A comprehensive electrocardiographic, molecular, and echocardiographic study of Brugada syndrome: Validation of the 2013 diagnostic criteria

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BACKGROUND The debate on the diagnostic value of high intercostal spaces (ICSs) and of the number of diagnostic leads in Brugada syndrome (BrS) has been settled by a recent expert consensus statement.

OBJECTIVE To test the validity, and the underlying anatomy, of the new electrocardiographic (ECG) diagnostic criteria using echocardiographic, molecular, and clinical evidence in 1 clinical study population with BrS.

METHODS We analyzed 114 patients with BrS and with a spontaneous or drug-induced type 1 ECG pattern recorded in 1 or more right precordial leads in fourth, third, and second ICSs. The right ventricular outflow tract (RVOT) was localized by using echocardiography. All probands were screened on the *SCN5A* gene.

RESULTS The percentage of mutation carriers (MCs) and the event rate were similar regardless of the diagnostic ICS (fourth vs high ICSs: MCs 23% vs 19%; event rate 22% vs 28%) and the number of diagnostic leads (1 vs $\geq$2: MCs 20% vs 22%; event rate 22% vs 27%). The concordance between RVOT anatomical location and the diagnostic ICSs was 86%. The percentage of the diagnostic ECG pattern recorded was significantly increased by the exploration of the ICSs showing RVOT by echocardiography (echocardiography-guided approach vs conventional approach 100% vs 43%; $P < .001$).

CONCLUSION The high ICSs are not inferior to the standard fourth ICS for the ECG diagnosis of BrS, and the interindividual variability depends on the anatomical location of the RVOT as assessed by using echocardiography. This approach significantly increases diagnostic sensitivity without decreasing specificity and fully supports the recently published new diagnostic criteria.

KEYWORDS Brugada syndrome; Electrocardiography; Echocardiography; Diagnostic criteria; *SCN5A*

ABBREVIATIONS **BrS** = Brugada syndrome; **ECG** = electrocardiogram/electrocardiographic; **FM** = family member; **ICS** = intercostal space; **MC** = mutation carrier; **RVOT** = right ventricular outflow tract

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Introduction

Brugada syndrome (BrS) is a rare heritable arrhythmogenic syndrome characterized by a coved-type ST-segment elevation in the right precordial leads and by an increased risk of life-threatening arrhythmias.[1] Diagnostic criteria for BrS, first proposed in 2002[2] and then updated in 2005[3] in an officially endorsed document, repeatedly agreed that the type 1 coved-type electrocardiogram (ECG) is diagnostic for BrS. By contrast, an unrelenting controversy has developed regarding the significance of a diagnostic pattern observed only in the high intercostal spaces (ICSs) and/or only in 1 precordial lead. A main concern was that the increased sensitivity obtained by the use of high ICSs[4–10] would be paid by a decrease in specificity. Several publications have challenged the criteria of the second consensus document[3] regarding either the number of precordial leads with a type 1 ECG pattern required for the diagnosis[11] or the diagnostic

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yield of their intercostal position.[7,12,13] On the basis of a general review of the literature, as well as on personal experience, a new diagnostic consensus opinion for BrS has recently been recommended[14] for a definitive diagnosis of BrS; namely, a type 1 ST-segment elevation observed either spontaneously or after drug-challenge tests in *at least 1* right precordial lead (V_1 or V_2) placed at a standard (fourth ICS) *and/or* a superior position (up to the second ICS) is diagnostic.

We assessed the appropriateness of these new ECG diagnostic criteria with a multidisciplinary approach in a single cohort of patients. Specifically, our first objective was to assess whether the percentage of mutation carriers (MCs) or the incidence of cardiac events would differ according to the diagnosis of BrS being made by the previous ECG criteria or exclusively by high ICSs or only with a single diagnostic lead. This approach allowed to test for the first time whether the newly proposed ECG criteria are associated with a decreased specificity.

Our second objective was to establish why is it that the diagnostic ECG pattern can be recorded in a specific ICS. It had been proposed that the explanation may lie in the association between the anatomical location of the right ventricular outflow tract (RVOT) and the ICS in which the Brugada ECG pattern is recorded.[13,15,16] However, these proposals were based on invasive and expensive technologies such as body surface mapping,[15] cardiac magnetic resonance imaging,[16] and right ventriculography.[13] We wanted to verify this association by using a simple, inexpensive, and noninvasive method such as echocardiography.

The design of our study allowed us to assess the robustness of the diagnosis of BrS made according to the new diagnostic criteria, through a comprehensive approach using anatomic, arrhythmic, and genetic aspects in the same cohort of patients.

Methods

Study population

The study population consisted of 114 patients from 107 distinct families having either a spontaneous or a drug-induced type 1 Brugada ECG pattern. All these patients were referred to the Department of Cardiology of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, and were studied retrospectively. Informed consent was obtained from all patients.

Clinical evaluation, diagnostic criteria, and drug challenge protocol

In all patients, a complete personal and family history of arrhythmic syncope, cardiac arrest, or sudden cardiac death was collected. For symptomatic patients, cardiac episodes were defined as unexplained syncope or documented sustained ventricular arrhythmias (ventricular tachycardia/ventricular fibrillation). Patients reporting palpitations, atypical chest pain, and/or a history of syncope strongly suggestive of vasovagal syncope were considered asymptomatic. Patients with an acquired cause for a type 1 ECG pattern were excluded.

A baseline 12-lead ECG was performed with leads V_1 and V_2 positioned in the fourth, third, and second ICSs. In addition, a 24-hour standard 12-lead ECG Holter monitoring was performed. The ECG was considered diagnostic for BrS if a type 1 ST-segment elevation ≥ 2 mm was present in 1 or more right precordial leads independently from the ICS in which it was recorded. Whenever the ECG pattern was only suspect (type 2 and type 3 ECGs) but not diagnostic, a flecainide test was performed, through the intravenous injection of 2 mg/kg flecainide, over a 10-minute period.

Echocardiographic examination

Of the 114 patients with BrS enrolled in the study, 77 consecutive patients underwent an echocardiographic examination at the time of their first visit or during follow-up. A single cardiologist (S.S.), blind to the diagnostic ICS at electrocardiography, performed a left parasternal short-axis view strictly perpendicular to the chest wall in the fourth, third, and second ICSs. RVOT location and measurement were performed in the subpulmonary region (Figure 1) according to the American Society of Echocardiography's recommendations[17] at both the aortic valve plane level and the subaortic plane level. For each patient, the body surface area was calculated by using the Mosteller formula: BSA $(m^2) = \{[\text{height (cm)} \times \text{weight (kg)}]/3600\}^{1/2}$.

Mutational analysis

After receiving informed consent, *SCN5A* was screened[18] through denaturing high-performance liquid chromatography and Sanger sequencing, as previously reported.[19] To be considered a putative pathogenic mutation, the *SCN5A* variant identified had to be (1) a nonsynonymous variant, (2) absent in at least 300 internal ethnically matched controls, and

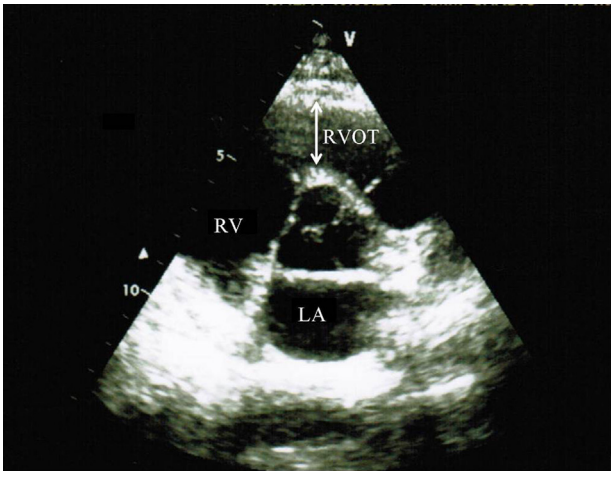

Figure 1 Standard approach for the measurement of the RVOT diameter at the aortic valve plane level, as recommended by the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group.[17] LA= left atrium; RV = right ventricle; RVOT = right ventricular outflow tract.