Impairment of cardiac autonomic function in patients with Duchenne muscular dystrophy: Relationship to myocardial and respiratory function

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Background Previous studies reported an impairment of nervous autonomic activity in patients with Duchenne muscular dystrophy (DMD). However, the relationship of the autonomic dysfunction to the impairment of cardiac mechanical function and of respiratory failure is not completely understood.

Methods We evaluated cardiac autonomic function by time- and frequency-domain heart rate variability (HRV) analysis on 24-hour Holter recordings in 60 patients with DMD (16.8 ± 4.8 years) and 28 healthy control patients (15.2 ± 4.6 years, P = not significant). The circadian rhythm of R-R interval, low frequency, high frequency, and low-frequency/high-frequency ratio was also assessed. In all patients, left ventricular ejection fraction was measured by 2D echocardiography; respiratory function was assessed by spirometry.

Results All HRV parameters were lower in patients with DMD than in control subjects, with the percentage of differences between adjacent R-R intervals >50 ms (11.6% ± 8.5% vs 27.3% ± 14.1%, P = .00001) and high frequency (23.9 ± 10.3 ms vs 36.1 ± 12.2 ms, P = .0001) showing the strongest differences. A significant circadian rhythm of HRV variables was present in both groups, but it was considerably flattened in patients with DMD. There was no correlation between left ventricular ejection fraction and HRV indexes except for a weak correlation with high frequency (r = 0.30, P = .02) and with low-frequency to high-frequency ratio (r = -0.29, P < .03). Similarly modest correlations were found between forced vital capacity and high frequency (r = 0.4, P = .007) and low-frequency/high-frequency ratio (r = -0.32, P = .026). Multiple regression analysis did not show any independent predictive variable for the autonomic impairment.

Conclusions Our data show a marked impairment of cardiac autonomic function in patients with DMD, which appears to mainly involve the parasympathetic branch and appears to have a multifactorial origin. (Am Heart J 2001;141: 808-12.)

Duchenne muscular dystrophy (DMD), a recessive sex-linked hereditary familial disorder, is characterized by degeneration, atrophy, and weakness of skeletal and cardiac muscle cells.1 The clinical features of the disease appear in early childhood, and patients become wheelchair-bound before 13 years of age, with most of them dying approximately at 20 years of age as the result of respiratory failure, heart failure, or both.2, 5 The frequent presence of sinus tachycardia, sweating, and chills suggests early neuroautonomic dysfunction in these patients.6 In recent years, heart rate variability (HRV) has frequently been used as a measure of cardiac autonomic activity in several diseases, including diabetes mellitus,7, 8 ischemic heart disease,9, 11 and congestive heart failure.12-14 With the use of HRV, some studies have shown an imbalance in autonomic activity in patients with DMD consisting of a decrease in parasympathetic activity and a predominance in sympathetic activity.15, 16 However, the relation of the impairment of cardiac autonomic function with cardiac mechanical dysfunction and respiratory failure in these patients is not completely understood.

Methods Study population

We studied 60 patients with DMD (16.8 ± 4.8 years) who were followed routinely at the Neuromuscular Center of the Unione Italiana Lotta Distrofia Muscolare in Rome, Italy. In 46
patients, the neurologic diagnosis was made by genetic study (deletion of dystrophin gene) and/or by muscular biopsy (absence of dystrophin protein); the remaining 14 patients showed a clear X-linked inheritance and/or a typical clinical evolution (neurologic signs before 3 years of age, high creatine-phosphokinase elevation, typical calf muscle hypertrophy). All patients were wheelchair-bound before 13 years of age. Patients received no medications for 48 hours before the study. An age-matched group of 28 male healthy patients (15.2 ± 4.6 years, P = not significant) was studied as control. Informed consent to participate in the study was obtained from each patient or his parents as necessary.

Holter monitoring
All patients and control subjects underwent 24-hour Holter recording with 3-channel real-time tape recorders (Diagnostic Monitoring, Irvine, Calif), monitoring the bipolar leads CM2, CM5, and modified aVF. Holter tapes were analyzed with the Oxford Medilog Excel 2.0 device (Abingdon, UK). For each patient, the total number of premature ventricular beats, ventricular couplets, and episodes of nonsustained ventricular tachycardia (defined as ≥2 consecutive premature ventricular beats with a rate ≥100 beats/min) were recorded.

HRV analysis
HRV was assessed, both in the time and frequency domain, on 24-hour Holter recordings after full revision of the electrocardiogram and editing of beats when indicated. Time-domain HRV variables included the mean of all R-R intervals for the entire 24-hour recording; the standard deviation of all R-R intervals; the mean of the standard deviations of all R-R intervals for all 5-minute segments; the standard deviation of the mean R-R intervals of all 5-minute segments; the square root of the mean squared differences of successive R-R intervals; and the percent of differences between adjacent R-R intervals >50 ms. In the frequency domain, HRV was assessed in the range of frequencies of 0 to 0.5 Hz by a fast-Fourier transform spectral analysis algorithm, with a spectral resolution of 0.0005 Hz, with the use of the version 7.0 Oxford HRV analysis package. The amplitude of the following frequency-domain HRV variables was obtained: total spectrum, very low frequency (0.0033 to 0.04 Hz), low frequency (0.04 to 0.15 Hz), high frequency (0.15 to 0.40 Hz), and the low-frequency/high-frequency ratio. The amplitude values of low frequency, high frequency, and low-frequency/high-frequency ratio were also obtained for each hour of the day.

Systolic myocardial function
Standard 2D echocardiograms were obtained with Hewlett-Packard Sonos 5500 equipment (Andover, Mass). Left ventricular ejection fraction (LVEF) was calculated from apical chamber views by the Simpson method. All measurements were obtained separately by two experienced cardiologists, and average values were used for analysis.

Respiratory function
Respiratory function was assessed in patients with DMD by means of the standard criteria of the American Thoracic Society. Spirometry was performed with the patients in a seated position with the use of a water-sealed spirometer (Baires II, Biomedin, Padua, Italy) and a reusable nose clip and blue vinyl soft plastic mouthpieces. Forced vital capacity was obtained as a measure of respiratory function by using CECA’s equation for patients ≥18 years of age and Polgar’s equation for younger patients.

Statistics
Continuous variables were compared by either t test or Mann-Whitney U test as indicated. The Fisher exact test was applied for comparison of discrete variables and the Spearman rank test for correlation analyses. To understand the factors involved in the impairment of HRV in patients with DMD, multiple regression analysis was applied to individuate the variables independently predictive of the reduction of high frequency, which appeared to be the most impaired HRV parameter, which also showed some correlation with myocardial and respiratory function. The presence of a circadian rhythm for R-R interval, low frequency, high frequency, and low-frequency/high-frequency ratio was assessed by cosinor analysis. With the use of this method, a cosine curve is fitted to the data by a least-squares method, and the rhythm is defined by 3 parameters: (1) mesor, that is, the rhythm-determined average; (2) amplitude, that is, one-half the difference between the highest and the lowest value in the derived cosine curve; (3) acrophase, that is, the lag from midnight and the time of the highest value of the variable in the curve fitted to the data. The significance of the circadian rhythms was evaluated by the zero-amplitude test. A value of P < .05 was considered statistically significant. Values are expressed as mean ± 1 SD.

Results
General results
The principal findings of patients and control subjects are summarized in Table I (age, LVEF, forced vital capacity, ventricular arrhythmias). LVEF was significantly reduced (46.2% ± 10.2% vs 58.1% ± 5.2%; P = .00001) and left ventricular end-systolic diameter was higher (36.4 ± 8.8 mm vs 30.3 ± 3.4 mm; P = .0001) in patients with DMD compared with control subjects. As expected, forced vital capacity was dramatically impaired in patients with DMD (mean, 42.8% ± 21.8%). Finally, no significant arrhythmias were found in healthy subjects, whereas frequent (≥30 premature ventricular beats/h) and/or repetitive ventricular arrhythmias were detected in 15 patients with DMD (25%, P = .002).

HRV data
HRV results are summarized in Table II. All time-domain HRV parameters were significantly lower in patients with DMD compared with control subjects, with the percentage of differences between adjacent R-R intervals >50 ms (11.6% ± 8.5% vs 27.3% ± 14.1%; P = .00001) showing the strongest difference. Similarly, almost all frequency-domain HRV parameters showed significant differences between the two
groups. In particular, low frequency and high frequency were lower in patients with DMD, whereas no significant difference was found for low-frequency/high-frequency ratio (1.4 ± 0.3 in patients with DMD vs 1.3 ± 0.3 in control subjects).

A significant circadian rhythm was found in both groups for R-R intervals and low frequency, high frequency, and low-frequency/high-frequency ratio (Table III). However, the circadian variation of R-R intervals, high frequency, and low-frequency/high-frequency ratio was considerably flattened in patients with DMD. This appeared to be caused by the absence of the...
increase in R-R interval and high-frequency power during the night (Figures 1 through 3).

**Variables correlated to HRV impairment**

There was no correlation in patients with DMD between age and most HRV variables; however, high frequency decreased (\( r = 0.30; P = .02 \)) and low-frequency/high-frequency ratio increased (\( r = -0.30; P = .02 \)) significantly with age.

Similarly, correlation analysis revealed no relevant relation in patients with DMD between LVEF and HRV indexes; only a weak correlation was found with high frequency (\( r = 0.30; P = .02 \)) and low-frequency/high-frequency ratio (\( r = -0.30; P = .02 \)).

Finally, a similar modest correlation was found in patients with DMD between forced vital capacity and some time-domain (the mean of the standard deviations of all R-R intervals for all 5-minute segments, \( r = 0.3, P = .039 \); the square root of the mean squared differences of successive R-R intervals, \( r = 0.31, P = .052 \); the percent of differences between adjacent R-R intervals >50 ms, \( r = 0.36, P = .013 \) and frequency-domain (high frequency, \( r = 0.4, P = .007 \); low-frequency/high-frequency ratio, \( r = -0.32, P = .026 \)) HRV variables, indicating a progressive impairment of vagal activity with the progressive worsening of respiratory function.

There were no significant differences in HRV parameters between patients with DMD with or without frequent and/or repetitive ventricular arrhythmias (data not shown).

**Multivariate analysis**

Multiple regression analysis in patients with DMD with age, LVEF, and forced vital capacity as independent variables and high frequency as dependent variable showed statistical significance of the model in predicting the impairment of high frequency (\( P < .01 \)). However, no independent value of any of the considered clinical variables was found, thus suggesting that the impairment of HRV had a multifactorial origin in these patients.

**Discussion**

Our data show that patients with DMD have a relevant impairment of cardiac autonomic function, as assessed by HRV analysis, both in time domain and in frequency domain. Moreover, the much stronger
impairment of the high-frequency increase during the night in patients with DMD suggests that the autonomic dysfunction mainly involves parasympathetic activity. This probably results in a prevalence of sympathetic tone during night hours, as suggested by the significantly higher low-frequency/high-frequency ratio values compared with control subjects during these hours (Figure 3).

Our data are in agreement with those obtained in previous studies, which also reported an impairment of HRV parameters in patients with DMD. These studies also showed that the severity of the disease was significantly correlated with the impairment of autonomic function. However, other possible causes of the autonomic alteration were not investigated in previous studies. In particular, patients with DMD have a dilated cardiomyopathy, which could contribute to HRV impairment, in agreement with the results reported in previous studies on other forms of dilated cardiomyopathy.

In this study we confirm that the HRV reduction is correlated to the severity of the disease. Indeed, the autonomic impairment was significantly correlated to the degree of respiratory failure. However, this correlation was only moderate, thus suggesting that other factors contribute to the autonomic alteration. In fact, our results showed a correlation of the autonomic impairment with age and with cardiac mechanical function as assessed by left ventricular function in patients with DMD, but these relations were fairly modest. Interestingly, multiple regression analysis did not show any independent variable for the alteration of high frequency.

Taken together, our data suggest that the strong impairment of cardiac autonomic function in patients with DMD cannot be explained by single abnormalities, but it probably is the result of multiple components, which may include not only respiratory and mechanical cardiac dysfunction but other factors such as structural and functional abnormalities of the sinoatrial node, neurohumoral changes caused by inactivity of patients, and abnormal mechanoreceptor- and metaboreceptor-mediated reflexes originating from the diseased skeletal muscles.

Previous studies in patients with ischemic heart disease or dilated cardiomyopathy have shown that reduced HRV is a strong predictor of cardiac death and arrhythmic events in these patients. This suggests that HRV analysis could also be of prognostic value in DMD cardiomyopathy. This important point should be appropriately investigated in future studies.

References


