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EDITORIAL COMMENT

Risk of Sudden Death in Asymptomatic Brugada Syndrome

Not as High as We Thought and Not as Low as We Wished . . . But the Contrary*

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For every 10 patients with Brugada syndrome presenting with syncope, 8 will be diagnosed only after a cardiac arrest (1). This 8:10 ratio of deadly to nonlethal events among consecutive patients with symptomatic Brugada syndrome is strikingly higher than the 8:60 ratio of deadly to nonlethal events reported for consecutive patients with symptomatic long-QT syndrome (2). Thus, although we still do not know what percentage of patients born with Brugada syndrome will ever have spontaneous arrhythmias, we do know that those who do are likely to experience cardiac arrest. This "1 strike and you're out" risk called for an aggressive approach to asymptomatic Brugada syndrome (3). However, widespread use of prophylactic implantable cardioverter-defibrillator (ICD) devices was soon associated with intolerably high rates of complications among young patients with Brugada syndrome (4,5). Clearly, continuous reassessment of the tests we use for risk stratification in Brugada syndrome is mandatory.

See page 1576

Risk stratification based on electrophysiologic studies. The weight of risk stratification in Brugada syndrome has been primarily placed on electrophysiologic study (EPS) (3). This approach was driven by data from Brugada showing that patients with inducible ventricular fibrillation (VF) have a 10-fold risk for developing spontaneous VF (6). Controversy started, however, when neither Priori et al. (7) nor Eckardt et al. (8) could reproduce such results. Controversy turned into disappointment when 2 independent meta-analysis, of reports published by 2006, showed that EPS is of little value for predicting spontaneous VF (1,9). Furthermore, 2 recent multicenter studies from Europe—the FINGER (France, Italy, Netherlands, Germany) study (10)—and Japan (11) questioned whether EPS has any prognostic value in Brugada syndrome.

In both studies (10,11), EPS included programmed stimulation at 2 right ventricular sites with as many as 3 extrastimuli. However, the minimal coupling interval of the extrastimuli (a strong determinant of VF-inducibility rate) was kept above 200 ms in the FINGER study but was brought down to ventricular refractoriness in the Japanese study. Consequently, the percentage of asymptomatic patients who had inducible VF was higher in the Japanese study (57%) than in the FINGER study (37%). However, the percentage of patients who had spontaneous VF during follow-up in the 2 studies was lower than predicted, on the basis of the numbers published by Brugada et al. (6), and did not appear to be influenced by the results of EPS (Fig 1). In both studies combined, only 2.6% of asymptomatic patients with inducible VF, as well as 1.8% of patients with negative EPS, had spontaneous VF during 4 to 5 years of follow-up ($p = 0.56$). Having said that, it is also premature to conclude that the long-term risk for patients with asymptomatic Brugada syndrome is negligible, because of the following: 1) Although the 460 patients with asymptomatic Brugada syndrome who underwent EPS in both studies represent the largest such cohort ever reported, the limited population size precludes narrowing the confidence interval of any prediction. Using 95% confidence limits, one can only conclude from these studies that the risk for spontaneous VF at 4 to 5 years of follow-up is very likely between 1% and 6% for asymptomatic adults with Brugada syndrome and inducible VF and between 1% and 4% for those with negative EPS. 2) Although the follow-up periods keep expanding, they are still inadequate to allow accurate estimation of the long-term risk for this inborn condition. In other words, we simply do not know if a 2.6% risk at 4 years translates into a 26% risk at 40 years. Nevertheless, in view of the minimal increment in prognostic value provided by the EPS results, the majority of electrophysiologists are now looking elsewhere for prognostication.

Clinical risk factors. The majority of Brugada patients who eventually have VF are male (12). However, 70% of all recognized patients with asymptomatic Brugada are also male (10). Consequently, sex is a weak prognosticator in Brugada syndrome (10). Importantly, the few females who actually have spontaneous VF have less often a type I Brugada electrocardiogram (ECG), have less degree of ST-segment elevation, and data on their response to flecainide or ajmaline challenge are limited (13). Similarly, the majority of Brugada patients who have arrhythmias are >20 and <60 years of age. Taking into consideration the limited accuracy of our prognostic tests and the high complication rates of ICD implantation (4,5), we believe that clinicians

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JACC Vol. 56, No. 19, 2010
November 2, 2010:1585–8

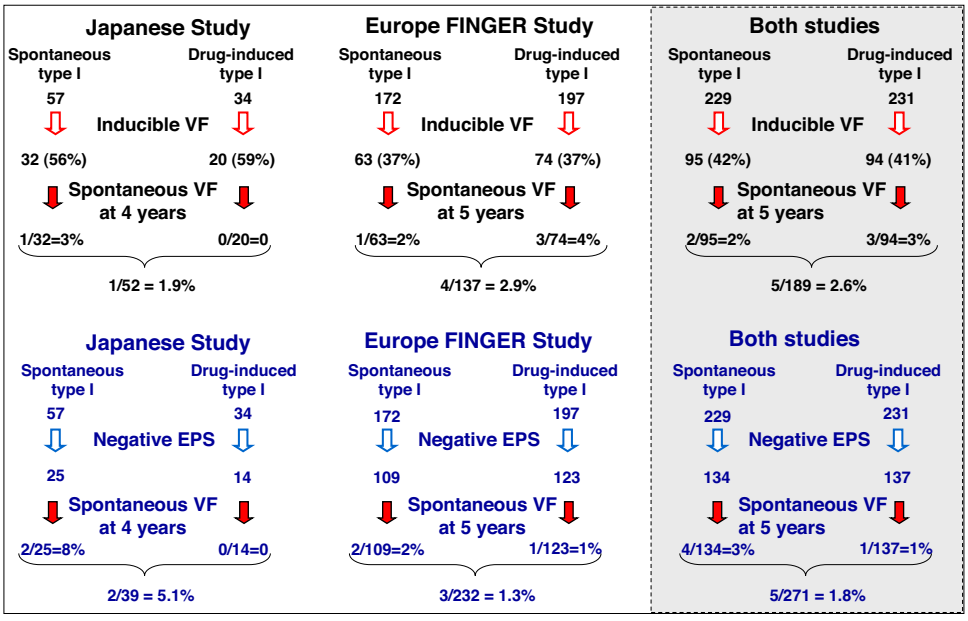

Figure 1 Outcomes of Patients With Asymptomatic Brugada Syndrome*

*Based on data from 2 recent large prospective studies (10,11). EPS = electrophysiologic study; VF = ventricular fibrillation.

should "look the other way" when dealing with women, elderly patients, or children with asymptomatic Brugada syndrome (14).

Electrocardiographic parameters. Numerous studies have shown that patients who have spontaneous type I (≥2 mm concave ST-segment elevation) Brugada ECG do worse than patients who only have a type I pattern when challenged with a sodium-channel blocker (9,10). However, classifying patients as either type I or non-type I is tricky because of the following: 1) Analysis of serial ECG recordings shows that the Brugada ECG pattern is highly variable over time. In patients with spontaneous coved-type ECG, only every third ECG is diagnostic, and every third ECG is normal (15). 2) Placing the V_1-V_2 recording electrodes at the second or third intercostal space (in addition to the standard fourth space location) increases the odds for recording a type I pattern (16). 3) With 24-h Holter recordings, one may detect transient type-I ST-segment elevation at night or after heavy meals (17). Thus, using Holter recordings with "high V_1-V_2" electrodes, one may double the percentage of patients with "spontaneous" type I ECG (18). Finally, Brugada patients may have a type I ECG only during fever, and may then have a malignant course (19).

The ECG features other than the degree of ST-segment elevation in V_1-V_2 are important. J-point elevation and "early repolarization" in the inferior leads are observed in 10% of patients with Brugada syndrome (20), and such patients appear to be at higher risk (11). Also, QRS wider than 120 ms in V_2 (21) and QRS fragmentation in V_1-V_3 are more frequently seen in Brugada patients with symptoms (22). In 1 study, QRS fragmentation performed better than EPS as a risk-stratification tool (22).

Response to exercise. Worsening of ST-segment elevation during the recovery phase of exercise tests in Brugada syndrome has been reported sporadically (23–25). Recently, Amin et al. (26) reported J-point elevation in Brugada patients during exercise and further elevation during the recovery period. Now, in this issue of the *Journal*, Makimoto et al. (27) report that ST-segment elevation during the recovery phase of exercise occurs in one third of Brugada patients and is a strong predictor of spontaneous VF (27).

The study by Makimoto et al. (27) included 93 patients with Brugada syndrome as well as 102 controls (including 47 with right bundle branch block), who underwent standard exercise testing. The ST-segment elevation in V_1-V_3 (defined as a ≥0.05 mV from their baseline) within 4 min of the end of exercise occurred in 37% patients with Brugada syndrome but in none of the controls ($p < 0.0001$). Patients with significant ST-segment rise during recovery also had more pronounced heart-rate slowing from peak exercise during the recovery period, reflecting greater vagal stimulation during recovery. Also, ST-segment elevation during recovery was associated with a *SCN5A* mutation, but not with a history of syncope or cardiac arrest. Importantly, during 6 ± 3 years of follow-up, arrhythmic events occurred in 44% of patients with Brugada syndrome who had ST-segment elevation during recovery from exercise, but in only 17% of Brugada patients who did not ($p = 0.004$). During univariate analysis, "history of VF," "ST-segment elevation after exercise," and "presence of *SCN5A* mutation" predicted arrhythmic events, whereas in-

duction of VF at EPS did not. Moreover, only the first 2 parameters remained significant independent predictors of outcome during multivariate analysis (27). Finally, among the 36 initially asymptomatic Brugada patients, 15 had ST-segment elevation after exercise, and 3 (20%) of them had arrhythmic events during follow-up. In contrast, none of the 21 asymptomatic patients without ST-segment elevation after exercise had arrhythmic events ($p = 0.039$). These results are in agreement with studies showing that vagal stimulation during pharmacologic challenge (28), heavy meals (17), or vagal syncope (29) increases the dispersion of ventricular repolarization and may be proarrhythmic in Brugada syndrome. However, 3 points argue against embracing the exercise test as the main tool for defining the need for therapy among asymptomatic patients: 1) the test failed to identify 68% of patients with a history of cardiac arrest; 2) the reproducibility of the test was not tested; and 3) the study included only 36 patients with asymptomatic Brugada syndrome, and that 8% of them had arrhythmic events during follow-up suggests that this was an a priori high-risk population (for comparison, ≤2% of initially asymptomatic patients had symptoms in the 2 recent multicenter studies already noted) (10,11).

What now? In the absence of well-established and reliable prognostic tests, we are now recommending prophylactic drug therapy with quinidine for asymptomatic Brugada syndrome in the context of an international study (30).

As explained in detail elsewhere (31), there are strong clinical and experimental data suggesting that quinidine could do for asymptomatic Brugada syndrome what beta-blockers have done for asymptomatic long-QT syndrome. It is, therefore, important to continue all efforts to prevent the disappearance of quinidine from the market (32–35).

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