

ORIGINAL ARTICLE

Electrocardiographic Abnormalities and Sudden Death in Myotonic Dystrophy Type 1

William J. Groh, M.D., M.P.H., Miriam R. Groh, M.S., Chandan Saha, Ph.D., John C. Kincaid, M.D., Zachary Simmons, M.D., Emma Ciafaloni, M.D., Rahman Pourmand, M.D., Richard F. Otten, M.D., Deepak Bhakta, M.D., Girish V. Nair, M.D., M.S., Mohammad M. Marashdeh, M.D., Douglas P. Zipes, M.D., and Robert M. Pascuzzi, M.D.

ABSTRACT

BACKGROUND

Sudden death can occur as a consequence of cardiac-conduction abnormalities in the neuromuscular disease myotonic dystrophy type 1. The determinants of the risk of sudden death remain imprecise.

METHODS

We assessed whether the electrocardiogram (ECG) was useful in predicting sudden death in 406 adult patients with genetically confirmed myotonic dystrophy type 1. A patient was characterized as having a severe abnormality if the ECG had at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block.

RESULTS

Patients with severe abnormalities according to the entry ECG were older than patients without severe abnormalities, had more severe skeletal-muscle impairment, and were more likely to have heart failure, left ventricular systolic dysfunction, or atrial tachyarrhythmia. Such patients were more likely to receive a pacemaker or an implantable cardioverter-defibrillator during the follow-up period. During a mean follow-up period of 5.7 years, 81 patients died; there were 27 sudden deaths, 32 deaths from progressive neuromuscular respiratory failure, 5 nonsudden deaths from cardiac causes, and 17 deaths from other causes. Among the 17 patients who died suddenly in whom postcollapse rhythm was evaluated, a ventricular tachyarrhythmia was observed in 9. A severe ECG abnormality (relative risk, 3.30; 95% confidence interval [CI], 1.24 to 8.78) and a clinical diagnosis of atrial tachyarrhythmia (relative risk, 5.18; 95% CI, 2.28 to 11.77) were independent risk factors for sudden death.

CONCLUSIONS

Patients with adult myotonic dystrophy type 1 are at high risk for arrhythmias and sudden death. A severe abnormality on the ECG and a diagnosis of an atrial tachyarrhythmia predict sudden death. (ClinicalTrials.gov number, NCT00622453.)

From the Department of Medicine, Krannert Institute of Cardiology (W.J.G., M.R.G., R.F.O., D.B., G.V.N., M.M.M., D.P.Z.), the Division of Biostatistics (C.S.), and the Department of Neurology (J.C.K., R.M.P.), Indiana University, Indianapolis; the Department of Neurology, Pennsylvania State University, Hershey (Z.S.); the Department of Neurology, University of Rochester, Rochester, NY (E.C.); and the Department of Neurology, State University of New York at Stony Brook, Stony Brook (R.P.). Address reprint requests to Dr. Groh at the Krannert Institute of Cardiology, Indiana University, 1800 N. Capitol, Rm. E406, Indianapolis, IN 46202, or at wgroh@iupui.edu.

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MYOTONIC DYSTROPHY IS AN AUTOSOMAL dominant disorder that is the most common muscular dystrophy presenting in adults.¹ It is characterized by myotonia (delayed muscle relaxation after contraction), progressive weakness and atrophy of the skeletal muscles, and systemic manifestations, including cardiac involvement.² Myotonic dystrophy type 1, the more common and typically the more severe of the two major types, is caused by an expanded cytosine–thymine–guanine (CTG) repeat on chromosome 19 in the 3′ untranslated region of a serine–threonine protein kinase gene called *DMPK* (dystrophia myotonica protein kinase).^{3–5}

Sudden death can occur in patients with myotonic dystrophy type 1 as a consequence of myocardial fibrosis and degeneration of the cardiac-conduction system.^{6–11} Cardiac involvement initially manifests as asymptomatic electrocardiographic (ECG) abnormalities, commonly prolongation of the PR interval and QRS duration. Arrhythmias can occur, including sinus-node dysfunction; progressive heart block; atrial tachycardia, flutter, or fibrillation; and ventricular tachycardia or fibrillation. Sudden death is believed to result from asystole after atrioventricular block or from a ventricular tachyarrhythmia.^{9,12} Because of the unpredictable progression of atrioventricular block, pacemakers have been recommended for patients with clinically significant conduction abnormalities.¹³ Implantable cardioverter–defibrillators have been used in patients with ventricular tachyarrhythmias.^{12,14,15}

Efforts to develop a method to identify patients with myotonic dystrophy type 1 who are at high risk for sudden death have been stymied because studies have failed to enroll and follow a sufficiently large, prospectively characterized population without referral bias. As a result, the optimal clinical approach to the diagnosis and treatment of arrhythmias is unclear, as is the effect of therapeutic interventions on the risk of sudden death.

There is evidence that patients with more severe conduction abnormalities, as quantified on the ECG, are at higher risk for arrhythmias.^{8,16} The ECG has therefore been recommended as an appropriate screening test, but its usefulness for the prediction of sudden death remains unknown.^{9,17} We tested the hypothesis that a severe abnormality on the ECG would predict sudden death in a population of patients with myotonic dystrophy type 1.

METHODS

STUDY ORGANIZATION

The study was conducted at 23 neuromuscular-disease clinics in the United States; it was initiated in April 1997, and follow-up is ongoing. All authors vouch for the completeness and accuracy of the data and its analysis and participated in writing the article. The institutional review boards of Indiana University and of each clinic approved the study.

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PATIENTS

Adult patients (18 years of age or older) with a clinical diagnosis of myotonic dystrophy were invited to participate. Analysis of the CTG repeat sequence was performed on leukocytes (at the Athena Diagnostics Laboratory) with the use of polymerase-chain-reaction assays and analysis of restriction-fragment-length polymorphisms, as well as the Southern blot technique.^{5,18} Only patients with an abnormal CTG repeat sequence (one or both alleles with ≥ 38 repeats) confirmatory of myotonic dystrophy type 1 were included.¹⁹ All patients provided written informed consent.

EVALUATION AT STUDY ENTRY

The clinical characteristics of the patients were ascertained from history and examination. An atrial tachyarrhythmia was diagnosed if the patient had a history of sustained atrial tachycardia, flutter, or fibrillation. A ventricular tachyarrhythmia was diagnosed if the patient had a history of sustained ventricular tachycardia or fibrillation. Cardiac-imaging studies assessing left ventricular function were reviewed, and a patient was considered to have systolic dysfunction if it was reported in the study results or if the ejection fraction was less than 50%. The severity of weakness was scored by a standardized five-point muscular-impairment rating scale, in which a score of 1 indicates no clinical muscular impairment, 2 minimal signs without distal weakness except for digit flexors, 3 distal weakness without proximal weakness except for elbow extensors, 4 moderate proximal weakness, and 5 severe proximal weakness.²⁰ For

analysis, patients with no or minimal weakness (muscular-impairment rating of 1 or 2) were grouped.

All patients underwent a 12-lead ECG that was analyzed by one investigator (Dr. Groh). A patient was classified as having a severe abnormality indicative of conduction disease if the ECG had at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block.

CAUSES OF DEATH

Follow-up was performed annually and could include a clinic visit, a newsletter with a reply questionnaire, or telephone contact. The decision to refer patients for cardiac evaluation was made by local care providers. New cardiac diagnoses were confirmed by a review of the records. Annual ECGs were recommended but not required. National death indexes were searched regularly.

Deaths were classified as sudden or nonsudden. Sudden death was defined as death occurring suddenly and unexpectedly in a patient who was stable before the event.^{21,22} Witnessed deaths were classified as sudden only if death occurred within 1 hour after the onset of new symptoms. Unwitnessed deaths were considered sudden if the patient was seen alive and stable during the previous 24 hours. If the temporal sequence was consistent with sudden death but a specific cause of death other than arrhythmia was confirmed, the death was classified as nonsudden. When available, ECG recordings were used to characterize the initial rhythm. Nonsudden deaths were subclassified into those related to progressive neuromuscular respiratory failure, cardiac deaths, and other deaths. Progressive neuromuscular respiratory failure was defined as death resulting from respiratory dysfunction related to myotonic dystrophy. Cardiac death was defined as death related primarily to a cardiac cause. Causes of death were adjudicated by a committee of study investigators who were unaware of all other patient data.

STATISTICAL ANALYSIS

Characteristics at study entry and non-time-dependent characteristics at follow-up were compared between patients with and those without severe abnormalities on the entry ECG with the use of Student's *t*-test for continuous variables and the

chi-square test or Fisher's exact test for categorical variables.

The times to new events occurring during follow-up were compared between patients with and those without severe ECG abnormalities with the use of Kaplan-Meier analysis and the log-rank test. The relative risks of sudden death, death due to progressive neuromuscular respiratory failure, and death from any cause were estimated for individual covariates with the use of a Cox proportional-hazards model. Variables associated with ECG abnormalities and death were entered into multivariate Cox proportional-hazards models in a stepwise selection procedure based on the likelihood-ratio test to determine the independent effect of patient characteristics on the relative risk of death. The follow-up time was the interval from study entry to the most recent evaluation or death and was censored at death for the determination of time to sudden death or death due to progressive neuromuscular respiratory failure in patients dying of other causes. Characteristics changing during follow-up were incorporated as time-dependent covariates. The sensitivity, specificity, and positive and negative predictive values of a severe abnormality on the ECG and a clinical diagnosis of an atrial tachyarrhythmia for sudden death were determined.

Two-sided *P* values were calculated for all analyses; values of 0.05 or less were considered to indicate statistical significance. Data were analyzed with SPSS software for Windows, version 14.0, and SAS software, version 9.3.1.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of 443 patients evaluated, 37 did not have an abnormal CTG repeat sequence and were excluded. The remaining 406 patients made up the study population. Of these, 310 did not have a severe ECG abnormality at study entry and 96 did. The characteristics of the patients at entry are shown in Table 1. Patients with severe ECG abnormalities were older, had more CTG repeats, and had more severe muscular impairment.

Seven of the 406 enrolled patients (1.7%) were lost to follow-up after study entry. None of these patients died during follow-up, according to a review of national death indexes. The mean and median durations of follow-up were 5.7 and 6.5

years, respectively. There was no difference in duration of follow-up between patients with and those without severe ECG abnormalities.

Table 1 also includes events occurring during follow-up according to the presence or absence of a severe ECG abnormality at study entry. There was no difference between the two groups in the rate of progression of muscular impairment during follow-up. Heart failure and left ventricular systolic dysfunction at entry or newly diagnosed during follow-up were more frequent in patients with severe ECG abnormalities at entry. Nineteen of the 23 patients with left ventricular systolic dysfunction had nonischemic cardiomyopathy attributed to myotonic dystrophy.

A diagnosis of atrial tachyarrhythmia was common, especially in those with severe ECG abnormalities at entry (29 of 96 patients). A diagnosis of ventricular tachyarrhythmia was less common. Pacemakers and implantable cardioverter-defibrillators were more frequently used in patients with severe ECG abnormalities. Among the 41 patients with pacemakers, 27 had either no or minimal symptoms and had received their pacemakers because of concern about conduction abnormalities. Nine of the 14 cardioverter-defibrillators were implanted in patients who did not have a diagnosis of spontaneous ventricular tachyarrhythmia.

There were no differences between the two groups in the likelihood of obtaining follow-up ECGs or in the interval between the first and last ECG. The ECGs typically showed concordant prolongation in the PR interval and QRS duration. Patients with severe ECG abnormalities at entry had greater rates of progression of the PR interval and of QRS duration and were more likely to have a new atrial tachyarrhythmia or a paced rhythm on subsequent ECGs. Sixty-nine patients without a severe ECG abnormality at study entry received a diagnosis of a severe abnormality on ECGs that were recorded during follow-up.

DEATH

Eighty-one of the 406 patients (20.0%) died during follow-up. The median age at death was 54 years. Twenty-seven (33.3%) of the deaths were sudden; details of events for the patients with sudden death are given in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

Nonsudden deaths were categorized as result-

ing from progressive neuromuscular respiratory failure in 32 patients (39.5%), cardiac causes in 5 (6.2%), and other causes in 17 (21.0%). Of the five nonsudden cardiac deaths, three were due to progressive heart failure in patients with a cardiomyopathy attributed to myotonic dystrophy and two to coronary artery disease.

The relationship between the characteristics of the patients and the cause of death is reported in Table 2. A univariate association with sudden death was identified for age, severe proximal muscle weakness, all the cardiac and arrhythmia diagnoses except ventricular tachyarrhythmia, the presence of a pacemaker or cardioverter-defibrillator, and each of the ECG indicators except paced rhythm. A significant univariate association with death due to progressive neuromuscular respiratory failure was identified for age, moderate and severe proximal muscle weakness, heart failure, atrial tachyarrhythmia, the presence of a pacemaker, and each of the ECG indicators except QRS duration. Death from any cause was significantly associated with ventricular tachyarrhythmia and with all the characteristics associated with sudden death and death from progressive neuromuscular respiratory failure.

Multivariate Cox regression models were constructed to determine which characteristics were independently associated with death (Table 3). Because a severe ECG abnormality was defined by the rhythm, PR interval, QRS duration, and presence of atrioventricular block, these individual covariates were not included in the multivariate models. All models were adjusted for age, the presence or absence of a pacemaker, and the presence or absence of a severe ECG abnormality, even when these variables were not significant predictors. A diagnosis of atrial tachyarrhythmia and a severe ECG abnormality were independent risk factors associated with sudden death. Other characteristics were not significant independent predictors of sudden death and had minimal effect on the multivariate model if they were included. Age, severe proximal muscle weakness, heart failure, and atrial tachyarrhythmia were independent risk factors for death from progressive neuromuscular respiratory failure. Age, severe proximal muscle weakness, heart failure, atrial tachyarrhythmia, and ventricular tachyarrhythmia were independent risk factors for death from any cause.

The presence of a severe ECG abnormality had

Table 1. Characteristics of the Patients at Study Entry and New Events at Follow-up According to the Presence or Absence of a Severe ECG Abnormality at Entry.*

Characteristic	No Severe Abnormality (N = 310)			Severe Abnormality (N = 96)			P Value†	
	Entry	Follow-up	Entry	Entry	Follow-up	Entry	Entry	Follow-up
Duration of follow-up — yr		5.7±2.3			5.5±2.2			0.56
Age — yr							<0.001	
Mean	40±12		49±11					
Median	39		48					
Male sex — no. (%)	153 (49.4)		52 (54.2)			0.41		
No. of CTG repeats	606±379		704±399			0.03		
Muscular-impairment score — no. (%)‡						<0.001		0.33
1 or 2	102 (32.9)	61 (19.7)	5 (5.2)		4 (4.2)			
3	91 (29.4)	79 (25.5)	26 (27.1)		20 (20.8)			
4	106 (34.2)	137 (44.2)	49 (51.0)		40 (41.7)			
5	11 (3.5)	33 (10.6)	16 (16.7)		32 (33.3)			
Heart failure — no. (%)	1 (0.3)	2 (0.11/yr)	4 (4.2)		6 (1.17/yr)	0.01		<0.001
Cardiac-imaging findings								
Patients who had an imaging study — no. (%)	76 (24.5)	65 (4.76/yr)	23 (24.0)		39 (9.67/yr)	0.91		<0.001
Left ventricular systolic dysfunction — no./total no. (%)§	5/76 (6.6)	4/65 (0.96/yr)	5/23 (21.7)		9/39 (3.62/yr)	0.05		<0.001
Atrial tachyarrhythmia — no. (%)¶	11 (3.5)	12 (0.71/yr)	10 (10.4)		19 (4.02/yr)	0.008		<0.001
Ventricular tachyarrhythmia — no. (%)	0	4 (0.23/yr)	0		4 (0.76/yr)			0.08
Pacemaker — no. (%)	1 (0.3)	9 (0.51/yr)	8 (8.3)		23 (4.69/yr)	<0.001		<0.001
Cardioverter-defibrillator — no. (%)	0	5 (0.28/yr)	0		9 (1.70/yr)			<0.001
ECG findings								
Patients who had ≥1 ECG at follow-up — no. (%)		271 (87.4)			79 (82.3)			0.20
Interval from first to last ECG — yr**		5.0±2.1			4.8±2.2			0.47
Patients who had a severe abnormality — no. (%)	0	69 (5.15/yr)	96 (100)		253±53	<0.001		<0.001
PR interval — msec††	186±24	206±30	232±50		8.8±12.9	—		0.001
Progression of PR interval — msec/yr‡‡		5.2±5.8			140±29	<0.001		<0.001
QRS duration — msec§§	96±10	103±16	129±24		140±29	<0.001		<0.001

Progression of QRS duration — msec/yr ¶¶	2.2±3.0	3.4±5.4	0.01
Atrial tachyarrhythmia — no. (%)	0 6 (0.45/yr)	6 (6.2) 13 (3.68/yr)	<0.001
Paced rhythm — no. (%)	0 5 (0.37/yr)	8 (8.3) 15 (4.26/yr)	<0.001
Second-degree or third-degree atrioventricular block — no. (%)	0	1 (1.0) 1 (0.27/yr)	

* A severe ECG abnormality was defined by the presence of at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block. Values given as percentages per year indicate the incidence of new events per year during the follow-up period in patients without the characteristic at entry. Plus-minus values are means ±SD.

† P values to detect differences in duration of follow-up, age, number of CTG repeats, interval from first to last ECG, PR interval, progression of PR interval, QRS duration, and progression of QRS duration were calculated with the use of Student's *t*-test. P values to detect differences in sex, muscular-impairment score, heart failure, cardiac-imaging findings, atrial tachyarrhythmia, presence of a pacemaker, and the number of follow-up ECGs were calculated by the chi-square test or Fisher's exact test. P values to detect differences in time during follow-up for progression of muscular impairment from muscular impairment at study entry, newly diagnosed heart failure, newly diagnosed left ventricular systolic dysfunction, newly diagnosed atrial tachyarrhythmia, newly diagnosed ventricular tachyarrhythmia, implantation of a pacemaker, implantation of a cardioverter-defibrillator, newly diagnosed atrial tachyarrhythmia, and newly diagnosed paced rhythm were calculated with the use of Kaplan-Meier survival analysis with the log-rank test.

‡ A score of 1 indicates no clinical muscular impairment; 2 minimal signs without distal weakness except for digit flexors; 3 distal weakness without proximal weakness except for elbow extensors; 4 moderate proximal weakness; and 5 severe proximal weakness.²⁰ Patients with no or minimal weakness (muscular-impairment rating of 1 or 2) were grouped for analysis.

§ A patient was considered to have left ventricular systolic dysfunction if it was reported in the results of the cardiac-imaging study or if the left ventricular ejection fraction was less than 50%.

¶ The diagnosis of atrial tachyarrhythmia includes sustained atrial tachycardia, flutter, or fibrillation.

¶¶ The diagnosis of ventricular tachyarrhythmia includes sustained ventricular tachycardia or fibrillation.

** Data were available for 271 patients in the group with no severe abnormalities and 79 in the group with severe abnormalities.

†† Data were available for 83 patients at entry and at follow-up in the group with severe abnormalities.

‡‡ Data were available for 270 patients in the group with no severe abnormalities and 61 in the group with severe abnormalities.

§§ Data were available for 89 patients at entry and at follow-up in the group with severe abnormalities.

¶¶ Data were available for 270 patients in the group with no severe abnormalities and 70 in the group with severe abnormalities.

a sensitivity of 74.1% for the prediction of sudden death, a specificity of 61.7%, a positive predictive value of 12.1%, and a negative predictive value of 97.1%. The presence of the combined risk factors of a severe ECG abnormality and a clinical diagnosis of an atrial tachyarrhythmia had a sensitivity of 81.5% for the prediction of sudden death, a specificity of 59.4%, a positive predictive value of 12.5%, and a negative predictive value of 97.8%.

DISCUSSION

Our study demonstrated that a severe abnormality on the ECG is an independent predictor, with moderate sensitivity, of sudden death in patients with myotonic dystrophy type 1. In a population of persons with genetically confirmed disease, we defined a severe ECG abnormality with the use of clinically relevant and easily measured parameters. During follow-up, 20% of the patients died, and one third of the deaths were sudden. Each of the indicators we used to define a severe ECG abnormality predicted the risk of sudden death when risk was evaluated on a univariate level; when combined, these indicators predicted the risk of sudden death in multivariate modeling. The presence of a severe ECG abnormality was specific for the prediction of sudden death; it was not an independent risk factor for nonsudden death from progressive neuromuscular respiratory failure or for death from any cause.

The presence of a severe ECG abnormality is indicative of cardiac conduction-system disease that is known to occur in myotonic dystrophy type 1. A prolonged PR interval and QRS duration correlate with the degree of conduction delay between the atria and the bundle of His and between the bundle of His and the ventricles and with the distribution and extent of conduction-system lesions found at autopsy.^{7,23,24} Conduction-system abnormalities can progress to complete atrioventricular block that can result in asystole and sudden death. In addition, conduction-system abnormalities can be associated with ventricular tachyarrhythmias that can result in sudden death.^{8,12,16,25} We had access to ECGs for more than half of the patients who died suddenly. A ventricular tachyarrhythmia was most commonly observed. Others have reported ventricular tachyarrhythmias as a cause of sudden death in patients with myotonic dystrophy.^{9-11,26,27} Whether the initial rhythm recorded after collapse was

Table 2. The Relation between the Characteristics of the Patients and Sudden Death, Death from Progressive Neuromuscular Respiratory Failure, and Death from Any Cause.*

Characteristic	Sudden Death (N=27)		Death from Progressive Neuromuscular Respiratory Failure (N=32)		Death from Any Cause (N=81)	
	Univariate Relative Risk (95% CI)	P Value	Univariate Relative Risk (95% CI)	P Value	Univariate Relative Risk (95% CI)	P Value
Age	1.46 (1.02–2.09)	0.04	1.98 (1.44–2.73)	<0.001	1.73 (1.41–2.12)	<0.001
Male sex	0.89 (0.42–1.90)	0.77	1.27 (0.63–2.55)	0.51	1.05 (0.68–1.62)	0.83
No. of CTG repeats	1.26 (0.87–1.82)	0.22	0.94 (0.66–1.34)	0.72	1.03 (0.83–1.29)	0.78
Muscular-impairment score†						
1 or 2	1.0		1.0		1.0	
3	1.40 (0.52–3.78)	0.50	0.77 (0.23–2.49)	0.66	1.45 (0.79–2.66)	0.23
4	1.67 (0.68–4.07)	0.26	2.27 (1.04–4.95)	0.04	1.96 (1.18–3.26)	0.009
5	3.61 (1.33–9.82)	0.01	10.26 (4.76–22.11)	<0.001	7.13 (4.25–11.97)	<0.001
Heart failure	4.13 (0.97–17.51)	0.05	5.49 (1.67–18.10)	0.005	5.10 (2.34–11.10)	<0.001
Left ventricular systolic dysfunction	3.93 (1.18–13.14)	0.03	0.97 (0.13–7.14)	0.98	2.54 (1.10–5.84)	0.03
Atrial tachyarrhythmia	8.19 (3.79–17.68)	<0.001	5.60 (2.70–11.64)	<0.001	5.36 (3.37–8.54)	<0.001
Ventricular tachyarrhythmia	7.09 (0.92–54.71)	0.06	4.07 (0.55–30.18)	0.17	10.78 (4.26–27.28)	<0.001
Pacemaker	3.77 (1.51–9.40)	0.004	4.09 (1.82–9.19)	<0.001	3.48 (2.03–5.96)	<0.001
Cardioverter-defibrillator	7.97 (1.75–36.16)	0.007			6.66 (2.37–18.66)	<0.001
ECG findings						
Severe abnormality‡	5.53 (2.33–13.17)	<0.001	4.78 (2.21–10.37)	<0.001	4.16 (2.60–6.65)	<0.001
PR interval	1.50 (1.01–2.24)	0.04	1.88 (1.48–2.39)	<0.001	1.69 (1.40–2.04)	<0.001
QRS duration	1.76 (1.28–2.43)	<0.001	1.33 (0.91–1.96)	0.14	1.43 (1.14–1.80)	0.002
Atrial tachyarrhythmia	9.34 (3.80–22.95)	<0.001	6.49 (2.64–15.96)	<0.001	6.64 (3.74–11.79)	<0.001
Paced rhythm	3.15 (0.94–10.52)	0.06	5.53 (2.26–13.56)	<0.001	4.90 (2.70–8.92)	<0.001

* Univariate relative risks and P values were calculated with the use of Cox proportional-hazards analysis for time to sudden death, death from progressive neuromuscular respiratory failure, and death from any cause. For continuous variables, the relative risk is expressed for an increase of 1 SD, which for age is 12 years, for number of CTG repeats is 386, for PR interval is 41 msec, and for QRS duration is 25 msec. For muscular impairment, the relative risks are calculated in comparison with the combined rating of 1 or 2, which was assigned a risk of 1.0. A relative risk left blank indicates that no patient with this characteristic died during follow-up. All covariates except age, sex, and number of CTG repeats were time dependent. CI denotes confidence interval.

† A score of 1 indicates no clinical muscular impairment, 2 minimal signs without distal weakness except for digit flexors, 3 distal weakness without proximal weakness except for elbow extensors, 4 moderate proximal weakness, and 5 severe proximal weakness.²⁰

‡ A severe ECG abnormality was defined by the presence of at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block.

also the initiating rhythm is unknown. Although our study used an accepted definition of sudden death, appropriate classification remains difficult.^{22,28} Mechanisms other than arrhythmias could have had a role in some of the sudden deaths.²⁵

Patients with severe abnormalities on the entry ECG were more likely to have or to receive a diagnosis of other factors that adversely affected outcome. These patients were older, had more mus-

cular impairment, and were more likely to have or to receive a diagnosis of heart failure, left ventricular systolic dysfunction, or atrial tachyarrhythmia. Nonetheless, when these characteristics were evaluated in the multivariate model, an abnormal ECG remained a significant predictor of sudden death, with an adjusted relative risk of 3.30.

Despite a substantial burden of sudden death, the major cause of death was respiratory failure associated with progressive muscular weakness

Table 3. The Relation between Patient Characteristics and the Risk of Death.*

Characteristic	Sudden Death		Death from Progressive Neuromuscular Respiratory Failure		Death from Any Cause	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Age†	1.16 (0.76–1.75)	0.50	1.81 (1.20–2.74)	0.005	1.46 (1.13–1.87)	0.003
Muscular-impairment score‡						
1 or 2			1.0		1.0	
3			1.28 (0.20–8.19)	0.80	1.13 (0.47–2.73)	0.79
4			2.85 (0.60–13.55)	0.19	1.47 (0.67–3.19)	0.33
5			13.07 (2.77–61.61)	0.001	4.54 (2.02–10.19)	<0.001
Heart failure			5.39 (1.46–19.82)	0.01	2.85 (1.20–6.74)	0.02
Atrial tachyarrhythmia	5.18 (2.28–11.77)	<0.001	2.41 (1.10–5.31)	0.03	2.59 (1.55–4.32)	<0.001
Pacemaker	1.35 (0.51–3.56)	0.54	1.80 (0.77–4.20)	0.17	1.46 (0.82–2.60)	0.19
Ventricular tachyarrhythmia					6.41 (2.30–17.89)	<0.001
Severe ECG abnormality§	3.30 (1.24–8.78)	0.02	1.33 (0.53–3.33)	0.55	1.58 (0.90–2.81)	0.11

* All multivariate Cox proportional-hazards models were adjusted for age, the presence or absence of a pacemaker, and the presence or absence of a severe ECG abnormality, even when their effects were not significant. All covariates except age were time dependent. CI denotes confidence interval.

† The relative risk is expressed for an increase of 1 SD (12 years).

‡ A score of 1 indicates no clinical muscular impairment, 2 minimal signs without distal weakness except for digit flexors, 3 distal weakness without proximal weakness except for elbow extensors, 4 moderate proximal weakness, and 5 severe proximal weakness.²⁰ The relative risk was calculated in comparison with the combined rating of 1 or 2, which was assigned a risk of 1.0.

§ A severe ECG abnormality was defined by the presence of at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block. Characteristics evaluated for inclusion in the models for sudden death, death from progressive neuromuscular respiratory failure, and death from any cause included age, number of CTG repeats, muscular impairment, heart failure, left ventricular systolic dysfunction, atrial tachyarrhythmia, ventricular tachyarrhythmia, the presence of a pacemaker, the presence of an implantable cardioverter-defibrillator, and the presence of a severe ECG abnormality. The characteristics were entered into the multivariate Cox proportional-hazards models by a stepwise procedure on the basis of the likelihood-ratio test. Characteristics that are not listed or for which no risk values are given were not included in the final model because their P values were greater than 0.05.

attributed to myotonic dystrophy, a finding similar to findings observed in other large registries.^{10,11} Independent predictors of death from progressive neuromuscular respiratory failure included older age, more severe muscular impairment, and a diagnosis of heart failure or atrial tachyarrhythmia. Because respiratory failure accounted for more deaths than did any other cause, these same characteristics were also independent predictors of death from any cause. The progressive muscular weakness observed in these patients affected their treatment after cardiac arrest and the subsequent outcomes. In three patients with acute unstable arrhythmias, resuscitative measures were aborted after the initial evaluation of rhythm because of advance health care directives. In another patient, resuscitative measures were stopped after defibrillation of a ventricular tachyarrhyth-

mia resulted in asystole. These four patients all had severe proximal muscle weakness, as assessed at the last study follow-up. It is likely that their stable but severe muscular involvement influenced decisions regarding emergency medical care.

The most common clinical arrhythmia observed was an atrial tachyarrhythmia. A diagnosis of atrial tachyarrhythmia was the only characteristic independently predicting both sudden death and death from progressive neuromuscular respiratory failure. Different mechanisms could be responsible for the association of an atrial tachyarrhythmia with these two causes of death. An atrial tachyarrhythmia could reflect the presence of atrial fibrosis indicative of conduction involvement and an increased risk of sudden death.⁷ Atrial tachyarrhythmias could also be more common in patients with pulmonary dysfunction who

are at higher risk for death due to progressive neuromuscular respiratory failure.²⁹

By the time of the last follow-up visit, 10 of the 96 patients with severe ECG abnormalities at study entry had received a diagnosis of heart failure. The majority of patients with heart failure had a diagnosis of nonischemic cardiomyopathy attributed to myotonic dystrophy.³⁰ A diagnosis of heart failure was associated with death from progressive neuromuscular respiratory failure and death from any cause. Screening patients with myotonic dystrophy type 1 for signs and symptoms of heart failure, especially those with an abnormal ECG, is appropriate.

On the basis of nonrandomized observations, some investigators have recommended pacemakers for patients with myotonic dystrophy and asymptomatic cardiac-conduction abnormalities.^{25,31} Pacing guidelines have been updated to reflect these recommendations.¹³ Such recommendations appeared to affect the use of pacemakers in our registry. By the time of the last follow-up visit, 10% of the patients had pacemakers, two thirds of which were prophylactic. However, we did not observe that pacemakers decreased the rates of sudden death or death from any cause. We and others have recognized that patients with myotonic dystrophy continue to die suddenly despite having functioning pacemakers.^{10,11,25,26}

A small number of the patients received implantable cardioverter-defibrillators, most of which were prophylactic. These devices are capable of delivering both pacing and defibrillation and therefore can treat both bradycardia and ventricular tachyarrhythmias. Sudden death occurred in two patients with implantable cardioverter-defibrillators. In one patient, postmortem evaluation of the cardioverter-defibrillator memory was available. The stored ECGs implicated an atrial tachyarrhythmia with recurrent delivery of inappropriate cardioverter-defibrillator therapy, provoking a later ventricular tachyarrhythmia and ultimately asystole not responding to pacing. The predominance

of ventricular tachyarrhythmias observed in patients at the initial evaluation of rhythm after collapse lends support to the concept that cardioverter-defibrillators could be beneficial in preventing sudden death. However, the effectiveness of cardioverter-defibrillators in reducing mortality in patients with myotonic dystrophy type 1 remains unknown. Mortality from progressive neuromuscular respiratory failure could limit the overall duration of benefit of implantable cardioverter-defibrillators in patients with myotonic dystrophy type 1.

In conclusion, our study shows that adult patients with myotonic dystrophy type 1 are at high risk for sudden death. The presence of a severe ECG abnormality and a clinical diagnosis of atrial tachyarrhythmia were the only independent predictors of sudden death detected in our analysis.

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