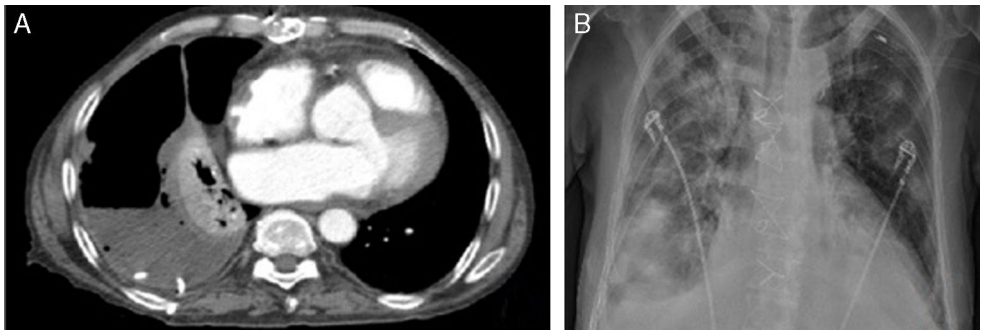

Figure. A, Computed tomography in patient 1, with correctly positioned chest drainage. B, Plain chest X-ray of patient 2 before chest drainage.

Antifungal combinations are reserved for cases of therapeutic failure. In these cases, a personalized approach is necessary.[5]

Pharmacological prophylaxis against fungal infections in recipients of solid organ transplants, such as heart transplants, is not general practice, but recent guidelines recommend considering fungal prophylaxis with echinocandins, voriconazole, or amphotericin B in patients considered at high risk (those undergoing hemodialysis, post-transplant surgical procedures, environmental colonization by *Aspergillus*, or documented prior cytomegalovirus infection).[3] Clinical suspicion and early treatment initiation are associated with lower mortality, but long-term therapy is often required and, at times, surgical resection is performed.

It is essential to conduct an individualized benefit-risk assessment. Clinicians should be aware at an early stage of the possibility of opportunistic infections and adjust accordingly the therapeutic algorithms in each hospital to individual risk factors (obesity, prior diagnosis of diabetes mellitus, repeat intervention for bleeding conditions, and the results of epidemiological surveillance).[6] In our center, monthly epidemiological surveillance is undertaken in areas of surgery related to the heart surgery department. There were no findings during the aforementioned period. Nevertheless, after isolation of *Aspergillus fumigatus* in 4 patients who underwent heart transplant (2 cases of parenchymal involvement and 2 of pleural empyema), we decided to return to universal prophylaxis for the first 6 post-transplant months with weekly inhaled amphotericin B. This drug was chosen because of its weaker interactions with immunosuppressants. After these first 6 months, treatment is individualized for each patient.

CONFLICTS OF INTEREST

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Antitachycardia Pacing Effectiveness for Monomorphic Ventricular Tachycardia in Brugada Syndrome After Quinidine Administration

Taquicardias ventriculares monomórficas en pacientes con síndrome de Brugada tratados con quinidina: eficacia de la estimulación antitaquicardia

To the Editor,

Implantable cardioverter-defibrillator (ICD) implantation is the first-line therapy for patients with Brugada syndrome (BrS) in secondary prevention after malignant ventricular arrhythmias (VA) or sudden death. After ICD implantation, the incidence of VA and high-energy shocks is high,[1] thereby resulting in a significant impact on quality of life and prognosis.

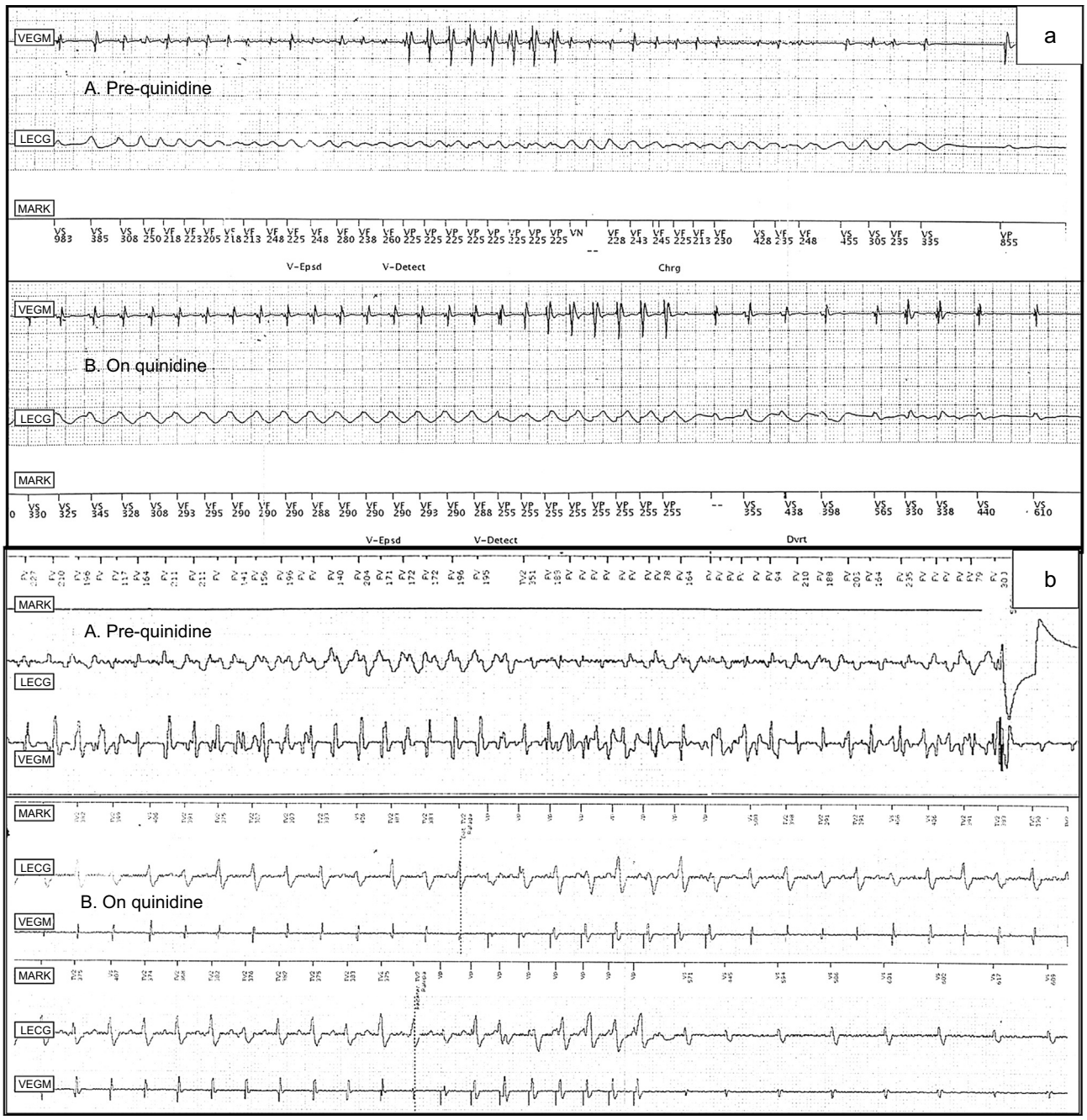

Figure. A: Pre-quinidine: syncopal polymorphic VT (230 ms cycle length) degenerating into VF treated with unsuccessful ATP and spontaneously terminated; On Quinidine: monomorphic fast VT accelerating from initial 320 ms to 290 ms successfully terminated by ATP. B: Pre-quinidine: polymorphic VT treated with shock; On Quinidine: monomorphic slightly irregular slow VT (390 ms cycle length) terminated by first ATP ramp after 3 failed ATP bursts (last failed bursts is shown before the successful ATP ramp. ATP, antitachycardia pacing; Chrg, charge; Dvrt, diverted therapy; LECG, "leadless" ECG; MARK, channel mark; V-Detect, ventricular detection; VEGM, ventricular electrogram; V-Epsd, ventricular episode; VF, ventricular fibrillation; VP, ventricular pacing; VS, ventricular sensing; VT, ventricular tachycardia.

Table
Patient Characteristics

Patient	Age, y	Sex	Familial BrS or SD	Atrial fibrillation	Clinical presentation	ECG pattern	RBBB	EPS	Genetic testing	Reason for quinidine initiation	Time ICD-quinidine (mo)	Follow-up on quinidine (mo)	Drug	Adverse effects
1	24	M	No	No	SD	Spontaneous type 1	No	Not performed	Not performed	Multiple syncopes for NS PVT	19	12	Hydroxiquinidine 1000 mg	Yes, diarrhea
2	64	M	No	No	Multiple syncopes	Drug induced type 1	No	VF inducible	BrS and ARVC negative	Multiple shocks (4) for PVT	24	50	Hidroxiquinidine 1000 mg	No
3	41	M	No	No	SD	Spontaneous type 1	Yes	Not performed	BrS negative	Multiples shocks (9) for VF	48	72	Quinidine bisulphate 600 mg	No

ARVC, arrhythmogenic right ventricular dysplasia; BrS, Brugada syndrome; ECG, electrocardiogram, EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; M, male; NS PVT, nonsustained polymorphic ventricular tachycardia; PVT, polymorphic ventricular tachycardia; RBBB, right bundle branch block; SD, sudden death; VF, ventricular fibrillation.

Recently, there has been increasing evidence of the use of quinidine as an adjuvant treatment[2] in ICD patients with frequent episodes of malignant VA. Quinidine inhibits outward transient K current (I_{to1}), which is believed to result in homogenization of the repolarization of the epicardial layers by restoring the action potential dome where I_{to1} currents are predominant, as in the epicardium of the right ventricular outflow tract.[3] Despite quinidine treatment, some patients continue to experience episodes of VA. The presence of monomorphic ventricular tachycardias (MVT) in BrS patients has been previously described, is linked to variable mechanisms and is sometimes responsive to antitachycardia pacing (ATP).[4] There have been no reports of the modification of malignant VA to MVT amenable to ATP termination in patients under quinidine treatment. We present a series of 3 patients showing a possibly novel effect of quinidine on the pattern of VA in patients with BrS.

We reviewed all episodes of VA among 29 patients with BrS under treatment with quinidine due to frequent ICD shocks included in a Spanish national registry.[5] We describe 3 patients from this registry who showed MVT terminated by ATP (Table). The general characteristics of the registry have been described elsewhere.[5]

Patient 1 presented with sudden death at the age of 24 years. He had spontaneous type 1 Brugada pattern in leads V_1-V_2. An ICD was implanted. After 19 months, he experienced an episode of syncope due to polymorphic ventricular tachycardia (PVT) and near-syncope episodes due to unsustained PVTs. Hydroxiquinidine (1000 mg/d) was started. The patient had not experienced any syncope or PVT since quinidine initiation, but after 12 months of follow-up he had 2 episodes of MVT terminated with a burst of ATP (Figure A).

Patient 2 had experienced several episodes of syncope at the age of 64 years. He showed type 2 Brugada pattern (type 1 after ajmaline). An ICD was implanted. Following ICD implantation, he had 4 episodes of ventricular fibrillation (VF) treated with shocks and therefore hydroxiquinidine was started (1000 mg/d). During 50 months of follow-up, he had no VF episodes; nevertheless, he had 62 episodes of MVT that were all terminated with bursts of ATP.

Patient 3 had an episode of aborted sudden death at the age of 41 years; his baseline electrocardiogram showed type 1 Brugada pattern. Four years after ICD implantation, quinidine bisulphate (600 mg) was initiated due to 9 episodes of VF treated with shocks. After 72 months of follow-up and no VF episodes, he had 1 episode of MVT (cycle 280 ms) terminated with a burst of ATP (Figure B). At present, the 3 patients are still on quinidine treatment (a mean treatment duration of 45 months) without no episodes of PVT or VF.

The most relevant finding of this case series is the modification of VA pattern in these BrS patients treated with quinidine, with no recurrence of PVT/VF but instead with MVT terminated by ATP without requiring high-energy shocks.

These results introduce new data on the analysis of the mechanism of VA in patients with BrS and the interaction between these mechanisms and the effect of quinidine.

According to the most accepted theories, the net outward shift of ionic currents during the end of phase 1 of the action potential results in an accentuation of the action potential notch, leading to the dispersion of repolarization and creating the substrate for phase 2 reentry and VA.[3] Recently, it has been suggested that alterations of depolarization are the mechanisms underlying the clinical manifestations of BrS: late potentials and fractionated electrogram have been observed in the epicardium of the right ventricular outflow tract.[6] Structural abnormalities have been described such as hypertrophy, fibrosis, and fatty infiltration in the right ventricular outflow tract, related to slowed conduction.

The presence of subtle structural abnormalities could favor the development of reentrant circuits and explain the finding of MVT in these patients. In this setting, quinidine could stabilize right ventricular outflow tract excitability and facilitate the conversion of malignant VA into more stable and regular MVT responsive to ATP. The positive response to ATP reinforces the idea of a reentrant circuit with excitable gap; it might be that quinidine-mediated slowing of conduction could facilitate the ATP burst to propagate to the circuit, depolarize the excitable gap, and extinguish reentry.

In view of this finding, it can be proposed that patients with BrS treated with quinidine due to frequent ICD shocks might benefit from the introduction of a fast VT zone with 1 or 2 ATP bursts since it has proven effectiveness in MVT termination and shock reduction. Further research is needed to confirm this uncommon VA pattern in BrS after quinidine treatment and elucidate its mechanism.

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Inconclusive Exercise Stress Echocardiography in Patients With Chest Pain: Prevalence and Clinical Determinants

Prevalencia y determinantes clínicos de ecocardiografía de esfuerzo no concluyente en pacientes con dolor torácico

To the Editor,

Chest pain is a common presenting complaint in the emergency room. The guidelines recommend using different techniques for diagnosis of chest pain of possible coronary origin.[1] The most important factor for choosing one technique over another is the competence of the local imaging laboratory. In Spain, the technique of choice is exercise stress echocardiography (ESE). This is a simple, inexpensive physiological test that is widely available. However, a certain percentage of ESE studies are inconclusive.

Our objective was to analyze the clinical determinants of inconclusive ESE in 452 consecutive patients who attended our emergency room for chest pain of probable coronary origin between January 2011 and December 2014. The symptom-limited Bruce protocol was used, although use of other protocols such as the modified Bruce protocol or the Naughton protocol was left to the discretion of the clinician, who also determined whether atropine or contrast echocardiography was used. ESE was considered inconclusive when the test was not positive for ischemia due to echocardiographic criteria and a heart rate (HR) of 85% the age-predicted maximum heart rate or a sufficient work load (6 MET for ages $\leq$ 75 years and 4 MET for ages above 57 years) was not reached or when contractility could not be assessed at the time of peak exercise.[2] For selection of the predictive logistic regression model, the *allsets* command of STATA version 13.0 was used and the coefficients of the regression model were calculated by binary logistic regression (*enter* method).

In total, 132 ESE (29%) were inconclusive (106 [80%] because they did not reach the HR target, 36 [27%] because they did not reach a sufficient work load, and 11 [8%] because it was impossible to assess segmental contractility at peak exercise). The characteristics of the study population are shown in Table 1. The patients with inconclusive ESE had a longer hospital stay (3 [1-4] days vs 1 [1-2] days; $P < .001$) and a higher number of additional tests (27% vs 4%; $P < .001$). In 23 patients with inconclusive ESE, coronary anatomy was studied and significant coronary artery disease was detected in 8 of these (34%).

Table 2 shows the best-fit model for predicting inconclusive ESE, with C statistic = 0.69 (95% confidence interval [CI], 0.63-0.74), Akaike information criterion index = 485, Bayesian information criterion = 509, and adequate calibration (Hosmer-Lemeshow test, $P = .87$). All factors included in the model for predicting inconclusive ESE were related to the criteria with an impact on the result. Obese patients and those with chronic obstructive pulmonary disease had a worse acoustic window and, along with patients with atrial fibrillation, usually had worse functional class. On the other hand, baseline HR < 70 bpm increased the probability that the HR target for a conclusive test was not reached.

Our study showed a rate of inconclusive ESE of 29%. In the literature, the rate of inconclusive provocation tests varies widely according to the type of study, the patient profile, and the level of care in which testing occurs. The series of simple ergometry in chest pain units have a rate of inconclusive studies of 22% to 39%.[3] Although ergometry includes electrocardiogram-dependent criteria, the main reason for an inconclusive study is not attaining target HR,[4] a criterion shared with ESE and one that was also a main reason for inconclusive results in our study. A meta-analysis of ESE or a pharmacologically-based test showed a rate of inconclusive studies of 27%.[5]

The importance of inconclusive ESE should not be ignored. On the one hand, patients with inconclusive ESE have a higher risk of