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Original article

# Assessment of cardiac autonomic function in patients with Duchenne muscular dystrophy using short term heart rate variability measures

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ABSTRACT

*Background:* Duchenne muscular dystrophy (DMD) is a hereditary neuromuscular disorder frequently associated with progressive cardiac dysfunction, and is one of the common causes of death in these children. Early diagnostic markers of cardiac involvement might help in timely intervention. In this study we compared the short term HRV measures of DMD children with that of healthy subjects.

*Method:* One hundred and twenty-four genetically confirmed boys with DMD and 50 age matched controls were recruited. Error-free, electrocardiogram was recorded in all subjects at rest in the supine position. HRV parameters were computed in time and frequency domains. Time domain measures included standard deviation of NN interval (SDNN), and root of square mean of successive NN interval (RMSSD). Frequency domain consisted of total, low frequency and high frequency power values. Ratio of low frequency and high frequency power values (LF/HF) was determined using customized software.

*Results:* HRV parameters were significantly altered in DMD children as compared to healthy controls. Following parameters [mean (SD)] were reduced in DMD as compared to controls; RMSSD (in ms) [52.14 (33.2) vs 64.64 (43.2); $p = 0.038$], High frequency component (nu) [38.77 (14.4) vs 48.02 (17.1); $p = 0.001$] suggesting a loss of vagal tone. In contrast, measure of sympathovagal balance LF/HF [1.18 (0.87) vs 0.89 (0.79); $p = 0.020$] was increased in DMD group.

*Conclusion:* In this cross sectional study we have demonstrated alteration in autonomic tone in DMD. Loss of vagal tone and an increase in sympathetic tone were observed in DMD children. Further prospective studies are required to confirm the utility of these measures as predictors of adverse cardiac outcome in DMD.



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## 1. Introduction

Duchenne muscular dystrophy (DMD) is X-lined neurological disorder presenting as a progressive muscular weakness. Though respiratory failure is the leading cause of death in these patients, with advancement in respiratory support technology, cardiac disorders are becoming an important issue.[1] Reduced heart rate variability has been shown to be a predictor of adverse cardiovascular events.[2] In particular, decreased vagal function and increased sympathetic activity is shown to be associated with higher risk of cardiovascular disease.[3] Several authors have reported impairment in electrocardiographic wave morphology and QT dispersion.[4–6] Yanagisawa et al., in their five year follow up study have demonstrated higher incidence of arrhythmia with increase in age.[5] It has been shown that combination therapy of angiotensin converting enzyme inhibitor and beta blockers can reverse signs of congestive cardiac failure in DMD patients.[7] Thus, early diagnostic markers are likely to help in deciding such intervention at an early phase.

Heart rate variability (HRV) is a non invasive tool to assess modulation of autonomic function. Several authors have used HRV to assess cardiac neural regulation.[8–10] In DMD brain dysfunction has been demonstrated by converging evidences from neuropathological and imaging studies[11,12]. Hence, HRV might be a good tool to study the dysfunction in central autonomic network. In this cross sectional study, we compared HRV of DMD children with healthy controls.

## 2. Materials and methods

This study was conducted in National Institute of Mental Health and Neurosciences a tertiary care neurology hospital. Institutional ethics committee approved the study. It was a prospective study from March 2009 to September 2012, where in 124 children with genetically confirmed DMD and 50 age matched normal boys, with no history of any neuromuscular symptoms or cardiac illness, were recruited after obtaining written assent consent. Our cohort were drug naive at the time of evaluation and were recruited for the study after genetic testing which was available within 3–4 weeks after clinical examination. Genetic confirmation was done by mPCR method for 30 exons of the DMD gene. The assessment protocol consisted of Modified Manual muscle testing, joint range of motion, muscular dystrophy functional rating scale (MDFRS), timed functional tests, intelligence Quotient with Stanford Binet Kamat Test, pulmonary function tests, heart rate variability (HRV), quality of life (QOL) with Pediatric quality of life Neuro muscular module, and Generic score. All children with DMD were started on the recommended daily dose of 0.75 mg/kg of prednisolone which was taken by children for about 2–3 weeks only at time of HRV assessment. The test was conducted in the autonomic laboratory under standard conditions as described earlier.[8,9,13]

## 3. Data acquisition

Artifact free, lead II electrocardiogram (ECG) was recorded in all subjects at rest in supine position and signals were conveyed through analog digital converter (Power Lab, 16 channels data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz. The raw ECG was converted into consecutive RR intervals for analysis. The data was analyzed offline using an automatic programme that allows visual checking of the raw ECG and breathing signals. It was ensured that subjects breathed with a respiratory rate of 12–15 breaths/min.[10,14] An error free 5 min ECG segment was taken for analysis and time and frequency domain parameters were calculated according to the Task force report on HRV.[2] Time domain parameters such as Standard deviation of RR intervals (SDNN) in milliseconds, Square root of the mean squared differences of successive intervals (RMSSD) in milliseconds, the number of NN intervals differing by $>$ 50 ms from the preceding interval (NN 50), the percentage of intervals $>$50 ms different from preceding interval (pNN50) and frequency domain parameters such as low frequency spectral power (LF) in $ms^2$, high frequency spectral power (HF) in $ms^2$, also in high frequency normalized units (HF.nu), low frequency normalized units (LF.nu) and low frequency and high frequency ratio (LF/HF) were computed using customized software.[8–10,13–15]

## 4. Statistical analysis

Groups were compared using independent sample *t*-test for continuous variables. HRV components obtained were not normally distributed and hence had to be square root

**Table 1 – HRV parameters in DMD patients versus controls.**

| Parameter | Cases [mean (SD)] | Controls [mean (SD)] | *p* Value |
|---|---|---|---|
| Heart rate (BPM) | 100.32 (15.47) | 85.75 (11.45) | <0.00** |
| SDNN (ms) | 53.40 (26.5) | 60.59 (28.9) | 0.095 |
| RMSSD | 52.14 (33.2) | 64.64 (43.2) | 0.038* |
| NN50 | 97.04 (77.8) | 121.42 (78.9) | 0.048* |
| pNN50 | 21.70 (18.81) | 30.3 (21.2) | 0.008* |
| Total power ($ms^2$) | 3405.46 (3408.6) | 4430.82 (4810.08) | 0.076 |
| Low frequency power ($ms^2$) | 868.17 (918.07) | 837.67 (650.16) | 0.668 |
| LF.nu | 36.80 (16.13) | 32.03 (14.9) | 0.088 |
| High frequency power ($ms^2$) | 1201.35 (1660.6) | 2077.09 (3625.3) | 0.015* |
| HF.nu | 38.77 (14.4) | 48.02 (17.1) | 0.001** |
| LF/HF | 1.18 (0.87) | 0.89 (0.79) | 0.020* |

*denotes $p < 0.05$. ** denotes $p < 0.01$.
Abbreviations: Bpm: beats per minute, HR: heart rate, SDNN: standard deviation of NN interval, RMSSD: root of square mean of successive NN interval, NN50: number of NN intervals with less than 50 ms, pNN50: percentage of number of NN interval with less than 50 ms, LF: low frequency power, LF.nu: low frequency power normalized unit, HF: high frequency power, HF.nu: high frequency power normalized unit, LF/HF: low frequency to high frequency ratio.