EDITORIAL

Type-I Paradox of Brugada Syndrome

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The electrocardiographic trademark of Brugada syndrome, historically referred to as "type-I" Brugada pattern, includes a coved-type ST-segment elevation of ≥2 mm in the right precordial leads.[1] In the original series, all patients had a type-I pattern spontaneously.[1] However, with longer follow-up periods it became evident that only 2% of patients with bona-fide Brugada syndrome display the type-I pattern at all times.[2] In fact, among patients with spontaneous type-I ECG who undergo repeated ECG recordings over time, only every third ECG is diagnostic, one third is suspicious, and every third one is normal.[2,3] This fact made it necessary to develop a reliable challenge-test to unravel the type-I ECG. Indeed, the sodium-channel-blocker (SCB) challenge test,[4] with intravenous injection of flecainide or ajmaline (in Europe), procainamide (in the United States), or pilsicainide (in Japan), proved to be effective for revealing the type-I ECG pattern when Brugada syndrome was suspected but the type-I pattern was not obvious.[1] Patients with a type-I ECG unraveled during a SCB test became known as patients with "drug-induced" Brugada syndrome.[1]

Given that practically all patients with Brugada syndrome have a type-I ECG that appears and fades away continuously over time, and since this type-I can be effectively unraveled by a SCB test, we intuitively expected patients with spontaneous and drug-induced type-I to have a comparable arrhythmic risk. However, in every single series, patients with drug-induced type-I end up having lesser risk.[5] We refer to this phenomenon, the somehow paradoxical and unexpected good prognosis of patients with drug-induced type-I, as the *type-I paradox* of Brugada syndrome. Here, we to try to explain it in light of the study by Ueoka et al, on the prognostic significance of the SCB test, in this issue of the *Journal of the American Heart Association* (*JAHA*).[6]

The Present Study: A Shift From Diagnostic to Prognostic Test?

Ueoka et al described 245 patients with Brugada syndrome who underwent a SCB test with pilsicainide. The patients were typical of Brugada syndrome: their mean age was 46 years, all but 2% were male, and the majority (62%) were asymptomatic at presentation.[6] Importantly, 74% of patients had previous documentation of spontaneous type-I, or had a spontaneous type-I at the onset of the test but *nevertheless* underwent a SCB test to assess its *prognostic* (rather than diagnostic) value. This is remarkable because, in view of the risks involved (see below) and perceived lack of diagnostic added-value, this test is generally considered contraindicated for patients who already have documentation of a type-I Brugada pattern on a resting ECG.[7] That "orthodox" view of the test, however, is evolving: SCB tests have been performed in patients with documentation of a type-I pattern during fever[8] or to better delineate the arrhythmogenic substrate during radiofrequency ablation.[9]

The appearance of ≥2 mm coved ST-segment elevation in response to a SCB challenge is generally accepted as the test end point, leading to an immediate halt of the drug infusion.[10] Here, Ueoka et al speculated that ECG changes of greater magnitude would identify patients at higher risk of spontaneous arrhythmias, and the infusion was continued irrespective of the ST-segment elevation height. In fact, 106 (43%) patients undergoing the test already had ≥2-mm ST-segment elevation *before* the SCB infusion, and a stunning 6-mm ST-segment elevation in response to the drug challenge was the rule.[6] With this audacious protocol, ≈10% of all patients developed ventricular arrhythmias during the test.[6] During 9 years of follow-up, 31 (13%) of the patients developed spontaneous ventricular fibrillation (VF).[6] As in previous studies,[5] cardiac arrest at presentation inferred a 3-fold higher risk of VF during follow-up. The new finding was that the development of ≥3-mm ST-segment elevation, or the appearance of ventricular arrhythmias in response to the SCB test, were also independent predictors of VF during follow-up, with hazard ratios of 2.8 and 3.6, respectively.[6] Risk

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stratification is of paramount importance for asymptomatic patients.[5] It is therefore important that, in the present study, the risk of spontaneous VF during follow-up for patients *asymptomatic* at presentation almost doubled if they developed ≥3-mm ST-segment elevation and was 15 times higher if they developed arrhythmias during the SCB challenge test.[6]

Insights From the Present Study for the "Type-I Paradox" of Brugada Syndrome

One can postulate 2 explanations, not mutually exclusive, for the "type-I paradox." Both imply that ST-segment elevation is mechanistically necessary for the development of spontaneous VF (even if that is not always the case).[11] According to the first explanation, patients who have spontaneous type-I at presentation simply have it more often and therefore have higher risk of developing VF.[12] After all, among patients with Brugada syndrome undergoing repeated ECGs or 12-lead Holter recordings with continuous ST-segment analysis, those with VF have longer time periods with ST-segment elevation.[13,14]

A second explanation for the "type-I paradox" could well be that patients with drug-induced type-I ECG consist of 2 subgroups: (1) patients presenting with a nondiagnostic ECG and a positive SCB test, who then develop a spontaneous type-I pattern at least once during follow-up; and (2) otherwise similar patients who never develop a spontaneous type-I ECG. This second group could be larger than we think: If we compare the incidence of VF among patients who have spontaneous versus drug-induced type I at presentation, a risk repeatedly reported as 1% versus 0.3% annual risk,[5] by then assuming that VF events in the drug-induced category occur *only* in patients who have "yet unrecognized" spontaneous type I, one may calculate that only 3 out of 10 patients with drug-induced type I will ever develop a spontaneous type I. In studies performing repeated ECG or Holter recordings after a SCB test, only 29%[2] to 35%[13] are "caught" with a spontaneous type I. Clearly, this partition will depend on the frequency of ECG recordings done over time and needs to be better defined. As discussed elsewhere,[15,16] *truly false-positive responses to a SCB test do exist* and such patients are expected to have an excellent prognosis.

The study by Ueoka et al[6] provides limited insight into this intriguing second possibility. There were 105 patients with a nondiagnostic ECG at the time of the SCB test. Of the 85 patients with a positive SCB test, roughly half had documentation of a spontaneous type-I ECG. All the arrhythmic events, including the arrhythmias provoked by the test and the few spontaneous arrhythmias taking place during follow-up, occurred in this group. The numbers of arrhythmic events, however, are too small to reach any valid conclusions, and studies looking at the prognosis of patients with drug-induced type-I who never have a spontaneous type-I ECG are urgently needed.

Implications of the Present Study: Which Patients Should Undergo a SCB Test? Who Should Not?

Anyone wishing to perform (or undergo) a SCB test should first become familiar with the publication by Poli on the risk of refractory VF that can be triggered by the test.[17] VF occurs in <1% of all tests and <2% of all positive tests,[18] but may become incessant.[17] With this *call for caution* in mind, we present our take-home message from the study by Ueoka, regarding patient subgroups that could potentially benefit from the well-described diagnostic aspects, and newly described prognostic value, of the test.

Patients Presenting With Cardiac Arrest and a Spontaneous Type-I ECG

Half of all Brugada syndrome patients presenting with cardiac arrest will not develop recurrent arrhythmias even after 10 years of follow-up.[5] One could therefore wonder if *the absence* of ventricular arrhythmias during a SCB test, using Ueoka's protocol,[6] could help select patients who do *not* need implantable cardioverter defibrillator implantation. The answer is clearly negative; it is clear from Ueoka's data that the risk is prohibitively high even in the absence of drug-induced arrhythmias.[6]

Patients With Cardiac Arrest But No Spontaneous Type-I ECG

All cardiac arrest survivors should undergo a full evaluation for candidate causes, rather than "carte-blanche implantable cardioverter defibrillator implantation." Their ultimate diagnosis has important implications for themselves and their family. For example, the risk of eventually developing a VF storm (potentially fatal even with an implanted defibrillator)[19] is sufficiently high (24%) after a first VF episode[5] to justify (or at least consider) quinidine therapy in addition to implantable cardioverter defibrillator implantation. False-positive SCB-test results are less likely in this patient group, but still possible,[10] especially when certain circumstances of the cardiac arrest (like an exercise-induced event) lower the pretest probability of Brugada syndrome.

Patients With Syncope

The most important step while evaluating patients with Brugada syndrome presenting with syncope involves the careful interpretation of the event. This is because patients with vagal syncope are at low risk of spontaneous VF, comparable to that of asymptomatic patients, even if they have a spontaneous or drug-induced type-I Brugada pattern.[20] In contrast, patients with syncope presumed to be arrhythmic on clinical grounds are likely to develop spontaneous VF.[20]

Ueoka et al[6] appropriately grouped patients with malignant syncope alongside cardiac arrest survivors, and interpretation of their data should be made accordingly.

Asymptomatic Patients With Spontaneous Type-I

Only a minority of patients in this category will ever develop arrhythmic symptoms but for those who do, cardiac arrest will often be the presenting symptom.[5] It is therefore tempting to adopt the strategy of Ueoka et al[6] (ie, performing a SCB test for risk stratification). We urge against such an approach until the results (in terms of risk stratification and safety) are reproduced in a prospective manner. Importantly, the efficacy-to-risk ratio of pilsicainide may not be comparable to that of other SCBs. Furthermore, in this study only 2% of patients were female and only 1 was younger than 18 years. This is important because the test appears to be not only less predictive,[21] but also less safe for women and children.[17]

Asymptomatic Patients Without a Spontaneous Type-I

Although this is the patient group for whom the SCB is generally recommended,[7] patients should be aware of the consequences of entering the path we call "rule out Brugada syndrome." As discussed elsewhere,[22] asymptomatic patients who *only* have their type-I pattern revealed by drugs are at low risk, presumably below the risk-threshold justifying therapeutic interventions in view of the risks inherent to our therapy. Patients diagnosed with Brugada syndrome who are then left untreated may develop unbearable anxiety that could lead to therapeutic interventions with limited proof of benefit.[22] In a recent study,[9] 84 asymptomatic patients with only drug-induced type-I ECG first underwent a prophylactic implantable cardioverter defibrillator implantation and, after remaining free of arrhythmias for an undisclosed time period, underwent prophylactic epicardial ablation of extensive areas of their right ventricle. *If* the second explanation for the type-I paradox is correct, it is possible that some of the patients undergoing these 2 invasive procedures do not even have the disease we call Brugada syndrome.

Disclosures

None.

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