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RHYTHM DISORDERS AND ELECTROPHYSIOLOGY

CLINICAL CASE

Ranolazine-Induced Type 1 Brugada Pattern

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ABSTRACT

BACKGROUND Brugada syndrome (BrS) is a rare inherited arrhythmia disease carrying a variable risk of sudden cardiac death. Diagnosis requires the type 1 Brugada electrocardiographic pattern, which can either be spontaneous or induced by sodium channel-blocking drugs. Ranolazine is an antianginal drug acting on the late sodium current with emerging antiarrhythmic properties; no information is available on the safety of ranolazine use in patients with BrS.

CASE SUMMARY We present the case of a 48-year-old man with recent history of ST-elevation myocardial infarction and residual microvascular angina who developed a type 1 Brugada pattern after starting therapy with ranolazine.

DISCUSSION Ranolazine has been demonstrated to be effective as an antiarrhythmic drug in several conditions in which other sodium-channel blockers are currently employed (eg, atrial fibrillation and type 3 long QT syndrome). Given the mechanism of action, it is plausible to hypothesize a potential role of ranolazine in unmasking the type 1 Brugada pattern.

TAKE-HOME MESSAGES Evidence of the safety of ranolazine in patients with BrS is lacking. A possible connection between ranolazine assumption and the unmasking of a type 1 Brugada pattern may question its use in these patients.

HISTORY OF PRESENTATION

A 48-year-old man with class 2 obesity, type 2 diabetes, hypercholesterolemia, smoking habit, and recent history of ST-segment elevation myocardial infarction (STEMI) underwent a stress/rest myocardial single-photon emission computed tomography 6 months after the acute event. The examination revealed a reversible perfusion defect of the mid-anterior and midanterolateral wall. Thus, a new coronary angiography was executed, showing good results of the previous intervention and no worsening of the coronary disease on the remaining vessels. A mild stenosis on the mid left anterior descending artery was functionally studied with fractional flow reserve, with negative result (fractional flow reserve: 0.88) (**Figure 1**). On the assumption of a microvascular disease, the patient was started on ranolazine 375 mg twice a day. Blood tests executed during his hospital stay showed normal

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ABBREVIATIONS AND ACRONYMS

BrS = Brugada syndrome

ECG = electrocardiogram

STEMI = ST-segment elevation myocardial infarction

liver and kidney function. The electrocardiogram (ECG) recorded at patient discharge is shown in Figure 2A. At the 1-month follow-up visit, ECG showed a type 1 Brugada pattern (Figure 2B).

PAST MEDICAL HISTORY

Six months earlier, the patient had undergone urgent coronary angiography for anterolateral STEMI. A thrombotic occlusion of a large first diagonal branch had been successfully treated with primary percutaneous coronary intervention. During that hospital stay, the patient had been diagnosed with type 2 diabetes and hypercholesterolemia; dapagliflozin, semaglutide, and high-dose atorvastatin had been initiated. The hospitalization had been uneventful, and the patient had been discharged 1 week after admission.

DIFFERENTIAL DIAGNOSIS

At the 1-month follow-up visit after the most recent hospitalization, at the time of Brugada syndrome (BrS) diagnosis, recent anamnesis was negative for chest pain, dyspnea, palpitations, or syncope; when asked some pointed questions, the patient reported a history of sudden death of uncertain cause in his maternal uncle. After the visit, 12-lead Holter monitoring was started and demonstrated the persistence of the type 1 Brugada pattern during the entire 24 hours recorded. Ranolazine was withdrawn, and 1 week later a complete regression of the electrocardiographic ST-segment modifications in V_1-V_2 was observed (Figure 2C). Genetic testing was recommended, however the patient declined.

TAKE-HOME MESSAGES

- Loss-of-function mutations in the *SCN5A* gene have been related to Brugada syndrome; accordingly, different sodium-channel blockers can unmask the type 1 Brugada pattern.
- Ranolazine inhibits the late I_{Na} current in cardiomyocytes and has demonstrated therapeutic properties in conditions associated with *SCN5A* gain-of-function mutations such as long QT syndrome type 3.
- This case suggests that ranolazine can unmask a type 1 Brugada ECG pattern; as a consequence, the safety of the drug when Brugada syndrome is suspected deserves targeted investigations.

INVESTIGATIONS

Three weeks after discontinuation of ranolazine, the patient experienced a sudden syncope which occurred after several episodes of nausea and emesis lasting for 2 days; the ECG was unremarkable. Referred to the cardiology unit for further examinations, the ajmaline test was executed and induced a type 1 Brugada pattern. In view of the uncertainty about the nature of the reported syncopal episode, a programmed electrical stimulation was performed and resulted in inducible ventricular tachycardia (Figure 2D).

MANAGEMENT

After a comprehensive assessment of the patient's risk profile and preference, a subcutaneous

FIGURE 1 Fractional Flow Reserve Evaluation of the Left Anterior Descending Artery

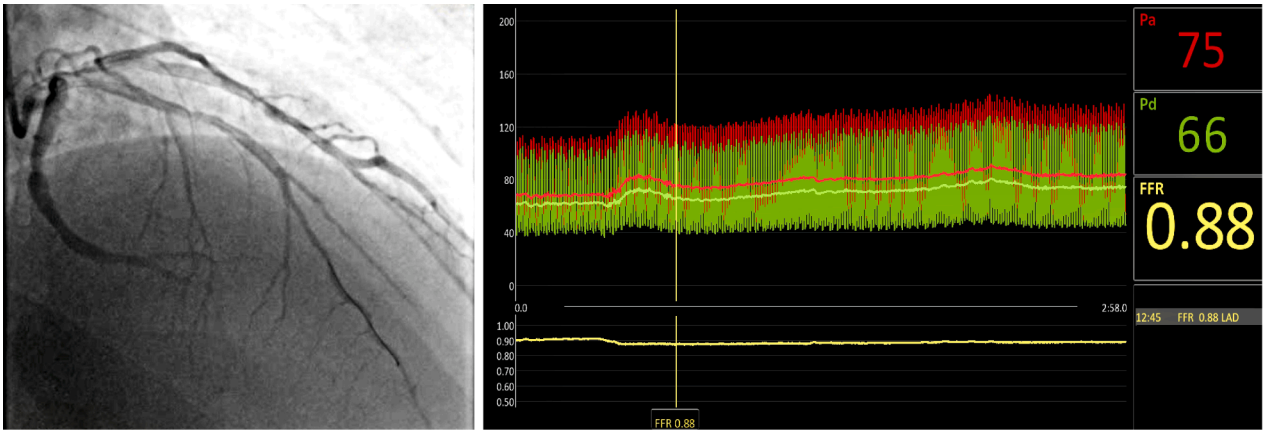
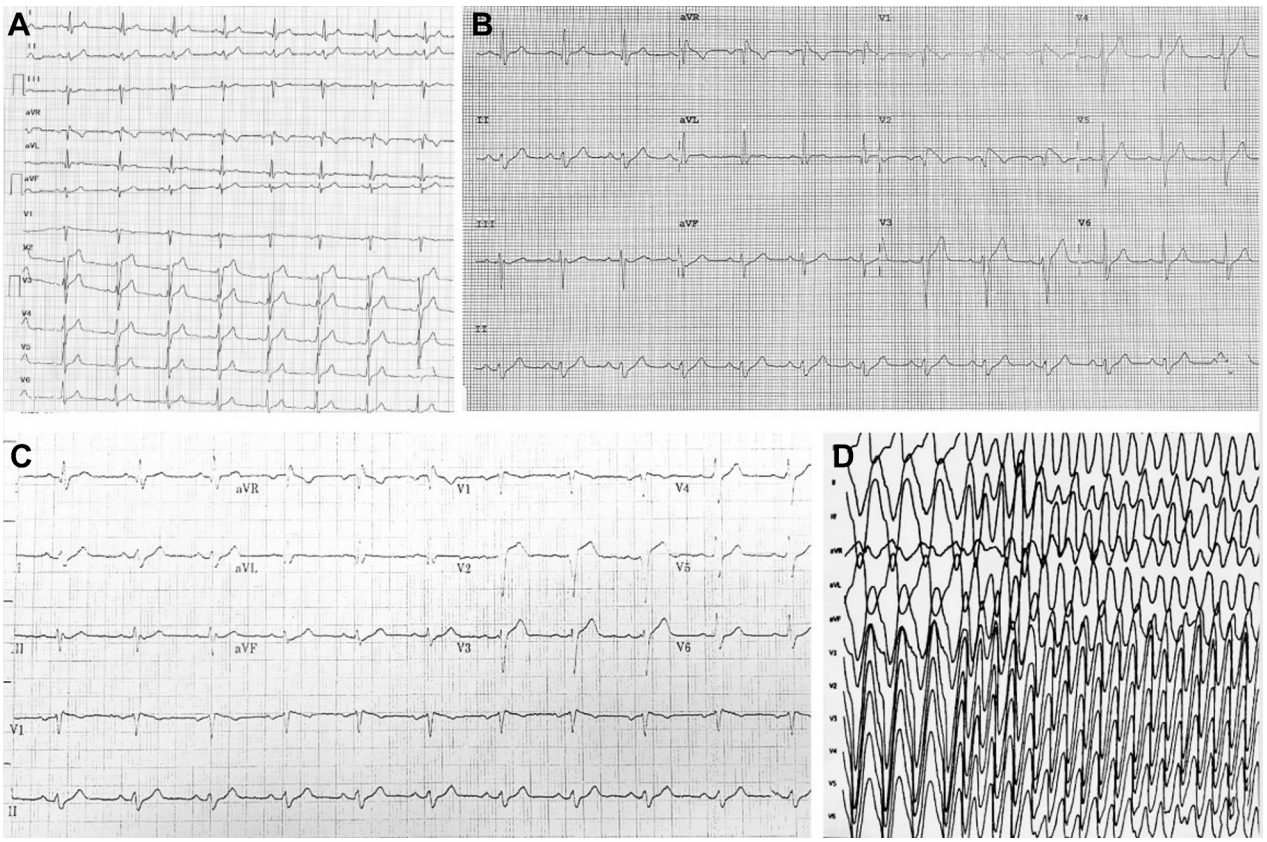


FIGURE 2 **ECG Tracings**



(A) ECG recorded at patient discharge. (B) ECG recorded after ranolazine administration (during the 1-month follow-up visit) showing type 1 Brugada pattern. (C) Complete regression of the ST-segment modifications after ranolazine was withdrawn. (D) Ventricular tachycardia induced by programmed electrical stimulation. ECG = electrocardiogram; STEMI = ST-segment elevation myocardial infarction.

implantable cardioverter-defibrillator was placed, and a follow-up visit at 6 months was planned.

DISCUSSION

BrS is a rare inherited arrhythmia disease associated with a variable risk of sudden cardiac death. The key to BrS diagnosis is the spontaneous type 1 Brugada ECG pattern, defined as the J point elevation of ≥0.2 mV with coved ST-segment elevation and T-wave inversion in at least 1 right precordial lead.[1,2] BrS is characterized by significant genetic heterogeneity, as an association with more than 20 genes have been reported. However, the strongest evidence-based clinical correlation has been demonstrated with the mutations of the *SCN5A* gene,[3] although present in only 20% of patients diagnosed with BrS. This gene encodes for the α-subunit of the $Na_v1.5$ sodium channel; its loss-of-function mutations result in later activation and earlier inactivation of the channel, leading to a shortening of the action potential duration by reducing I_{Na} peak during phase 0.[4] Based on these molecular features, sodium-channel blockers have been used for diagnostic purposes to unmask the type 1 Brugada pattern in ambiguous ECGs.[5] Antiarrhythmics with a predominant action on $Na_v1.5$ of both class 1a (ajmaline and procainamide) and 1c (flecainide and pilsicainide) are indeed routinely used in provocation tests.[6]

Ranolazine is conversely a piperazine derivative with antianginal effects primarily attributed to the inhibition of the late I_{Na} current in cardiomyocytes, which modulates the Na^+/Ca^{2+} intracellular balance, preventing calcium overload; the latter is known to increase myocardial oxygen consumption and left ventricular filling pressure, thus ischemia. The antiarrhythmic properties of ranolazine seem to be due to the suppression of early afterdepolarizations (EADs). At high concentrations, ranolazine also inhibits the delayed rectifying potassium current (I_{Kr})

and the L-type calcium current ($I_{Ca,L}$); this multiple-channel action could explain the negligible effect on QT interval and the low risk of torsades de pointes.[7] The drug has also demonstrated a potential role in the management of arrhythmias usually responsive to other sodium-channel blockers; the RAFFAELLO study supported the auxiliary role of ranolazine in the cardioversion of atrial fibrillation and the maintenance of the sinus rhythm.[8] Moreover, in the clinical setting of long QT syndrome type 3, a disease related to the *SCN5A* gene gain-of-function mutations, ranolazine demonstrated a significant repolarization time shortening[9] and has been proposed as a therapeutic alternative to flecainide.[10]

On these grounds, it is possible to speculate on a potential role of ranolazine in unmasking the type 1 Brugada pattern. Other similar evidence is nevertheless lacking. To the best of our knowledge, to date, there is just 1 case report in the literature, which was reported as an adverse drug reaction.[11] Furthermore, the safety of ranolazine in patients with BrS has never been questioned, and concordantly the drug is not mentioned among those to avoid in this clinical condition according to the current guidelines and position papers.[1,2,12] The rarity of reports such as ours may be owing to the low incidence of BrS and the concomitant scarce use of ranolazine within the management of chronic coronary syndrome (compared with other anti-ischemic drugs). Moreover, patients with BrS usually present symptoms and reach a diagnosis in the third and fourth decade of life, whereas ranolazine is typically prescribed to patients with complex coronary artery disease and a history of multiple revascularizations, thus in most cases at older ages.

FOLLOW-UP

At the 6-month follow-up visit, no new syncopal episodes were reported by the patient, no recurrence of Brugada ECG pattern was found, and no arrhythmic events were detected by the subcutaneous implantable cardioverter-defibrillator.

CONCLUSIONS

The present case supports the hypothesis of a correlation between ranolazine assumption and the unmasking of a type 1 Brugada pattern. In fact, none of the ECGs recorded before the ranolazine treatment showed any anomalous pattern, and complete ECG normalization was observed after the ranolazine was withdrawn. If confirmed, the potential proarrhythmic effect of ranolazine in BrS seems noteworthy since, as yet, evidence of the safety of ranolazine with respect to BrS is lacking.

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REFERENCES

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126.

2. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018;72:1046–1059.

3. Hosseini SM, Kim R, Udupa S, et al. Reappraisal of reported genes for sudden arrhythmic death: evidence-based evaluation of gene validity for Brugada syndrome. *Circulation*. 2018;138:1195–1205.

4. Zhang ZS, Tranquillo J, Neplioueva V, Bursac N, Grant AO. Sodium channel kinetic changes that produce Brugada syndrome or progressive cardiac conduction system disease. *Am J Physiol Heart Circ Physiol*. 2007;292:H399–H407.

5. Rolf S, Bruns HJ, Wichter T, et al. The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J*. 2003;24:1104–1112.

6. Krahn AD, Behr ER, Hamilton R, Probst V, Laksman Z, Han HC. Brugada syndrome. *JACC Clin Electrophysiol*. 2022;8:386–405.

7. Schram G, Zhang L, Derakhchan K, Ehrlich JR, Belardinelli L, Nattel S. Ranolazine: ion-channel-blocking actions and in vivo electrophysiological effects. *Br J Pharmacol*. 2004;142:1300–1308.

8. De Ferrari GM, Maier LS, Mont L, et al. Ranolazine in the treatment of atrial fibrillation: results of the dose-ranging RAFFAELLO (Ranolazine in Atrial Fibrillation Following An ELectricaL CardiOversion) study. *Heart Rhythm*. 2015;12:872–878.

9. Chorin E, Hu D, Antzelevitch C, et al. Ranolazine for congenital long-QT syndrome type III: experimental and long-term clinical data. *Circ Arrhythmia Electrophysiol*. 2016;9:e004370.

10. Cano J, Zorio E, Mazzanti A, et al. Ranolazine as an alternative therapy to flecainide for SCN5A V411M long QT syndrome type 3 patients. *Front Pharmacol*. 2020;11:580481.

11. Ranolazine. *React Wkly*. 2019;1764:288.

12. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart Rhythm*. 2009;6:1335–1341.

KEY WORDS Brugada syndrome, chronic coronary syndrome, ranolazine