Heat Wave: A Trigger of Electrical Storm in a Patient With Brugada Syndrome

Ola de calor: desencadenante de tormenta arrítmica en un paciente con síndrome de Brugada

To the Editor,

Brugada syndrome (BrS) is a hereditary arrhythmogenic disease characterized by a specific electrocardiographic pattern and a higher risk of sudden cardiac death due to ventricular tachyarrhythmias in patients with no structural heart disease[1]. The electrocardiographic pattern is dynamic and drug challenge to provoke a Brugada electrocardiographic pattern is an essential tool in the diagnosis of this syndrome[2]. Fever has been identified as a factor that can unmask the electrical pattern of BrS and trigger ventricular arrhythmias. The pathophysiological role of fever as an inductive mechanism in BrS has yet to be defined, but it is thought to be due to sodium channel inactivation secondary to body temperature in patients with mutations in the *SCN5A* gene[3].

We report a case of electrical storm in a BrS patient triggered by the extremely high temperatures experienced during the record heat wave that occurred in Spain and other parts of Europe during the summer of 2015. The patient was a 34-year-old man who presented to the emergency department of a university hospital after an episode of syncope and repeated shocks from his implantable cardioverter-defibrillator (ICD).

The patient had visited the emergency department 8 months earlier after experiencing a sudden loss of consciousness in a crowded discotheque. On arrival, the electrocardiogram (ECG) revealed the typical Brugada pattern with right bundle branch block morphology and ST-segment elevation in V_1 and V_2 (coved morphology). Echocardiography showed the heart to be structurally normal. He was diagnosed with BrS and underwent ICD implantation.

The patient experienced no new events until July 3, 2015. That afternoon, he was playing in a park with his 5-year-old son when the episode of syncope occurred and he received repeated shocks from the ICD. At that time, the thermometers were registering one of the highest temperatures of that summer, 42.7 °C (108.86 °F). On admission, the patient was stable and the physical examination was normal, except for an axillary temperature of 37.5 °C, with no signs or symptoms of infection. The ECG showed the typical Brugada pattern (Figure 1A). The results of the laboratory tests were normal (serum potassium, magnesium and calcium concentrations and inflammatory markers). Isoprenaline therapy was begun, and there were no new episodes of ventricular tachycardia or premature ventricular contractions, the patient's body temperature fell with no need for additional measures, and the ECG returned to normal within 24 hours (Figure 1B). Device interrogation showed that all the parameters were normal. Four episodes of ventricular fibrillation were correctly detected, and shocks were delivered at 41 joules (Figure 2). After 3 days of observation, the patient was discharged with strict recommendations to avoid being outdoors during the hours of maximum heat and exposure to indoor settings with high temperatures and was given advice on the usual measures to prevent fever. After 9 months of follow-up, the patient remained asymptomatic and had reported no further events.

Several mutations in the *SCN5A* gene have been identified that encode for sodium channels in up to 20% to 30% of BrS patients. The genetic basis of this disease includes loss-of-function mutations in the genes encoding the cardiac sodium channels, which reduce the normal duration of the action potential. The effect is more pronounced in regions where the refractory periods are heterogeneous (with normal and mutated sodium channels), as occurs in the right ventricular epicardium. These differences lead to reentry

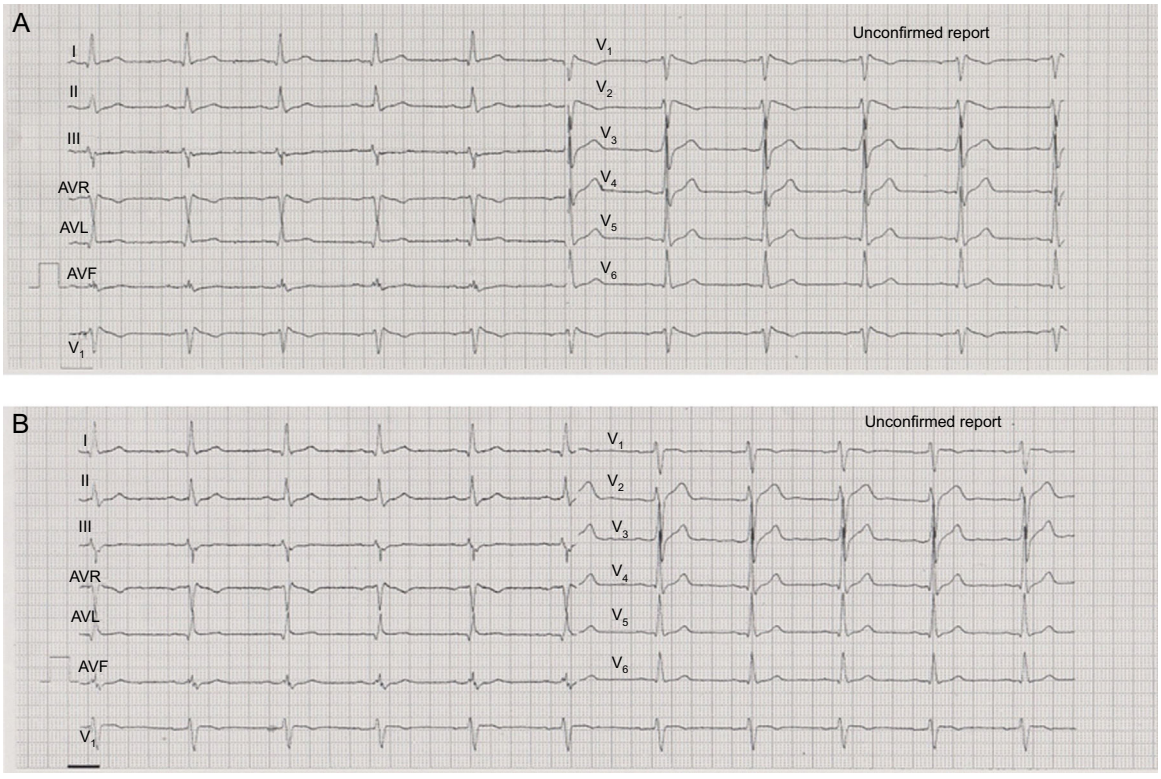

Figure 1. A: Admission electrocardiogram showing Brugada type 1 pattern. B: normal electrocardiogram 24 hours later.

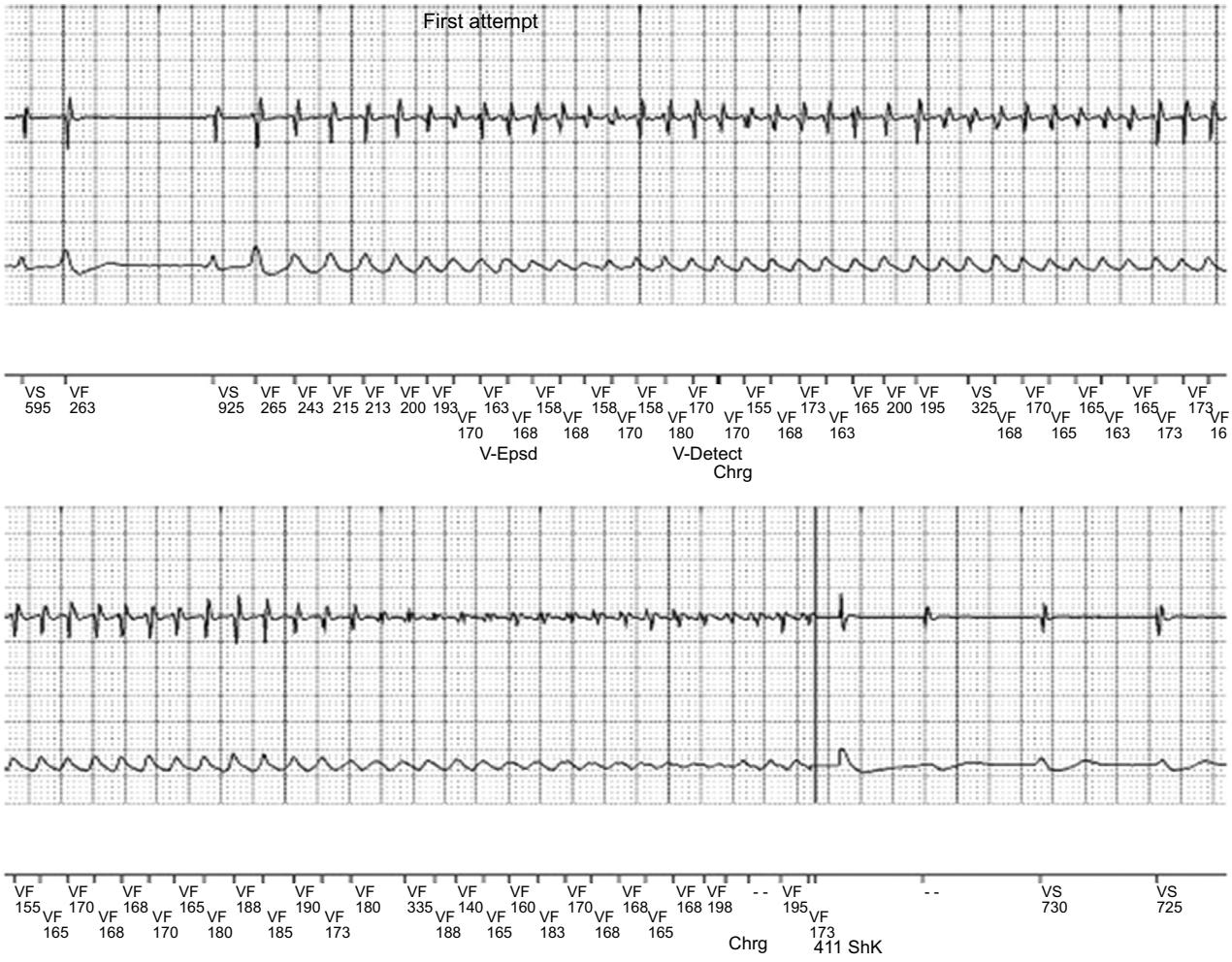

Figure 2. Implantable cardioverter defibrillator tracing showing an episode of ventricular fibrillation treated by electric shock.

circuits that result in the development of premature ventricular contractions and ventricular arrhythmias.

A number of conditions have been proposed as possible triggers of the Brugada electrocardiographic pattern, including fever, electrolyte disturbances, drugs, or medication (for example, cocaine, anesthetics, antiarrhythmic agents, antidepressants, and antihistaminic agents)[3].

Fever is one of the factors most frequently reported to be a trigger of the Brugada electrocardiographic pattern, provoking episodes of ventricular tachyarrhythmia. In a large series of BrS patients, fever was the factor triggering the arrhythmias in 18% of the participants[4]. The hypothesis proposed to explain the causal mechanism of this triggering factor was temperature-dependent inactivation of the sodium channel in patients with the *SCN5A* mutation.

Moreover, the literature includes a few isolated cases of the unmasking of the Brugada electrocardiographic pattern by a heatstroke[5,6]. However, to date, there is absolutely no evidence of the triggering of ventricular arrhythmias in this setting.

In July 2015, a heat wave hit Spain and other European countries, with temperatures of over 40 °C (104 °F). Our patient experienced ventricular arrhythmias on one of the hottest days in Spain, with temperatures of up to 42.7 °C (108.86 F). This report illustrates a case in which the high outdoor temperatures may have contributed to sodium channel inactivation, triggering the Brugada electrocardiographic pattern and the recurrent episodes of ventricular fibrillation.

Isabel Molina Borao,* Naiara Calvo Galiano, Javier Urmeneta Ulloa, Elena Rivero Fernández, Teresa Olóriz Sanjuan, and Antonio Asso Abadía

Unidad de Arritmias, Servicio de Cardiología, Hospital Universitario Miguel Servet, Zaragoza, Spain

* Corresponding author:
E-mail address: imborao@hotmail.com (I. Molina Borao).

Available online 26 September 2016

REFERENCES

1. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al.; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002;106:2514–9.
2. De-Riva-Silva M, Montero-Cabezas JM, Fontenla-Cerezuela A, Salguero-Bodes R, López-Gil M, Arribas-Ynsaurriaga F. Respuesta positiva diferida al test de flecainida en pacientes con sospecha de síndrome de Brugada: un hallazgo preocupante. Rev Esp Cardiol. 2014;67:674–5.

3. Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, et al. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res. 1999;85:803–9.
4. Amin AS, Meregalli PG, Bardai A, Wilde AA, Tan HL. Fever increases the risk for cardiac arrest in the Brugada pattern. Ann Intern Med. 2008;149:216–8.
5. Canpolat U, Bayazit Y, Aytemir K. Brugada syndrome unmasked by heat exhaustion. Ann Noninvasive Electrocardiol. 2016 Mar 28 [Epub ahead of print]. Available at: http://dx.doi.org/10.1111/anec.12356.
6. Lacunza J, San Román I, Moreno S, García-Molina E, Gimeno J, Valdés M. Heat stroke, an unusual trigger of Brugada electrocardiogram. Am J Emerg Med. 2009;27:634.

http://dx.doi.org/10.1016/j.rec.2016.06.011
1885-5857/

Relaxin Concentrations in Acute Heart Failure Patients: Kinetics and Clinical Determinants

Concentración de relaxina en pacientes con insuficiencia cardiaca aguda: comportamiento y determinantes clínicos

To the Editor,

In recent decades, animal experiments have shown numerous cardiovascular benefits for the hormone relaxin, traditionally known for its effects during pregnancy[1]. Relaxin lowers peripheral vascular resistance, reduces pulmonary congestion, improves cardiac output, and increases renal flow. By increasing nitric oxide, it produces vasodilating, anti-inflammatory, antiplatelet, and antioxidant effects. In addition, there have been descriptions of relaxin cardiac receptors and release in atria and ventricles[2]. Serelaxin, a recombinant form of endogenous relaxin, has emerged as a therapeutic option in acute heart failure (AHF) and shows promising results in the RELAX-AHF trial[3]. However, the role of relaxin in the pathophysiology of AHF has not been established, and there are only a few published clinical studies[4–6]. To date, it has not been shown that endogenous relaxin production is an important compensatory mechanism, a useful biomarker, or a hormone with prognostic value in patients with AHF.

The aim of our study was to analyze the role of relaxin as a neurohormonal mediator in patients with AHF. To conduct the research, we selected 43 consecutive patients (age, 69.8 ± 9.4 years; men, 63%) who had been hospitalized with a diagnosis of AHF. Plasma relaxin concentrations were determined upon arrival at the emergency room and at 30 days after discharge and in stable condition. All concentrations were measured using a previously validated enzyme-linked immunoassay (Immunodiagnostik; Bensheim, Germany)[2,4–6]. The patients' clinical, analytical, and echocardiographic variables were retrospectively collected from their medical history.

On arrival at the emergency room, relaxin was undetectable in 3 patients (7%); the median for all other patients was 14.3 [interquartile range, 5.8-48.0] (range, 1.5-878) pg/mL. Table lists the characteristics for the entire study population and according to median concentration. No significant associations were found with any clinical variables, including age, sex, left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide, echocardiographic variables, and New York Heart Association functional class. After the acute event, relaxin concentration at 30 days had a median of 26.5 [11.4-47.3] (0.85-1031) pg/mL and strongly correlated with concentration on admission ($r_s = 0.536$; $P < .001$). The repeated measures analysis showed no significant change between measurements in the emergency room and at 30 days ($P = .204$, Wilcoxon test) or a uniform pattern of kinetics (Figure). During follow-up (median, 654 [332-932] days), 8 of 21 patients above and 8 of 22 below the relaxin median died or were readmitted for heart failure ($P = .91$).

Our study is the first to investigate relaxin kinetics in patients with AHF and its relationship with a broad set of variables related to the disease. Relaxin concentrations showed considerable variability, as observed in the few published studies, with variations between 600 and 900 (pg/mL)[4–6], similar to those of our population (878-1031 pg/mL). These studies included patients with chronic heart failure, with reduced[5,6] or preserved[6] left ventricular ejection fraction, and after discharge following an episode of AHF[4]. The lack of an association with clinical variables plus the fact that hormone concentrations do not depend on the time point, whether the patient is in the emergency room with AHF or stabilized at 30 days, indicates that relaxin, as an endogenous hormone, does not actively participate in the pathophysiology of AHF. Once the patient has arrived at the emergency room, sample collection at different time points should have no influence, given the correlation with 30-day fasting values and the lack of a circadian effect on relaxin in previous studies. The results of our study are consistent with the those of series that found similar

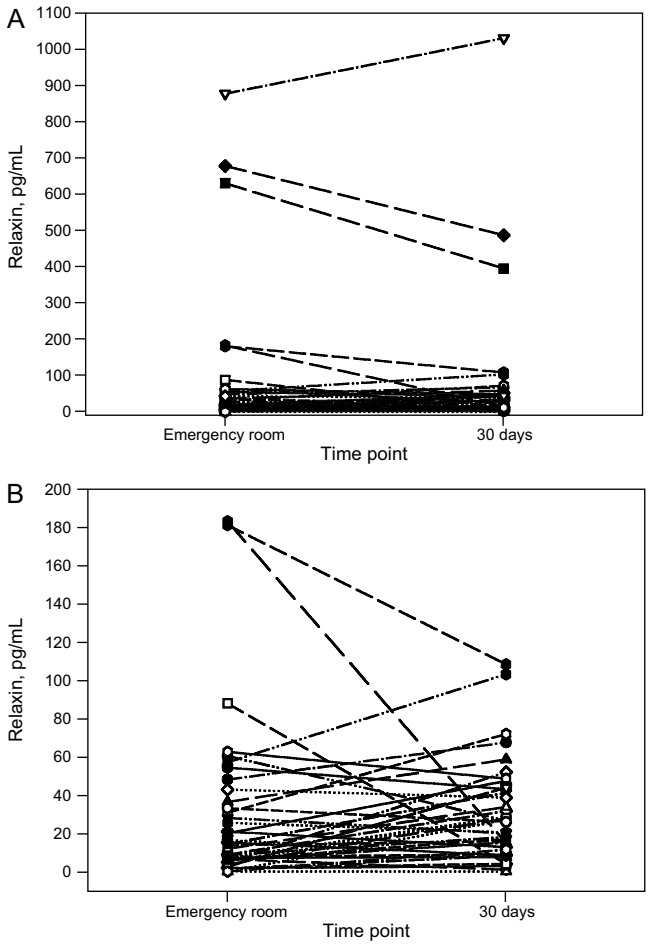

Figure. Changes in relaxin concentrations on arrival to the emergency room and at 30 days (A) and enlargement of the area between 0 and 200 (pg/mL) (B).