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Long-Term Follow-Up of Patients With Long-QT Syndrome Treated With β -Blockers and Continuous Pacing

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Background—The long-QT syndrome is associated with sudden cardiac death. Combination of β -blocker and pacing therapy has been proposed for treatment of drug-resistant patients. The purpose of this study was to summarize our long-term experience with combined therapy in patients with long-QT syndrome.

Methods and Results—A total of 37 patients with idiopathic long-QT syndrome were treated with combined therapy consisting of continuous cardiac pacing and maximally tolerated β -blocker therapy and followed up for 6.3 ± 4.6 years (mean \pm SD). The group consisted of 32 female and 5 male patients with a mean age of 31.6 years. The mean paced rate was 82 ± 7 bpm (range, 60 to 100 bpm). On follow-up, recurrent symptoms caused by pacemaker malfunction were documented in 3 patients. Four patients died during the follow-up period: 2 adolescents stopped β -blocker therapy, 1 patient died suddenly while treated with combined therapy, and 1 patient died of unrelated causes. In addition, 3 patients had resuscitated cardiac arrest while on combined therapy, and 1 patient had repeated, appropriate implantable cardioverter-defibrillator discharges on follow-up.

Conclusions—Because 28 of 37 patients remain without symptoms with β -blocker therapy and continuous pacing, combined therapy appears to provide reasonable, long-term control for this high-risk group. However, the incidence of sudden death and aborted sudden death (24% in all patients and 17% in compliant patients) strongly suggests the use of a “back-up” defibrillator, particularly in noncompliant adolescent patients. Implantable cardioverter-defibrillator therapy, however, may be associated with recurrent shocks in susceptible patients. (*Circulation*. 1999;100:2431-2436.)

Key Words: syncope ■ death, sudden ■ cardioversion ■ defibrillation ■ pacemakers

The association of sudden cardiac death with idiopathic long-QT syndrome is well documented.¹⁻⁹ Despite recent significant advances in elucidation of the genetic mechanism,¹⁰⁻¹⁸ treatment of long-QT syndrome continues to present a challenge. The benefits of β -blocker therapy have been well documented in several studies, preventing syncope in 75% to 80% of patients with long-QT syndrome.^{1,19} Even with β -blocker therapy, however, there is a 20% to 25% risk of syncope and a continued risk for sudden cardiac death.¹⁹ Because the sympathetic nervous system was thought to play a crucial part in the underlying pathophysiology of the disease, either as a primary defect causing sympathetic imbalance or as a trigger, patients underwent left cervicothoracic sympathetic denervation, again with limited success.²⁰ More recently, combined therapy with β -blockers and continuous cardiac pacing was introduced as therapy for patients with long-QT syndrome, and initial reports were quite favorable.^{8,21,22}

The purpose of this study was to describe our long-term follow-up of patients with long-QT syndrome treated with combined β -blocker therapy and continuous pacing to place this treatment in proper perspective. We found that even with

combined therapy, these patients remain at significant risk for sudden death.

Methods

We performed a retrospective study of 37 patients with idiopathic long-QT syndrome treated with combined β -blocker and pacing therapy. Medical records and follow-up histories of these 37 patients were reviewed. The first 16 patients were part of a cohort studied by Eldar et al²² and were reviewed retrospectively. Subsequent patients were entered prospectively and followed up with the cohort. All patients except 3 had a documented long-QT interval on surface ECG. These 3 patients had aborted sudden death (n=2) or syncope (n=1) and family histories supportive of the diagnosis of long-QT syndrome. In these patients, 2 had ≥ 2 family members who had long-QT syndrome, and 1 patient developed prolongation of the QT interval with time, but her family history was negative. Prolongation of the QT interval was defined as a baseline corrected interval >440 ms in male patients and >460 ms in female patients. All patients treated with combined β -blocker and pacemaker therapy were included in this study. Clinical characteristics and follow-up of the study patients were noted.

Patients were followed up by either a cardiologist or the referring physician. Patients presented between 2 months and 61 years of age; the duration of follow-up was 6.3 ± 4.6 years (mean \pm SD). Failed β -blocker therapy was defined as recurrent syncope or palpitations,

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usually associated with dizziness or presyncope; aborted sudden death on β -blocker therapy; or the inability to tolerate at least several different β -blockers at doses high enough to note a β -blocker response (documented by Holter). A β -blocker response was defined as a 20% decrease in baseline heart rate in response to medication in children. Each patient served as his or her own control. A heart rate of <60 bpm was achieved in all adults. In addition to a baseline decreased heart rate, children were monitored for a diminished chronotropic response during exercise as defined by a $\geq 20\%$ decrease in maximal heart rate response to exercise appropriate for age. Failed left cervicothoracic sympathectomy was defined as recurrent syncope or aborted sudden death after surgical sympathectomy. Fourteen patients received combined β -blocker and pacemaker therapy at the time of diagnosis without prior failed β -blocker therapy. Three patients who had recurrent symptoms while being treated with combination therapy received an implantable cardioverter-defibrillator (ICD). Four additional patients received ICDs after presenting with aborted sudden death. In addition, all patients underwent regular pacemaker evaluation every 6 months with 12-lead ECG evaluations and 24-hour Holter evaluations as clinically indicated. Compliance evaluation with medical therapy was measured by history, interrogation of the baseline unpaced sinus rate, pill count in some patients, and the need for prescription refills. Thirty patients were followed up at the University of California at San Francisco; 7 were followed up elsewhere. Follow-up data were derived from the referring physicians' reports at the respective referring institutions. One patient was lost to follow-up during our study period and was censored from the study.

Results

Among the 37 patients, age at the time of follow-up ranged from 6.4 to 78.6 years (mean, 32.1 ± 17.3 years). One patient had Jervell-Lange-Nielsen syndrome; another 14 had family histories of long-QT syndrome; and the remaining 22 patients had sporadic long-QT syndrome. In these patients, a family history was negative for sudden cardiac death, and the 12-lead ECGs of immediate relatives did not reveal long-QT syndrome. Sixteen patients (43%) experienced aborted sudden death, and all but 3 (92%) had syncope. Table 1 summarizes the clinical characteristics. There were 32 female and 5 male patients. All patients except 1 were symptomatic with long-QT syndrome and had histories of syncope and/or sudden cardiac death; the 1 asymptomatic patient had a long-QT interval with a positive family history of sudden death of a sister. Sixteen experienced ≥ 1 episodes of aborted sudden death, and 18 (49%) had documented polymorphic ventricular tachycardia. Eleven patients with documented polymorphic ventricular tachycardia did not have an episode of sudden death. Four patients had AV conduction block either at baseline ($n=3$, documented by Holter or ECG) or induced during pacing ($n=1$). This patient was noted to have infranodal block during pacing at cycle lengths slightly shorter than the sinus cycle length. One patient had sinus node disease. The remaining 32 patients had normal heart rates. Attempted treatments in this patient population are outlined in Table 1. Twenty-three patients were initially treated with β -blockers, as outlined under prior therapy. Some patients were treated with >1 type of β -blocker and/or had other therapies. These patients are labeled with BB (for >1 β -blocker tried) and/or have additional therapies listed in the column for other therapies. The most commonly used β -blocker was atenolol ($n=16$), followed by propranolol ($n=8$). A variety of other β -blockers were also used. The types of β -blocker therapy are summarized in Table 2. No

patient received labetalol. The dose of β -blocker therapy is summarized in Table 1. All children (<18 years of age) received ≥ 1.5 to $4.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ of β -blocker therapy, which was adjusted as the child's weight increased with age every 6 months to 1 year. Of the 23 patients who received pacemakers after they failed β -blocker therapy, 4 had a left cervicothoracic sympathectomy and subsequently were treated with continuous pacing. Another patient received a left cervicothoracic sympathectomy after recurrent symptoms with combination therapy (Figure 1). The 5 patients with sudden death or aborted sudden death were treated with similar types and doses of β -blocker therapy compared with those patients without recurrent symptoms (Table 2).

All patients were treated with maximally tolerated doses of β -blocker therapy and permanent pacing. Twenty-eight patients were paced in the DDD, 3 in the AAI, and 6 in the VVI mode. Three patients were upgraded from the VVI or AAI to the DDD mode. One patient had recurrent symptoms of syncope, and the other had symptoms of near syncope. Another patient was upgraded from the AAI to DDD mode. This patient did not have any symptoms. All patients were 100% paced as documented by Holter evaluation. The minimum mean paced rate was 82 ± 7 bpm (range, 60 to 100 bpm). One patient was initially paced at the lower rate of 60 bpm, which was subsequently increased to 80 bpm. Episodes of aborted sudden death occurred both before and after the minimum paced rate was increased to 80 bpm. The mean paced QT was 425 ± 49 ms (range, 320 to 560 ms); the mean paced QTc interval was 497 ± 41 ms (range, 390 to 552 ms). All patients were followed up by either a pediatric or an adult cardiologist for a mean of 6.3 ± 4.6 years and were treated with maximally tolerated doses of β -blocker therapy and continuous pacemaker therapy.

Five patients were noted to have documented pacemaker malfunction; 3 experienced recurrent symptoms in association with pacemaker malfunction: a pacemaker lead fracture in 1 and pacemaker ventricular lead undersensing in another. One patient was upgraded to a dual-chamber system after a syncopal episode in association with atrial lead malfunction. Symptoms resolved once the pacing problems were addressed appropriately (Figure 1). Two patients remained asymptomatic in association with documented pacemaker malfunction. However, 1 patient suffered an episode of aborted sudden death in association with pregnancy 4 years after the pacing malfunction was addressed (6 years after pacing therapy was initiated), at which time her pacemaker was noted to function appropriately.

Follow-up data are summarized in Figure 1. Four patients died during the follow-up period. One died of carcinoma at 34 years of age; her death was unrelated to long-QT syndrome. Two adolescents died suddenly after discontinuing β -blocker therapy. A pacemaker check a few months previously had revealed appropriate pacemaker functions with lower programmed rates of 80 and 85 bpm, respectively. One of these patients had a β -blocker blood level of 0 at the time of autopsy. One adult patient died suddenly despite good compliance and a recent pacemaker evaluation. There was no association between the length of the QTc and risk of sudden death. Seven patients were treated with ICDs. Of these, 3

TABLE 1. Clinical Characteristics and Therapy Before Combination Therapy

| Patient | Age at Diagnosis, y | Age at PM, y | Sex | Syncope | ASD | T de P | Baseline QTc, ms | Duration of Prior BB Therapy | Other Therapy |
|---------|---------------------|--------------|-----|---------|-----|--------|------------------|------------------------------|---------------|
| 1 | 1.5 | 3.5 | F | Y | Y | | 650 | 2.0 | |
| 2 | 11.0 | 12.6 | F | Y | N | | 621 | 1.6 | |
| 3 | 21.5 | 30.0 | F | Y | Y | Y | 402 | 8.4 | LCTS |
| 4 | 2.0 | 26.0 | F | Y | N | | 502 | 23.9 | BB+LCTS |
| 5 | 5.3 | 11.2* | F | Y | N | Y | 600 | 5.9 | |
| 6 | 8.8 | 11.2* | M | Y | Y | | 550 | 2.4 | BB |
| 7 | 10.1 | 12.1 | F | Y | N | Y | 600 | | |
| 8 | 21.8 | 21.8 | F | Y | N | Y | 670 | | |
| 9 | 24.8 | 24.8 | F | Y | N | Y | 660 | | |
| 10 | 24.9 | 27.9 | F | Y | N | | 600 | | |
| 11 | 34.0 | 38.5 | F | Y | Y | | 498 | 4.5 | |
| 12 | 35.6 | 36.3 | F | Y | Y | Y | 459 | 0.8 | |
| 13 | 8.5 | 9.8 | M | Y | N | | 440 | 1.3 | BB |
| 14 | 6.5 | 6.5 | F | Y | N | Y | 440 | | |
| 15 | 34.0 | 44.2 | M | Y | N | Y | 581 | 10.2 | |
| 16 | 33.4 | 33.4* | F | Y | N | Y | 639 | | |
| 17 | 17.9 | 17.9 | F | Y | N | Y | 510 | | |
| 18 | 10.9 | 12.8 | F | Y | Y | | 591 | 1.3 | BB |
| 19 | 40.8 | 40.8 | F | Y | N | Y | 550 | | |
| 20 | 28.0 | 28.0 | F | N | Y | | 510 | | |
| 21 | 24.7 | 24.7 | F | N | N | | 600 | | |
| 22 | 17.0 | 39.6 | F | Y | Y | Y | 639 | 22.6 | LCTS |
| 23 | 9.4 | 11.4 | F | Y | N | Y | 566 | 1.9 | BB |
| 24 | 28.4 | 28.4 | F | Y | N | | 697 | | |
| 25 | 63.5 | 68.5 | F | Y | Y | Y | 450 | 5.0 | |
| 26 | 7.2 | 11.3 | M | Y | Y | | 590 | 4.1 | BB |
| 27 | 20.5 | 41.4* | F | Y | N | | 500 | 20.9 | |
| 28 | 4.1 | 5.2 | F | Y | N | | 533 | 1.1 | |
| 29 | 49.1 | 49.1 | M | Y | Y | | 560 | | |
| 30 | 8.0 | 57.4 | F | Y | N | Y | 520 | 49.4 | |
| 31 | Birth | Birth | F | Y | Y | Y | 545 | | |
| 32 | 16.8 | 16.9 | F | N | Y | Y | 439 | | |
| 33 | 6.0 | 42.7 | F | Y | Y | | 509 | 36.6 | |
| 34 | 23.2 | 26.9 | F | Y | Y | Y | 565 | 3.7 | |
| 35 | 6.5 | 13.1 | M | Y | N | | 510 | 6.6 | |
| 36 | 9.0 | 13.6 | F | Y | Y | | 552 | 4.6 | BB+LCTS |
| 37 | 23.1 | 28.4 | F | Y | N | | 565 | 5.3 | BB |

PM indicates pacemaker; ASD, aborted sudden death; T de P, documented torsade de pointes; BB, β -blockers; and LCTS, left cervicothoracic sympathectomy.

*Patient died during follow-up.

ICDs were placed because of recurrent symptoms (syncope and aborted sudden death in 1 and aborted sudden death in 2) despite combination therapy, and 4 were placed as initial therapy after patients presented with resuscitated cardiac arrest. Of 30 compliant patients receiving combination therapy, 3 required ICD insertion because of resuscitated cardiac arrest. One additional patient experienced repeated, appropriate discharges of her ICD (17 discharges in 2 hours) 4 years after ICD insertion. This patient's lower rate was programmed to 80 bpm. These data reflect a 17% incidence (5 of

30 patients) of malignant events defined as aborted cardiac arrest or sudden cardiac death in patients treated with appropriate combined therapy (ie, continuous pacing and β -blocker therapy).

Figure 2 demonstrates symptom-free survival curves for our patients. The first curve shows the recurrence of symptoms for the group as a whole and includes both noncompliant patients and those who developed recurrent syncope or aborted sudden death related to pacemaker malfunction. The recurrence rate of symptoms (sudden death, aborted sudden

TABLE 2. Clinical Follow-Up Data for 37 Patients With Long-QT Syndrome

| Patient | Current BB Therapy | BB Dose, mg/d ⁻¹ | PM Mode | Minimum Programmed PM Rate, bpm | F/U, y | F/U Events |
|---------|--------------------|-----------------------------|---------|---------------------------------|--------|-------------------------------------|
| 1 | Propranolol | 80* | DDD | 90 | 3.08 | |
| 2 | Atenolol | 100* | DDD | 70, 80 | 7.15 | |
| 3 | Atenolol | 50 | AAI | 90 | 14.96 | Syncope, ICD storm |
| 4 | Atenolol | 100* | VI | 85 | 19.83 | |
| 5 | Propranolol | 120* | AAI | 80 | 5.19 | SCD: noncompliant |
| 6 | Atenolol | 75* | DDD | 80 | 4.59 | SCD: noncompliant |
| 7 | Metoprolol | 400 | DDD | 80 | 3.38 | |
| 8 | Metoprolol | 200 | DDD | 80 | 1.65 | |
| 9 | Metoprolol | 200 | DDD | 80 | 1.64 | |
| 10 | Metoprolol | 200 | DDD | 80 | 1.62 | |
| 11 | Toprolol | 50 | VI† | 90 | 2.88 | |
| 12 | Atenolol | 100 | AAI | 90 | 9.62 | ASD |
| 13 | Propranolol | 120* | DDD | 90 | 4.78 | |
| 14 | Propranolol | 60* | DDD | 80 | 1.99 | |
| 15 | Nadolol | 120 | VI | 80 | 1.72 | |
| 16 | Metoprolol | 50 | DDD | 100 | 0.66 | Died (cancer) |
| 17 | Atenolol | 200 | VI† | 70 | 9.37 | ASD with and without PM malfunction |
| 18 | Propranolol | 120* | DDD | 80 | 2.10 | |
| 19 | Propranolol | 160 | DDD | 80 | 3.25 | |
| 20 | Propranolol | 160 | DDD | 80 | 8.01 | |
| 21 | Bisoprolol | 10 | DDD | 90 | 1.80 | |
| 22 | Nadolol | 120 | VI | 85 | 2.71 | |
| 23 | Atenolol | 100* | DDD | 80 | 4.78 | |
| 24 | Atenolol | 100 | DDD | 70 | 7.92 | |
| 25 | Metoprolol | 50 | DDD | 80 | 11.34 | ASD with PM malfunction |
| 26 | Propranolol | 120* | VI | 80 | 8.07 | |
| 27 | Atenolol | 50 | DDD | 80 | 3.91 | SCD |
| 28 | Propranolol | 64* | DDD | 80 | 3.21 | |
| 29 | Atenolol | 50 | VI | 85 | 8.84 | |
| 30 | Atenolol | 100* | DDD | 80 | 12.90 | |
| 31 | Propranolol | 80* | DDD | 90 | 8.52 | |
| 32 | Atenolol | 50 | VI | 85 | 8.45 | |
| 33 | Atenolol | 100 | DDD | 60, 80 | 1.45 | ASD |
| 34 | Atenolol | 100 | DDD | 80 | 8.90 | |
| 35 | Atenolol | 100* | DDD | 80 | 6.64 | |
| 36 | Nadolol | 80* | AAI† | 70 | 15.55 | Syncope with PM malfunction |
| 37 | Atenolol | 50 | DDD | 70, 85 | 9.11 | |

F/U indicates follow-up; SCD, sudden cardiac death; and other abbreviations as in Table 1.

*Patient experienced ASD in association with pacemaker malfunction; †patient underwent pacemaker upgrade from either AAI or VI mode to DDD mode (see text for description of modes).

death, appropriate ICD discharge, or syncope) was 24% for the whole group at the time of follow-up (mean, 6.3 years). The second curve shows data for those patients who had continuous appropriate pacing and β -blocker therapy. The recurrence rate of symptoms (sudden death, aborted sudden death, appropriate ICD discharge, or syncope) was 17% in compliant patients. In noncompliant patients, defined as those who failed to take β -blockers or who had pacemaker malfunction, the incidence of morbid events (sudden death, aborted sudden death) was 57% (4 of 7 patients; Figure 1).

Although the symptom-free survival rate was less for the group as a whole compared with those patients who had continuous pacing and β -blocker therapy, these differences were not statistically significant. Of note is the gradual increase in return of symptoms (or death) with time, particularly starting 1.5 years after the onset of combined therapy.

Discussion

This report outlines the clinical course of patients the long-QT syndrome treated with combined β -blocker and

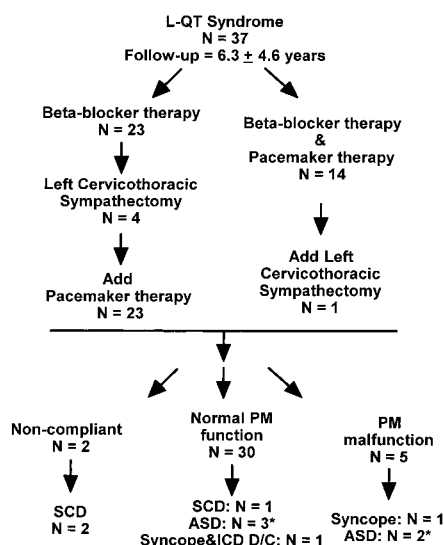


Figure 1. Summary of clinical follow-up in 37 patients treated with combined therapy for long-QT syndrome. ASD indicates aborted sudden death; D/C, discharge; and SCD, sudden cardiac death. *One patient had aborted sudden death in association with pacemaker (PM) lead malfunction and subsequently experienced another episode of aborted sudden death with pacemaker functioning appropriately.

continuous pacemaker therapy and represents the largest cohort with the longest follow-up interval so treated. We found that although all but 1 of the 37 patients were symptomatic owing to syncope or cardiac arrest at baseline, over a mean follow-up interval of 6.3 years, 28 patients (76%) remained totally asymptomatic with continuous pacing and β -blocker therapy. Knowledge of the nature of failure to respond to therapy is important for the clinician to place combination therapy in proper perspective. For example, 2 of our young patients died suddenly and had discontinued β -blocker therapy. In addition, 5 patients had pacemaker malfunctions. We recognize that this reflects a higher malfunction rate than traditionally expected, but we would like to point out that this cohort includes young patients in which pacemaker malfunction, especially lead fracture, may be higher. In the compliant group, 1 patient died suddenly, and 3 required ICD therapy because of documented recurrences

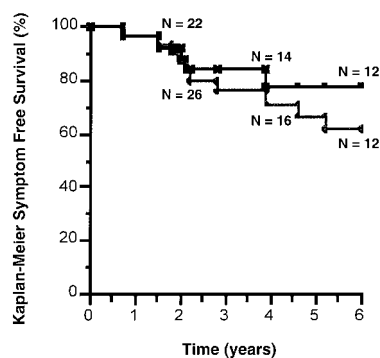


Figure 2. Kaplan-Meier survival curve analysis of patient cohort with long-QT syndrome reflecting incidence of total events in cohort in lower curve and incidence of events in compliant patients in upper curve. Numbers of patients followed at 2-, 4-, and 6-year intervals are given.

of symptoms. The failure rate for compliant patients (defined as recurrent sudden cardiac death, aborted sudden death, appropriate ICD discharge, or syncope) is significant (17%, or 5 of 30 patients). One concern with ICD therapy is that the electrical discharge may result in enhanced sympathetic tone, which may initiate multiple episodes of torsade de pointes. When this occurs, a patient may receive many ICD discharges in association with repeated, recurrent episodes of ventricular arrhythmias, otherwise known as an ICD storm. This appeared to be the case in 1 of our patients who eventually stabilized with intravenous β -blockers and pacing at a more rapid rate. However, repeated ICD discharges or an ICD storm does not seem to represent a substantial risk, as reflected by the relatively low incidence of an ICD storm in patients followed up with ICD implantation for the long-QT syndrome.^{23,24} In a follow-up study of patients treated with ICDs, the incidence of an ICD storm in patients with long-QT syndrome was 5%.²⁴ Because of the persistent risk of sudden death and the preliminary results of this study, ICD implantation was performed in 4 of our patients who presented with sudden death in the past 2 years. This more aggressive approach may be effected in part by greater patient acceptance and improvements in technological advances associated with ICD insertion.

Examination of the Kaplan-Meier curve shows an increased incidence of events with time, particularly after 1.5 years of combined therapy. This explains the difference between the present results and those of a previous study.²¹ Thus, our findings show that combination therapy may not provide adequate protection against recurrent sudden cardiac death or syncope in patients with long-QT syndrome.

The limitations of this review include the fact that this is not a controlled prospective analysis but rather an observational study. It is difficult to compare our patients with other previously reported groups. Initially, our policy was to initiate combined therapy only in those who failed to respond to standard therapy (ie, β -blocker or cervicothoracic sympathectomy). In view of the excellent initial experience, we accepted symptomatic patients (syncope or aborted sudden death) without prior failure of standard therapy. In total, 23 of 37 patients had failed either β -blocker therapy or sympathectomy before combined therapy. We do not know if we are dealing with an especially resistant group of patients. Moreover, initial therapy for patients with cardiac arrest has switched to favor ICD placement. This is supported by a study describing the incidence of appropriate ICD discharges in a "high-risk" population of patients with long-QT syndrome to be 60% at a 31-month follow-up.²³ This population is small but reflects the limited experience available with patients with this rare syndrome. Our recurrence rate may be overly pessimistic for long-QT patients as a group, because a significant proportion of our patients failed other therapy. Finally, because the QT or QTc intervals just before sudden death are not available, we cannot exclude the possibility that reprogramming would have prevented death, because higher pacing rates may have further shortened the QT interval and therefore possibly decreased the possibility of sudden death. Further follow-up studies are needed to define a more accurate relative risk of malignant events.

In conclusion, exciting advances in our understanding of the genetic abnormalities promise to lead to even more effective therapeutic breakthroughs. For example, 1 type of long-QT syndrome has been shown to be due to abnormalities in the Na⁺ channel gene (SCN5A), and preliminary observations relative to mexiletine therapy have been reported.²⁵ However, the very malignant nature of this disease and the age of patients afflicted mandate that optimal therapy be used as quickly as possible. Our results reveal that over a 6.3-year period, the incidence of sudden death, aborted sudden death, or syncope was 24% (although 2 deaths occurred in noncompliant patients). However, even in the compliant group, we found a significant incidence (17%) of morbidity or potentially morbid events. The overriding clinical concern is that this failure rate is unacceptable. Until "curative" therapy is available, we recommend strong consideration of the use of the ICD as a back-up therapy for all patients who present with sudden cardiac death or for those who develop recurrent symptoms while on combined therapy.

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