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Long-Term Follow-Up of Arrhythmias in Patients With Myotonic Dystrophy Treated by Pacing

A Multicenter Diagnostic Pacemaker Study

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OBJECTIVES We hypothesized that pacemaker (PM) implantation in patients with myotonic dystrophy (MD) with a prolonged HV interval, even asymptomatic, may protect them against sudden death related to atrioventricular (AV) block. We sought to prospectively document the true incidence of AV block episodes in this high-risk population and accurately trace, in the long term, by the PM, the occurrence of arrhythmias that may remain undetected during conventional follow-up.

BACKGROUND Myotonic dystrophy is associated with a high risk of sudden death, commonly attributed to AV block or ventricular arrhythmias, but cardiac pacing is only recommended as a secondary prevention.

METHODS Patients with MD with an HV interval ≥70 ms, even in the absence of related symptoms, prospectively received a cardiac PM, including an algorithm capable of diagnosing episodes of bradycardia and tachyarrhythmias.

RESULTS The population consisted of 49 patients (45.5 ± 8.9 years old) followed for 53.5 ± 27.2 months. Paroxysmal arrhythmias were recorded in 41 patients (83.7%), consisting of complete AV block (n = 21), sino-atrial block (n = 4), or atrial (n = 25) or ventricular (n = 13) tachyarrhythmias. No patient died of AV block during follow-up, but 10 deaths occurred, 4 of them sudden. An arrhythmic cause could be excluded by postmortem PM interrogation in two cases of typical sudden death.

CONCLUSIONS Arrhythmias are common in patients with MD with infrahisian conduction abnormalities. The prophylactic implantation of a pacing system when the HV interval is ≥70 ms seems appropriate. The PM protects the patient against the clinical consequences of paroxysmal profound bradycardia and facilitates the diagnosis and management of frequent paroxysmal tachyarrhythmias. (J Am Coll Cardiol 2002;40:1645–52) © 2002 by the American College of Cardiology Foundation

Myotonic dystrophy (MD) is a serious autosomal-dominant hereditary disease with an estimated incidence of 1 in 8,000 births (1–3). Death is a major concern in MD, although its reported incidence varies widely, and may be related to muscular weakness or respiratory failure, or sometimes it may be sudden (4–13). The most often proposed mechanisms of sudden death in MD are atrioventricular (AV) conduction disorders and ventricular tachyarrhythmias (4,6,8,9,11,14–21). Practice guidelines recommend the implantation of a cardiac pacemaker (PM) in patients with MD in case of acquired third-degree AV block (class I indication) or if there is the incidental finding, during electrophysiologic (EP) study, of a markedly prolonged HV interval (>100 ms) in asymptomatic patients (class IIa indication) (22).

In our study, we put forward the hypothesis that implantation of a PM in patients with MD with an HV interval ≥70 ms, even asymptomatic, may protect them against the risk of sudden death related to AV block. The aims of this multicenter study were: 1) to prospectively justify the PM indication by automatic recording of spontaneous AV block episodes in patients with MD without previously documented bradycardia; and 2) to use the PM to accurately record the occurrence of cardiac bradyarrhythmias and tachyarrhythmias that may remain undetected during conventional clinical follow-up.

METHODS

Patient recruitment and testing. The study was approved by the Ethical Review Committee of the Cochin School of Medicine. After having given their written, informed consent to participate, the patients were enrolled into the study in eight medical centers, between 1993 and 1996. The Appendix lists the institutions and investigators participating in this study. Molecular genetic testing was performed as previously described (23). The diagnosis of MD was confirmed by the finding, on deoxyribonucleic acid extracted

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Abbreviations and Acronyms

AV = atrioventricular
ECG = electrocardiogram/electrocardiographic
EP = electrophysiologic
MD = myotonic dystrophy
PM = pacemaker
SA = sino-atrial

from peripheral blood samples, of an expansion of the cytosine-thymine-guanine triplet over 50.

Electrophysiologic testing was performed, as previously described (24), in the presence of symptomatic or asymptomatic AV conduction abnormalities (first-degree or higher AV block and/or widening of the QRS complex >100 ms), palpitations or documented arrhythmias, or near syncope or syncope, or preoperatively in preparation for major surgery under general anesthesia.

The main study inclusion criteria consisted of an HV interval ≥70 ms, even in the absence of related symptoms. Patients with documented bradycardia requiring cardiac pacing could also be included, with the sole objective of recording spontaneous tachyarrhythmias.

Before implantation of a diagnostic dual-chamber PM (Chorus RM 7034, Ela medical, Le Plessis Robinson, France), a 12-lead rest electrocardiogram (ECG), 24-h ambulatory ECG, signal-averaged ECG, transthoracic echocardiogram, and right and left ventricular radionuclide angiograms were obtained.

Algorithm specifications. A specific diagnostic algorithm was downloaded to the random-access memory of the PM, allowing the diagnosis of bradycardias and tachycardias at the ventricular level during the VDI mode (ventricular pacing and sensing plus atrial sensing). Two types of bradycardic events—"pauses" and "bradycardias"—were defined (Fig. 1). The diagnosis of "tachycardia," based on ventricular rate analysis, was made when the following criteria were present: 1) a beat-to-beat heart rate acceleration ≥25% at the initiation of the tachycardia; 2) a heart rate >154 beats/min; and 3) for more than five consecutive cycles. With each event, the time and date were memorized, along with marker chains, all retrievable by PM interrogation. Each marker chain included atrial and ventricular events preceding and following the diagnostic cycle, allowing clarification of the nature of the event (Fig. 2).

Patient follow-up. Follow-up visits were scheduled every six months, at which time the patients' clinical status and surface ECG were recorded, and a complete PM interrogation was performed, including retrieval of the diagnostic algorithm data. Important clinical events were recorded by interviewing the patient, the family, or the patient's primary physician. In case of death, if possible, the PM was interrogated to determine whether the death was arrhythmic.

Statistical analyses. Data are reported as the mean value ± SD. The rates of AV block, sino-atrial (SA) block, and atrial and ventricular tachyarrhythmias were analyzed for the entire follow-up period by life-table analysis. Kaplan-Meier survival curves were constructed; the patients who died or were no longer being followed up were censored. The prognostic values of factors measured at baseline, that could be related to the occurrence of AV block, SA block, and tachyarrhythmias, were tested by the log-rank test. Cox proportional hazards models were used to study the effect of several factors simultaneously and to adjust for the potential confounding effect of age. All computations were performed with the SAS package (SAS User's Guide Statistics 1990, version 6, SAS Institute Inc., Cary, North Carolina).

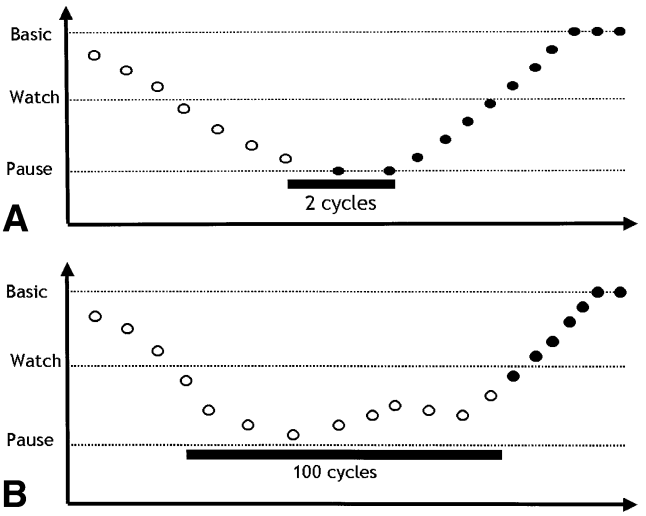

Figure 1. Diagnostic algorithm for bradycardic events. In addition to a backup rate (basic), a watch rate (50 beats/min) and a pause rate (30 beats/min) are defined. The spontaneous ventricular rate (Vs) may fall below the backup rate to the pause rate, at which point ventricular pacing (Vp) is initiated. **(A)** A "pause" is confirmed after two consecutive ventricular cycles paced at the pause rate of 30 beats/min, triggering the memorization of a marker chain. **(B)** A marker chain of "bradycardia" is stored after 100 consecutive ventricular cycles between the watch and pause rates. Thereafter, rescue ventricular pacing begins, gradually rising to the backup rate. **Open circle** = Vs; **Closed circle** = Vp. Vs = ventricular sensed event; Vp = ventricular paced event.

RESULTS

Study population. The study population consisted of 49 patients (24 men and 25 women; 45.5 ± 8.9 years old). Their main baseline clinical characteristics are summarized in Table 1. Forty-five patients had no history of documented bradycardia before study entry. In this group, 11 complained of palpitations, 16 experienced syncope or fainting episodes before EP testing, and 25 had no cardiac symptoms and underwent EP testing because of conduction disturbances on the surface ECG. Only two patients had a normal ECG and underwent EP testing for investigation of syncope in one case and for palpitations and near syncope in the other.

Four patients had documented bradycardia before study inclusion: asymptomatic infrahisian 2:1 AV block (n = 1), infrahisian complete AV block with syncope (n = 1),

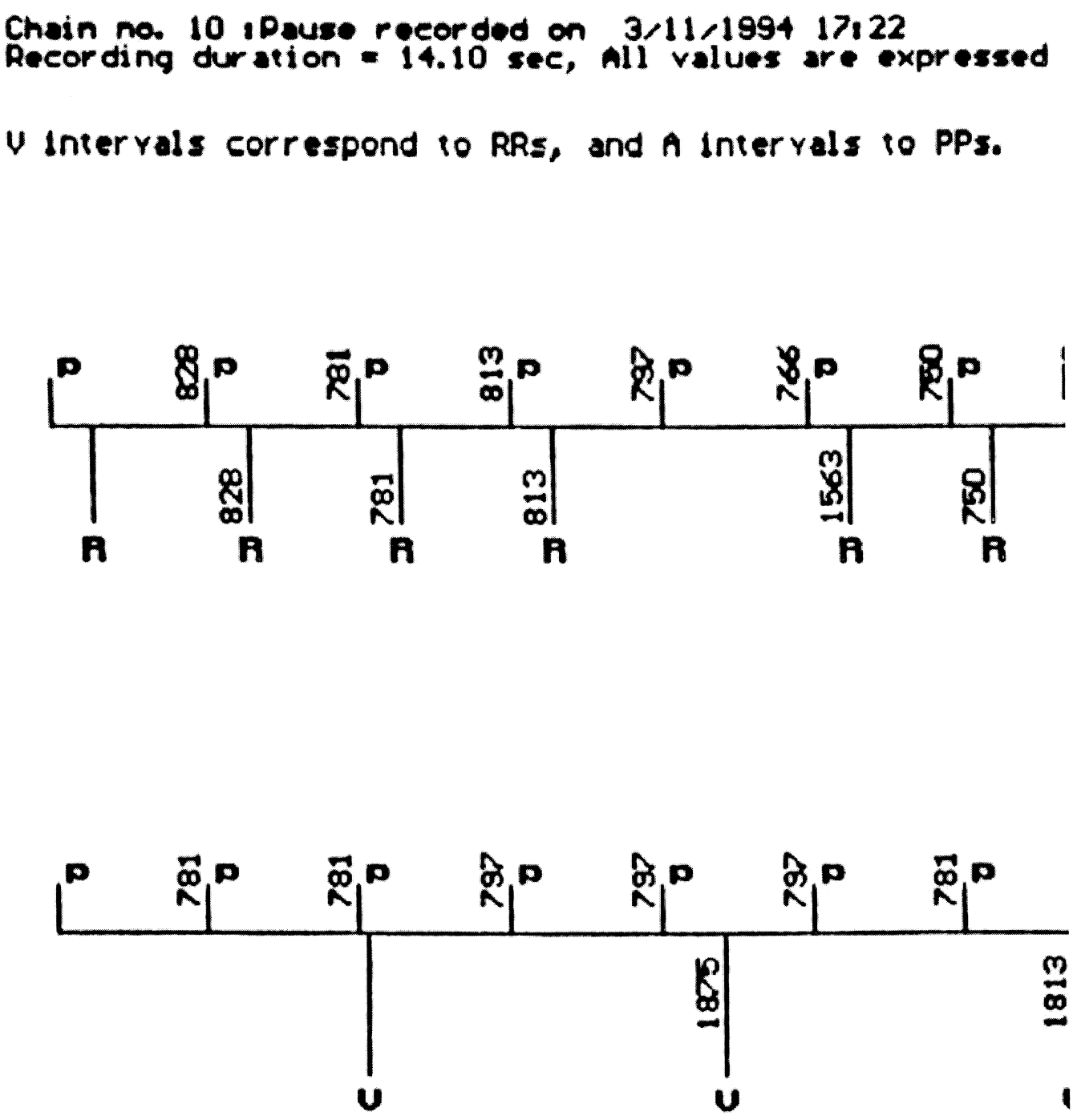

Figure 2. Marker chain of paroxysmal complete atrioventricular block. The intervals displayed correspond to RRs or PPs intervals. P = spontaneous P-wave; R = spontaneous R-wave; V = paced ventricle.

asymptomatic paroxysmal third-degree AV block on the 24-h ambulatory ECG (n = 1), and complete absence of atrial activity, without ventricular escape, following electrical cardioversion of atrial flutter (n = 1).

Long-term follow-up. Over a mean observation period of 53.5 ± 27.2 months (median 57.5 months, maximum 101.4 months), 10 patients died and 4 patients left the study on their physician's recommendation (n = 2), because of PM memory failure (n = 1), or because of study protocol violation (n = 1). The circumstances of the 10 deaths, including 4 sudden deaths, were clarified in all but 2 cases (Table 2). In two patients who died suddenly, PM interrogation performed shortly after death excluded an arrhythmic death, because no arrhythmia was stored by the diagnostic algorithm. Their heart rate trend only showed a moderate acceleration of sinus rhythm a few minutes before death.

During 425 follow-up visits (range 1 to 18 follow-up visits per patient), 21 patients (43%) reported symptoms

Table 1. Baseline Characteristics of Patient Population

	Mean ± SD	Range
Age (yrs)	45.5 ± 8.9	19–67
CTG repeat sequences (n)	921 ± 441	185–1,750
Vital capacity (ml)	2447 ± 813	980–4,488
Radionuclide LVEF (%)	59 ± 10.6	38–79
Radionuclide RVEF (%)	35.9 ± 9.7	9–51
Left atrial diameter (mm)	33.2 ± 6.2	20–48
PACs on 24-h ambulatory ECG (n)	426 ± 994	0–4,413
PVCs on 24-h ambulatory ECG (n)	452 ± 965	0–5,410
PR interval (ms)	223 ± 36	160–320
QRS duration (ms)	127 ± 30	60–200
SA conduction time (ms)	150 ± 99	20–369
Corrected sinus node recovery time (ms)	427 ± 266	50–1,200
AH interval (ms)	110 ± 37	45–200
H duration (ms)	23 ± 8	10–45
HV interval (ms)	79 ± 11	70–125
Atrial refractory period (ms)	218 ± 35	160–320
Ventricular refractory period (ms)	249 ± 30	190–320

	# of Patients
Arrhythmic history	
Atrial fibrillation/flutter	3/3
Monomorphic PVCs (> 200 per 24 h)	2
Torsades de pointes	1
Sustained monomorphic VT	1
Surface ECG	
First-degree AV block	27
2:1 AV block	1
Third-degree AV/SA block	1/1
LAFB	13
Incomplete/complete RBBB	1/5
Incomplete/complete LBBB	5/8
LAFB and RBBB	2
Nonspecific IVCD	5

Programmed stimulation	Nonsustained	Sustained
Atrial (n = 39)		
Atrial fibrillation	1	6
Atrial flutter	0	2
Atrial tachycardia	1	1
Ventricular (n = 43)		
Monomorphic VT	0	2
Polymorphic VT	6	0
Ventricular fibrillation	1	1

AV = atrioventricular; CTG = cytosine-thymine-guanine; ECG = electrocardiogram; IVCD = intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB and RBBB = left and right bundle branch block, respectively; LVEF and RVEF = left ventricular and right ventricular ejection fraction, respectively; PAC = premature atrial complex; PVC = premature ventricular complex; SA = sino-atrial; VT = ventricular tachycardia.

consisting of dyspnea (n = 6), palpitations (n = 9), fainting (n = 9), or syncope (n = 1). In 18 patients, no rythmologic explanation was found for symptoms sometimes atypical; in 3 patients, the symptoms coincided with an arrhythmia memorized by the PM: palpitations related to atrial fibrillation (n = 1) or bitachycardia (n = 1) and dyspnea due to 2:1 AV block (n = 1).

Marker chain analysis. In 41 (83.7%) of the 49 patients, marker chains indicative of arrhythmias were retrieved from the PM's memory. A marker chain of "pause" was present in 23 (51.1%) of 45 patients without previously documented bradycardia (Fig. 3) due to high-degree paroxysmal AV block (n = 21) and/or paroxysmal complete SA block (n = 4). The cumulative incidences of pauses at 6, 12, 24, and 48 months were 22.2%, 37.8%, 46.7%, and 48.9%, respectively. Pauses were exclusively nocturnal in 35% of cases of AV block and in all cases of SA block.

Algorithm criteria of "bradycardia" due to marked sinus bradycardia were confirmed in 24 patients (53%), mostly (75.1%) during the night.

In 28 patients (57.1%), "tachycardia" (Fig. 4) was recorded due to atrial arrhythmias with rapid AV conduction in 25 patients (51%) and/or ventricular tachycardia in 13 patients (26.5%). The cumulative incidences of tachycardias at 6, 12, 24 and 48 months were 22.4%, 32.7%, 40.8%, and 51%, respectively. Atrial and ventricular arrhythmias were strictly diurnal in 54.5% and 72.7%, respectively, and strictly nocturnal in only 13.6% and 18.2%, respectively.

Statistical analysis. No statistical association was found between the occurrence of AV or SA block and several variables, including age, gender, severity of muscle disease, rest heart rate, conduction intervals (PR, QRS, and HV, or H duration), corrected sinus node recovery time, SA conduction time, signal-averaged ECG, anti-arrhythmic treatment, or history of syncope or near syncope.

After adjustment for age, the occurrence of atrial arrhythmias was associated with the number of supraventricular extrasystoles recorded on the 24-h ambulatory ECG, with a relative risk of 4.2 (95% confidence interval 1.3 to 12.9) beyond 1,000 extrasystoles per 24 h. Atrial arrhythmias were not associated with age, gender, severity of muscular disease, corrected sinus node recovery time, SA conduction time, right atrial refractory period, induction of atrial arrhythmia by programmed stimulation, left atrial diameter, vital capacity, or history of palpitations.

No direct or age-adjusted statistical association was found between the incidence of ventricular arrhythmias and age, gender, muscular weakness, anti-arrhythmic treatment, ventricular extrasystoles on the 24-h ambulatory ECG, right ventricular refractory period, induction of ventricular arrhythmia by programmed stimulation, results of the signal-averaged ECG, left or right ventricular ejection fraction, or history of palpitations, syncope, or near syncope.

The occurrence of death was positively associated with age ($p = 0.005$, $r = 1.1$) and the degree of muscular weakness ($p = 0.01$, $r = 1.76$), and negatively correlated with the pulmonary vital capacity ($p = 0.01$, $r = 0.93$) and anti-arrhythmic drug treatment with amiodarone or beta-blockers ($p = 0.03$, $r = 0.18$).

Surface ECG findings. Among the 45 patients without documented bradycardia before study entry, surface ECG recordings during follow-up visits revealed the development of high-degree AV block in 5 patients at 25, 51, 56, 64, and 88 months of follow-up (Fig. 5). Of these five patients, two patients had no history of syncope or fainting; two patients had fainting episodes; and one patient reported syncope before implantation of the PM. In three of five cases, paroxysmal third-degree AV block was detected by the PM

Table 2. Fatal Outcomes in 10 Patients

Pt. No.	Post-Implant Follow-Up (months)	Sudden Death	Pacemaker Interrogated	Cause of Death
1	10	Yes	Yes	Undetermined; arrhythmia excluded by pacemaker interrogation
2	49	Yes	Yes	Undetermined; arrhythmia excluded by pacemaker interrogation
3	53	Yes	No	Asystole during acute decompensation of chronic respiratory failure and severe ischemic cardiomyopathy
4	23	Yes	No	Unknown
5	57	No	No	Acute decompensation of chronic respiratory failure
6	58	No	No	Chronic respiratory failure
7	82	No	No	Acute decompensation of chronic respiratory failure
8	83	No	No	Embolic cerebral/vascular accident
9	59	No	No	Massive pulmonary embolism
10	56	No	No	Unknown

Autopsy was not performed in any of the patients.

algorithm during the first month after implantation. Two patients had no previous marker chain recording of AV block because, against the study protocol, their device had been reprogrammed 11 to 20 months earlier to the DDD mode, which is a mode that does not allow the identification of bradycardic events.

One patient developed permanent SA block on the surface ECG at 81 months, as predicted by the PM that stored a marker chain of complete SA block 16 months after implantation.

Seven patients had atrial fibrillation on routine ECG recordings, becoming chronic in 5 cases after 7 to 77 months of follow-up. In all cases, an episode of paroxysmal atrial fibrillation with a rapid ventricular rate had been previously diagnosed by the PM.

One patient complained of dizziness 71 months after implantation, related to a sustained bitachycardia (monomorphic ventricular tachycardia and atrial flutter) present both on the surface ECG and in the PM's memory.

DISCUSSION

To our knowledge, this study is the first to use an implantable diagnostic device providing an accurate diagnosis of spontaneous bradycardias and tachyarrhythmias, even when the patient is asymptomatic, associated with antibradycardia support. This diagnostic tool was applied to patients with MD (Steinert's disease) in the largest series published thus far of paced patients with this disorder, which is associated with a high risk of arrhythmias and sudden death.

High incidence of AV block. A high incidence of arrhythmic events was observed. Indeed, 41 (83.7%) of the 49 patients had an arrhythmic event recorded by the PM's diagnostic algorithm during follow-up. High-degree paroxysmal AV block was recorded in 46.7% of patients who had no known bradycardia on study entry. All but one of the bradycardic events were asymptomatic, as they were brief or associated with pauses limited by backup pacing. The PM protected our 49 patients from the consequences of pro-

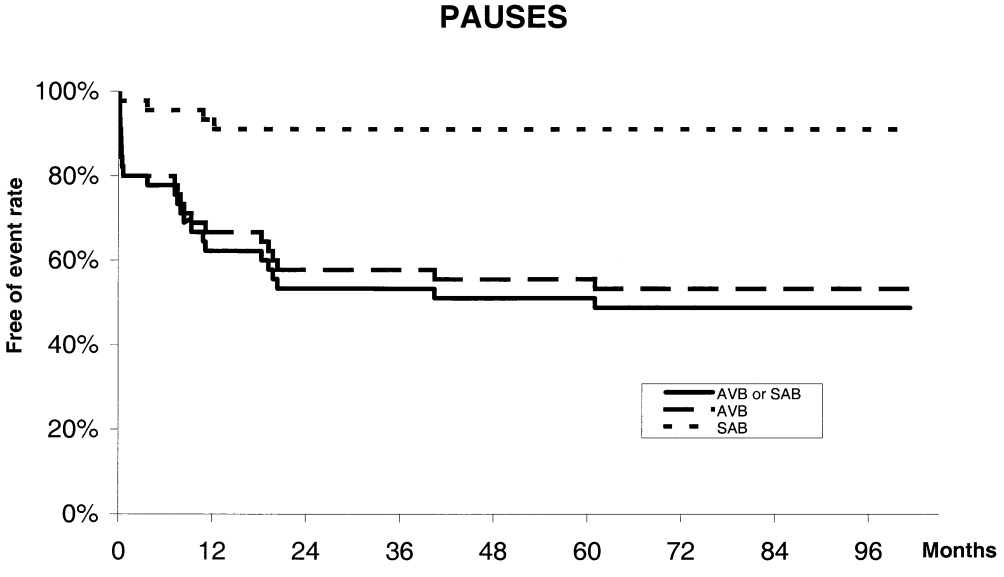

Figure 3. Kaplan-Meier analysis of the incidence of bradyarrhythmias observed during follow-up, diagnosed as "pauses" by the pacemaker algorithm, and corresponding to either complete sino-atrial block (SAB) or high-degree atrioventricular block (AVB).

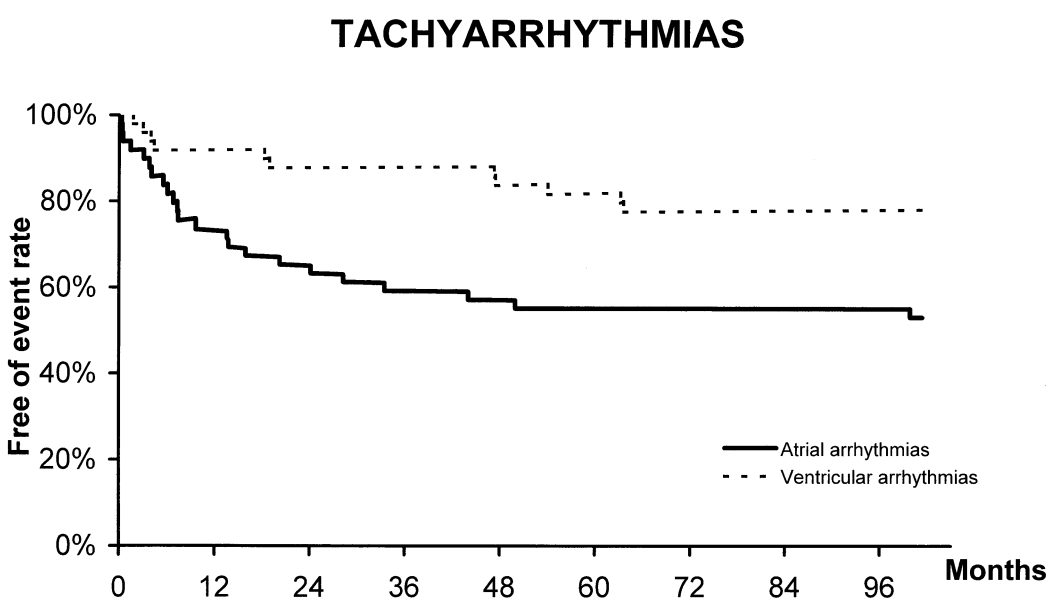

Figure 4. Kaplan-Meier analysis of the incidence of atrial and ventricular tachyarrhythmias observed during the follow-up period.

found bradycardia. Reprogramming the PM to the DDD mode (sequential atrioventricular sensing and pacing) after documentation of paroxysmal AV block prevented subsequent symptomatic bradyarrhythmias. The strictly nocturnal occurrence of some of the episodes of AV block may suggest a functional precipitant—for example, sleep apnea, a disorder often associated with MD (25,26). However, the diurnal occurrence of most episodes of AV block, as well as prolongation of the HV interval at study entry, points to the importance of infrahisian disease. In addition, the observation of fixed 2:1 or third-degree AV block on the surface ECG in five patients, months after the recording of paroxysmal third-degree AV block by the PM, supports the hypothesis of an organic etiology. The data stored by the PM during follow-up confirm the validity of PM implantation. Considering these results, prophylactic permanent pacing should be considered in patients with MD when the HV interval is ≥70 ms, even without related symptoms, and not when the HV interval exceeds 100 ms, as previously recommended (22).

Severe sinus node dysfunction with paroxysmal third-degree SA block, later observed on the surface ECG in one case, was documented in only 9% of patients, exclusively at night. This observation militates in favor of a functional precipitant, perhaps sleep apnea, although one of the four patients had an abnormal sinus node recovery time on study entry.

Atrial and ventricular arrhythmias. The high number of paroxysmal atrial arrhythmias recorded confirms their frequent occurrence in patients with MD (24). Although no statistically significant relationship was established in this study, the high incidence of atrial arrhythmias recorded during follow-up was consistent with the patients' history of atrial arrhythmias and the results of programmed atrial stimulation before PM implantation. A density of atrial extrasystoles >1,000 per 24 h on the 24-h ambulatory ECG was the only variable associated with the subsequent occurrence of atrial arrhythmias. It is noteworthy that the actual incidence of atrial arrhythmias was probably underestimated, because their detection was limited to episodes associated with rapid AV node conduction, as the diagnostic algorithm accounts only for the ventricular rate. The importance of these atrial arrhythmias is illustrated in the development of chronic atrial fibrillation in 5 patients between 0 and 28 months after the first recorded arrhythmic episode.

Of the several variables examined, the number of atrial extrasystoles on the 24-h ambulatory ECG was the sole predictor of atrial arrhythmias. In view of the small size of our study population, we were able to identify relative risks of 2 and 3 with powers of 20% and 75%, respectively, by statistical analysis, except for ventricular arrhythmias, which occurred so infrequently as to preclude a power calculation. Consequently, predictive factors of an only moderate relative risk may have been missed.

Spontaneous ventricular tachycardia was recorded in 13 patients. Although highly symptomatic ventricular arrhythmias have been described in MD (4,6,8,9,11,15–19), no poorly tolerated episode was observed among our patients. Only one patient complained of palpitations during bitachycardia. The predominantly diurnal incidence (72.7%) of these arrhythmias suggests their facilitation by sympathetic activity. Although a negative correlation has been found between age and arrhythmia induction by programmed ventricular stimulation (24), no correlation was found in this study between the results of EP testing and subsequent recordings of ventricular arrhythmias.

All tachyarrhythmias were identified by the PM algorithm before being diagnosed by conventional follow-up methods. Furthermore, when anti-arrhythmic drug treat-

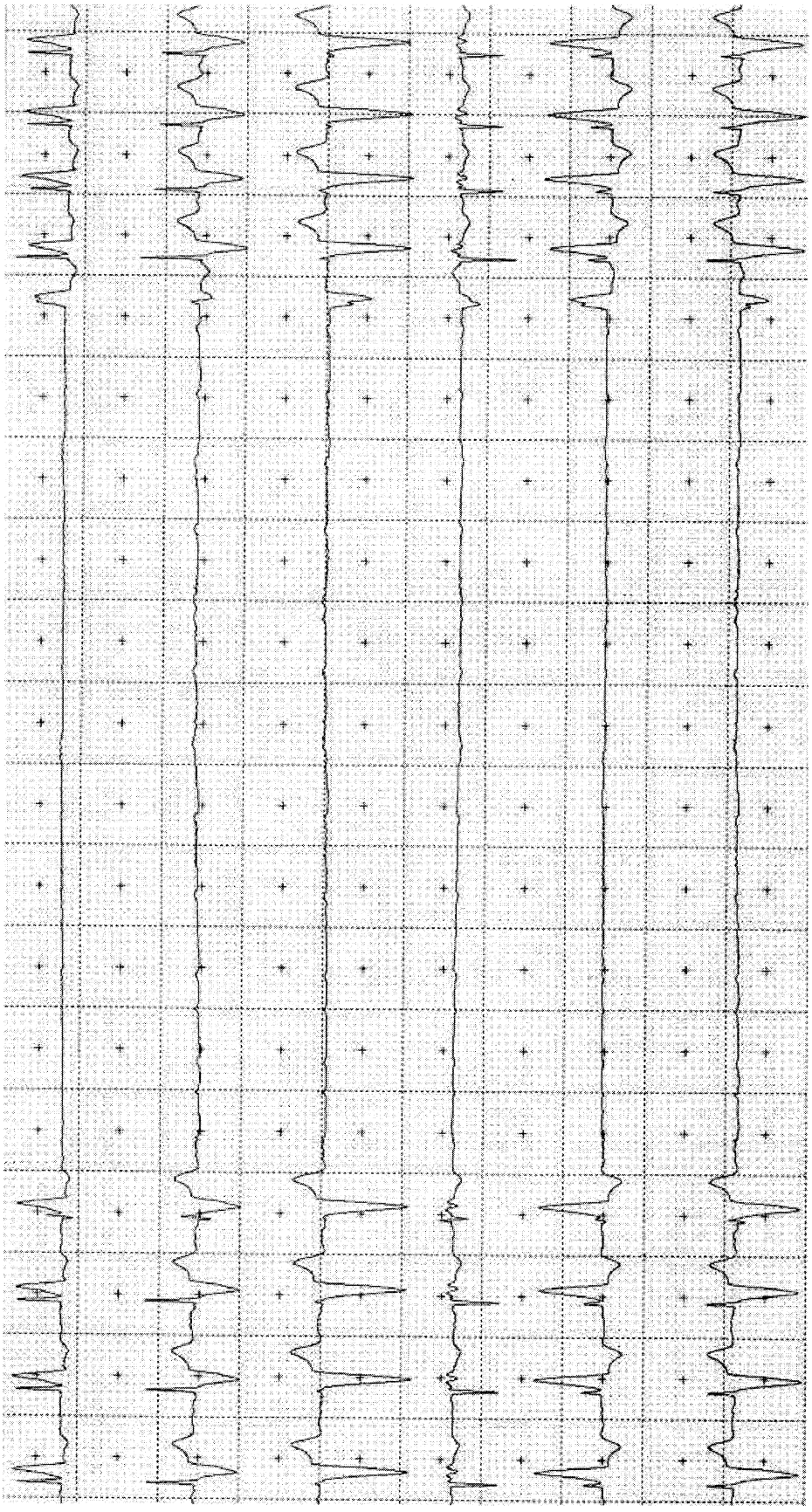

Figure 5. In March 1994, the presence of asymptomatic conduction disturbances on the surface electrocardiogram (ECG) prompted electrophysiologic testing in this 51-year-old woman with myotonic dystrophy. After the finding of a prolonged HV interval (70 ms), a pacemaker was implanted. During the first month after implantation, marker chains of paroxysmal high-degree atrioventricular (AV) block were recorded. In September 2000, 2:1 AV block was observed on the surface ECG. In March 2002, pacemaker dependency was demonstrated during temporary pacemaker inhibition, with underlying complete AV block, as shown on this ECG tracing (paper speed 25 mm/s).

ment was indicated, the PM allowed us to monitor the efficacy of the therapy.

Causes of death during long-term follow-up. No death related to AV block occurred. Four of the 10 deaths, one of which was sudden, were due to acute respiratory insufficiency. This 40% rate is comparable to the 42% death rate from respiratory failure in the Canadian population described by Mathieu et al. (12) in a cohort of unselected patients with a common ancestor. It is consistent with the finding, in our study, of a statistical link between the risk of death and a lower vital capacity or more severe muscular weakness. As in the Canadian study, we observed a higher incidence of sudden death than that expected in a young population. However, this incidence was considerably higher in our population, reaching 8.2% at 53.5 months, as compared with 2.2% at 120 months in the Canadian study. Furthermore, mortality may have been limited by permanent pacing, preventing death from AV block, as well as by the early treatment of asymptomatic paroxysmal tachyarrhythmias, reducing the risk of a spontaneous adverse evolution. Anti-arrhythmic drug treatment with amiodarone or beta-blockers demonstrated a protective effect in our study.

No arrhythmic cause was identified in three of our four patients who died suddenly. This demonstrates that typical sudden death can be nonarrhythmic in MD.

Conclusions. As expected, we found a high incidence of paroxysmal complete AV block in patients with MD with infrahisian conduction abnormalities, even without history of related symptoms. The prophylactic implantation of a pacing system when the HV interval reaches 70 ms should then be recommended to protect patients against the clinical consequences of paroxysmal profound bradycardia. A PM including detailed diagnostic functions also facilitates the diagnosis and management of frequent paroxysmal tachyarrhythmias that may remain undetected during conventional clinical follow-up.

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APPENDIX

Participating medical institutions and investigators. FRANCE: Hopital d'Angers, Angers (J. Victor and F. Dupuis); Hopital Gabriel Montpied, Clermont-Ferrand (D. Lamaison); Hopital Louis Pradel, Lyon (H. Bussillet); Hopital Cochin, Paris (A. Lazarus, J. Varin, H. M. Bécane, P. Laforet, B. Eymard, S. Weber, and D. Duboc); Hopital Pontchaillou, Rennes (P. Mabo and J. C. Daubert); Hopital Charles Nicolle, Rouen (F. Anselme and N. Saoudi); Hopital Trousseau, Tours (D. Babuty); and Hopital Rangueil, Toulouse (M. Salvador-Mazenq).