Dealing with biological variation in the Brugada syndrome

See page 2290, doi:10.1053/euhj.2001.2691 for the article to which this Editorial refers

If events occur according to a probabilistic approach it is likely to be as a result of a complicated series of functions and not to a binary formula such as ‘yes’ or ‘no’. Life is something like: 'maybe, or maybe not'. The function varies depending on the system being studied. Because many biological phenomena behave in a cyclical manner, any biological observation will have to deal with the manifestations of their cyclic changes. Medicine deals with biology and as such cannot escape these rules. That is why there exists no test in clinical medicine with 100% sensitivity and 100% specificity.

The electrocardiogram diagnostic of the Brugada syndrome is not difficult to recognize if one knows what it looks like. Even a child can recognize the ‘coved’ pattern of ST segment elevation in leads V1 to V3. However, even the most expert rhythmologist will have difficulty in mathematically defining the aspects that make an electrocardiogram diagnostic of the Brugada syndrome. That is only one of the difficulties, because there are others requiring very careful consideration at the time of diagnosis: (1) the degree of abnormality of the electrocardiogram before or after drug administration (the initial conditions); (2) the spontaneous variation of the electrocardiogram (cyclical behaviour); (3) the methodology employed (position of the electrocardiographic electrodes, and physiological variations in body shape).

The excellent paper by Sangwatanaroj et al. in this issue[1] deals with all the aspects of the electrocardiographic diagnosis of the Brugada syndrome and adds important information to our present knowledge, increasing the power of the electrocardiogram as a diagnostic tool.

The initial conditions

It is easy to understand that the more abnormal the electrocardiogram is, the easier it is to recognize the abnormality. This is beautifully illustrated in Fig. 3 of their paper where panel B (saddle-back type) was considered ‘questionable’ in terms of diagnosis and panel D (coved type after procainamide) was considered diagnostic. Indeed we cannot agree more that a coved type ST segment elevation has to be present (spontaneously or after drug) for the electrocardiogram to be diagnostic, because a saddle-back type can be mimicked by incomplete right bundle branch block, pectus excavatum, Steiner’s disease and other conditions.

The spontaneous variation of the electrocardiogram

In about half the patients with the Brugada syndrome the electrocardiogram normalizes spontaneously at one moment or another. This observation is based on electrocardiograms usually recorded at the outpatient clinic during routine follow-up visits. A more systematic analysis of the electrocardiogram (for instance with continuous monitoring) suggests that the electrocardiogram of the Brugada syndrome changes continuously. This is not surprising, because it has been shown that many factors modulate the electrocardiographic manifestations of the Brugada syndrome: body temperature, glucose and insulin levels, exercise, adrenaline, changes in heart rate, respiratory variation, and of course administration of drugs (antiarrhythmic, antimalaria, neuroleptic, antihistaminic, antidepressive, cocaine). Fortunately, the administration of antiarrhythmic drugs (class I) can be used to unmask electrocardiographic abnormalities. Sangwatanaroj et al. used procainamide in their study. Ajmaline is probably a better option for two reasons: a short half-life that makes the test safer, and a strong sodium channel block that increases sensitivity (we have observed negative tests with procainamide that were positive with ajmaline).

The methodology employed

The major contribution of the study by Sangwatanaroj et al. is the use of additional precordial leads. No two individuals have the same body and heart shape, but we always record the electrocardiogram in the same way. If the electrical abnormalities in the Brugada syndrome are in agreement with the present hypothesis (for review see reference[2]) it is a disease caused by increased electrical heterogeneity between the right ventricular endo- and epicardium. The degree of electrical heterogeneity may vary from one individual to another.

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with the Brugada syndrome. It may be greater in the free wall in some, the outflow tract in others, or even in the inferior wall. The ST-segment elevation may then be recorded at the normal precordial position of V₁–V₃ in the first situation, at one or two intercostal spaces higher in the second, and in the inferior leads II, III and aVF in the third situation, as reported in a variant of the Brugada syndrome[3]. The value of recording additional precordial leads in the study by Sangwatanaroj et al. was impressive. The sensitivity of the test to recognize the Brugada syndrome increased by more than 20% in survivors of near sudden death. Recording additional precordial leads before or after drug challenge tripled the number of relatives recognized to carry the disease. The pedigree shown in their Fig. 4 serves as the best example of the additional diagnostic value of the higher placed precordial leads.

It is difficult to explain all these findings without having an ‘in vivo’ method with which to study the electrical heterogeneity within the ventricular wall. Body configuration may also play a role in the findings because many Thai men have a lean body configuration. In any case, this study helps us understand that some false-negative tests reported in the literature[4] might not be false negatives but simply the result of methodological problems.

Sangwatanaroj et al. correctly point out other limitations, such as not having the exact genotype of each individual, but so it is in all clinical studies published so far. In spite of that, the study by Sangwatanaroj et al. represents an important addition to our understanding of the electrocardiographic manifestations of the Brugada syndrome and indicates that the additional precordial leads shown in their Fig. 1 should be systematically recorded when screening for this disease.

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References