Further Confirmation That a Conduction Disturbance Underlies the Electrocardiographic Pattern of the So-Called Brugada Syndrome

To the Editor:

It is a privilege to acknowledge the scientific accuracy of Dr Wilde and coworkers who admitted that some depolarization abnormalities underlie the so-called Brugada syndrome.

In a previous article, Dr Wilde wrote, “Both theoretical considerations and in vivo experiments support the idea that heterogeneity of repolarization across the wall of the right ventricular outflow tract (RVOT) contribute to the ECG patterns and the genesis of arrhythmias in the Brugada syndrome” (p 669).

This recent admission gives further credit to our observation on a patient with the syndrome 20 years ago. This still-healthy patient, who can be seen on page 70 of http://digitalaberlibero.it/martini_syndrome/, had a documented 4. Martini B, Nava A, Thiene G, Buja GF, Canciani B, Scognamiglio R, Boldrini Hospital Cardiovascular Unit Boldrini Hospital 36016 Thiene (VI) Italy bmartini@tiscal.it

QRS delay at the right ventricular outflow tract. Prolonged PR and HV intervals, left axis deviation, and late potentials both spontaneously and after flecainide were all reported in this syndrome. All are consistent with organic disease of the conduction system as documented at necropsy.

Bortolo Martini, MD


Response

We thank Dr Martini for providing additional supportive evidence for our observation that right ventricular conduction slowing is critically involved in the pathophysiology of Brugada syndrome. Despite Dr Martini’s suggestion to the contrary, this is by no means a departure from our previous work, but a continuation thereof. For instance, conduction slowing as a leitmotiv was presented in our previous demonstration that Brugada syndrome patients with a SCN5A mutation (the gene encoding the cardiac sodium channel, which is responsible for impulse propagation) are distinguished from those without such a mutation by significantly more conduction slowing. Nevertheless, we must emphasize that the present evidence (including our most recent study) does not rule out a pathophysiological role of severe abbreviation of the subepicardial action potential, as proposed by Antzelevitch. Of note, we have provided experimental and modeling evidence that conduction slowing and severe action potential abbreviation are intimately linked, and both can result from reduced sodium current produced by SCN5A mutations. The dominant clinical presentation (isolated conduction disease or Brugada syndrome) is simply determined by the amount of sodium current reduction, with more severe sodium current reduction resulting in Brugada syndrome.

We feel that a strict dichotomy in theories surrounding the electrophysiological basis of Brugada syndrome (conduction slowing versus action potential abbreviation), although philosophically attractive, may not reflect reality and may hamper true understanding of this syndrome. Similar to common diseases, we witness the emerging insight that “monogenic” model diseases such as Brugada syndrome have multiple phenotypes and, by inference, multiple mechanisms. In the present genomic era, a solution to this complexity will undoubtedly be found along our pervasive search for modifier genes. Thus, our present study may not only provide novel leads for rational management of Brugada syndrome, but also directions to the search for modifier genes.

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