A Novel Form of Short QT Syndrome (SQT3) Is Caused by a Mutation in the \(\text{KCNJ2}\) Gene

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Abstract—Short QT syndrome (SQTS) leads to an abbreviated QTc interval and predisposes patients to life-threatening arrhythmias. To date, two forms of the disease have been identified: SQT1, caused by a gain of function substitution in the HERG \(I_{K_s}\) channel, and SQT2, caused by a gain of function substitution in the KvLQT1 \(I_{K_ch}\) channel. Here we identify a new variant, “SQT3”, which has a unique ECG phenotype characterized by asymmetrical T waves, and a defect in the gene coding for the inwardly rectifying Kir2.1 \(I_{K_1}\) channel. The affected members of a single family had a G514A substitution in the \(\text{KCNJ2}\) gene that resulted in a change from aspartic acid to asparagine at position 172 (D172N). Whole-cell patch-clamp studies of the heterologously expressed human D172N channel demonstrated a larger outward \(I_{K_1}\) than the wild-type \(P<0.05\) at potentials between \(-75\) mV and \(-45\) mV, with the peak current being shifted in the former with respect to the latter (WT, \(-75\) mV; D172N, \(-65\) mV). Coexpression of WT and mutant channels to mimic the heterozygous condition of the proband yielded an outward current that was intermediate between WT and D172N. In computer simulations using a human ventricular myocyte model the increased outward \(I_{K_1}\) greatly accelerated the final phase of repolarization, and shortened the action potential duration. Hence, unlike the known mutations in the two other SQTS forms (N588K in HERG and V307L in KvLQT1), simulations using the D172N and WT/D172N mutations fully accounted for the ECG phenotype of tall and asymmetrically shaped T waves. Although we were unable to test for inducibility of arrhythmia susceptibility due to lack of patients’ consent, our computer simulations predict a steeper steady-state restitution curve for the D172N and WT/D172N mutation, compared with WT or to HERG or KvLQT1 mutations, which may predispose SQT3 patients to a greater risk of reentrant arrhythmias. (Circ Res. 2005;96:800-807.)

Key Words: genetics ■ arrhythmias ■ ion channels ■ cellular electrophysiology

Short QT syndrome (SQTS)\(^1\) is a novel inherited disorder that occurs in individuals with a structurally intact heart and an increased susceptibility to arrhythmias and sudden death. The disease is characterized by a remarkably accelerated repolarization that is reflected in a shorter than normal QTc. Clinical manifestations of SQTS overlap with those of other genetic arrhythmic syndromes caused by ion channel abnormalities,\(^2\) including the long QT Syndrome (LQTS), Brugada Syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), and range from syncopal events to cardiac arrest; affected and asymptomatic individuals have also been identified.\(^1,3\)

Although few families with SQTS have been described, two genetic loci (responsible for SQT1 and SQT2, respectively) have already been linked to the disease, demonstrating that SQTS is a genetically heterogeneous disease, allelic to LQTS. SQT1 is caused by a gain of function mutation in the \(\text{KCNH2}\) gene\(^4\) encoding the \(\alpha\)-subunit of the HERG \(I_{K_s}\) channel: loss-of-function mutations in this gene cause LQT2. SQT2 is caused by a gain of function mutation in the \(\text{KCNQ1}\) gene\(^5\) encoding the \(\alpha\)-subunit of the KvLQT1 \(I_{K_ch}\) channel: loss of function mutations in this gene cause LQT1.

We report a novel locus associated with SQTS: we demonstrate for the first time that a gain of function mutation in the \(\text{KCNJ2}\) gene encoding for the strong inwardly rectifying channel protein Kir2.1 is associated with an accelerated repolarization process. We classify it as type 3 short QT syndrome or SQT3.

Materials and Methods

Clinical Cases

An asymptomatic 5-year-old child presented an “abnormal ECG” during routine clinical evaluation. She had a markedly short repolarization time and conspicuously narrow and peaked T waves. A

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short QT syndrome was suspected, and the child and her family were referred to our attention. A detailed family history was collected during genetic counseling, and the child, her parents, and grandparents underwent clinical evaluation. Resting standard 12-lead ECG, Holter monitoring, maximal exercise stress test, echocardiogram, and signal-averaged ECG were obtained in all individuals. Blood samples were collected for genetic investigations. All patients signed an informed consent form to undergo molecular evaluation. The Internal Review Board of the Maugeri Foundation approved the study protocol.

Genetic Analysis
DNA was extracted from peripheral blood lymphocytes using a standard enzymatic phenol-chloroform method. The entire open reading frames of KCNQ1, KCNH2, SCNSA, KCNE1, KCNE2, and KCNJ2 were analyzed by DHPLC (Wave, Transgenomics) after PCR amplification of 150 to 350 bp fragments. All abnormal chromatograms were sequenced (310 Genetic Analyzer, ABI Prism) and compared with 600 alleles from healthy subjects with normal ECG.

Cloning of Human Kir2.1 cDNA
The coding region of human intronless KCNJ2 (AF153819) gene was amplified directly from a human genomic DNA with 5'-CCAGAGGATATCTGGAG-3' and 3'-UTR-Kir2.1 R (5'-GGTTGTGTCGCAACACATTTC-3') primers using the Gene Amp XL-PCR Kit (Roche). The D172N mutation was introduced by site-directed mutagenesis using the QuickChange mutagenesis kit (Stratagene). The entire coding region of the mutant clone was sequenced with a BigDye terminator kit (Applied Biosystems) and an automatic DNA sequencer (ABI type 310). Wild-type (WT) or mutant Kir2.1 cDNA was subcloned into the eucariotic vector pGEM-dT Easy Vector (Promega). The D172N mutation was activated in the hyperpolarized direction by 20 mV, and the activation kinetics for $I_{Ks}$ were made faster (by multiplying the activation time constant by 0.5).

The steady-state cardiac action potentials in all cases were obtained by pacing the ionic model for 10 seconds at 1 Hz. For simplicity, the ionic concentrations in the single-cell model were clamped to constant values.

The propagation of the cardiac impulse was simulated in a rectangular lattice of area $2 \times 0.2$ cm, consisting of $200 \times 20$ nodes (ventricular cells), and no-flux boundary conditions at the edges. We used the Euler method to integrate the voltage at each node, which was governed by the conventional reaction-diffusion equation, assuming isotropic tissue and uniform electrophysiological properties throughout:

$$\frac{\partial V}{\partial t} = -\frac{I_m}{C_m} + D \left( \frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2} \right)$$

where $V$ is the membrane voltage, $I_{ion}/C_m$ is the total membrane ionic current (in pA/pF), and $D$ is the diffusion coefficient. The time step for integration was 0.005 ms, the space step was 0.1 mm, and the value of the $D$ was 0.07 mm$^2$/ms. One edge of the strand was paced at 1 Hz for 10 seconds, and used to compute and contrast the pseudo-ECGs in the wild-type and the mutant cases. The pseudo-ECG ($\phi$) was calculated as the sum of all the dimensionless far-field extracellular potentials, resulting from the spatial gradients of transmembrane potential $\vec{V}_{m}$ in the rectangular lattice:

$$\phi = - \sum_{2D~sheet} \frac{\vec{V}_{m} \cdot \vec{r}}{r}$$

where $r$ is the radius vector between the position of the transmembrane potential and the position of the ECG lead electrode, which was located 2 cm away from the pacing electrode.

All simulations were coded in “C”, and solved on a 32-bit processor, parallel computer (MicroArray cluster machine).

Results
Clinical Evaluation
ECG of the proband is shown in Figure 1 (traces III-1). Her QTc interval was 315 ms. The QT wave was short and the T wave was noticeably narrow and peaked. The ECG of the 30-year-old mother was unremarkable (Figure 1, traces I-1) her history was negative for sudden cardiac death or juvenile arrhythmias. In contrast, the 35-year-old father presented a short QT interval (QTc 320; Figure 1 traces II-2), and reported a history of presyncopal events and palpitations since age 15. He had undergone multiple ECG and Holter recordings after nocturnal episodes characterized by sudden awakening and palpitations. The wife reported that on several occasions the husband had experienced seizure-like activities followed by awakening, lamenting tachycardia, shortness of breath, and palpitations; all episodes resolved spontaneously. His parents had unremarkable ECGs (Figure 1, traces I-1 and I-2) and reported no family history of sudden cardiac death. The family pedigree is presented in Figure 1.
Interestingly, the QT intervals recorded on the ECGs of the proband and her father were identical and were characterized by asymmetrical T waves with a rather normal ascending phase and a remarkably rapid terminal phase (see Figure 1, bottom traces II-2 and III-1). This pattern was consistently present throughout the Holter recording and had been present in the first ECG of the father at age 15. The diagnosis of Short QT Syndrome was established in the two patients and electrophysiological testing was recommended to the father for risk stratification, but he declined to undergo any further clinical investigation. A clinical geneticist evaluated the patients for the presence of extracardiac abnormalities or dysmorphic features. Patients were interrogated for symptoms that would indicate skeletal muscle disease, but nothing could be identified in both patients.

**Genetic Analysis**

No mutation was identified in the father or the proband in the two genes previously associated with SQTS (**KCNQ1** and **KCNH2**). We therefore screened for other cardiac ion channel transcripts that we considered potential candidate genes for SQTS. We identified in both affected individuals a single base pair substitution (G514A) in **KCNJ2**, resulting in an amino acid change from aspartic acid to asparagine at position 172 in the Kir2.1 potassium channel (Figure 2). This substitution was absent in all the clinically unaffected family members.  

![Figure 1. Family pedigree and ECG recordings in the SQTS family with **KCNJ2** mutation. Leads V1, V2, and V3 (top, middle, and bottom) are depicted. Duration of QTc interval in lead V2 is reported. Horizontal calibration bars correspond to 400 ms. Arrow indicates the proband; filled symbols indicate clinically and genetically affected individuals; empty symbols indicate clinically and genetically unaffected individuals.](http://circres.ahajournals.org/)

![Figure 2. A, Wild-type (top trace) and mutated (bottom trace) DNA sequences performed on genomic DNA of individuals II-2 and III-1 (see Figure 1). Nucleotides 505 to 542 are reported. Bottom trace shows heterozygous substitution of guanine to adenine resulting in the D172N mutation. B, Cartoon of the predicted transmembrane topology of the Kir2.1 channel showing the localization of D172N. C, Amino acidic sequence alignment of Kir2.1 channels from various species in the region surrounding codon 172 (highlighted). A remarkable level of conservation is evident, suggesting the functional relevance of this region.](http://circres.ahajournals.org/)
Potential range between gene in CHO cells resulted in an inward current at the
not shown). Overexpression of the KCNJ2
CHO cells, which are devoid of endogenous Kir2.1 members (I-1, I-2, II-1), suggesting that the mutation may have occurred as a de novo in the father of the proband and it involved a highly conserved region of Kir2.1 (Figure 2).

Cellular Electrophysiology
We performed functional characterization of the mutant in CHO cells, which are devoid of endogenous $I_{K1}$ currents (data not shown). Overexpression of the KCNJ2 WT or mutant gene in CHO cells resulted in an inward current at the potential range between $-120$ and $-90$ mV, consistent with the reversal potential calculated for the solutions used in the experiments. At more positive voltages the outward current rectified in the inward direction and inactivated completely near $-30$ mV. Figure 3A shows representative current traces of Kir2.1 WT (n=5), D172N (n=7), and WT/D172N (n=20), elicited by voltage-clamp steps (duration 400 ms) from $-120$ mV to $+20$ mV, applied from a holding potential of $-60$ mV. In the I-V relationship shown in Figure 3B, the voltage is adjusted to the liquid junction potential of 15 mV, and the current is normalized to the current recorded at $-100$ mV (ie, $-115$ after adjustment for liquid junction potential).\(^{10}\) At potentials between $-75$ and $-45$ mV, the D172N channel exhibited a significantly larger outward current than the WT ($P<0.05$). Furthermore, the peak of the current recorded in the D172N mutant was shifted by 10 mV as compared with the WT (from $-75$ mV in the WT to $-65$ mV in the D172N). As expected, the cotransfection of the WT and mutant constructs gave an intermediate result; the outward current was significantly larger at $-65$ and $-55$ mV when compared with the WT alone ($P<0.05$), and significantly smaller in the range between $-75$ and $-55$ mV when compared with the D172N ($P<0.05$).

In Silico Characterization of D172N
We used modifications of the Priebe-Beuckelmann (PB) computer model of the human ventricular action potential\(^{6}\) to investigate the potential electrophysiological consequences of the D172N mutation. Figure 4A shows superimposed action potentials obtained in simulations featuring the I-V relations of barium sensitive currents ($I_{K1}$) of CHO cells expressing the WT (black), homozygous (red; D172N), and heterozygous (broken red; WT/D172N) mutant Kir2.1 channels. At a pacing rate of 1 Hz, the increased outward component of $I_{K1}$ caused by the D172N mutation produces an abrupt increase in the rate of final repolarization. In the homozygous, action potential duration measured at 90% repolarization (APD$_{90}$) was reduced by $\sim 50$ ms, whereas in the heterozygous the APD$_{90}$ is reduced by $\sim 30$ ms. For comparison, the filled blue tracing in Figure 4A shows a simulation in which the recently reported V307L mutation in the KvLQT1 channel was used.\(^5\) The combined shift of activation and decrease in activation time constant of $I_{K1}$ diminish APD$_{90}$ by $\sim 80$ ms. Similarly, as shown by the broken blue tracing, the N588K mutation in the HERG channel\(^4\) led to an APD$_{90}$ abbreviation of $\sim 95$ ms at 1 Hz in this model.

Although these results demonstrate that the D172N mutation can lead to APD abbreviation, when paced at a rate of 1 Hz, the changes predicted by the model are smaller than those of the KvLQT1 and HERG mutations that have been reported for SQTS patients. To determine the behavior at higher activation frequencies, we investigated the APD restitution kinetics of the Priebe-Beuckelmann model for each one of the ion channel mutations shown in Figure 4A. We used the S1-S2 protocol and measured the APD$_{90}$ of the S2 response as a function of the preceding diastolic interval (DI). The results are presented in Figure 4B. The restitution curves associated with all mutations are appreciably lower than the wild-type (black). However, the D172N and WT/D172N mutant curves (red) are much steeper than the other two. These data, together with our previous experimental studies\(^{11,12}\) demonstrating the role of the outward component of $I_{K1}$ in reentrant dynamics, strongly suggest that myocardial tissues carrying
the D172N mutation in the Kir2.1 channel should be capable of sustaining stable functional reentry at higher frequencies than tissues carrying the wild-type channel (see Discussion).

**D172N Mutation and T-Wave Morphology**

As illustrated in Figure 1, an important characteristic of the ECGs of the proband and her father was the tall and asymmetrical T waves with an exceedingly rapid terminal phase. We hypothesized that such a peculiar ECG appearance may have been related to the sudden acceleration of the final phase of action potential repolarization in the D172N and WT/D172N mutant cells (Figure 4A, red tracings). We tested this hypothesis by carrying out additional simulations of action potential propagation (Figure 5). We used a rectangular lattice of cardiac cells (2×0.2 cm) that was paced at a constant frequency of 1 Hz. Action potentials propagated from left to right at a constant velocity of 50 cm/s. We calculated the ECGs in the WT and the mutant cases by placing a unipolar lead on the left side of the lattice, to simulate recordings from a right precordial lead (see Materials and Methods for details). As illustrated in the bottom panel of Figure 5, both the HERG and KvLQT1 mutations greatly reduced the QT intervals without significantly affecting the T-wave morphology. In contrast, both homozygous and heterozygous substrates of the D172N mutation resulted in simulated ECG traces whose T-wave morphologies were very similar to that of the proband, reproduced on the far right of Figure 5.

**Discussion**

**Major Findings**

We identify here a new variant of Short QT syndrome, SQT3, which is characterized by asymmetrical T waves and a genetic defect in the KCNJ2 gene that causes a significant increase in the outward component of the I-V relation of IK1.

The electrocardiographic pattern identified in the two affected family members was clearly different from those previously reported in patients affected by SQTS,1,3–5 thus...
suggesting that affected members of this family present a novel substrate for the short repolarization. Accordingly, genetic analysis performed on the KCNJ1 and KCNH2 genes encoding for the alpha subunits of the potassium channels that conduct \( I_{Kr} \) and \( I_{Ks} \), respectively, failed to demonstrate the presence of mutations that could account for the shortening of repolarization. However, the screening of the KCNJ2 gene encoding the cardiac inward rectifier Kir2.1 channel disclosed the presence of a single base pair mutation resulting in a D172N substitution in the second transmembrane region of the channel.

The aspartate at position 172 is highly conserved in Kir2.1 channels in different species and is considered to form a binding site of the channel blocker spermine or to be located in close proximity to a binding site of this cytoplasmatic blocker of \( I_{Kr} \). The substitution of the acidic residue at position 172 with a neutral amino acid such as asparagine has been shown to alter the rectification properties of the channel when expressed in Xenopus Oocytes. It also alters its binding affinity for long bis-amines. Altogether these data support the view that the mutation identified in our patients is unlikely to be functionally silent. We therefore devised a series of biological and numerical experiments aimed at establishing a functional link between the mutation, its likely functional consequences in terms of action potential characteristics and electrocardiographic morphology. When the mutant construct was expressed in CHO cells by itself, it caused a gain of function, manifested as an increased outward current that reflects the channel.

\( I_{Ks} \) Mutations and Arrhythmogenesis

\( I_{Ks} \) plays an important role in stabilizing the resting membrane potential, in modulating excitability, and in causing the final repolarization phase of the action potential in both atria and ventricles. The current shows strong rectification between -80 and -40 mV. Interestingly, as expected, the cotransfection of the WT and D172N plasmids, mimicking the heterozygous substrate of the patients, gave a wide range of possibilities for the \( I-V \) relationship that, on average, yielded an intermediate situation between the WT and/or the D172N alone. Random coassembly of the four subunits forming the Kir2.1 channel could explain these results. It is therefore reasonable to speculate that, in a heterozygous situation, the coassembly of the WT subunit is preferred over the coassembly of the mutants, but it is also possible that one or more WT subunits coassemble with one or more mutated subunits to result in a whole range of possible currents. Thinking of the heart as a cellular syncytium, it is reasonable to expect that the mutation should result in an increased outward current that reflects the characteristics of both the WT and D172N mutant subunits and that lays somewhere between the normal and the “homozygous”.

We hypothesized that an increase in outward current would accelerate ventricular repolarization, thus causing a shortening of the terminal phase of the cardiac action potential. Hence, the D172N mutation would fully account for the electrocardiographic phenotype and induce an asymmetrically shaped T wave with a rapid descending limb. Such a hypothesis is borne out by our simulation results (APD and T wave), which further show that whereas the SQTS phenotype can be induced by gain of function in different repolarizing currents (\( I_{Ks}, I_{Kr}, I_{Ks} \)), the peculiar asymmetry of the T wave could be seen only in the Kir2.1 mutation.

Clinical Criteria in SQTS

The identification of SQTS has highlighted the concept that genetic abnormalities leading to abbreviated repolarization may predispose to tachyarrhythmias. The values of QTc that are diagnostic for SQTS are not yet defined even if most of the patients identified so far have a QTc \( \leq \) 300 ms. It is likely that less dramatically abbreviated repolarizations may also be arrhythmogenic. It took years to realize that the Long QT syndrome included a majority of patients with more modest prolongation of repolarization who were at risk of cardiac events. Similarly, it will require the identification of a larger number of genetically affected individuals to be able to define the clinical criteria for the diagnosis of SQTS. Viskin et al recently provided evidence that 35% of their patients affected by unexplained VF are individuals with a short QTc defined as a QTc < 360 ms. This value represents the lowest 0.5% of the distribution in the normal population. Based on Viskin’s observations, it is tempting to speculate that the two extremes of the Gaussian distribution of the QT interval may identify individuals at increased risk of VF. Because it has been suggested that LQT loci might be quantitative trait loci for the QT interval in the population, it is also possible that QT loci may have a similar role. It will be interesting to systematically search for common allelic variants in the genes that cause SQTS and to quantify their role in abbreviating repolarization and in contributing to susceptibility to tachyarrhythmias in the general population.

I_{Kr} Mutations and Arrhythmogenesis

I_{Kr} overexpression significantly increased \( I_{Kr} \) density in guinea pig myocytes, and conversely, overexpression of the dominant-negative Kir2.1AAA significantly decreased \( I_{Kr} \). Additionally, in agreement with our simulations in the human model (see Figure 4), Miao et al demonstrated that \( I_{Kr} \) overexpression significantly increased the rate of change in membrane potential (dV/dt) during the final phase of repolarization, whereas \( I_{Kr} \) suppression had the opposite effect. Li et al developed a dominant-negative transgenic mouse model with suppressed \( I_{Kr} \) resulting from targeted expression of a nonconducting Kir2.1-AAA subunit in the mouse heart (TG-AAA mice). Although TG-AAA mice displayed an altered cardiac excitability, the susceptibility of
these animals to cardiac arrhythmias was equal to that of control mice.

Interestingly, loss of function mutations in the KCNJ2 gene27 have been identified in patients affected by Andersen Syndrome,28 which is also referred to as the type 7 form of the Long QT syndrome (LQT7) and is characterized by prolonged repolarization and by periodic hypokalemic paralysis.29 In the Andersen syndrome, reduction of \( I_{K1} \) leads to prolongation of the QT interval and predisposes to cardiac arrhythmias.27 In contrast, an increase of \( I_{K1} \) has been demonstrated to shorten repolarization, evidenced by shortening of the monophasic action potential and the QT interval, and to exert a proarrhythmic effect both in the atria and the ventricles in a transgenic mouse model of upregulation of Kir2.1,30 although changes in repolarization characteristics are not necessarily similar to upregulation of \( I_{K1} \). In fact, studies to characterize these differences are underway in our laboratory using a transgenic mouse model of the D172N mutation.

D172N Mutation and Ventricular Vulnerability

The proband of this study has no history of cardiac arrhythmias; during exercise stress testing, she developed isolated premature ventricular complexes with left bundle branch block morphology that were asymptomatic. The father of the proband and carrier of the D172N mutation had experienced repeated episodes of nocturnal palpitation and a syncopal event; however, no documentation of arrhythmias is currently available. Overall, in analogy with other patients with the electrocardiographic diagnosis of SQTS,1,3 our patients do not present clinically documented tachyarrhythmias. In silico data, however, support the view that, by increasing the outward component of \( I_{K1} \), the D172N mutation creates a vulnerable substrate that may facilitate development of atrial and ventricular tachycardias even in a heterozygote substrate.

Indeed, whereas the increased outward current resulting from the D172N mutation is expected to reduce the likelihood of early or delayed afterdepolarizations, it is reasonable to surmise that the steeper restitution associated with such a mutation would enhance the possibility of T-wave alternans.31,32 thereby increasing vulnerability to fibrillation when the heart rate is high.33 In addition, as demonstrated by experimental and simulation studies, a significant correlation exists between the stability and frequency of rotors responsible for VF and the magnitude of the outward component of \( I_{K1} \).10,11,34 Hence, at the range of frequencies of VF, a larger outward current should result in shorter APD to allow higher frequency rotors to stabilize.34 By inference, SQTS patients with demonstrated D172N mutation are expected to have an increased vulnerability to sustained VF.

Limitations

Our study has certain limitations that need to be considered. First, although the use of the PB equations6 of the human cardiac myocyte allowed us to reproduce accurately the morphology of the T wave in the proband and her father, the 2-D simulations were performed in a simplistic model in the absence of structural or cellular heterogeneities. Nevertheless, it is striking that even such an apparently oversimplified model can so accurately reproduce the ECG data. Furthermore, despite the fact that the in-silico data predict that the mutation increases susceptibility to reentrant arrhythmias, we could not investigate if an arrhythmogenic substrate is present in the patients because they refused to undergo electrophysiological testing.

Conclusions

We report on a new form of Short QT syndrome (SQTS) that is associated with a D172N substitution in the Kir2.1 channel. The electrocardiographic characteristics resulting from the genetic defect are unique in that they include tall and asymmetrical T waves with a slow ascending and an exceedingly rapid descending limb. Computer simulations demonstrate that this phenotype is the result of an accelerated repolarization produced by an excessive outward component of the inward rectifier current \( I_{K1} \).

Note Added in Proof

After acceptance of the manuscript the patient expressed the wish to undergo electrophysiologic investigation. The protocol used was ventricular stimulation from two sites (right ventricular apex and right ventricular outflow tract), with 2 cycle lengths (600, 430 ms) and up to 3 extra stimuli. The effective refractory period was 160 msec. Programmed electrical stimulation induced ventricular fibrillation with 3 premature extra stimuli at a basic drive of 600 msec.

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