistence of typical type 1 ECG pattern and ventricular tachyarrhythmias inducibility may represent a marker of sudden cardiac death. These findings open up new lines of research to better identify patients with new-onset lone AF and latent BrS at potential risk of sudden cardiac death.

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Conflict of interest: none declared.

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