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# **Novel *SCN5A* Mutation (Q55X) Associated with Age-Dependent Expression of Brugada Syndrome Presenting as Neurally Mediated Syncope**

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## ABSTRACT

**BACKGROUND:** The association of Brugada syndrome and neurally mediated syncope (NMS) has been recently described. Although mutations in *SCN5A* have been identified in Brugada syndrome, the genetic link between Brugada syndrome and NMS has not been determined.

**OBJECTIVES:** The purpose of the study was to clinically and genetically characterize a man with recurrent syncope that was originally diagnosed as NMS at the age of 8 who subsequently manifested Brugada syndrome at the age of 17.

**METHODS:** The proband underwent clinical examinations including head-up tilt test, Na channel provocation test, and electrophysiological study. Genetic screening of *SCN5A* was carried out for the proband and the family members. Biophysical properties of mutant *SCN5A* channel in a heterologous expression system were studied by whole-cell patch clamp technique.

**RESULTS:** The proband showed positive head-up tilt test, coved-type ST elevation recorded from the 3<sup>rd</sup> intercostal space, and the positive picrocainide provocation test. Ventricular fibrillation was inducible at programmed electrical stimulation, consistent with characteristics of both Brugada syndrome and NMS. A novel nonsense *SCN5A* mutation (Q55X) was identified in the proband, mother and his asymptomatic brother. The heterologously-expressed mutant channel was non-functional.

**CONCLUSION:** We first genetically determined an *SCN5A* mutation in a patient showing combined phenotype of NMS and Brugada syndrome. It is suggested that NMS and Brugada syndrome may share, at least in part, a common pathophysiological mechanism.

**KEY WORDS:** Brugada syndrome; neurally mediated syncope; *SCN5A*; tilt test

## INTRODUCTION

Brugada syndrome is an autosomal dominant disorder characterized by ST elevation in the right precordial leads and syncope or sudden death due to malignant ventricular arrhythmias<sup>1</sup>. Brugada syndrome typically predisposes men between 30-50 years to syncope, and mutations in the gene encoding the cardiac Na channel  $\alpha$  subunit *SCN5A* have been identified in 20-30% of Brugada-syndrome patients. The ECG signature of the Brugada syndrome is dynamic and often concealed, and the prevalence of a Brugada-type ECG in the juvenile population is very low<sup>2</sup>. The most common cause of syncope in young individuals is neurally mediated syncope (NMS), a disorder of regulation of autonomic tone, which is triggered by a wide variety of stimuli including orthostatic and emotional stress. The prognosis of NMS in young individuals is generally benign. Brugada syndrome and NMS are distinct causes of syncope by definition; however, the association of these conditions has been suggested in several case reports<sup>3-6</sup>. Furthermore, a recent clinical study showed that the head-up tilt (HUT) test was positive in 35% of patients with a coved-type ST elevation<sup>7</sup>. Here, we present the first case of NMS with a subclinical *SCN5A* mutation that manifested Brugada syndrome during adolescence. Our report emphasizes the genetic and clinical heterogeneity of Brugada syndrome, and suggests that at least some individuals with NMS manifest Brugada syndrome age-dependently, possibly influenced by multiple factors including a hormonal and genetic substrate.

## CASE REPORT

A 17-year-old man was referred for evaluation of recurrent syncope. Non-specific intraventricular conduction delay and 1<sup>st</sup> degree AV block were recognized at a medical checkup when he was 8 years old (Fig 1A). The physical examination, chest X-ray, echocardiography and treadmill exercise testing were normal, and no ST elevation or

arrhythmias were observed at that time. Six months later, he had a first episode of syncope during prolonged standing. Since the syncopal attacks typically occurred while he was in an upright posture or under emotional stress, his condition was diagnosed as NMS, although it was not proved at that time. At the age of 11, saddle-back ST elevation became apparent in leads V2-3 (Fig. 1B). At the age of 17, a coved-type ST elevation was recorded from the 3rd intercostal space (Fig. 1C).

On admission, a provocation test with a Na channel blocker was performed with intravenous administration of 50 mg of pilsicainide to test for conversion of a saddle-back ST elevation to a coved-type in the standard right precordial leads. Pilsicainide significantly augmented the J wave and ST elevation in V2 (0.2 mV), although it did not convert the ECG to coved-type (Fig 2A). A signal-averaged ECG was positive for late potentials. He experienced an 8.3 sec episode of sinus arrest during venipuncture before electrophysiological study (EPS). EPS showed sinus node dysfunction (corrected sinus node recovery time: 833 ms; sino-atrial conduction time measured by Narula's method: 473.5 ms) and AV node dysfunction (Fig 2B). VF was induced by double extrastimuli from the RV apex (Fig 2C). A HUT test provoked hypotension followed by 12 sec of sinus arrest, indicating a mixed type I NMS.

There was no family history of sudden cardiac death, but his mother had sick sinus syndrome with 1<sup>st</sup> degree AV block, and his asymptomatic brother had 1<sup>st</sup> degree AV block and non-specific intraventricular conduction delay (Fig 3A). Genetic screening revealed a novel *SCN5A* mutation at exon 2 resulting in a premature stop codon (Q55X) of the proband as well as his mother and brother (Fig 3A, B). This mutation is predicted to prematurely

truncate the N-terminal of the Na channel (Fig 3C). The heterologously expressed mutant Q55X channel showed no observable Na current (Fig 3D).

An implantable cardioverter defibrillator was recommended for the proband, but was declined. He has been treated with cilostazol, a phosphodiesterase inhibitor, to prevent severe bradycardia<sup>8</sup> and possible arrhythmias due to the Brugada syndrome<sup>9</sup>. The proband's mother and brother did not agree to undergo EPS or pharmacological testing.

## DISCUSSION

In the present case, the mode of syncope and clinical examinations including the HUT test strongly favored NMS before the age of 11. However, the clinical manifestation gradually changed to Brugada syndrome during adolescence. A spontaneous coved-type ST elevation, inducible VF, and the loss-of-function *SCN5A* mutation are all consistent with the diagnosis of Brugada syndrome in this case that could potentially give rise to lethal arrhythmias. It was reported that some patients with Brugada syndrome, like the present case, exhibit only a coved-type ST elevation when the ECG is recorded from a higher intercostal space in the presence or absence of Na channel blockers<sup>10, 11</sup>. Therefore, the proband suffered from two apparently distinct conditions: NMS and Brugada syndrome. The autonomic nervous system has been implicated in both diseases<sup>12, 13</sup>, and several case reports have described patients exhibiting clinical phenotypes of both NMS and Brugada syndrome<sup>3-5</sup>. Furthermore, a recent study demonstrated that 12 (35%) out of 34 patients with a coved-type ST elevation showed a vasovagal response to a HUT test<sup>7</sup>. These observations suggest an association between NMS and Brugada syndrome rather than a simple coincidence, although identification of the causes of syncope in such patients are often difficult and therefore, treatment of these patients remains a therapeutic challenge<sup>5</sup>. Our report provides a genetic

and biophysical basis for the first time that supports an association of NMS and Brugada syndrome.

The ECG signature of Brugada syndrome is dynamic and often concealed. The age-dependent manifestation of Brugada syndrome correlates well with previous observations that the ECG penetrance in the mutation carriers of Brugada syndrome is considerably lower in children than adults (17% vs. 100%, respectively)<sup>14</sup>. Furthermore, in a large family with overlapping phenotypes of Brugada syndrome and long QT syndrome due to an *SCN5A* mutation 1795insD, QT prolongation was recognized from birth onward, whereas ST elevation became apparent only after 5 years<sup>15</sup>. We speculate that at least some episodes of syncope before the age of 11 in the present case may have been caused by arrhythmias due to the concealed Brugada syndrome substrate. Autonomic and hormonal influences including testosterone may be another candidate for the age-dependent manifestation of the Brugada-syndrome phenotype, as the Brugada-type ECG pattern disappeared following surgical castration for prostate cancer in a case report<sup>16</sup>. Moreover, based on a recent observation that *SCN5A* is expressed not only in the myocardial cells but also in intracardiac ganglia<sup>17</sup>, it is speculated that the nonsense mutation of *SCN5A* may not only provide the substrate for Brugada syndrome in the myocardium, but also an imbalance in intracardiac ganglia activity, which in turn results in autonomic dysfunction implicated in both Brugada syndrome and NMS. Alternatively, some genetic modifiers other than *SCN5A* may contribute to the age-dependent manifestation of the Brugada-syndrome phenotype as well as the apparent phenotype-genotype dissociation observed between the proband and two mutation carriers.

In summary, we demonstrated a novel nonsense *SCN5A* mutation in a case of Brugada syndrome that was previously diagnosed as NMS. The functional consequences of *SCN5A* mutations are diverse, possibly influenced by multiple factors including age, hormones, or genetic modifiers. Moreover, the prognosis of NMS may not necessarily be benign, because at least some NMS patients, like the present case, may also have Brugada syndrome due to a subclinical genetic substrate that may potentially give rise to lethal arrhythmias.

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#### FIGURE LEGENDS

##### **Figure 1. Age-dependent ECG changes in the proband**

- (A) ECG at the age of 8 showed non-specific intraventricular conduction delay without ST elevation.
- (B) Saddle-back ST elevation was evident in V2-3 at the age of 11.
- (C) Coved-type STS elevation was observed in leads V1-3 from the 3rd intercostal space at the age of 17.

##### **Figure 2. Provocation test with a Na channel blocker and the electrophysiological study**

- (A) Intravenous administration of 50 mg pilsicainide augmented the J wave and induced ST elevation in V2, although none of the standard right precordial leads

converted to a coved-type.

- (B) Intracardiac recording shows prolonged AA, AH, AV and PR intervals.
- (C) VF was induced from RV apex by double extrastimuli (S1S1=800 ms, S1S2=250 ms, S2S3=230 ms).

**Figure 3. Electrocardiographic and genetic evaluation of the pedigree, and the functional characterization of the mutation**

- (A) Pedigree of the family with Brugada syndrome. Arrow indicates the proband. Electrocardiograms from the V2 lead are shown. Open symbol indicates the unaffected individual. Closed and shaded symbols indicate genetically affected individuals with or without symptoms, respectively.
- (B) Sequence electropherogram of *SCN5A* of the proband shows heterozygous nonsense mutation (arrow) of a stop codon (TAG) for Gln-55 (CAG).
- (C) Predicted topology of Nav1.5 and the location of Q55X.
- (D) WT and Q55X channels were transiently transfected into tsA-201 cells and the whole-cell Na current were recorded as previously described<sup>18</sup>. Representative current traces elicited by test pulses (from -90 to +60 mV in 10 mV steps) from a holding potential of -120 mV are shown.

**REFERENCES**

1. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: Report of the second consensus conference: Endorsed

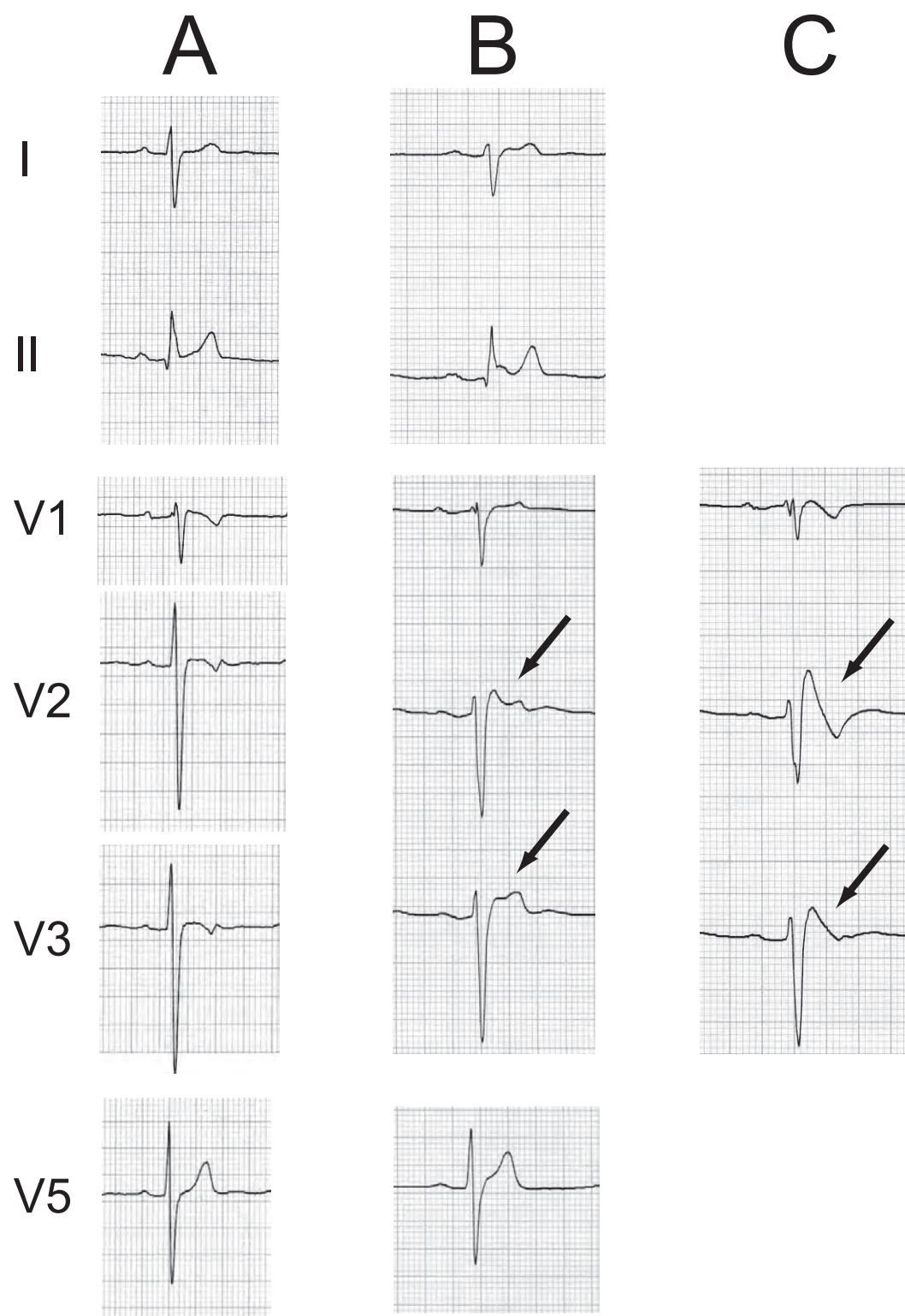
by the Heart Rhythm Society and the European Heart Rhythm Association.  
Circulation. 2005;111:659-670.

2. Yoshinaga M, Anan R, Nomura Y, Tanaka Y, Tanaka Y, Sarantuya J, Oku S, Nishi S, Kawano Y, Tei C, Arima K. Prevalence and time of appearance of Brugada electrocardiographic pattern in young male adolescents from a three-year follow-up study. Am J Cardiol. 2004;94:1186-1189.
3. Marquez MF, Rivera J, Hermosillo AG, Iturralde P, Colin L, Moragrega JL, Cardenas M. Arrhythmic storm responsive to quinidine in a patient with Brugada syndrome and vasovagal syncope. Pacing & Clinical Electrophysiology. 2005;28:870-873.
4. Patruno N, Pontillo D, Anastasi R, Sunseri L, Giamundo L, Ruggeri G. Brugada syndrome and neurally mediated susceptibility. Ital Heart J. 2005;6:761-764.
5. Samniah N, Iskos D, Sakaguchi S, Lurie KG, Benditt DG. Syncope in pharmacologically unmasked Brugada syndrome: indication for an implantable defibrillator or an unresolved dilemma? Europace. 2001;3:159-163.
6. Patruno N, Pontillo D. Brugada syndrome and vasovagal syncope. Pacing & Clinical Electrophysiology. 2006;29:215-215.
7. Yokokawa M, Sato Y, Kitamura S, Tanaka K, Nagai T, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Shimizu W. Neurally-mediated syncope as a cause of syncope in patients with type 1 Brugada ECG. Heart Rhythm. 2006;3:S58-S58.
8. Atarashi H, Endoh Y, Saitoh H, Kishida H, Hayakawa H. Chronotropic effects of cilostazol, a new antithrombotic agent, in patients with bradyarrhythmias. J Cardiovasc Pharmacol. 1998;31:534-539.

9. Tsuchiya T, Ashikaga K, Honda T, Arita M. Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol.* 2002;13:698-701.
10. Sangwatanaroj S, Prechawat S, Sunsaneevitayakul B, Sitthisook S, Tosukhowong P, Tungsanga K. New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. *Eur Heart J.* 2001;22:2290-2296.
11. Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, Suyama K, Kurita T, Aihara N, Kamakura S. Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. *J Cardiovasc Electrophysiol.* 2000;11:396-404.
12. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Col Cardiol.* 1996;27:1061-1070.
13. Wichter T, Matheja P, Eckardt L, Kies P, Schafers K, Schulze-Bahr E, Haverkamp W, Borggrefe M, Schober O, Breithardt G, Schafers M. Cardiac autonomic dysfunction in Brugada syndrome. *Circulation.* 2002;105:702-706.
14. Schulze-Bahr E, Eckardt L, Breithardt G, Seidl K, Wichter T, Wolpert C, Borggrefe M, Haverkamp W. Sodium channel gene (SCN5A) mutations in 44 index patients with Brugada syndrome: different incidences in familial and sporadic disease. *Hum Mutat.* 2003;21:651-652.
15. Beaufort-Krol GCM, van den Berg MP, Wilde AAM, van Tintelen JP, Viersma JW, Bezzina CR, Bink-Boelkens MTE. Developmental aspects of long QT syndrome type

- 3 and Brugada syndrome on the basis of a single SCN5A mutation in childhood. *J Am Coll Cardiol*. 2005;46:331-337.
16. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing & Clinical Electrophysiology*. 2003;26:1551-1553.
17. Scornik FS, Desai M, Brugada R, Guerchicoff A, Pollevick GD, Antzelevitch C, Perez GJ. Functional expression of "cardiac-type" Nav1.5 sodium channel in canine intracardiac ganglia. *Heart Rhythm*. 2006;3:842-850.
18. Makita N, Sasaki K, Groenewegen WA, Yokota T, Yokoshiki H, Murakami T, Tsutsui H. Congenital atrial standstill associated with coinheritance of a novel SCN5A mutation and connexin 40 polymorphisms. *Heart Rhythm*. 2005;2:1128-1134.

**Figure 1**



**Figure 2**

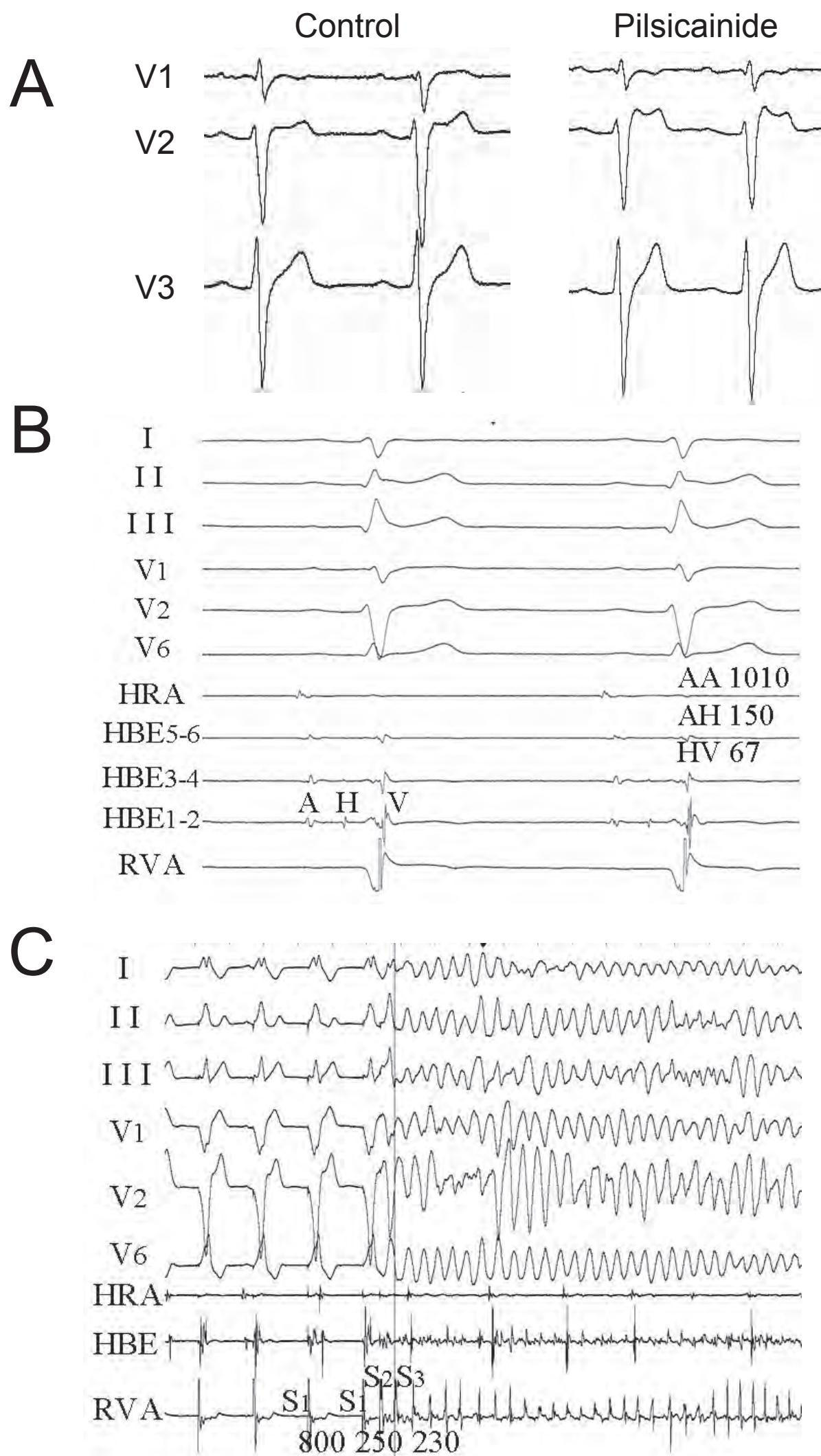


Figure 3

