Brugada syndrome diagnosed from the EKG leads in the High Intercostal Spaces: Searching for Answers from a Higher Source?

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As is well known, Brugada syndrome is an autosomal dominant inherited disorder with variable expressivity that is characterized by ST-segment elevation in the right precordial leads and an increased risk of ventricular fibrillation and sudden cardiac death.¹ Since the seminal report of this condition by Brugada and Brugada in 1992,² no other inherited arrhythmogenic disorder has perhaps generated more passionate debate than BrS, with many controversies related to the underlying mechanism, methods of risk stratification, prognosis of its phenotypic manifestations and its long term management.^{1,3} Of paramount importance are two competing theories of the underlying mechanism of arrhythmogenesis. The depolarization hypothesis proposes that defective sodium channel function (leading to a weak inward sodium current during phase 1 of the action potential), in combination with a unopposed transient outward current (I_{to}), which is most prominent in the right ventricular outflow tract (RVOT) epicardium leads to an accentuation of the action potential notch in the RV epicardium rather than the endocardium, resulting in an accentuated J wave and ST segment elevation characteristic of the Brugada pattern EKG.¹ Arrhythmias are thought to develop because of inhomogeneous repolarization in different areas of the RV epicardium leading to phase 2 re-entry and to the development of closely coupled extrasystoles leading to ventricular arrhythmias.¹ In contrast, recent evidence suggests that the RVOT epicardium in BrS harbors morphological and ultrastructural abnormalities not detectable by current imaging modalities, but demonstrable with electrophysiologic mapping,⁴⁻⁷ leading slow and discontinuous conduction that in turn conspire to produce an arrhythmogenic substrate, which may progress over time.⁸ Indeed, it is likely that a combination of the two mechanisms explains the arrhythmogenicity of BrS.⁹ Whilst the underlying mechanism is keenly

debated, there is uniform agreement that it is the RVOT, which harbors the arrhythmicogenic substrate in BrS.

To that end, the EKG remains the pivotal tool in establishing a diagnosis as leads V1 and V2, when placed in the standard position of the right and left fourth intercostal spaces (ICS) respectively, provide a vantage point for the detection of RV abnormalities. However, a number of prior studies have suggested that an EKG recorded from a high precordial location (2nd or 3rd, rather than the 4th ICS) may increase the sensitivity of diagnosis of BrS by providing an even more accurate vantage point, especially for the RVOT.¹⁰⁻¹⁷ Based on this rationale, the most recent expert consensus statement formally expanded the definition to include the Brugada EKG pattern with leads V1 and V2 positioned in the 2nd, 3rd, or the 4th ICS, rather than standard lead placement in the 4th ICS alone as diagnostic of BrS.¹⁸ This naturally creates a new category of patients in whom BrS EKG pattern is only evident by recordings from the high ICS. However there is limited data about the natural history and prognosis of such patients.

In this edition of the *Journal*, Curcio and colleagues,¹⁹ examined the role of high ICS lead placement in the diagnosis of BrS and the prognosis of such patients diagnosed *exclusively* by the high ICS. The authors report 300 patients in whom the diagnosis of BrS was not established using the former 2002²⁰ or the 2005²¹ criteria (using standard EKG lead placement), both at baseline and after provocative testing with sodium-channel blocking agents. In these patients, BrS was suspected on the basis of history of syncope (21% of patients), cardiac arrest (2.6%), minor symptoms (40.7%), or were asymptomatic (35.7%). A family history of sudden cardiac death was present in 19% and a family history of BrS in 3% of patients. No patients had evidence of structural heart disease. A

large number high ICS EKGs without provocation (1819, with a median of 5 EKGs/patient) were systematically analyzed and the most severe EKG used for classification. Of the 300 patients, only 4 patients (1.3%) had a spontaneous type I Brugada EKG detectable with high ICS placement, but not with standard placement. After provocative testing, a diagnostic type I Brugada EKG developed in the high ICS leads in a further 60 patients. Thus, 64 out of 300 were diagnosed with BrS using high ICS lead placement, either spontaneously or with provocative testing, amounting to a 21% increase in the yield of diagnosis. In follow up, only 3 of the 64 patients (4.7%) developed cardiac events, that included two resuscitated cardiac arrests and one sudden cardiac death. These events occurred after a mean of ~3 years after initial clinical assessment. It is critical to note all 3 of these events occurred in patients in whom a spontaneous type I EKG pattern was evident in the high ICS space only. None of the patients with a drug-provoked type I EKG pattern in the high ICS developed cardiac events. The authors note that the 64 patients diagnosed using the high ICS space alone experienced a lifetime annual incidence of cardiac events of only 0.11% over a mean observation time of 41 years. The authors' surmise that this was truly a low risk group as the event rate in this "new" population was similar to patients diagnosed only after drug provocation using the 2002 criteria using standard ICS lead placement. Moreover, the event rate was significantly lower than patients with a spontaneous type I pattern diagnosed with standard lead positioning using the 2002 criteria, with or without a history of syncope.

The findings of Curcio et al.,¹⁹ highlight the fundamental role of the EKG in dictating both, the diagnoses and prognosis of BrS. Whilst standard placement of V1 and

V2 in the 4th ICS place can diagnose BrS, a number of imaging and detailed mapping studies have shown that there are significant patient-specific differences in the electrical projection of the RVOT on chest surface. In an 87-electrode body surface mapping study, Shimizu et al¹⁰ showed that 28% of BrS patients had maximal ST segment elevation evident only in the 2nd and 3rd ICS whilst the 4th ICS showed only mild saddleback ST segment elevation in such patients. Using right ventriculography, Nagase et al¹¹ showed significant anatomic variation in the RVOT in relation to the 3rd and 4th ICS; indeed the RVOT overlay the 4th ICS in only 18% and the 3rd ICS in 82% of patients. A type I EKG was recorded at the 4th ICS in 82% of patients in whom the RVOT overlay the fourth ICS; however in 84% of patients in whom the RVOT overlay the 3rd ICS, a type I ECG was not seen at the 4th ICS, but was seen at the 3rd ICS instead. Similarly, using cardiac MRI, Veltman et al¹⁷ showed that the RVOT was located over the 3rd ICS in all patients in their cohort and that the location of the type I EKG highly correlated with the anatomic location of the RVOT.¹⁷ Savastano et al¹⁶ showed that a diagnostic Brugada ECG was present exclusively in the high ICS in 44% of patients in their cohort. In that study, echocardiographic guided EKG lead placement over the visualized RVOT markedly improved the diagnostic yield of BrS. Clearly, individual variation in location of the RVOT in relation to the intercostal space will critically influence whether the standard lead position will consistently capture the anatomic location of the RVOT. When coupled with the day-to-day variation in the typical type I BrS pattern,²² EKG lead placement directly overlying the RVOT, using imaging, if necessary will most likely play a future role in improving the diagnostic yield of BrS. Moreover, if the disease is heterogeneous in its mechanism¹ (and possibly in its progression)⁸, it is plausible that a sub-population

detectable only with high ICS lead placement representing “early” or a milder phenotype may emerge.

Prior studies, have also shown a 20-40% increase in the yield of detecting a Brugada EKG pattern,¹²⁻¹⁵ either spontaneously or with drug provocation, consistent with the 21% increase in yield reported by Curcio et al.¹⁹ In contrast to the benign prognosis of patients diagnosed exclusively on the basis of high ICS leads reported by Curcio et al.,¹⁹ prior studies have reported that such patients face a similar incidence of adverse cardiac events when compared to patients diagnosed using the standard ICS leads.^{15, 16} However, a valid comparison between these studies may not be plausible, as the populations studied were quite different. For example, the studies by Miyamoto et al¹⁵ and Savastano et al¹⁶ included a very high incidence of patients detected exclusively using the high ICS (28% and 44% respectively compared with 21% in Curcio et al¹⁹); moreover, the proportion of symptomatic patients, the proportion of patients with spontaneous versus drug-provoked Brugada EKG pattern and the geographical location of the population also varied. Furthermore, prior studies were of smaller sample size and included patients with the Brugada EKG from both standard and high ICS lead placement, whilst Curcio et al,¹⁹ exclusively studied patients in whom a Brugada pattern was not seen using standard ICS lead placement. Importantly, none of the patients diagnosed with Brugada EKG exclusively on high ICS lead placement after drug provocation in the study by Curcio et al,¹⁹ experienced any cardiac events which was similar to the prognosis of patients who were diagnosed with drug provocation using standard ICS lead placement. This group is likely to represent a truly low risk group.³ However the prognosis of patients diagnosed exclusively with high ICS lead placement in the absence of drug provocation needs

further study, as the numbers of such patients in the present study were small (4 patients) and the follow up duration was limited (36 months).

Predictions on diagnostic yield on high ICS and long-term prognosis are clearly influenced by the baseline incidence of BrS amongst different population. For example, the Type I ECG is observed more frequently in Asia (0-0.36%) and Europe (0-0.25%) than the USA (0.03%). Similarly, the type 2 or 3 ECG is also observed more frequently in Asia (0.12-2.23%) and in Europe (0-0.6%) than in the USA (0.02%).¹ Further study is therefore needed to determine the incidence of the Brugada type EKG from the high ICS amongst large, geographically diverse populations. Moreover, cardiac event rates may also vary according to the geographic population, warranting further definition. As this new population of patients emerge, there is no doubt questions will arise seeking clarification of the prognosis patients diagnosed exclusively with high ICS who experience syncope, and the prognostic role of electrophysiologic testing in such patients who are asymptomatic. Finally, the low diagnostic yield with genetic testing (positive in 20-30% of BrS patients) also means that there is an absence of a gold standard by which conclusions about diagnostic yield can be accurately judged. As this was a retrospective study, larger prospective and multi-center studies are needed to clarify the prognosis of patients with a Brugada EKG pattern diagnoses exclusively by high ICS lead placement.

The study by Curcio et al.¹⁹ is not only systematic but is also timely, insightful and sourced from a highly experienced center with a fine legacy of seminal observations in inherited arrhythmogenic disorders. The study sheds light onto a rapidly emerging group of patients who will be reclassified with BrS or a Brugada-like EKG, and are now formally recognized by the guidelines.¹⁸ The study provides great impetus in further

characterizing the prognosis of such patients. It also confirms the pivotal role of the EKG in diagnosis and risk stratification and suggests that further work is needed to refine lead placement to match RVOT position to improve the diagnostic accuracy of the EKG in detected BrS.

Author contributions

Dr. Saurabh Kumar: Drafting article; critical revision of the article.

Dr. Jonathan Kalman: Critical revision of the article.

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