Long-term follow-up of patients with myotonic dystrophy: an electrocardiogram every year is not necessary

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A high risk of arrhythmias was reported in myotonic dystrophy (MD). The purpose of the study was to evaluate the value of non-invasive and invasive investigations for the arrhythmias detection and when to repeat the investigations. 129 patients, mean age 41 ± 14 years, with MD, were asymptomatic, except 4. Electrocardiogram (ECG), left ventricular ejection fraction determination, Holter monitoring, signal-averaged ECG, electrophysiological study (51) were obtained and repeated each year in patients without conduction abnormalities. Electrocardiogram and Holter monitoring were normal in 72 and 89 patients, respectively. Standard deviation of the mean RR intervals (SDNN) was 100 ms in 30 patients. Late potentials were present in 32 patients, without ventricular tachycardia (VT) correlation. Ejection fraction was normal in all but six patients (60 ± 10.5%). HV interval was prolonged in 0 of 8 patients with normal ECG, 1 of 9 with isolated first degree atrioventricular block, 9 of 16 with hemiblock, and 10 of 15 with bundle branch block. Atrial fibrillation (AF) was induced in 22 patients, non-sustained VT in 6 patients, and sick sinus syndrome noted in 10 patients. The mean time for the ECG change was 5 ± 1 years. After 10 ± 7.5 years, AF occurred in 15 patients; 12 patients died. Multivariate analysis indicated that both AF at ECG and SDNN lower than 100 ms were independent predictors of death. HV increase was noted only in patients with abnormal ECG. The most frequent arrhythmia was AF and was associated with a high risk of death. The repetition of ECG every year is probably not useful.

Keywords
Myotonic dystrophy • Sudden death • Atrial fibrillation

Type-I myotonic dystrophy (MD1) was first described in 1909, by Steinert. Type-1 MD1 is associated with a high risk of atrioventricular (AV) conduction disturbances and also supraventricular and ventricular arrhythmias. Myotonic dystrophy-related arrhythmic risk was frequently reported, but the methods for monitoring the disease and the rate of examination repetition remain unknown.

The purpose of this study was (i) to analyse the contribution of non-invasive techniques and invasive methods in early detection of conduction and rhythm disorders, (ii) to report the relationships between age, the abnormalities of electrocardiogram (ECG), and the data of electrophysiological study (EPS), (iii) to look for the time noted between a normal evaluation and the development of ECG abnormalities, and (iv) to evaluate the nature of arrhythmias during the follow-up.

Population
One hundred and twenty-nine patients with confirmed type-I MD were consecutively recruited; there were 61 men and 68 women aged from 16 to 70 years (mean 41 ± 14 years). Age did not show significant differences between men and women.

Diagnosis of DM1 was attested by clinical examination and confirmed by molecular genetic testing either in the subject (n = 76) or a first degree relative (n = 53). The patients were recruited in the internal medicine department of orphan disease (P.K.) or in the neurology department (L.S.) and sent to the cardiology department for systematic investigations. The enrolment began in 1986 and ended in July 2009. These patients were living in Lorraine, which is in eastern France.
All of them but four were asymptomatic; three patients had dizziness, and one had presented a sustained well-tolerated ventricular tachycardia (VT) at 30 years during exercise.

Methods

The studies were approved by the Ethic Committee of Nancy (France).

The following non-invasive studies were prospectively performed in the department of cardiology after informed consent:

- A 12-lead ECG was recorded.
- Left ventricular ejection fraction (LVEF) was measured at echocardiography.
- A 24 h ECG Holter monitoring was recorded. Major abnormalities at Holter monitoring were defined as the occurrence of a second degree AV block or a sinus bradycardia (<40 bpm) or a sinus pause >3 s or a sustained atrial fibrillation (AF; >1 min) or VT (>30 s). Minor abnormalities were defined as the occurrence of a first degree AV block or a sinus bradycardia (>40 bpm, <50 bpm) or a sinus pause of >2 s and <3 s or the presence of frequent atrial or ventricular premature beats (>1%), non-sustained (NS) episodes of atrial fibrillation (AT) or fibrillation or VT. Heart rate variability (HRV) in the time domain was calculated every 5 min with the Elatec medical arrhythmia analysis program (ELA/SORIN; France); standard deviation of the mean RR intervals (SDNN; ms) during the 24 h period was determined.
- A signal-averaged ECG (SAECG) was recorded at 40 Hz high-pass filtering (Cardionics system, Belgium). As criteria for the presence of late potentials (LP) in patients without bundle branch block (BBB), we used the combination of two of the three parameters, a filtered QRS duration >120 ms, a low-amplitude signal (LAS) duration >40 ms, and a root mean square voltage of the last 40 ms (RMS 40) of QRS <20 μV. When the noise was >0.7 μV, the patient was excluded from the analysis.

Electrophysiological study was performed in the absence of cardioactive drugs in the 51 patients with abnormal ECG or symptoms (n = 4) and in 4 patients for an abnormal SAECG. The protocol was previously reported and included the assessment of sinus node function and AV conduction, a programmed atrial stimulation using one and two extrastimuli and a programmed ventricular stimulation using one and double ventricular extrastimuli, introduced at right ventricular apex and right ventricular outflow tract. A third extrastimulus was added if a sustained VT or fibrillation (VF) was not induced. The shortest coupling interval was 200 ms.

Abnormal electrophysiological findings were categorized according to the criteria previously used by our group as follows: (i) sinus node dysfunction if the corrected sinus node recovery time was longer than 550 ms; (ii) conduction disturbances, if AV Wenkebach block occurred at a pacing rate <90 bpm, or if the HV interval was >60 ms in the case of fine QRS complex or Right BBB (RBBB), >70 ms in the case of Left BBB or if infrahisian second degree AV block occurred at a pacing rate <150 ms; (iii) inducible supraventricular tachyarrhythmia if it was sustained, i.e. lasting at least 3 min, either spontaneously terminating but reproducible or permanent; (iv) inducible ventricular tachyarrhythmia was considered as pathological if it was sustained, i.e. lasting at least 30 s or requiring termination before 30 s due to haemodynamic intolerance. Induced ventricular tachyarrhythmias were categorized as monomorphic VT (<270 bpm) or ventricular flutter (>270 bpm) or VF.

Follow-up

Non-invasive studies were repeated each year in patients with a normal evaluation. They were not repeated when EPS was abnormal and pacemaker implantation was indicated. Pacemaker was indicated in asymptomatic patients when HV interval was prolonged at electrophysiology as previously defined. In patients requiring antiarhythmic drug for supraventricular arrhythmias, pacemaker was also indicated in the case of supraventricular conduction abnormalities or sinus node dysfunction as previously defined. The comparisons were made between initial evaluation and the last date of evaluation.

Follow-up duration ranged from 1 to 23 years, with a mean duration of 10 ± 9 years.

Statistical analysis

Data are expressed as the mean ± 1 standard deviation. For comparison of means, statistical analysis used the Mann–Whitney U test, or the Wilcoxon matched-paired test for paired data. Testing contingency tables was performed using a χ² test, with Yate’s correction for continuity if necessary. Sensitivity, specificity, and relative risk (RR) with 95% confidence interval (95% CI) were calculated for predictive value of binary variables. Probabilities of survival and that of cardiac events were calculated using the Kaplan–Meier method. Cox proportional hazard analysis was used to identify predictors of cardiac events or death in univariate and multivariable analysis. All baseline above-described clinical and laboratory variables were entered in a univariate Cox regression analysis. Variables associated with long-term mortality or cardiac event in univariate analysis were entered into the multivariable models. A P-value of <0.05 was considered significant.

Results

Baseline data

The ECG was normal in 72 patients (55.8%). First degree AV block was present in 17 patients, left anterior hemiblock (LAHB) in 12 patients, complete right or left BBB in 8 patients, first degree AV block and left hemiblock in 6 patients, and first degree AV block and BBB in 5 patients. Permanent AF or flutter was noted in 11 patients and AF was the single abnormality in 9 patients; the rate in AF was spontaneously rapid in all patients but 1; 2 patients had a right BBB associated with AF.

Patients with abnormal ECG were significantly older than the others (46.3 ± 12.2 vs. 36.4 ± 13.9 years; P < 0.001). Left ventricular ejection fraction tended to lower than in remaining patients (57.7 ± 12.9 vs. 62.5 ± 8.4%; P = 0.06). Men more frequently had a complete BBB or atrial flutter or AF than women; 60% of patients with abnormal ECG are men (P < 0.05).

Table 1 reports the predictive values of age, LVEF, and QRS duration for the presence of conductive defect at ECG. Age remained the only independent variable in multivariate analysis to explain abnormal ECG.

Holter monitoring was normal in 69% of the patients with a normal ECG. Minor abnormalities as frequent atrial premature beats (n = 4) or ventricular premature beats (n = 3), sinus bradycardia and nocturnal sinus pauses (n = 7) were noted in 14 patients. Non-sustained episodes of AF or fibrillation were noted in eight patients and NS VTs in three patients; both NS AT and VT occurred in one patient and episodes of second
Long-term follow-up of patients with MD

Table 1  Sensitivity, specificity, RR, and odds ratio of several variables in prediction of conduction defect at in patients with type-1 MD (first degree AVB, left hemiblock, bundle branch block, associated first AV block with left hemiblock, or bundle branch block) (5% confidence interval in parenthesis)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>RR</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>71.9 (54.4–80.5)</td>
<td>54.1 (44.2–64.6)</td>
<td>2.33**</td>
<td>3.01 (1.29–7.05)</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>20.0 (9.3–37.8)</td>
<td>92.3 (84.6–96.4)</td>
<td>2.08**</td>
<td>3.00 (0.96–9.40)</td>
</tr>
<tr>
<td>QRS = 119 ms</td>
<td>48.0 (30.1–66.5)</td>
<td>89.7 (80.7–95.9)</td>
<td>3.83**</td>
<td>8.08 (2.83–23.04)</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; LHB, left hemiblock; BBB, bundle branch block; AF, atrial fibrillation.

**P-value of

**P-value < 0.05.

Table 2  Sensitivity, specificity, RR, and odds ratio of several variables in prediction of infranhisian block in type-1 MD patients (5% confidence interval in parenthesis)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>RR</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal conduction at ECG</td>
<td>100 (81.4–100)</td>
<td>34.5 (20.0–52.8)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Abnormal conduction at ECG (first AV block excepted)</td>
<td>90.5 (69.6–98.4)</td>
<td>58.6 (40.7–74.4)</td>
<td>5.82** (1.77–19.13)</td>
<td>13.46 (2.99–60.52)</td>
</tr>
<tr>
<td>Conduction abnormality at Holter</td>
<td>19.0 (7.3–40.7)</td>
<td>82.8 (64.8–92.7)</td>
<td>1.07 (0.50–2.29)</td>
<td>1.13 (0.28–4.53)</td>
</tr>
<tr>
<td>QRS &gt;119 ms</td>
<td>58.8 (36.0–78.3)</td>
<td>71.4 (49.7–96.3)</td>
<td>1.96 (0.98–3.91)</td>
<td>3.57 (0.96–13.24)</td>
</tr>
<tr>
<td>QRS &gt;130 ms</td>
<td>58.8 (36.0–78.3)</td>
<td>81.0 (59.3–92.7)</td>
<td>2.45** (1.25–4.81)</td>
<td>6.07 (1.50–25.54)</td>
</tr>
<tr>
<td>Late potential</td>
<td>64.7 (41.1–82.7)</td>
<td>61.9 (40.8–79.2)</td>
<td>1.83 (0.89–3.80)</td>
<td>2.98 (0.821–10.8)</td>
</tr>
</tbody>
</table>

NC, not calculable; first degree AV block is defined as a PR interval ≥ 200 ms; conduction abnormality at Holter was defined as the presence of paroximal second AV block or a sinus pause ≥ 2.5 s.

**Indicates a P-value of <0.05.

degree AV block in three patients. Sustained AF was noted in 11 patients, but all of them had AF on ECG.

Heart rate variability was normal or near normal in all patients in whom SDNN can be measured: SDNN varied from 58 to 251 ms (mean 128 ± 43); SDNN was longer than 100 ms in 72 patients and moderately decreased between 50 and 100 ms in 30 patients. No significant relationship was found between SDNN and age or LVEF.

A signal-averaged ECG: the recording has been interpreted in 103 patients. QRS duration was <120 ms in 83 patients and >119 ms in 20 patients (mean 107 ± 23 ms). Left ventricular ejection fraction was similar in both groups (61 ± 9 and 60 ± 12%, respectively). Root mean square voltage of the last 40 ms was >20 μV in 53 patients and lower than 20 μV in 50 patients. Left ventricular ejection fraction was similar among patients with decreased RMS 40 (60 ± 9%) and patients with normal RMS 40 (62 ± 10%). Low-amplitude signal lasted >39 ms in 50 patients and <240 ms in 73 patients. Left ventricular ejection fraction was 61.5 ± 9% in patients with increased LAS and 60 ± 11% (NS) in patients with normal LAS. Late potentials were present in 35 patients (34%).

Echocardiography: Left ventricular ejection fraction varied from 15 to 80% (mean 60.8 ± 10.7%). Heart disease was present in 12 patients; all of them were older than 40 years, from 42 to 68 (mean 50 ± 9 years); sequelae of myocardial infarction were present in 3 patients, valvular aortic stenosis in 1 patient and dilated cardiomyopathy in 5 patients. Only six patients with underlying heart disease had an LVEF lower than 40%.

Electrophysiological abnormalities were noted in 48 of 51 patients. Only three patients had a normal EPS; two patients had a normal ECG, and the remaining one had a left anterior hemiblock.

Infranhisian conduction abnormalities were noted in 20 patients (39%), never in 8 patients with normal ECG, in 1 of 9 (11%) with first degree AV block, in 6 of 10 (60%) with left hemiblock, in 6 of 8 (75%) with BBB, 3 of 6 (50%) with the association first AV block and left hemiblock, and 4 of 7 (57%) with first degree AV block and BBB; 3 patients with only AF and fine QRS complex have a normal infranhisian conduction.

These patients may have multiple abnormalities associated with infranhisian conduction disturbances as supranhisian conduction abnormalities in 16 patients, induction of atrial flutter or fibrillation in 22 patients, induction of monomorphic VT lasting from 15 to 30 s in 6 patients, and/or sinoatrial dysfunction in 10 patients.

Patients with infranhisian AV block had a higher mean QRS duration than the others (137.8 ± 32.2 vs. 112.8 ± 19.8 ms; P < 0.02). However, neither age (50.4 ± 9.0 vs. 49.4 ± 11.2 years; P = 0.8), nor LVEF (56.9 ± 14.0 vs. 54.0 ± 16.5%; P = 0.9), nor SDNN (130 ± 57 vs. 132 ± 50 ms; P = 0.8), nor RMS40 (13.2 ± 9.4 vs. 20.2 ± 14.4 μV; P = 0.06) nor LAS (48.0 ± 28.7 vs. 33.9 ± 14.4 ms; P = 0.13) significantly differed between the patients with and without infranhisian AV block. Abnormal conduction noted at ECG was significantly sensitive to predict infranhisian block, as well as QRS duration higher than 130 ms (Table 2). Multivariate analysis indicated that only abnormal conduction at ECG (first
degree AV block associated with a left hemiblock or a BBB or isolated BBB) was an independent predictor for infrahisian block.

All patients with a normal ECG had a normal HV interval; however, some of them had a sinoatrial dysfunction \((n=2)\), an increase of AH interval \((n=2)\), or the induction of a supraventricular tachycardia \((n=5)\).

### Follow-up \((10 \pm 9 \text{ years})\)

#### General survival and clinical events

Fifteen patients developed supraventricular arrhythmias, AF in eight patients, and permanent atrial flutter \((n=7)\) requiring ablation in five of them. Atrial fibrillation was relatively rapid in six patients and spontaneously slows in two patients.

The 30-year-old man who presented a VT is well. He had no heart disease and a diagnosis of idiopathic outflow tract tachycardia was made by EPS. Beta-blockers were stopped 5 years later without recurrences of VT after a follow-up of 22 years.

Three patients received mexiletine to attempt to improve the myocardy. Two patients with paroxysmal AF were treated by disopyramide.

Pacemaker was implanted in 31 patients, mainly for an increased HV interval \((n=29)\). Only three asymptomatic patients received a pacemaker for a sinus node dysfunction \((n=2)\) or supraventricular conduction abnormalities because they needed an antiarrhythmic drug. In one asymptomatic 43-year-old patient with dilated cardiomyopathy, resynchronization with defibrillator was indicated.

Twelve patients died and two of them were resuscitated: one patient, with myocardial infarction, dizziness, and inducible VT in whom a defibrillator was not implanted, died suddenly. One patient died after administration of class I antiarrhythmic drug; eight patients died from progressive cardiac and neuromuscular respiratory failure; four of them had AF at the time of death.

The rate in AF was rapid in these patients \((>100/\text{min})\); two patients were resuscitated from sudden death. They were in rapid AF with tachycardia-induced dilated cardiomyopathy in one of them. Improvement of LVEF was noted 3 months later. Table 3 reports the data of patients who died.

### Changes of studies during the follow-up of 104 patients

The comparisons were made between initial evaluation and the last date of evaluation.

The ECG did not change in 65% of MDs; in 49 patients with normal ECG, the ECG remained normal in 32 of them; first degree AV block developed in 11 patients, left hemiblock in 3 patients, and complete BBB in 3 patients. Three patients with a BBB developed another localization of conduction disturbance.

Using Kaplan–Meier analysis, the probability of being free of significant ECG change was 100% at 3 years, and 97% \((5\% \text{ CI: } 91–100\%)\) at 5 years in patients with normal baseline ECG. The shorter time of the occurrence of a significant modification was >4 years (Figure 1). However, to be sure to detect a significant change and risk of arrhythmias, a period of 3 years could be proposed.

The Holter monitoring, repeated in 61 patients with initially normal study, remained normal in 44 patients \((72\%)\); sinus pauses were noted in 6 patients and NS VT in one patient. Of 19 patients with initial abnormalities, Holter monitoring became normal in 10 of them.

Mean values of SDNN did not change significantly between the first inclusion \((129 \pm 39 \text{ ms})\) and the last study \((131 \pm 45 \text{ ms})\). Standard deviation of the mean RR intervals, initially normal in 53 patients \((>100 \text{ ms})\), remained unchanged \((141 \pm 42 \text{ ms})\) at the second study; however, SDNN was <100 ms in 5 of these patients. Standard deviation of the mean RR intervals, initially decreased between 50 and 100 ms in 19 patients at the beginning of the study \((\text{mean } 78.6 \pm 11.4 \text{ ms})\) tended to increase at the second study \([95.9 \pm 35.1 \text{ ms}, \text{not significant}, 0.8]\).

At SAECG, QRS duration increased from 99.8 ± 17.6 to 106.8 ± 23.0 ms \((P < 0.0001)\). Root mean square voltage of the last 40 ms decreased from 29.9 ± 14.9 to 18.9 ± 15.1 μV \((P < 0.0001)\) and LAS increased from 29.1 ± 12.0 to 38.6 ± 17.1 ms \((P < 0.001)\). Consequently, the criteria of LP initially present in 10 patients were noted in 24 patients at the second study. One

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**Table 3** Data of patients who died compared with alive patients

<table>
<thead>
<tr>
<th></th>
<th>Deaths (12)</th>
<th>Alive (117)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51 ± 14</td>
<td>40 ± 14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex (male) (%)</td>
<td>8 (67)</td>
<td>53 (45)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55 ± 19</td>
<td>61 ± 9</td>
<td>(0.09)</td>
</tr>
<tr>
<td>Abnormal ECG (%)</td>
<td>8 (67)</td>
<td>50 (43)</td>
<td>NS</td>
</tr>
<tr>
<td>AF or A Fl (%)</td>
<td>5 (42)</td>
<td>10 (8.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SDNN &lt;100 ms (%)</td>
<td>6/8 (75)</td>
<td>24/100 (24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Late potentials (%)</td>
<td>2/7 (28/5)</td>
<td>30/93 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>HV &gt;70 ms (%)</td>
<td>4/9 (44)</td>
<td>16/42 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>4 (33)</td>
<td>28 (24)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results of investigations performed at initial evaluation. Late potentials: combination of two of the three parameters; QRS duration > 120 ms. LAS >40 ms, and RMS 40 < 20 μV. A Fl, atrial flutter.

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**Figure 1** Probability of being free of significant ECG change in DM1 patients according to baseline surface ECG.
patient had NS VT on Holter monitoring, but this patient had no induced VT. No patient with LP had induced VT at EPS. HV interval was prolonged in five of them and was normal in other patients.

Left ventricular ejection fraction did not change significantly (61 ± 11 at first study, 58 ± 11% at second study). However, in 14 patients in whom LP appeared at the second study, LVEF was significantly lower than in others (56.3 ± 7.5 vs. 61.3 ± 6.7%, P < 0.05).

Electrophysiological study was repeated in two patients with initially normal EPS. One man, 30 years old with normal ECG developed a first degree AV block at 43 years; HV interval was similar (60 ms at first study, 65 ms 13 years later). A woman, 32 years old with RBBB and LAHB, QRS duration of 178 ms, had a normal HV interval in 2003 (56 ms). In 2009, QRS duration was 191 ms, PR interval increased from 180 ms to 280 ms, and HV interval was very long (134 ms).

Factors associated with pacemaker indication
Table 4 reported the univariate Cox hazard analysis results of baseline data for the prediction of pacemaker implantation. Age, ECG conduction defect, CTG repeat expansion, LP were significant predictors of pacemaker implantation (Figure 2), while older age than 40 years [hazard ratio (HR) = 3.6, 5% CI: 1.8–8.2, P = 0.0001] and significant ECG conduction defects (HR: 13.0, 5% CI: 4.3–40, P < 0.0001) remained independent predictors of pacemaker implantation using a multivariate model. Probability of being free of pacemaker implantation was 98% (5% CI: 95–100%), 96% (5% CI: 92–100%), and 94% (5% CI: 87–100%) at 1 year, 3 years, and 5 years, respectively, in patients with normal baseline ECG.

In these patients, only two pacemakers were implanted during the first 3 years of follow-up, both because of sinus node dysfunction. In contrast, probability of pacemaker implantation was 26% (5% CI: 12–39%), 37% (5% CI: 22–52%), and 45% (5% CI: 37–63%), respectively, at 1 year, 3 years, and 5 years when baseline ECG was abnormal (Figure 2).

Factors associated with death (12 patients)
Univariate Cox hazard analysis indicated that age, male gender, conduction defects in surface ECG, SDNN were significant predictors of death (Table 4). Age (HR = 1.12, 5% CI: 1.05–1.2, P < 0.0001), male gender (HR = 5.2, 5% CI: 1.1–24.1), and ECG conduction defects (HR = 5.4, 5% CI: 1.4–20.5, P < 0.00001) remained independent predictors of death using multivariate Cox hazard model. All patients who died were older than 40 years.

Moreover, patients who developed AF or AT had a risk of death, respectively, 6.7 higher (5% CI: 2.7–17.1) and 4.2 higher (5% CI: 1.6–11.2) than those who were free of rhythm disturbances.

Summary of the value of investigations
The analysis of the value of each investigation indicated the superiority of the simple surface ECG recording over investigations as Holter monitoring, SAECG, or echocardiography for the determination of the risk of infrahisian conduction disturbance in case of left hemiblock or complete BBB and for the determination of the risk of death when AF or atrial flutter was present. Furthermore, the repetition of the studies every 6 months or each year did not seem useful. In the present study, we noted that in patients with initially normal ECG, at least 3 years are required to detect significant changes of the ECG recording.

Discussion
We find a relatively low incidence of serious arrhythmias in type-1 MD compared with the literature and a slow evolution; the repetition of investigations every 6 months or each year is not useful. A large proportion of ECG are normal (56%). However, after a mean follow-up of 10 years, the electrophysiographic conduction disorders increase in some patients. At least 3 years are necessary to note a significant change of ECG. Only the patients with abnormal ECG have infrahisian conduction abnormalities. The QRS duration could be another factor in favour of HV interval

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**Table 4 Results of univariate Cox proportional hazard analysis of factors contributing to pacemaker indication and death in patients with myotonic dystrophy**

<table>
<thead>
<tr>
<th></th>
<th>Pacemaker</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (5% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.04–1.11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &gt;40 years</td>
<td>3.6 (1.6–8.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CTG &gt;850</td>
<td>2.7 (1.2–6.2)</td>
<td>0.023</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.7 (0.8–3.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>13.0 (4.3–40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HB and/or BBB at ECG</td>
<td>7.4 (3.3–16.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Holter ECG disturbances</td>
<td>2.0 (0.8–5.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>SDNN</td>
<td>1.00 (0.99–1.10)</td>
<td>0.99</td>
</tr>
<tr>
<td>Late potentials</td>
<td>2.5 (1.1–5.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>LVEF &lt;45%</td>
<td>2.25 (0.78–6.6)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

CTG, CTG repeat expansion; abnormal ECG, lengthening of PR interval or AF or left hemiblock, bundle branch block; HB and/or BBB at ECG, left hemiblock and/or bundle branch block at surface ECG; Holter ECG disturbances, minor and major abnormalities; SDNN, standard deviation of the mean RR intervals; LVEF (<100 ms); late potentials, presence of late potentials; LVEF, left ventricular ejection fraction; HR, hazard ratio; 5% CI, 5% confidence interval.
increase. Atrial fibrillation is associated with a significant risk of death in association with the age of the patient. Ventricular arrhythmias are rare in our study group. Several studies reported the type-1 MD-related arrhythmias. The main known arrhythmia in type-1 MD is the early occurrence of infrahisian conduction disturbances3–5 but also of other arrhythmias as sinus node dysfunction6 or supra-ventricular arrhythmias in 10 to 30% of MDs.7–9 The frequency of ventricular arrhythmias varied from 0 to 15%.10,11 Bundle branch re-entry would be frequent, explained by the conduction disturbances,12 but did not occur in our population. The incidence of sudden death in the type-1 MD was estimated between 2 and 11%. The aetiology of sudden deaths in type-1 MD could be related to cardiac arrhythmias as a complete AV block or ventricular tachyarrhythmia,10–13 but also it could be related to acute respiratory failure or pulmonary embolism. In the study of Lazarus et al.,14 10 deaths among 49 patients occurred, including 4 sudden deaths, but 2 were related to an arrhythmia.

Several investigations were proposed to stratify the risk of cardiac death associated with type-1 MD. The severity of cardiac injury could be correlated with age and CTG repeat length,15 but the data were not confirmed by Lazaruset al.14 Advanced age was associated with the mortality but not associated with the severity of conduction abnormalities.

The surface ECG remains the most important investigation to detect infrahisian conduction disturbance. Electrocardiographic abnormalities were observed in 40–85% of MDs. Patients with cardiac events had a significantly prolonged PR interval in the study of Colleran et al.16 We do not confirm these data in patients with a normal QRS width. Groh et al.15 reported that PR interval ≥240 ms, QRS duration ≥120 ms, or second degree AV block predicted the risk of sudden death.

Signal-averaged ECG is used in patients with VT. Some studies suggested that the prolongation of QRS duration and the duration of the LAS on the SAECG were related to delayed activation of the His and Purkinje tissue rather than true LP.17–19 These data were confirmed in the present study: QRS duration prolongation was a significant factor in our study of HV interval increase, but the decrease of RMS 40 was not specific.

Saé et al.20,21 suggested that Holter monitoring should be performed on a regular basis, at intervals not >6 months. Rhythmic and conductive disorders were reported in 45–90% of type-1 MD.21–23 Sinus bradycardia was the most frequent arrhythmia, but could be explained by sleep apnoea.23 Most of our patients had a normal Holter monitoring or minor abnormalities; only patients with abnormal ECG had significant abnormalities. A decline of HRV with age was reported,25 but was not confirmed in our study. An impairment of heart rate turbulence was reported as a predictor of ventricular tachyarrhythmias.26 If we found an initial lower HRV in patients who died, we did not find any correlation with documented ventricular arrhythmias.

The echocardiography is a simple means to detect a cardiomyopathy.27 This heart disease was uncommon in our group except in
old patients who frequently had another heart disease or in patients with AF. Our data differ from those reported by Bhakta et al. who reported signs of left ventricle impairment in most of the patients.

The EPS remains the main investigation for the detection of AV conduction disturbances. These authors reported that a normal ECG did not exclude an abnormal conduction. However, all our patients with a normal ECG had normal infrahisian AV conduction. But, abnormal ECG must lead to an EPS. A lengthening of the HV interval varied from one study to another; HV interval is frequent in type-1 MD. The definition of the lengthening of the HV interval is frequent in type-1 MD. The definition of the lengthening of the HV interval varied from one study to another; HV > 55 ms and then > 70 ms were retained as pathological. More than one-third who had abnormal infrahisian conduction (HV > 70 ms) would develop a paroxysmal complete AV block in the 3 years.

The general prognosis of type-1 MD is debated. The risk of death related to paroxysmal AV block is now easily prevented by a pacemaker implantation. Groh et al. reported 81 deaths among 406 patients (20; 27 of them were sudden (7%). The mortality was also high in study of Lazarus et al. (10/49; 20%). The mortality was only 9% in our study and the incidence of sudden death only 2% for a similar mean age and a longer follow-up. A low risk of sudden death was recently reported by a Canadian study. However, we confirm the negative impact of AF on the prognosis as reported by Groh et al.

The follow-up of patients with type-1 MD is recommended. Several studies underline the interest of the surface ECG recording and recommend repeating the ECG 1–2 times per year. This short delay seems excessive in patients with normal ECG. A change of ECG required at least 5 ± 1years. The appearance of a left hemiblock or a BBB and the occurrence of AF or flutter are the main risk factors of AV conduction abnormality and death. The RAMYD study has been undertaken by an Italian group to evaluate the best strategies in type-1 MD.

In conclusion, the annual follow-up of patients with a MD with a systematic Holter monitoring and SAECG is not useful. The simple follow-up of the ECG every 3 years could be enough. The abnormalities concern principally the older patients and the men. If this ECG remains normal, the risk of event is very low. The most frequent clinical event is the development of a supraventricular arrhythmia. Careful management of AF and atrial flutter should be considered because these arrhythmias are associated with a high risk of heart failure and death. Ventricular arrhythmias are rare and generally related to an associated cardiomyopathy.

Conflict of interest: none declared.

References