Genetic and environmental factors in cardiac sodium channel disease

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A refined protocol of flecainide testing in Brugada Syndrome

From ambiguous assessment towards definite diagnosis

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Brugada syndrome (BrS) is diagnosed in individuals with ≥2-mm ST elevation with coved-type (type I) morphology in the right precordial leads. This typical ECG pattern often fluctuates in time, from a diagnostic to a non-diagnostic pattern or vice versa, modulated by factors such as autonomic tone, fever, and sodium channel blocking drugs. Consequently, in suspected BrS cases with a nondiagnostic ECG pattern, drug challenge testing is required to unmask BrS.

Various sodium channel blocking drugs are used to provoke type I ECG, while these agents also block other cardiac ion channels such as I_{to}, leading to varied effects on ST-segment and eventually to different diagnostic yields. A study comparing the effect of intravenous ajmaline vs flecainide reported that flecainide failed to induce type I ECG in 32% of individuals with ajmaline-positive BrS. Therefore, ajmaline ideally should be used in every drug challenge test to avoid false-negative results. However, flecainide remains a diagnostic tool in clinical practice as ajmaline is not available in all countries.

The current standard protocol of flecainide testing is intravenous infusion of 2 mg per kilogram of body weight over 10 minutes. Yet, recent case reports showed that type I ECG may appear 100 to 120 minutes after flecainide infusion. This points out that a 10- to 30-minute monitoring time of the test may be too short in some cases.

In this issue of Heart Rhythm, Calvo et al. present their effort to work out this problem. They studied 59 patients with nondiagnostic BrS ECG pattern at baseline (but only at the 3rd and 2nd intercostal spaces) and performed flecainide testing. For 30 minutes from the start of flecainide infusion, 12-lead ECG was monitored continuously with the right precordial leads placed at the 3rd intercostal space. Two other ECG recordings were also made at 30 minutes and 90 minutes using the 3rd and 2nd intercostal spaces. Overall, 11 of the 59 patients (18.6%) showed a positive test: one-third at an early time period (0-10 minutes), another one-third at a ‘delayed’ period (10-30 minutes), and the remaining one-thirds at a ‘late’ period (90 minutes). Furthermore, ECG parameters during the first 30 minutes were compared between 4 late responders and non-responders (48 patients). QRS width >110 ms could differentiate the late responders from the non-responders (sensitivity 100%, specificity 86%, positive predictive value 88% and negative predictive value 100%). The authors also attempted to find pharmacogenetic backgrounds to explain the diverse responses to flecainide by screening polymorphisms in CYP2D6 and CYP3A5, liver enzymes involved in flecainide metabolism.

Although the study methods (only 3rd intercostal space was used for continuous monitoring during flecainide testing) possibly limited the authors’ ability to reveal the true ratio of delayed and late responders as well as to study pharmacogenetics in flecainide testing of BrS, several interesting points merit discussion.

First, two-thirds of the flecainide-positive subjects failed to develop a positive test in 10 minutes, meaning these patients would have fallen into the false-negative category if the standard monitoring period of 10 minutes had been applied. This is a surprisingly
large number. In our series of 159 subjects with non-type1 BrS ECG at baseline who underwent flecainide testing, no patient developed type1 ECG during a 10- to 30-minute monitoring period. In addition, the overall positive rate is quite low (18.6%) in the study by Calvo et al. compared to ours (40%, [64/159]). This may be explained by differences in the methods between the 2 studies, such as selection of study subjects (number and age of subjects, symptoms or family history of BrS, more symptomatic and familial cases in our series), different ECG lead use for continuous monitoring (3rd intercostal space in the study by Calvo et al. vs 4th and 3rd intercostal space in our study) and the proportion of SCN5A mutation carriers (3% in the study by Calvo et al. vs 27% in our study).

Another reason may be flecainide metabolism. When flecainide is intravenously injected in healthy men, its mean plasma half-life is 11 hours (range, 7-15 hours) and its pharmacokinetics appears to be linear. Several factors contribute to its wide range of half-life. Aging, hepatic and renal dysfunction, heart failure, and polymorphisms of hepatic enzymes (eg, CYP2D6) are known to delay flecainide metabolism. Given that BrS patients are usually young with normal hepatic or renal function, polymorphisms of hepatic enzymes are attractive candidates for evaluation.

So, how do we find individuals with a delayed response to flecainide testing, and how long do we need to monitor them after flecainide infusion? The authors attempted to answer these questions by (1) seeking ECG parameters indicative of late responders (at 90 minutes) and (2) screening polymorphisms of hepatic enzymes (CYP2D6 and CYP3A5) to find subjects with poor flecainide metabolism.

As to ECG parameters, the authors reported that a QRS width >110 ms during the first 30 minutes after flecainide infusion was useful to distinguish late responders from nonresponders. However, the analysis included too small a number of cases (4 late responders vs 48 nonresponders) to draw a definite conclusion. Of note, in our series, by using logistic regression analysis, we also attempted to find baseline ECG parameters which may predict the outcome of flecainide testing. Our results showed that QRS width in lead V1, J-point elevation in lead V2, S wave duration in lead II contributed significantly to the prediction. In a future study, ECG parameters measured both before and after flecainide should be tested to find any ECG parameters useful for predicting the outcome of flecainide testing.

Finally, with regard to flecainide metabolism as a possible factor of delayed/late response to the drug, the association between the time of occurrence of type1 ECG and CYP2D6 polymorphisms was inconclusive. As for CYP3A5, all patients were homozygous for a minor allelle. One of the reasons may be that a limited number of ECG leads for continuous monitoring led to underestimation of the development of type1 ECG and to misclassification of CYP2D6 polymorphisms related to the time points of type1 ECG appearance. In fact, although CYP2D6 is known to be the major metabolizer of flecainide, little is known about the effects of CYP2D6 polymorphisms and their interaction with
other hepatic enzymes\textsuperscript{10}. Current knowledge is drawn from few clinical studies with a small number of patients who were treated not only with flecainide but also other antiarrhythmic drugs\textsuperscript{7,11}. The results of these studies are also discordant\textsuperscript{10}. The effects of \textit{CYP2D6} polymorphisms on flecainide metabolism certainly need to be reevaluated. A study population consisting of BrS patients seems ideal to test the pure effect of \textit{CYP2D6} polymorphisms because it is a rather young cohort without concomitant diseases.

The results shown by Calvo et al. certainly are intriguing and call for revision of the flecainide testing protocol to improve its diagnostic yield in patients with BrS. To do so, the establishment of a large international registry of flecainide testing is encouraged so that the questions raised here can be reevaluated before a refined protocol of flecainide testing is finally established.
REFERENCES


