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CASE REPORT

# A combination of quinidine/mexiletine reduces arrhythmia in dilated cardiomyopathy in two patients with R814W *SCN5A* mutation

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## Abstract

*SCN5A* gene mutations are described in 2% of patients with dilated cardiomyopathy (DCM) and different rhythm disturbances, including multifocal ectopic Purkinje-related premature contractions. Recent data indicate that sodium channel blockers are particularly effective monotherapy in carriers of the R222Q *SCN5A* variant. Our purpose is to describe the effectiveness of antiarrhythmic treatment in a family with genetically determined arrhythmogenic DCM associated with the R814W variant in the *SCN5A* gene. We examined a family with arrhythmogenic DCM (multifocal ectopic Purkinje-related premature contractions phenotype, atrial tachyarrhythmias, automatism, and conduction disorders) and described antiarrhythmic treatment efficacy in heart failure symptoms reduction and myocardial function improvement. We found a heterozygotic mutation R814W in *SCN5A* by whole exome sequencing in the proband and confirmed its presence in all affected subjects. There were two sudden cardiac deaths and one heart transplantation among first-degree relatives. The 58-year-old father and his 37-year-old daughter had full spectrum of symptoms associated with R814W *SCN5A* mutation. Both had implanted cardioverter defibrillator. In the father, adding mexiletine to quinidine therapy reduced ventricular arrhythmia (50–60% → 6–8% of whole rhythm) and reverted long-standing atrial fibrillation to sinus rhythm. In the daughter, mexiletine and overdrive pacing were effective in ventricular arrhythmia reduction (25% → 0.01%). Because of a growing number of atrial fibrillation recurrences, a reduced dose of quinidine (subsequently flecainide) was added, resulting in arrhythmia significant reduction. In both cases, antiarrhythmic effectiveness correlated with clinical improvement. In *SCN5A* R814W-associated DCM, a combination of Class I antiarrhythmics and overdrive pacing is an effective treatment of severe ventricular and atrial arrhythmias.

**Keywords** R814W *SCN5A* variant; Arrhythmogenic dilated cardiomyopathy; Multifocal ectopic Purkinje-related premature contractions

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## Introduction

There is a growing recognition of inherited arrhythmogenic cardiomyopathy, with desmosomal and other genes, for example, *LMNA*, *PLN*, *RBM20*, and *SCN5A*, as contributors.[1,2]

More than 20 mutations identified in *SCN5A* are related to dilated cardiomyopathy (DCM).[3] In particular, the p.R222Q *SCN5A* variant is recurrently associated with arrhythmogenic DCM.[1,4–8] Quite a few researchers, including these authors,[5,6,8] have found that sodium channel blocking agents cause a substantial reduction in refractory ventricular arrhythmia (VA) and improvement in left ventricular (LV) function in the mutation carriers.

This family report shows our experience with management of severe arrhythmia in relation to R814W *SCN5A*-linked DCM.

## Case report

In 2006, following two sudden cardiac deaths in the family, the proband (then a 22-year-old woman; *Figure 1*: III:5) with treatment-resistant VA was referred to the Institute of Cardiology, Warsaw. Heart palpitations started when she was 14. With time, increasing VA and dilation of the LV with impairment of LV systolic function was observed, despite antiarrhythmic and heart failure (HF) therapy. On admission, she had Class III HF symptoms according to the New York Heart Association (NYHA), severe systolic dysfunction [LV ejection fraction (LVEF) 20%], and life-threatening VA containing >80% of whole rhythm, consisting of frequent single ventricular ectopic beats (VEBs), nonsustained ventricular tachycardia (nsVT) and sustained ventricular tachycardia, idioventricular rhythm (IVR) as well as persistent atrial fibrillation (AF). A single-chamber implantable cardioverter defibrillator (ICD) was implanted. In electrophysiological study, multifocal ectopic Purkinje-related premature contractions (MEPPC) phenotype was diagnosed. Ablation of complex VA failed. Amiodarone treatment caused complete regression of ventricular and atrial arrhythmia with LV systolic function improvement (LVEF 50%). After 2 years, we observed a growing number of both ventricular and atrial arrhythmias and deterioration of LV function, which brought the proband to heart transplantation in 2010.

Clinical screening, including standard 12 lead electrocardiogram (ECG), echocardiography, and 24 h ECG registration by Holter method, was performed in the family, and genetic testing was offered. All affected family members were treated at our institute. General characteristics of the family is described in *Table 1*.

### Genetic testing methodology

After obtaining written informed consent, blood samples for DNA testing were taken from the proband and all living family members. In addition, a blood sample from deceased proband's sister was also screened. DNA was isolated from the peripheral blood by phenol extraction. Whole exome sequencing (WES) was performed on HiSeq 1500 using TruSeq Exome Enrichment Kit (Illumina, San Diego, CA, USA) as described previously.[9] *SCN5A* variant identified with WES was followed up in relatives with Sanger sequencing.

### Genetic results

We found a heterozygotic mutation NM_198056.2: c.2440C > T:(p.Arg814Trp/R814W) in *SCN5A* by WES in the proband and confirmed its presence in all affected subjects (*Figure 1*). No other pathogenic/likely pathogenic variants in genes related to arrhythmia or cardiomyopathies were identified.

**Figure 1** Results of genetic study in relation to the family pedigree with R814W *SCN5A* mutations. Left, Integrative Genomics Viewer view, chromatogram of *SCN5A* NM_198056.2:c.2440C>T:(p.Arg814Trp/p.R814W) variant and family pedigree. Above, pedigree: squares represent male subjects, and circles represent female subjects. Black arrowhead denotes the proband. Red arrowheads denote studied patients. A diagonal line marks deceased individuals. Solid black symbols denote dilated cardiomyopathy. Open symbols with asterisk denote unaffected individuals. The presence or absence of a heterozygous mutation is indicated by a +/− symbol.

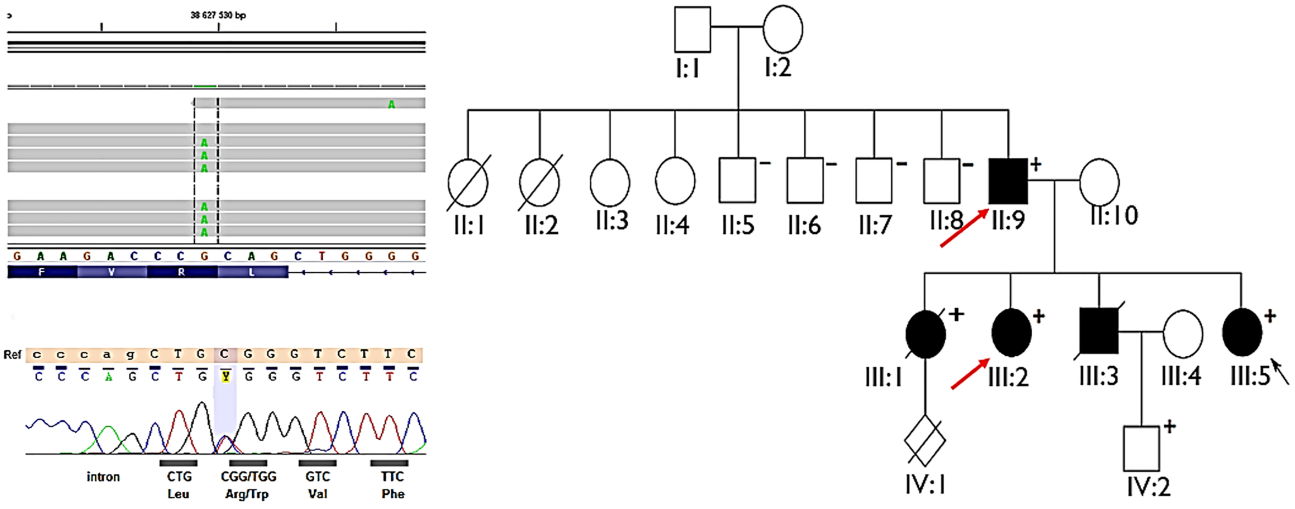



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**Table 1** Characteristics of affected family members and description of antiarrhythmic treatment

| Characteristics of affected family members | | | | | |
|---|---|---|---|---|---|
| Subject | II:9 | III:1 | III:2 | III:3 | III:5 |
| Age at onset/now | 35/58 | 15/24[a] | 32/37 | 22/22[a] | 14/35 |
| Sex | M | F | F | M | F |
| Symptoms | Palpitations<br>presyncope<br>HF | Palpitations<br>HF<br>SCD | HF | SCD | Palpitations<br>presyncope<br>HF<br>SCD with successful ICD therapy |
| NYHA functional class | III | II | II/III | ND | II–>IV<br>OHT |
| LVDd (mm)/EF (%) | 58/38 | 64/30 | 60/25 | ND/LV hypertrophy | 66/10 |
| DCM | Yes | Yes | Yes | No | Yes |
| Conduction disorders | AVB I/II, RBBB | ND | AVB I | ND | AVB I/II, RBBB |
| Arrhythmias | AF/AFL/MEPPC nsVT/IVRT | AF, MEPPC, VT/VF | AF/AFL/MEPPC | ND | AF/MEPPC VT/VF |
| ICD | Yes | No | Yes | No | Yes → CRT-D<br>OHT in 2010<br>Now PM |
| Concomitant diseases | HT, DM2, CAD | — | — | — | — |
| Others | CTI ablation 2003, 2016—bidirectional block | SCD in 8 month pregnancy | EPS/ablation MEPPC<br>AAI pacing 500 ms—without VEBs | — | EPS/ablation not successful—MEPPC |

| Chronologic description of antiarrhythmic treatment with quinidine and mexiletine or combination of both | | |
|---|---|---|
| Subject | **II:9** | **III:2** |
| Quinidine alone | Yes—partially successful (2014–10.2016) | Yes—unsuccessful, poor tolerance (01.2015—stopped in 03.2015) |
| VEBs before/after quinidine treatment/24 h | ~45 000/~8000 | ~25 000/~30 000 |
| Echo findings before/after quinidine | | |
| LVEF (%) | 38/55 | 60/25 |
| LVDd (mm) | 50/58 | 48/50 |
| LVSd (mm) | 42/43 | 32/46 |
| LA area ($cm^2$) | 30/25.4 | 21.6/20.8 |
| PWd (mm) | 10.9/11 | 8.3/8 |

(*Continues*)


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**Table 1** (continued)

| Chronologic description of antiarrhythmic treatment with quinidine and mexiletine or combination of both | | |
|---|---|---|
| Subject | **II:9** | **III:2** |
| Others | AF long-standing persistent → conversion to SR!<br>10.2016—VEBs 46 500/day | Beginning AF episodes<br>EPS/ablation of MEPPC<br>07.2015—ineffective |
| ICD therapy after quinidine | Zones: VT 162/min, 6 ATP, 4 HV, VF 214/min, ATP during charging, 6HV<br>Monitored nsVT, without therapy | 08.2015:<br>ICD-VR → ICD-DR, then AAI overdrive 90/min<br>Zones: VT 181/min, 5 ATP, 4 HV, VF 230/min, ATP during charging, 6 HV<br>No episodes, without therapy |
| Mexiletine alone | Yes—unsuccessful (10.2016–01.2017) | Yes—good effect (08.2015 till now) |
| VEBs before/after mexiletine treatment/24 h | 46 500 → 30 000 → 60% whole rhythm | ~25 000/200 4600 |
| Echo findings after mexiletine | | |
| LVEF (%) | 44–47 | 40–50 |
| LVDd (mm) | 61 | 48 |
| LVSd (mm) | 43 | 36 |
| LA area ($cm^2$) | 34.9 | 19.7 |
| PWd (mm) | 9.3 | 8.5 |
| Others | SR → persistent AF<br>No | AF recurrences, Mode Switch 15% (in ICD control)<br>No |
| ICD therapy after mexiletine | | |
| Monitored nsVT episodes | | |
| Drug combination | Quinidine + mexiletine (since 01.2017) | Mexiletine + quinidine (low dose 2 × 100 mg) (06.2018–10.2018) |
| VEBs before/after combination treatment/24 h | From 30 000 to 60% whole rhythm/6000–8800 | 4300/single |
| Echo findings after combination | | |
| LVEF (%) | 52 | 50 |
| LVDd (mm) | 54 | 47 |
| LVSd (mm) | 42 | 36.5 |

(*Continues*)

**Table 1** (continued)

| Chronologic description of antiarrhythmic treatment with quinidine and mexiletine or combination of both | | |
|---|---|---|
| Subject | **II:9** | **III:2** |
| LA area ($cm^2$) | 25 | 18 |
| PWd (mm) | 11 | 7.5 |
| Atrial tachyarrhythmias before/after combination | AF persistent → SR | Reduction in AF recurrence, Mode Switch 15% → 3% |
| ICD therapy after combination | No | No |

AF, atrial fibrillation; AFL, atrial flutter; AVB, atrioventricular block; ATP, antitachycardia pacing; CAD, coronary artery disease; CRT-D, cardiac resynchronization therapy with defibrillator; CTI, cavo-tricuspid isthmus; DCM, dilated cardiomyopathy; DM2, diabetes mellitus type 2; EF, ejection fraction; EPS, electrophysiological study; F, female; HF, heart failure; HT, hypertension; HV, high voltage shock; ICD, implantable cardioverter defibrillator; ICD-VR, implantable cardioverter defibrillator single chamber; ICD-DR, implantable cardioverter defibrillator dual chamber; IVRT. idioventricular rhythm; LA, left atrium; LV, left ventricular; LVDd, left ventricular diastolic diameter; LVSd, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; M, male; MEPPC, multifocal ectopic Purkinje-related premature contractions; ND, not defined; nsVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; PM, pacemaker; PWd, posterior wall diameter; RBBB, right bundle brunch block; SCD, sudden cardiac death; SR, sinus rhythm; VEBs, ventricular ectopic beats; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Death.

## Studied subjects

We focused on the cases of a 58-year-old father (II:9) and his 37-year-old daughter (III:2). The father had a 20-year history of HF and a complex of VA (VEBs/nsVT/IVR), which constituted 50–60% of whole rhythm, and 10-year long-standing AF/atrial flutter (AFL), coexistent diabetes mellitus type 2, hypertension, and coronary artery disease. He has moderate impairment of LV systolic function (LVEF 38%) and HF symptoms in II/III NYHA class.

Since she was 32, the daughter has been symptomatic, after a significant increase in ventricular and supraventricular arrhythmias (supraventricular extrasystoles ~1500/24 h; VEBs ~25 000/24 h). She has been followed up for 15 years in an outpatient clinic due to familial sudden cardiac death high risk. Both patients (II:9 and III:2) have had an ICD implanted since 2006.

## Antiarrhythmic treatment

### *II:9*

On the basis of the published data,[5,6] antiarrhythmic treatment with quinidine was administered to the father. Before quinidine therapy, he had severe HF (dyspnoea and fluid retention in the pulmonary and systemic circulations), as well as vertigo and frequent presyncope that correlated with nsVT (*Figure 2A*). After optimization of HF therapy, quinidine in standard doses (2 × 200 mg/day) was added. We observed a significant reduction in VA (*Table 1*), HF symptoms regress (NYHA II/III → NYHA I/II), and an improvement of LV systolic function (LVEF 38% → 55%) with normalization of LV end-diastolic dimension (54 mm) (*Figure 2C* and *D*). After 8 months of treatment, a return of sinus rhythm was observed. A consecutive 24 h ECG registration by Holter revealed sinus bradycardia, episodes of typical AFL, and conduction disorders: first-degree atrioventricular block, right bundle branch block, and reduced number of VA (~4500/day). Due to typical AFL, ablation was performed to obtain a bidirectional conduction block in the cavo-tricuspid isthmus. Stable antiarrhythmic effect was constant during the 2 year observation. Then, there occurred an increasing number of VEBs/nsVT. Mexiletine (standard dose 3 × 200 mg/day) in monotherapy was unsuccessful. On the basis of earlier antiarrhythmic success of quinidine, we used a combination of quinidine and mexiletine in the patient with standard doses of both drugs (mexiletine 3 × 200 mg/day and quinidine 2 × 200 mg/day) without side effects. After combined therapy, there was a significant arrhythmia reduction (VEBs/nsVT/IVR from 47 000/day to 6000–8000/day and sinus rhythm restoration—*Figure 2B*) as well as an increase in LVEF to 55% and a reduction in HF symptoms on subsequent follow-up visits. This treatment has been effective for 1.5 year follow-up.

### *III:2*

In the daughter, antiarrhythmic treatment with quinidine was started in 2015. There was no antiarrhythmic effect (VEBs 25 000/day → 30 000/day), and poor tolerability was observed. Therefore, treatment was discontinued after 6 weeks. Acceleration of VA (VEBs/bigeminy with right bundle branch block-like morphology and narrow QRS; *Figure 3A*) caused worsening of LV systolic function (LVEF 60% → 25%; *Figure 3C*) and significant exacerbation of HF symptoms (NYHA II → III). AF/AFL episodes were also present. In electrophysiological study, the connection of VEBs with Purkinje fibres was confirmed. Ablation of VA in His–Purkinje fibre signals in LV was performed at the same time but was ineffective. It was also proved that AAI overdrive pacing 500 ms was suppressing the arrhythmia. After that, an upgrade to dual chamber ICD was done. Overdrive stimulation was partially successful. Mexiletine (standard dose 3 × 200 mg/day) was administered. When treatment was effective in VA reduction (VEBs 30 000/day → 50/day; *Figure 3B*), LVEF improved (25% → 40–50%; *Figure 3D*), and HF symptoms (NYHA III → I/II) regressed. This antiarrhythmic success is constant with regard to VA. Because of a growing number of AF/AFL recurrences (in ICD control mode switch raised up to 15%), we used a combination of mexiletine with a reduced dose of quinidine (2 × 100 mg/day) with a significant reduction in atrial arrhythmia (mode switch decrease from 15% → 3%) in 12 month follow-up. The drug combination was well tolerated by the patient, like in the father's case. We also tried to use flecainide with full success in VEBs number and AF/AFL recurrence reduction, but the side effects (vision disturbances) disqualified that therapy in our patient.

A history of antiarrhythmic treatment is chronologically described in *Table 1*.

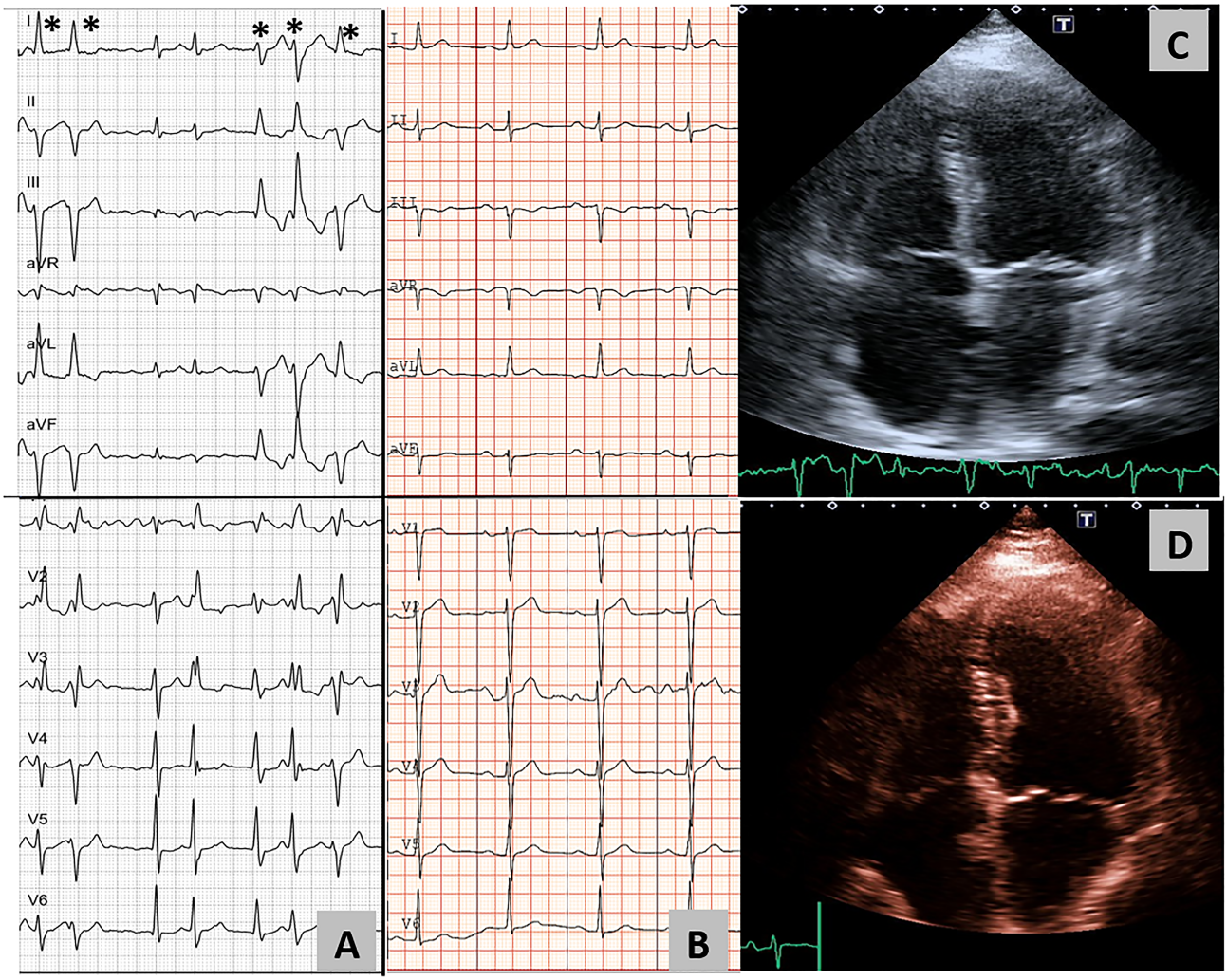
# Discussion

This study shows that successful antiarrhythmic treatment with a combination of Class I antiarrhythmics can reduce life-threatening VA, restore sinus rhythm, and alleviate HF symptoms in patients with arrhythmogenic DCM caused by R814W *SCN5A* mutation. There were no side effects in personalized doses during the therapy. Treatment with a combination of these drugs has not been described, as yet. It is also the first study describing success of antiarrhythmic drugs in regression of HF symptoms due to DCM caused by R814W mutation in *SCN5A* gene. In one of the cases, the treatment was associated with overdrive pacing.

## R814W *SCN5A* mutation

The identified variant affects positively charged arginine at position 814, which lies on S4 segment of DII domain (DII/

**Figure 2** Patient II:9: (A and B) Electrocardiographic and (C and D) echocardiographic images before and after antiarrhythmic treatment (AAT) with sodium channel blockers combination. (A) Twelve lead surface electrocardiogram before AAT; atrial fibrillation, 1st, 2nd, and 7th evolution—ventricular ectopic beats (VEBs) with right bundle brunch block (RBBB) + left anterior fascicular block (LAFB)-like morphology, 5th and 6th evolution—VEBs with RBBB-like and right axis deviation morphology (stars show VEBs), and 3rd and 4th QRS are proper rhythm evolutions (3rd QRS 100 ms; 4th with RBBB, QRS 140 ms). (B) Twelve lead electrocardiogram after successful combined AAT—sinus rhythm 60/min., PR 260 ms, QRS 100 ms., QT/QTc 430/430 ms. (C) Echo 2-D before AAT, four-chamber view at systole; dilation of left ventricle, left ventricular ejection fraction 35%. (D) Echo 2-D after successful AAT, four-chamber apical view at systole; normalization of left ventricular diameter, left ventricular ejection fraction 55%.




S4) of sodium channel $Na_v1.5$ α subunit—one of the four sodium channel voltage sensors.[10] Previously, heterozygous R814W substitution arising *de novo* in a patient with sporadic DCM was reported.[11] Nguyen *et al*. performed functional studies on this mutation.[12] R814W mutant displayed abnormal kinetics of activation and deactivation, the hyperpolarized shift of the conductance–voltage relationship, and the altered voltage dependence of activation and deactivation.[12] This can lead to an altered force–frequency relationship—an important regulatory mechanism of the heart contractility.[12] R814W is a gain-of-function variant; it could be responsible for hyperexcitability of the His–Purkinje system that leads to incomplete repolarization in Purkinje cells and premature ventricular action potentials and thus enhanced automaticity. A high burden of ectopic beats may lead to development of DCM phenotype in the end.[6,13] In patients with arrhythmogenic DCM, mutations in S4 DI and DII domains are associated with cardiac arrhythmias (AF and VEBs), cardiac conduction disorders, sick sinus syndrome, and DCM.[12,14] Other potential mechanisms of contractile dysfunction include abnormal calcium handling, improper pH regulation, and disrupted mitochondrial function.[13,15]


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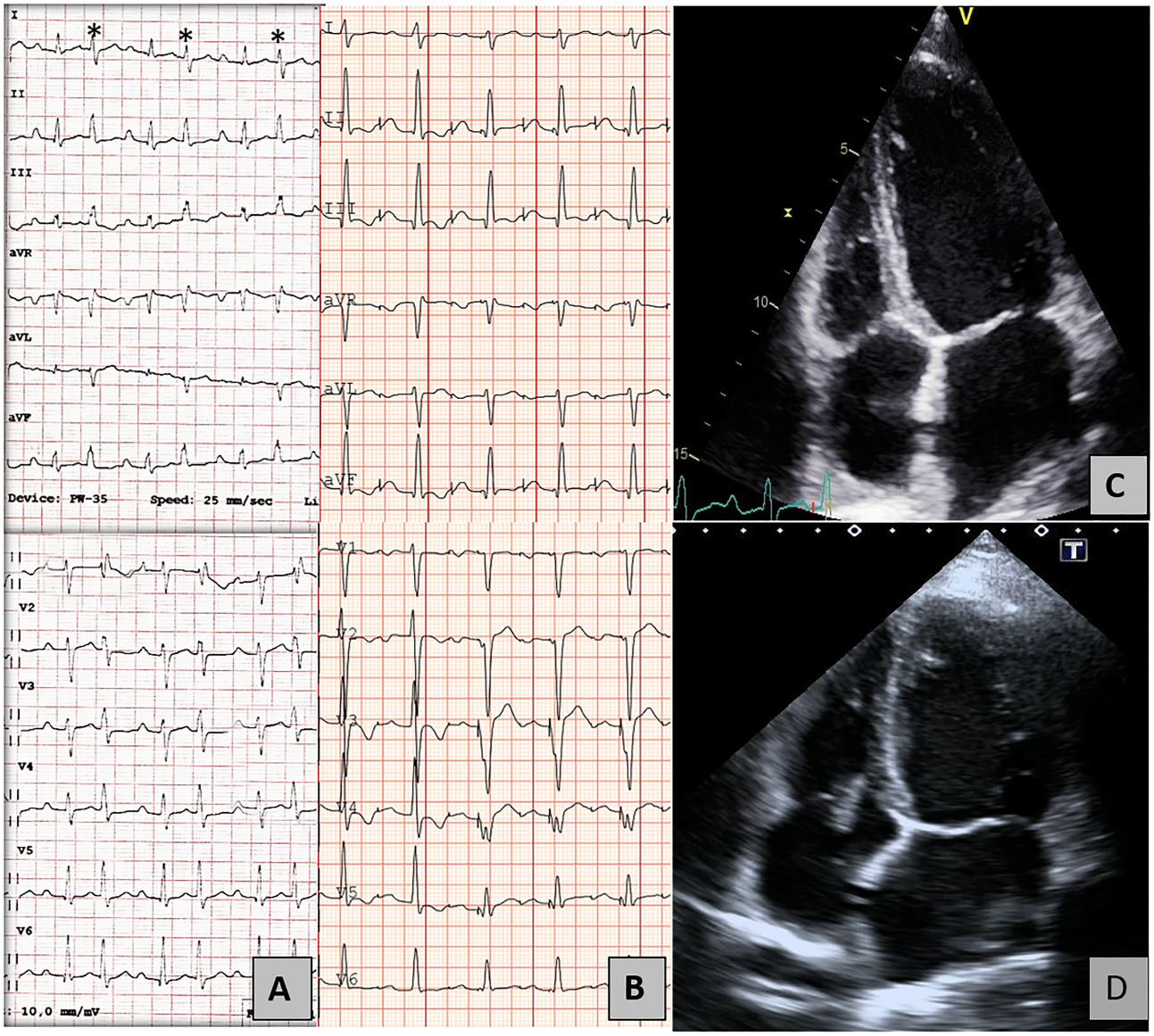
**Figure 3** Patient III:2: (A and B) Electrocardiographic (ECG) and (C and D) echocardiographic images before and after antiarrhythmic treatment (AAT) with sodium channel blockers' combination. (A) Twelve lead surface ECG before AAT; sinus beats with PR 240 ms, QRS 110 ms, QT 380 ms ventricular bigeminy (stars show ventricular ectopic beats) with RBBB-like morphology and narrow QRS 120 ms. (B) Twelve lead ECG after AAT and upgrade to ICD-DR; 1st and 2nd evolution—AAI pacing 90/min, QRS 110 ms, QT 360 ms and the 3rd, 4th, and 5th evolution—DDD pacing 90/min, QRS complexes have fusion beat morphology. (C) Echo 2-D before AAT, four-chamber apical view, systolic phase; dilation of left ventricle, left ventricular ejection fraction 25%. (D) Echo 2-D after successful AAT, four-chamber apical view, systolic phase; normalization of left ventricular diameter, left ventricular ejection fraction 50%.




## Antiarrhythmic treatment in dilated cardiomyopathy caused by *SCN5A* mutation

Published data show that successful antiarrhythmic therapy with sodium channel blockers (quinidine, flecainide, and amiodarone) in *SCN5A* gene mutations can reverse HF symptoms and restore LV contractile function.[5,6,8,16] This has been shown in particular with R222Q variant but also with other mutations, namely, with recently published A204E[16] variant where quinidine eliminated VA and for L828F[17] variant where flecainide had the same effect. In our patients with R814W variant, we had to include a combination of Class I antiarrhythmics to attain acceptable treatment results. There is little data on long-term results of sodium channel blockers' effectiveness (>5 years of treatment) in this specific group of arrhythmogenic DCM patients.[16,17] Also, the advantageous effect of overdrive pacing in the daughter should be emphasized.

Of note, we show intrafamilial variability of the response to antiarrhythmics in patients with the R814W *SCN5A* variant. Significant reduction of atrial arrhythmia and VA on flecainide or amiodarone was also reported in one family with the G213D variant described by Calloe *et al.*[18] However, we emphasize that the difference in the response to treatment especially in the elder subject (father, II:9) but not in the younger subject (daughter, III:2) may be partly explained by possible influence of concomitant diseases, like coronary artery disease.

Another issue refers to ablation of VA in the patients. Current guidelines suggest the possibility of considering ablation therapy in patients with DCM and drug refractory VA while emphasizing the complexity of the arrhythmic substrate (as in MEPPC) and the limited effectiveness of this strategy.[19] We performed ablation of VA in the proband (III:5) with no effect, and that is why at the time, she was referred for orthotopic heart transplantation. In III:2 patient, ablation of VA was ineffective, too. In MEPPC syndrome, Doisne *et al.* performed catheter ablation of VEBs with recurrence of the arrhythmia 3 months later[16]; on the other hand, quinidine treatment was effective.

In conclusion, in *SCN5A* R814W-associated DCM rather than monotherapy, a combination of Class I antiarrhythmics and overdrive pacing may be needed for controlling severe arrhythmia. Furthermore, physicians should be aware of possible recurrence of different types of arrhythmia, both supraventricular and ventricular with time, and of the need for close and vigilant follow-up.

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## Conflict of interest

The authors declare no conflict of interest. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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## Author contributions

J.Z.-K. contributed to the conception, design, data acquisition, and interpretation and drafted the paper; Z.T.B. contributed to the conception and analysis and drafted and revised the paper; W.E. contributed to data acquisition, analysis, and revision; G.T.T. and M.F. contributed to data acquisition and interpretation and drafted genetic methodology; G.W., R.B., and K.K. contributed to data acquisition and interpretation; P.U. and M.O. contributed to data analysis and interpretation; Ł.S. and R.P. contributed to data analysis and revision; M.B. contributed to data analysis, interpretation, and revision.

## Ethics approval and consent to participate

All members of the family signed a written informed consent form for the genetic examination and the consent for publishing all the data. The study was approved by the Institutional Ethics Committee on Human Research of the Cardinal Stefan Wyszynski Institute of Cardiology 7.06.2011; consent number: 1276/2011.

## Consent for publication

All members of the family signed a written consent form for publishing all the data.

## Availability of data and materials

All relevant data are included in the manuscript. The data sets used and/or analysed during the current study are available from the corresponding author upon request.

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