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.4 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,2 and we identified SCN5A as 1 of the causative genes of early repolarization syndrome.1 Furthermore, mutations in the cardiac L-type Ca2+ 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.1,3 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 al13 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.5 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.6 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.

Hiroshi Watanabe, MD, PhD, FESC
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Akihiko Nogami, MD, PhD
Division of Heart Rhythm Management
Yokohama Rosai Hospital
Yokohama, Japan

Kimie Okubo, MD, PhD
Division of Cardiology
Department of Medicine
Niohn University School of Medicine
Tokyo, Japan

Hiro Kawata, MD, PhD
Division of Arrhythmia & Electrophysiology
Department of Cardiovascular Medicine
National Cerebral & Cardiovascular Center
Suita, Japan

Yuka Hayashi, MD
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Taisuke Ishikawa, DVM
Department of Molecular Pathogenesis
Medical Research Institute
Tokyo Medical & Dental University
Tokyo, Japan

Takeru Makiyama, MD, PhD
Department of Cardiovascular Medicine
Kyoto University Graduate School of Medicine
Kyoto, Japan

Satomi Nagao, MD
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Nobue Yagihara, MD
Division of Cardiology
Niigata University School of Medicine
Niigata, Japan

Naofumi Takehara, MD, PhD
Yuichiro Kawamura, MD, PhD
Department of Internal Medicine
Division of Cardiovascular Respiratory & Neurology

(Circ Arrhythm Electrophysiol. 2012;5:e60-e61.)
© 2012 American Heart Association, Inc.
Circ Arrhythm Electrophysiol is available at http://circrep.ahajournals.org
DOI: 10.1161/CIRCEP.112.971507
References


11. Yoshifu Aizawa MD, PhD. Division of Cardiology National Cerebral & Cardiovascular Center Suita, Japan

12. Minoru Horie MD, PhD. Department of Cardiovascular & Respiratory Medicine Shiga University of Medical Science Otsu, Japan

13. Yoshifusa Aizawa MD, PhD. Division of Cardiology National Cerebral & Cardiovascular Center Suita, Japan

14. Wataru Shimizu MD, PhD. Division of Cardiology Cardiovascular Center Tachikawa General Hospital Nagaoka, Japan

15. Masaomi Chinushi MD, PhD. Department of Cardiology Niigata University School of Medicine Niigata, Japan

16. Naomasa Makita MD, PhD. Department of Molecular Physiology Nagasaki University Graduate School of Biomedical Sciences Nagasaki, Japan

17. Ichiro Watanabe MD, PhD, FHRS. Division of Cardiology National Cerebral & Cardiovascular Center Suita, Japan
Response to Letter Regarding Article, "Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization"


_Circ Arrhythm Electrophysiol._ 2012;5:e60-e61
doi: 10.1161/CIRCEP.112.971507

_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/5/2/e60

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Arrhythmia and Electrophysiology_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Arrhythmia and Electrophysiology_ is online at:
http://circep.ahajournals.org/subscriptions/