Response to Letter Regarding Article, “Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization”

We appreciated hearing from Casado-Arroyo et al regarding our recently published article, “Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization,” showing that SCN5A is a novel causative gene of early repolarization syndrome. In this study, we identified 3 SCN5A mutations in 3 unrelated patients with idiopathic ventricular fibrillation associated with early repolarization (or early repolarization syndrome). Because all of the patients had J-point elevation in the right precordial lead(s) in addition to J-point elevation in the inferior/lateral leads, Casado-Arroyo et al suggested that all of our patients have Brugada syndrome based on their recent findings that the risk of arrhythmia events is similar between patients with the Type 1 Brugada electrocardiographic pattern in 1 of the right precordial leads and patients with the Type 1 electrocardiographic pattern in >1 lead. However, we respectfully disagree because our patients never met the diagnostic criteria for Brugada syndrome. The diagnosis of Brugada syndrome is made when patients have a Type 1 Brugada electrocardiographic pattern, which is characterized by a prominent coved ST-segment elevation displaying a J-wave amplitude or ST-segment elevation ≥0.2 mV followed by a negative T-wave in ≥2 of the right precordial leads in the absence or presence of sodium channel blockers. Although the J-point elevation was ≥0.2 mV in 1 (Patients 2 and 3) or 2 (Patient 1) of the right precordial leads in our patients, there was no clear negative T-wave such that these patients did not exhibit a Type 1 electrocardiogram. The results of a sodium channel blocker challenge are positive in almost all patients with Brugada syndrome as shown by studies performed by our group and by the Brugada group, but the results were negative for all of our patients. Although Patient 3 had an R367H SCN5A mutation, which has been identified in another family affected by Brugada syndrome, the penetrance is incomplete in Brugada syndrome and identical mutations in SCN5A can result in different phenotypes, indicating the importance of genetic modifiers and environmental influences in determining disease susceptibility. Furthermore, the same mutation in KCNJ8 has recently been identified in patients with Brugada syndrome and in those with early repolarization syndrome, further supporting the hypothesis.

The letter by Casado-Arroyo et al presents important recent issues: the similarities and differences in both the genetic backgrounds and clinical characteristics between early repolarization syndrome and Brugada syndrome. Mutations in SCN5A have been identified in up to 30% of patients with Brugada syndrome, and we identified SCN5A as 1 of the causative genes of early repolarization syndrome. Furthermore, mutations in the cardiac L-type Ca2+ channel genes and those in KCNJ8 have been linked to both diseases. Because early repolarization syndrome and Brugada syndrome share genetic backgrounds, it is not surprising that both diseases also share clinical characteristics. J-point elevation is often found in the right precordial leads in patients with early repolarization syndrome, and our patients with early repolarization syndrome carrying an SCN5A mutation had J-point elevation in the right precordial lead(s). In contrast, inferolateral early repolarization is found in approximately 10% of patients and is associated with an increased risk of arrhythmia events in patients with Brugada syndrome. There are further similarities in the clinical characteristics, including a male preponderance, bradycardia-dependent augmentation of J-point elevation, reduction or elimination of J-point elevation during exercise, conduction abnormality, and responses to isoproterenol and quinidine. The similarities have led Antzelevitch et al to propose that both diseases represent different manifestations of a single disease termed “J wave syndromes.” However, important differences also exist between the 2 diseases. The modes of initiation of ventricular fibrillation are different. The early repolarization pattern is not generally associated with abnormalities in the T-wave, but the diagnostic Type 1 Brugada electrocardiogram includes a negative T-wave. In the signal-averaged electrocardiogram, abnormal late potentials are frequently found in patients with Brugada syndrome but are rare in patients with early repolarization syndrome. Sodium channel blockers augment ST elevation in the right precordial leads for patients with Brugada syndrome, whereas the drugs attenuate J-point elevation in patients with early repolarization syndrome. Interestingly, J-point elevation was augmented and ventricular fibrillation was induced by pilsicainide in 2 of the 3 patients carrying an SCN5A mutation, suggesting a unique characteristic of early repolarization syndrome associated with SCN5A mutations. Further studies are needed to elucidate the mechanism(s) responsible for the genotype–phenotype type correlations of the diseases associated with J-point elevation.


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