Relationships Among Electrophysiological Findings and Clinical Status, Heart Function, and Extent of DNA Mutation in Myotonic Dystrophy

A. Lazarus, MD; J. Varin, MD; Z. Ounnougnene, MD; H. Radvanyi, MD; C. Junien, PharmD, PhD; J. Coste, MD; P. Laforet, MD; B. Eymard, MD; H.M. Becane, MD; S. Weber, MD; D. Duboc, MD

**Background**—Impulse-conduction abnormalities and arrhythmias are common in myotonic dystrophy (MD). This study was performed to determine whether a correlation exists between electrophysiological (EP) testing data and clinical status, heart function, or size of the DNA abnormality (cytosine-thymine-guanine sequence repeat).

**Methods and Results**—Eighty-three MD patients underwent invasive EP studies prompted primarily by the presence of asymptomatic conduction abnormalities. AV conduction disturbances were common and mainly distal (HV interval, 66.2 ± 14 ms). AV conduction observed from the surface ECG was generally concordant with endocardial measurements. However, 11 of 20 patients with normal surface ECGs had abnormal subhisian conduction. Atrial arrhythmias were inducible in 41% of cases and correlated with prolongation of the AH interval (P = 0.02) and a shorter atrial refractory period (P = 0.04). Induction of ventricular arrhythmias (18%) correlated strongly with age (P = 0.0003). After adjustment for age, the extent of DNA mutation correlated with the Walton score (P = 0.0018) but not with conduction abnormalities or induction of arrhythmias.

**Conclusions**—Prolongation of the HV interval is the most common conduction abnormality in MD and can be reliably recognized only by invasive EP testing. It raises the issue of prophylactic pacing to limit the incidence of sudden death in MD. Atrial and ventricular arrhythmias are often inducible, although their predictive value remains to be determined. Young age emerged as the most powerful predictor of inducible ventricular tachyarrhythmias. Conversely, we found no relationship between ECG or EP abnormalities recorded during invasive testing and the DNA mutation size or severity of peripheral muscle involvement. *(Circulation. 1999;99:1041-1046.)*

**Key Words:** myotonic dystrophy ■ arrhythmia ■ heart block

Myotonic dystrophy (MD) is a common autosomal-dominant hereditary disease in adults. Its incidence is estimated to be 1 in 8000 births. It is a multisystemic disorder, with cardiac complications considered by some to be the most common cause of death. Sudden cardiac death is indeed common in patients suffering from MD, although its reported incidence varies widely among published series. The mechanisms of sudden death most often proposed are AV conduction disorders and ventricular tachyarrhythmias. Therefore, invasive electrophysiological (EP) studies are often performed to estimate the individual risk of arrhythmias.

The multisystemic manifestations of the disease are due to a mutation in the length of a cytosine-thymine-guanine (CTG) trinucleotide repeat situated in the 3’ noncoding exon of a gene that encodes a serine-threonine protein kinase (DMPK). This pleiotropic disorder is characterized by a highly variable expression. The MD region includes 3 genes (59, DMPK, and DMAHP). Studies of the DMPK gene have suggested multiple mechanisms at the DNA, RNA, and protein levels. However, the 59 and DMAHP genes may also play an important pathogenic role. The mutation displays intergenerational instability, accounting for anticipation and somatic instability. The size of the enlarged CTG-repeats fragment varies among affected siblings and increases in successive generations, in parallel with increasing severity of the disease. Thus, a loose correlation has been observed between the size of the CTG-repeat expansion and disease severity. For example, the number of CTG triplets has been found to correlate with the evolution of conduction abnormalities recorded on the surface ECG and with abnormalities in metabolism and perfusion of the myocardium.

This study describes the EP abnormalities observed in 83 patients with MD who were referred for invasive testing according to a systematic study protocol. Furthermore, pos-
sible correlations were examined between these findings and surface ECG data, length of CTG triplet expansion, severity of peripheral muscle dysfunction, and general cardiac status.

Methods

Patient Recruitment and Testing

All patients were enrolled in the study between 1991 and 1996 from a multidisciplinary clinic dedicated to neuromuscular disorders. The diagnosis of MD was made on the basis of family history, presence of cataract, and facial and peripheral muscle dysfunction associated with clinically apparent myotonia, confirmed by electromyography when necessary. Expansion of the CTG triplet was systematically looked for as soon as routine genetic diagnostic testing for MD became available. DNA was extracted from peripheral blood samples, and molecular genetic testing was performed as previously reported.

All patients underwent a cardiovascular examination, 12-lead resting ECG, 24-hours ambulatory ECG, and echocardiography. The severity of peripheral muscle dysfunction was scored according to the system of Walton. Left atrial size was measured by 2-dimensional echocardiography from a long-axis, left parasternal view. The 24-hour ambulatory ECG was recorded before invasive EP testing. Right and left ventricular ejection fractions were measured by radionuclide angiography after injection of 20 mCi of technetium-labeled autologous erythrocytes.

EP testing

Intracardiac EP studies were performed in the presence of symptomatic or asymptomatic AV conduction abnormalities (first-degree or higher AV block with or without widening of the QRS complex >100 ms), palpitations or documented arrhythmias, or near syncope or syncne or preoperatively in preparation for major surgery under general anesthesia. EP testing was performed by use of standard techniques with 1 bipolar and 1 quadripolar electrode introduced into the femoral vein and advanced to the right atrium and right ventricle, respectively. Programmed stimulation was performed with ≤3 extrastimuli at a strength equal to twice end-diastolic threshold delivered during spontaneous rhythm and after paced trains at rates of 100 and 150 bpm from the right high atrium and from 2 right ventricular sites (usually apex and pulmonary outflow tract). A tachyarrhythmia was defined as sustained if it lasted >30 seconds or was hemodynamically unstable enough to require immediate termination by DC shock.

Statistical Analyses

Because of the limited sample size in some subgroups and skewed distribution of the results, the nonparametric Wilcoxon pairwise test, Fischer exact test, and Spearman rank correlation test were used to examine the relationships between variables. Logistic regression models tested the independent prognostic value of each variable on induced arrhythmias. A forward stepwise procedure was used to limit inclusion in the final model to the factors with significant explanation of outcome (enter and remove P=0.10). The analyses were performed with the SAS package (SAS Institute Inc). All data are reported as mean±SD. A 2-tailed value of P<0.05 was considered statistically significant.

Results

Of 204 consecutive MD patients seen in the multidisciplinary clinic, 97 were candidates for EP testing. Eleven patients already had pacemakers, and 3 declined EP testing and were excluded from analysis. The remaining 83 patients were studied. These 37 women and 46 men were 40.8±11.8 years old and belonged to 73 kindreds, 66 of which had each a single study participant and 7 of which included between 2 and 4 study participants.

Molecular genetic testing was performed in 66 patients. Seventeen patients were enrolled in the study before the routine availability of this test. The mean number of CTG triplets was 573.7±408.4 (range, 62 to 1666), 760.3±426 (range, 100 to 1670), and 827.3±303.6 (range .500 to 1335) in patients with mild (39.5%), moderate (43%), or severe (17.5%) disease, respectively. A significant correlation (P=0.01, r=0.30) was confirmed between severity of peripheral muscular involvement by Walton score and CTG measurements. In contrast, a significant relationship was not found between CTG and surface or intracardiac AV conduction measurements or between CTG and inducibility of tachyarrhythmias (Table 1).

Indications for EP testing consisted of abnormal AV conduction in 55 patients, high-degree AV block in 3 (1 permanent 2:1 AV block on standard ECG, and 2 paroxysmal AV blocks noted on 24-hour ambulatory ECG), presyncope or syncne in 12, palpitations in 11, and preoperative evaluation in 2. No sustained tachyarrhythmia was recorded on 24-hour ambulatory ECG, although 1 run of nonsustained ventricular tachycardia was observed in 1 patient and 5 patients had histories of atrial tachyarrhythmias (AAs).

First-degree AV block was present in 41 patients, and 1 had fixed 2:1 block. Nonspecific changes were found in 10 patients, complete or incomplete right bundle-branch block in 11, complete or incomplete left bundle-branch block in 14, and isolated fascicular block or block associated with right bundle-branch block in 24.

During invasive testing, 11 patients (13%) had an AH interval >140 ms, 10 (12%) had a His electrogram duration >25 ms, and 34 (41%) had HV intervals prolonged to ≥70 ms (Table 2). An HV interval <55 ms was measured in only 21 patients (25%). Sinus node recovery time was >550 ms in 15 patients and >1000 ms in 4 asymptomatic patients.

Table 2 summarizes the correlations observed between surface and intracardiac AV conduction measurements. AH interval correlated with PR interval (P=0.0001), and His electrogram duration correlated with duration of the QRS complex (P=0.048). HV interval, on the other hand, correlated with both PR interval (P=0.002) and QRS duration (P=0.0001). Twenty patients had normal conduction intervals (PR ≤200 ms and QRS ≤100 ms) on surface ECGs. Eleven (55%) had prolonged HV intervals between 60 and 80 ms. In these 11 patients, a short AH interval balanced the
TABLE 2. Relationships (Spearman Correlation) Between Surface and Intracardiac AV Conduction Measurements

<table>
<thead>
<tr>
<th></th>
<th>PR Interval, (212.7±37.1 [140–340]) ms</th>
<th>QRS Duration, (113.6±25.4 [80–200]) ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH interval</td>
<td>108.4±33.4 (65–240) ms</td>
<td>0.0001 (r=0.73)</td>
</tr>
<tr>
<td>H duration</td>
<td>17.2±4.7 (10–30) ms</td>
<td>NS</td>
</tr>
<tr>
<td>HV interval</td>
<td>66.2±14 (30–125) ms</td>
<td>0.002 (r=0.34)</td>
</tr>
</tbody>
</table>

TABLE 3. Intracardiac Conduction Parameters in Patients With Normal PR and QRS Durations and Prolonged or Normal HV Values

<table>
<thead>
<tr>
<th></th>
<th>Normal HV Interval</th>
<th>Prolonged HV Interval</th>
<th>P, Student’s t Test (Bilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH interval, ms</td>
<td>101.1±16.3</td>
<td>82.7±14.5</td>
<td>0.018</td>
</tr>
<tr>
<td>H duration, ms</td>
<td>15.8±4.4</td>
<td>15.9±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>HV interval, ms</td>
<td>54.1±1.8</td>
<td>64.5±6.5</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

prolongation of HV, explaining the absence of apparent abnormality on surface ECG (Table 3). No significant relationship was found between patient age and surface or intracardiac ECG measurements except for PR (P=0.0001; r=0.43) and AH (P=0.002; r=0.33) intervals. Programmed atrial stimulation was performed in 75 patients. It was withheld in the 5 patients who had histories of documented sustained AA, in 1 young female patient whose procedure was abbreviated because of uncontrollable agitation, and in 2 patients in whom serious ventricular arrhythmias (VAs) were induced before the performance of programmed atrial stimulation.

AA was induced in 31 patients (41%) and was sustained in 77% of patients, consisting of atrial fibrillation in 15 patients, atrial flutter in 12, and atrial tachycardia in 4. Logistic regression analysis showed that AA inducibility correlated positively with AH interval duration (P=0.02) and negatively with the right atrial refractory period (P=0.04). In contrast, no relationship was found between AA inducibility and patient age, number of CTG triplets, Walton score, left atrial size, P-wave duration, or other EP measurements, such as sinus node recovery time (Table 4).

Programmed ventricular stimulation was performed in all but the young, agitated patient. VA was induced in 15 patients (18%), consisting mainly of polymorphous ventricular tachycardia (n=10), usually nonsustained (n=8). Ventricular fibrillation and nonsustained monomorphic ventricular tachycardia were induced in 3 and 2 patients, respectively. Most arrhythmias were induced with short-coupled (≈200 ms) triple extrastimuli. No sustained monomorphic ventricular tachycardia was induced. A strong inverse correlation was found between patient age and VA inducibility (P=0.0003). In contrast, no correlation was found with number of CTG triplets, Walton score, conduction intervals, right ventricular refractory period, or ventricular ejection fractions (Table 5). No patient with inducible VA had spontaneous ventricular ectopy on 24-hour ambulatory ECG.

Discussion

This study is the largest EP observation reported to date in MD and confirms the predominance of subhisian conduction abnormalities reported in earlier smaller series.6,9,34–36 The potentially malignant nature of these abnormalities makes it important to identify noninvasive markers that would assist in their detection. Measurement of the conduction intervals on surface ECG represents a first step because it bears a significant relationship with intracardiac measurements. However, this relationship is neither simple nor reliable. Indeed, the HV interval correlates with both PR interval and QRS complex duration, with comparable correlation coefficients.

Therefore, neither surface ECG measurement itself allows reliable estimation of the quality of subhisian conduction. This may explain the finding of a prolonged HV interval at EP testing in over one half of the patients whose conduction intervals were within normal limits on surface ECGs. Although as suggested by Hawley et al37 the PR interval might be a simple indicator of the course of cardiac involvement in MD, it does not allow us to precisely judge the state of subhisian conduction.

Amplification of the CTG triplets repeat is characteristic of the mutation causing MD. Its relationship with clinical muscle weakness is well known38 and was confirmed in our series. Melacini et al29 observed a relationship between ECG conduction disorders and length of expansion of CTG triplets. Such a linear correlation between the extent of CTG repeat and various measurements of conduction on surface and intracardiac ECG was not found in this study. However, methodological differences are noteworthy: (1) grouping of the patient according to length of CTG expansion in the study of Melacini et al versus continuous variable analysis in our study and (2) dissimilar populations with a less important familial representation in our study, which included 66 patients from 56 kindreds versus 42 patients from 24 kindreds in the Melacini et al analysis. Indeed, as shown by Tokgozoglu et al11 and underscored by Hawley et al,37 the strongest correlation between CTG and conduction time intervals has been found in families with clinical myotonic heart disease. Finally, ours was not a study of the long-term evolution of the disease; rather, it was a search for an instantaneous direct correlation because surface ECG, EP
testing, and measurement of DNA mutation size were performed simultaneously. In individual cases, the length of CTG expansion does not allow prediction of the quality of AV conduction, which can be examined reliably only by intracardiac recordings in these patients.

Similarly, AA or VA inducibility did not correlate with length of the CTG repeat. It should be mentioned, however, that most studies that have attempted to correlate length of CTG expansion with a given systemic anomaly have used the length of mutation measured in lymphocyte DNA.1 It is conceivable that a stronger correlation would be found if the mutation size were measured directly in the tissue affected by the pathological process, although this has not been confirmed in striated muscle. Such cardiac testing would be difficult to justify ethically, particularly at the level of the conduction system. Long-term follow-up of our patients will tell more precisely the value of the measurement in the lymphocyte as a predictor of conduction disturbances, keeping in mind that somatic instability is a life-long phenomenon.

Sinus dysfunction was infrequent (18%), usually mild and asymptomatic. The sometimes marked prolongation of the HV interval noted in these mostly asymptomatic patients raises the issue of impending catastrophic events, including sudden death from asystole. Should a prophylactic pacemaker be recommended? Our observational study does not offer a clear

### Table 4. Relationships Between Response to Programmed Atrial Stimulation and Selected Study Variables

<table>
<thead>
<tr>
<th></th>
<th>Inducible AA, Mean±SD (Range)</th>
<th>No AA, Mean±SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.9±11.6 (15–64)</td>
<td>39.6±11.7 (13–65)</td>
</tr>
<tr>
<td>DNA mutation size, CTG number</td>
<td>604.8±266.1 (62–1335)</td>
<td>781.4±484.4 (100–1670)</td>
</tr>
<tr>
<td>Walton score, n</td>
<td>2.2±2.1 (0–7)</td>
<td>2.4±1.8 (0–8)</td>
</tr>
<tr>
<td>Left atrium size, mm</td>
<td>33.1±5.1 (19–41)</td>
<td>31.5±4.3 (24–43)</td>
</tr>
<tr>
<td>24-h ambulatory ECG</td>
<td>159.9±701.6 (0–3858)</td>
<td>102±203 (0–976)</td>
</tr>
<tr>
<td>Premature atrial complexes, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricular ejection fraction, %</td>
<td>35.4±8 (10–48)</td>
<td>38.7±8.2 (16–53)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>64.3±8.9 (42–78)</td>
<td>64.9±8.9 (43–79)</td>
</tr>
<tr>
<td>P-wave duration, ms</td>
<td>108.1±17.8 (80–160)</td>
<td>103.9±12.2 (80–120)</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>220.8±42.5 (150–340)</td>
<td>207±33 (160–300)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>112.6±22.9 (80–200)</td>
<td>111.9±22.7 (80–180)</td>
</tr>
<tr>
<td>Sinus node recovery time, ms</td>
<td>411±175 (180–1020)</td>
<td>528.4±898.8 (50–6200)</td>
</tr>
<tr>
<td>AH interval, ms</td>
<td>120.3±37.7 (70–240)*</td>
<td>101.9±28.5 (65–200)</td>
</tr>
<tr>
<td>H duration, ms</td>
<td>16.4±4.7 (10–25)</td>
<td>17.4±4.8 (10–30)</td>
</tr>
<tr>
<td>HV interval, ms</td>
<td>64.8±11.5 (50–100)</td>
<td>65.4±15.2 (30–125)</td>
</tr>
<tr>
<td>Right atrium ERP, ms</td>
<td>218.9±29.5 (160–300)†</td>
<td>233.4±32.4 (160–320)</td>
</tr>
</tbody>
</table>

ERP indicates effective refractory period.

*P=0.023; †P=0.047 (Wilcoxon).

### Table 5. Relationships Between Response to Programmed Ventricular Stimulation and Selected Study Variables

<table>
<thead>
<tr>
<th></th>
<th>Inducible VA, Mean±SD (Range)</th>
<th>No VA, Mean±SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.1±10 (15–50)*</td>
<td>43.3±10.8 (13–65)</td>
</tr>
<tr>
<td>DNA mutation size, CTG number</td>
<td>778.2±383.4 (300–1335)</td>
<td>688.6±415.7 (62–1670)</td>
</tr>
<tr>
<td>Walton score, n</td>
<td>2.2±2 (0–7)</td>
<td>2.3±1.9 (0–8)</td>
</tr>
<tr>
<td>Right ventricular ejection fraction, %</td>
<td>35.9±9.2 (10–50)</td>
<td>36.9±8.9 (9–53)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>64.1±9.8 (48–78)</td>
<td>63.3±9.6 (38–79)</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>212.7±33.5 (180–300)</td>
<td>213.9±37.3 (150–340)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>117.3±34.3 (80–200)</td>
<td>113.3±23 (80–180)</td>
</tr>
<tr>
<td>AH interval, ms</td>
<td>104.7±25 (80–180)</td>
<td>109.8±35 (65–240)</td>
</tr>
<tr>
<td>H duration, ms</td>
<td>19.4±3.1 (10–25)</td>
<td>16.9±4.8 (10–30)</td>
</tr>
<tr>
<td>HV interval, ms</td>
<td>70.3±14.7 (45–100)</td>
<td>65.5±13.7 (30–125)</td>
</tr>
<tr>
<td>Right ventricular ERP, ms</td>
<td>231.4±24.8 (190–280)</td>
<td>247.6±31.4 (180–340)</td>
</tr>
</tbody>
</table>

ERP indicates effective refractory period.

*P=0.0003 (Wilcoxon).
answer to that question. Only the long-term outcome of these patients or the implantation of devices containing long-term ECG monitoring functions in memory may help determine the best approach.40

One other important observation in this study was the frequent inducibility of usually sustained AA in patients otherwise free of arrhythmic symptoms. Only 11 patients had reported palpitations, often atypical, remotely suggestive of paroxysmal tachyarrhythmias. Among the predictive factors identified, a shorter atrial refractory period is consistent with our current understanding of atrial arrhythmogenic substrates. On the other hand, P-wave duration, which signals the presence of intra-atrial conduction disturbances, did not emerge as a statistically significant predictor. However, an accurate measurement was often difficult in these patients because of flattening of the P wave and prominent artifacts of muscular origin.

Life-threatening VA occurring spontaneously or sometimes as a proarrhythmic complication of antiarrhythmic therapy has been reported by several authors in patients with MD.2,18,19,22–24,41,42 Some have been able to reproduce them with programmed ventricular stimulation.19,22–24,42 In this study, VA was induced in 18% of the patients who underwent programmed ventricular stimulation. These arrhythmias are generally considered nonspecific, especially when induced in asymptomatic patients. However, in patients with MD, their significance with respect to the prediction of serious spontaneous arrhythmic events remains unclear and will have to be scrutinized during long-term follow-up.

We observed a highly significant correlation between the VA inducibility and age; the younger patients had inducible arrhythmias more often. The explanation for this relationship remains unclear. If programmed ventricular stimulation were to have prognostic value, the sudden death of these patients exposed at a young age to a malignant arrhythmia could account for the low percentage of patients with inducible arrhythmias later in life. To illustrate this hypothesis, 1 of our patients with symptomatic conduction abnormalities and inducible nonsustained ventricular tachycardia died suddenly while wearing a pacemaker. The Holter functions of the device memory storing ventricular intervals revealed the presence of frequent short ventricular cycles at the time of death and in the preceding days, perhaps a forerunner of sudden death from VA.

No other measurement, such as the typically predictive ventricular ejection fraction, was found to correlate with VA inducibility. However, the size of our patient sample may have been insufficient, particularly because few of them presented with advanced left ventricular dysfunction.

In conclusion, our study of patients with MD found no relationship between severity of peripheral muscle involvement or length of CTG triplet repeats and EP abnormalities recorded during invasive testing. A long-term prospective follow-up is the only way to determine the prognostic value of the abnormalities observed, such as conduction disorders and ventricular and atrial arrhythmias, and to identify MD patients at highest risk of serious arrhythmic events.

Acknowledgments
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References


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