# Heart Rate Variability in Myotonic Dystrophy Type 1 Patients

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## Abstract

**Background: Cardiac involvement is common in myotonic dystrophy (MD) patients. Heart rate variability (HRV) is a simple and reliable technique that can be useful for studying the influence of the autonomic nervous system on the heart.**

**Objective: Study heart rate variability in patients with type 1 MD.**

**Methods: We studied HRV during 5-minute recordings in MD patients and in a healthy control group. We analyzed frequency domains (LF and HF) in normalized units (nu) and sympathovagal balance, in the sitting and supine position.**

**Results: Seventeen patients (10 men and 7 women) and seventeen matched healthy individuals (10 men and 7 women) were studied. Sympathetic and parasympathetic modulations of the heart increased in male MD patients from supine to sitting position in 19% of LFnu and the LF/HF ratio rose by 42.3%. In the sitting position, male MD patients exhibited significantly higher sympathovagal balances in 50.9% compared to healthy control individuals. HRV was influenced by both gender and disease. Gender influenced LFnu in the supine position while the LF/HF ratio and HFnu were affected in both positions. Post hoc analyses showed that gender significantly impacts MD patients and healthy individuals in different ways ($p < 0.01$). The low frequency domain in the sitting position (LFnu) was significantly influenced by the disease.**

**Conclusion: The results of this study suggest that the sympathetic drive in middle-aged male MD patients who are not severely impaired and present moderate disease duration seems to be greater than in healthy matched individuals. (Arq Bras Cardiol 2012;98(4):353-361)**

**Keywords: Heart rate; myotonic dystrophy; spectrum analysis; autonomic nervous system.**

## Introduction

Myotonic dystrophy (MD) is the most frequent form of muscular dystrophy in adults[1,2]. Clinical manifestations of MD are myotony, muscle weakness, cardiac abnormalities, cataracts, endocrine and digestive tract disturbances; sleep disorders and baldness[3-5]. Heart problems experienced by patients with MD are well known[1,6]. Most patients are asymptomatic; however, alterations in cardiac physiology are common, as observed in electrocardiograms[6]. Clinical manifestations include conduction delay, rhythm disturbances and myocardial disease. Electrocardiographic disorder indicates abnormalities in intraventricular and atrioventricular conduction, atrial fibrillation and ventricular arrhythmias. Histopathology data show fibrosis in the conduction system and in the sinoatrial node associated to myocyte hypertrophy[7]. Patients with greater skeletal muscle impairment are older and experience heart problems more frequently[8].

The autonomic nervous system plays a crucial role in heart rate (HR) modulation. A decrease in its variability is a predictor of morbidity and mortality[9,10]. Earlier research found that healthy women showed greater vagal dominance over HR, which seems to account for their enhanced cardioprotection compared to men, although these differences decrease with age[11]. The study of heart rate variability (HRV) has therefore been proposed as a simple, inexpensive and non-invasive method that provides information on neurocardial integrity. A number of investigations on the overall function of the autonomic nervous system in patients with MD show that the presence of autonomic neuropathy is highly unlikely[1,12,13]. However, studies on autonomic modulation of HR in patients with MD have obtained conflicting results[14-18]. The present study aimed to evaluate the possible differences in autonomic modulation of HR between the sexes for patients with MD and healthy individuals in different body positions and the influence of interaction between sex and disease on autonomic modulation of HR in different body positions.

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## Methods

### Individuals

Patients diagnosed with MD by the neurologist of a university hospital and matched healthy control groups were invited to take part in the study. Patients with a history of respiratory or heart disease, hypertension, diabetes mellitus, thromboembolic disease, thyroid disease, stroke, depression, tobacco use or alcoholism were excluded. No individuals took anti-hypertensive drugs, anti-arrhythmic drugs or other medication that could affect the autonomic control of HR. None were undergoing physiotherapy treatment or participating in any regular aerobic exercise program. Patients had no other diseases that could influence the autonomic nervous system and presented no conduction disturbance on previous electrocardiogram (ECG) analyses. The control group consisted of healthy volunteers recruited from the academic community via advertisement. Control individuals were matched for gender, height and weight, did not use any drugs and were judged healthy according to history and physical examination. All participants gave written consent and the study was approved by the hospital's Ethics Committee (protocol number 151/07). The study complies with the Principles of Helsinki declaration[19].

### Clinical classification of muscular impairment

All patients were categorized into five degrees of impairment, using the Muscular Impairment Rating Scale (MIRS), in accordance with distal to proximal progression of peripheral muscle involvement characteristic of MD: degree 1 – absence of clinical signs of muscular impairment; degree 2 – minimal signs such as myotony and facial weakness, palpebral ptosis and/or slight or moderate proximal weakness; degree 3 – distal weakness without proximal compromise; degree 4 – slight or moderate proximal weakness; degree 5 – severe proximal weakness, with the patient confined to a wheelchair[20].

### Assessment of heart rate variability

Participants were evaluated in the morning to avoid differences caused by circadian changes. Laboratory temperature was maintained between 22°C and 24°C and relative air humidity between 50 and 60%. Patients were informed about the protocol, instructed to abstain from stimulants or alcoholic beverages during the 24 hours preceding the test and to ingest a light meal at least 2h before assessment.

On the day of the test, patients were questioned and examined as for their overall well being, a good night's sleep (7-8 hours) and compliance with instructions. After a 20-minute rest period, systemic blood pressure (Missouri-Mikato, SP, Brazil) and radial pulse (Nonin Medical, MN, USA) were measured to determine if basal conditions were adequate for the test.

To obtain HR data, volunteers were monitored in the supine position for 15 minutes using a Polar S810i® monitor (Polar Electro Oy®, Finland) after 5 minutes of signal stabilization. The Polar S810i® monitor is a practical and reliable device to monitor beat-by-beat HR for HRV analysis; the equipment captures R-R intervals through 2 adhesive electrodes. Electrodes were placed on the skin, on top of the xiphoid process and on the middle axillary line at the level of the xiphoid process. Data obtained by the Polar monitor were transferred to the computer using an interface with an infrared device for signal emission. This system detects ventricular depolarization, corresponding to the R wave on the ECG, with a sampling rate of 500 Hz and a temporal resolution of 1 millisecond[21], validated by Loimaala et al [22]. The infrared interface was placed at a maximum distance of 8 inches and at a 15° angle to the Polar S810i®[20]. HR signals were processed to calculate HRV values using a specific MatLab® program (Math Works, USA), which calculates HRV values based on the R-R intervals obtained on the device. HRV was evaluated in both time and frequency domains, using the region of greatest stability in tracing R-R intervals, provided it exhibited at least 256 consecutive beats. Frequency domains were analyzed by fast Fourier transform applied in a single window after linear subtraction of tendency in previously selected R-R intervals. Analysis in the frequency domain was carried out using total power, low (LF: 0.04 to 0.15 Hz) and high (HF: 0.15 to 0.4 Hz) frequency bands in normalized units (*nu*) and an LF/HF ratio. The LF band is modulated by both sympathetic and parasympathetic nervous systems and the HF band is related to cardiac vagal control[23].

### Statistical analysis

Participants were characterized using descriptive statistics, obtaining the means and standard deviations of age, body mass index (BMI) and length of time since diagnosis. Normal data distribution was verified by the Shapiro walk test. The paired t- test was applied to compare intra-group HRV data. Ordinary two-way ANOVA was used in MD patients and the control group to determine the influence of disease and gender on heart rate variability. Results were considered statistically significant for $p < 0.05$. The *GraphPad Prism*® 5.0 program was used for analyses.

## Results

Twenty-six patients were invited to take a part in the study. Three were excluded due previous disease history and four declined to participate due to lack of interest. The final sample was composed of 17 patients (10 men and 7 women) and 17 matched healthy individuals (10 men and 7 women). As demonstrated in table 1, no differences were found between anthropometric characteristics between the two groups.

### Clinical characteristics in MD patients

Among individuals with MD, male patients showed longer time since diagnosis than females and were therefore in a more advanced stage of the disease, according to clinical classification of muscular impairment. Almost all male patients exhibited slight to moderate peripheral muscular impairment (minimal signs or distal weakness), while most women were classified as grade 3 (Table 2). None of the participants were wheelchair-bound and all were capable of executing the activities of daily living.

**Table 1 – Anthropometric characteristics of 17 MD patients and 17 healthy individuals included in the study**

| | MD | CG | p | MD | CG | p |
|---|---|---|---|---|---|---|
| | Female (n = 7) | Female (n = 7) | | Male (n = 10) | Male (n = 10) | |
| Age (years) | 42.3 ± 13.8 | 40.14 ± 8.33 | p > 0.05 | 38.2 ± 7.9 | 41.2 ± 2.9 | p > 0.05 |
| BMI (kg/m²) | 25.1 ± 5.6 | 24.40 ± 1.2 | p > 0.05 | 22.7 ± 3.1 | 24.5± 3.3 | p > 0.05 |

*MD - Myotonic dystrophy; CG – Control Group; BMI - Body mass index.*

**Table 2 - Clinical characteristics of 17 patients with MD**

| | Male (n=10) | Female (n=7) | All (n=17) |
|---|---|---|---|
| Length of time since diagnosis, years | 9.5 ± 9.5 | 4.9 ± 3.4 | 7.6 ± 7.8 |
| Degree of muscular impairment (MIRS) | | | |
| Grade I - no muscular impairment | 0 | 2 (28.6%) | 2 (11.8%) |
| Grade II - minimal signs, without distal weakness | 3 (30%) | 3 (42.8%) | 6 (35.3%) |
| Grade III - distal weakness | 2 (20%) | 2 (28.6%) | 4 (23.5%) |
| Grade IV - slight to moderate proximal weakness | 5 (50%) | 0 | 5 (29.4%) |
| Grade V - severe proximal weakness | 0 | 0 | 0 |

*Data expressed as mean ± standard deviation. MIRS - Muscular Impairment Rating Scale[17]. MD - Myotonic dystrophy*

### Heart rate variability: gender differences between MD patients

Significant inter-gender differences were found in MD patients in the sitting position. LF/HF values and LF*nu* were 73% and 25% higher among males respectively, while HF*nu* was 51.2% higher in women (Table 3). The LF/HF ratio was greater in men in the supine and sitting positions. Significant changes also were observed from the supine to the sitting position in male patients, with a 19% decrease in HF*nu*, 19% increase in LF*nu* and 42.3% rise in the LF/HF ratio (Table 3).

### Heart rate variability: gender differences in healthy individuals

As per table 4, the control group showed no differences between gender and during changes in body position from supine to sitting. LF*nu* in the supine position was 22.8% higher for women in relation to men. Body position changes from supine to sitting lowered the HF*nu* by 30.8% among healthy females. The LF/HF ratio rose for men and women during changes in body position by 50% and 132%, respectively.

### Influence of gender and disease on HRV in healthy individuals and MD patients

In the sitting position, male MD patients presented sympathovagal balances significantly high compared to healthy control individuals in 50.9% (Table 5). Influence of gender and disease on HRV in healthy individuals and MD patients is illustrated in Figure 1 and 2 and demonstrated in tables 5 and 6. Considering influences of disease and gender on HRV in MD patients and healthy individuals, we observed significant gender-influence on the LF/HF ratio, HF*nu* in the sitting and supine position and LF*nu* in the supine position. Post hoc analyses show that gender significantly impacts MD patients and healthy individuals in different ways ($p < 0.01$). The low frequency domain in the sitting position, LF*nu,* was significantly influenced by the disease.

## Discussion

This study proposes to assess inter-gender autonomic modulation of HR in patients with MD and healthy individuals in different body positions, as well as the influence of gender and disease and their interaction in both groups. HRV results in MD patients comparing genders suggest a difference in LF*nu*, HF*nu* and LF/HF ratio, with a decrease in parasympathetic modulation and increase in sympathetic modulation for males assessed in the sitting position. Sympathetic and parasympathetic modulations of the heart evaluated by LF*nu*, sympathovagal balance and LF/HF ratio increase for male MD patients with a change in body position. Sympathovagal balances are significantly high in male MD patients compared to healthy controls. HRV was affected by both gender and disease. Gender influenced LF*nu* in the supine position while the LF/HF ratio and HF*nu* was affected in both positions. Disease significantly influenced low frequency domain, LF*nu*.

In contrast to other research[14-18], this study assesses HRV during short time periods in sitting and supine positions, in addition to analyzing the magnitude of gender differences. Methodological procedures were based on the fact that

**Table 3 - Comparison of HRV in MD patients between supine and sitting positions**

| MD patients | Male | Female | Δ Male vs. Female |
|---|---|---|---|
| Total Power | | | |
| Supine | 2008 ± 1119 | 1334 ± 1304 | 674 |
| Sitting | 2098 ± 1127 | 1999 ± 1443 | 99 |
| Δ total power | 90 | 665 | |
| LFnu | | | |
| Supine | 0.620 ± 0.15 | 0.500 ± 0.14 | 0.120 |
| Sitting | 0.890 ± 0.12* | 0.600 ± 0.11‡ | 0.290 |
| Δ LFnu | 0.120 | 0.100 | |
| HFnu | | | |
| Supine | 0.380 ± 0.15 | 0.500 ± 0.14 | -0.120 |
| Sitting | 0.210 ± 0.12 | 0.430 ± 0.11‡ | -0.220 |
| Δ HF,nu | -170 | -70 | |
| LF/HF ratio | | | |
| Supine | 2.10 ± 1.45 | 1.13 ± 0.64 | 0.970 |
| Sitting | 5.52 ± 3.63* | 1.50 ± 0.63‡ | 4.02 |
| Δ LF/HF ratio | 3.42 | 0.37 | |

*Data expressed as mean ± standard error. * p < 0.01 between males in different positions and ‡ p < 0.01 between genders in sitting position. MD - Myotonic dystrophy; LFun - low frequency in normalized units; HFun – High frequency in normalized units; LF/HF - low frequency/ High frequency ratio or sympathovagal balance; Δ - delta or variation.*

**Table 4 – Comparison of HRV in healthy gender between supine and sitting positions**

| Healthy subjects | Male | Female | Δ Male vs. Female |
|---|---|---|---|
| **Total Power** | | | |
| Supine | 1848 ± 401 | 1595 ± 519 | 253 |
| Sitting | 1948 ± 882 | 1365 ± 534 | 583 |
| Δ total power | 100 | -230 | |
| **LFnu** | | | |
| Supine | 0.603 ± 0.141 | 0.491 ± 0.107 | 0.112 |
| Sitting | 0.653 ± 0.205 | 0.620 ± 0.147 | 0.033 |
| Δ LFnu | 53 | 129 | |
| **HFnu** | | | |
| Supine | 0.369 ± 0.131 | 0.496 ± 0.107 | -0.127 |
| Sitting | 0.343 ± 0.205 | 0.379 ± 0.147 | -0.036 |
| ΔHFnu | -26 | -117 | |
| **LF/HF ratio** | | | |
| Supine | 1.87 ± 1.17 | 1.06 ± 0.45 | 0.81 |
| Sitting | 2.81 ± 1.81 | 2.26 ± 2.06 | 0.59 |
| Δ LF/HF ratio | 0.94 | 1.2 | |

*Data expressed as mean ± standard error. LFun - low frequency in normalized units; HFun – High frequency in normalized units; LF/HF - low frequency/ High frequency ratio or sympathovagal balance; Δ - delta or variation.*

**Table 5 - HRV in male MD patients and healthy subjects in different body positions**

| Male | MD patients | Healthy | Δ Male vs. Male |
|---|---|---|---|
| **Total Power** | | | |
| Supine | 2008 ± 1119 | 1848 ± 401 | 160 |
| Sitting | 2098 ± 1127 | 1948 ± 882 | 150 |
| **LFnu** | | | |
| Supine | 0.620 ± 0.15 | 0.603 ± 0.141 | 0.017 |
| Sitting | 0.890 ± 0.12 | 0.653 ± 0.205 | -0.237 |
| **HFnu** | | | |
| Supine | 0.380 ± 0.15 | 0.369 ± 0.131 | 0.011 |
| Sitting | 0.210 ± 0.12 | 0.343 ± 0.205 | 0.133 |
| **LF/HF ratio** | | | |
| Supine | 2.10 ± 1.45 | 1.87 ± 1.17 | 0.23 |
| Sitting | 5.52 ± 3.63 | 2.81 ± 1.81‡ | 2.71 |

*Data expressed as mean ± standard error. ‡ p < 0.01 for significant difference between healthy individuals and MD patients in the sitting position. MD - Myotonic dystrophy; LFun - low frequency in normalized units; HFun – High frequency in normalized units; LF/HF - low frequency/ High frequency ratio or sympathovagal balance; Δ - delta or variation.*

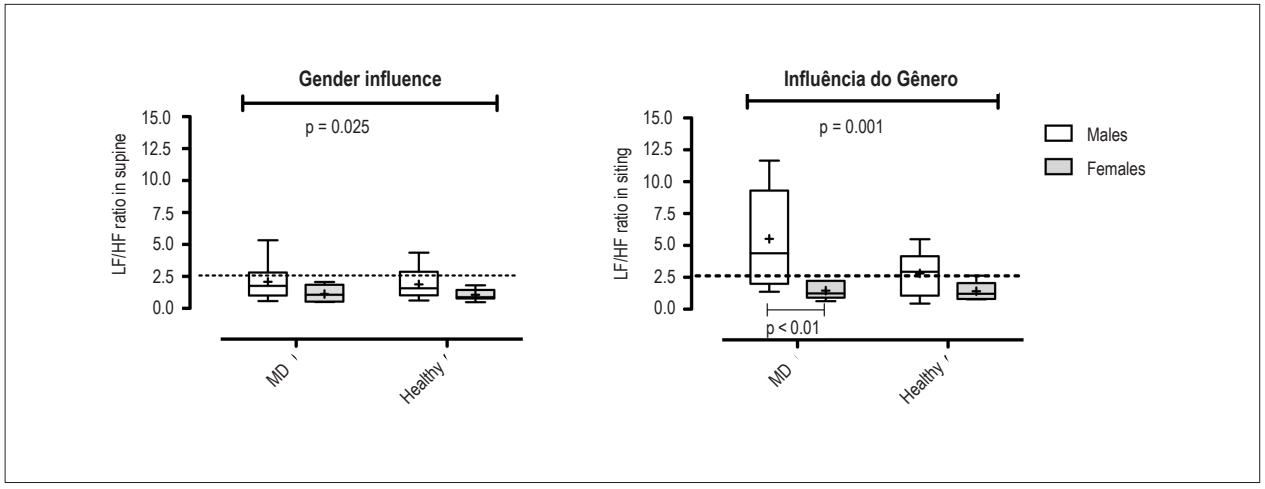


**Figure 1 -** *Gender influence on LF/HF ratio in MD patients and healthy individuals in both positions.*

HRV measurements obtained with 5-minute recordings demonstrated good reproducibility, as well as being fast and easy to analyze[24-26]. Additionally, HRV responses to postural changes are considered a better predictor of heart events[27]. Nevertheless, HRV is relatively simple to assess, although results can be difficult to interpret[28]. Modulation of heart rate is strongly influenced by several factors, including body position, humor, mental stress and environmental conditions[29]. HRV assessment also depends on local conditions such as noise, temperature, spontaneous and quiet breathing[30,31]. As previously stated[32], due to physiological differences between males and females, it is essential to compare inter-gender differences in HRV indices. Finally, HRV must be analyzed considering frequency domains in normalized units. This is the most recommended form of analysis since it accurately represents variations of sympathetic and parasympathetic modulation[23].

To our knowledge, five previous studies on autonomic modulation of Heart Rate in patients with MD have been published. Discrepant results obtained in the past may be due to different analytical methods, autoregressive or fast Fourier, which were not interchangeable[33,34], as well as diverse postural positions during HRV measurement in each study. Inoue et al[14] were the first authors to investigate HRV in MD type 1 patients. They analyzed HRV using the autoregressive method in 10 MD patients (4 male and 6 female) without cardiac conduction disturbance, in addition to 10 age and gender-matched healthy controls at rest in the supine position. The authors found that LFms$^2$ and HFms$^2$ decreased by 642% and 452% respectively, and that the

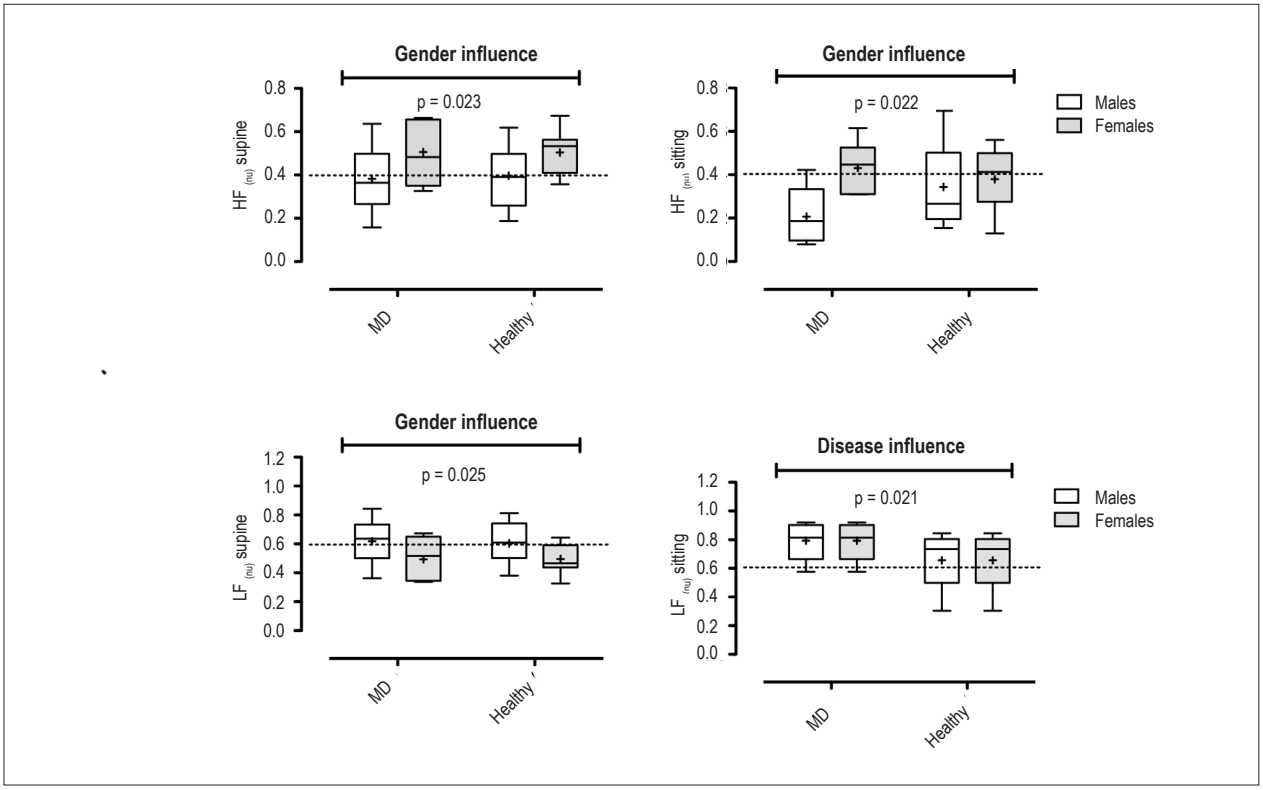


**Figure 2 -** *Gender and disease influence on HFun and LFun in MD patients and healthy individuals in both positions.*

LF/HF ratio increased 158% in MD patients in relation to healthy individuals. The study did not consider the time since diagnosis and muscle impairment. However, the authors state that at the moment of investigation all patients were capable of walking and performing daily activities without assistance, corresponding to MIRS classification 1 to 4. The significant difference between MD patients and healthy individuals has never been confirmed by other studies. Flachenecker et al[15] investigated the response of cardiovascular autonomic function, including HRV, analyzed by the fast Fourier method, in MD type 2 patients. However, they recorded a reduction of 53.7% for LF$ms^2$ in MD type 2 patients compared to healthy volunteers. Recent research has identified significant variations in severity, type, and distribution of electrical myotony in MD type 1 and MD type 2, as well as a correlation between muscle weakness and myotony in the two disorders[35]. Hence, comparison between this study and the results obtained by these authors is not appropriate. In a study similar to ours, Di Leo et al[17], investigated HRV in MD type 1 patients using the autoregressive method with different body positions. In 23 MD patients and a control group, they observed a significant decrease in LF$ms^2$, a marker of sympathetic activity, for MD patients in the supine position. The results of this study can only be partially considered for comparison with ours. The authors did not describe baseline characteristics of the control group, HRV analysis was performed using the autoregressive method and the MD group included men and women with a substantial age variation between 15 years and 51 years. These factors may influence results, in that physiological differences are established by HRV in men and women of different ages.

Other two previous studies applied the fast Fourier method to analyze HRV in patients with MD. In a multicenter study, Hardin et al[16] evaluated 289 MD patients in the supine position during short HRV acquisition periods. They did not include a control group since the study aims were to evaluate ambulatory ECG in a large and diverse population with MD type 1, in which clinical factors were associated to HRV by analyzing low frequency domains LF$ms^2$, HF$ms^2$ and LF/HF ratio. Furthermore, the investigation was conducted at several centers. HRV data showed wide variability, with standard deviation greater than the mean and higher than commonly found in HRV studies. These authors observed a decrease in total power and predominance of sympathetic drive compared to normal HRV values. Finally, Rakocević-Stojanović et al[18] analyzed HRV in twenty patients and fifteen healthy controls. The study does not clearly describe patient and control group characteristics such as age, gender, time since diagnosis and presence of minor or major disability. Total power fell by 64.6% in MD patients in relation to healthy controls, while LF$ms^2$, HF$ms^2$ and LF/HF ratios were not significantly lower in MD patients. The authors concluded that sympathetic dysfunction may occur in patients with MD type 1.

This study builds on this prior investigation in several important ways. Firstly, time since diagnosis is critically important for the development of comorbidities in MD patients and was not considered in any previous studies,

Table 6 - HRV in Female MD patients and healthy subjects in different body positions

| Female | MD patients | Healthy | Δ Female vs. Female |
|---|---|---|---|
| **Total Power** | | | |
| Supine | 1334 ± 1304 | 1595 ± 519 | - 261 |
| Sitting | 1999 ± 1443 | 1365 ± 534 | 634 |
| **LFnu** | | | |
| Supine | 0.500 ± 0.14 | 0.491 ± 0.107 | 0.009 |
| Sitting | 0.600 ± 0.11 | 0.620 ± 0.147 | -0.020 |
| **HFnu** | | | |
| Supine | 0.500 ± 0.14 | 0.496 ± 0.107 | 0.004 |
| Sitting | 0.430 ± 0.11 | 0.379 ± 0.147 | 0.051 |
| **LF/HF ratio** | | | |
| Supine | 1.13 ± 0.64 | 1.06 ± 0.45 | 0.007 |
| Sitting | 1.50 ± 0.63 | 2.26 ± 2.06 | -0.76 |

*MD - Myotonic dystrophy; LFun - low frequency in normalized units; HFun – High frequency in normalized units; LF/HF - low frequency/ High frequency ratio or sympathovagal balance; Δ - delta or variation.*

whereas this study defined time since diagnosis for the patient group. Secondly, it is important to perform HRV analyses separately for men and women, adopting a control group. Thirdly, using normalized units to study frequency domains is highly recommended in order to analyze the influence of sympathetic and parasympathetic autonomic modulation on the heart. All procedures should be adopted considering that there are no established HRV reference values. Finally, since HRV study is a matter of great interest in clinical and physiological research, HRV measurement must be obtained under rigorous conditions to reduce factors that may influence results. According to data provided by our results, a starting point on HRV in myotony dystrophy type 1 can be established.

This study contains several strengths; however, the main limitation lies in the small sample of participants and extrapolation of the results should be done carefully. An important objective of this work, not previously investigated, was the study of cardiac autonomic modulation in MD, considering both male and female patients and influence of postural body change.

The present findings suggest that in middle-aged males, MD patients who are not severely impaired and present a moderate duration of disease, sympathetic drive seems to be greater than in healthy matched individuals.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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