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.[1] 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.[2] However, we respectfully disagree because our patients never met the diagnostic criteria for Brugada syndrome.[3] 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.[3] 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,[4,5] 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,[6] 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.[7,8] 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.[9]

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,[3] and we identified *SCN5A* as 1 of the causative genes of early repolarization syndrome.[1] Furthermore, mutations in the cardiac L-type Ca^{2+} channel genes and those in *KCNJ8* have been linked to both diseases.[9–11] 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).[1,12] 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.[13] 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.[1,5] The similarities have led Antzelevitch et al[14] 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.[12] 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.[3] 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.[5] 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.[5] 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.[1] Further studies are needed to elucidate the mechanism(s) responsible for the genotype–phenotype correlations of the diseases associated with J-point elevation.

Disclosures

None.

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