SCIENTIFIC LETTER

Is heart rate variability a valid parameter to predict sudden death in patients with Becker's muscular dystrophy?

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Becker's muscular dystrophy (BMD) is an X linked recessive muscular dystrophy caused by dystrophin anomalies in striated muscles, with myocardial involvement^{1,2} and consequent dilated cardiomyopathy, rhythm and conduction disorders, and a high risk of sudden cardiac death.^{3,4} Heart rate variability (HRV) is a measure of the cyclical variations of beat-to-beat (RR) intervals that reflects cardiac autonomic function and sympathovagal balance.^{5,6} A predominance of sympathetic tone in cardiac activity induces tachycardia and reduced beat-to-beat variations, whereas parasympathetic nerve activity reduces heart rate and increases HRV.⁷ HRV is a well-correlated non-invasive parameter used to stratify arrhythmic risk in patients with chronic failure. In general, higher HRV is desirable, and lower HRV has been found to be a significant independent predictor of cardiac mortality and morbidity.^{8–9}

The objective of our study was to evaluate the prognostic value of HRV for sudden death in a population of patients with BMD and dilated cardiomyopathy.

METHODS

The study population consisted in 30 men (mean age 44.2 (SD 12) years) with BMD and a variable stage of myocardial involvement. The control group consisted of 30 healthy men (age 39 (3.2) years). All patients included in study underwent physical examination, blood analyses, 12-lead surface ECG and echocardiographic evaluation. Table 1 shows the data obtained.

The diagnosis of the type of muscular dystrophy in the patients group was confirmed by DNA analysis (polymerase chain reaction) and by immunohistochemical examination of muscular biopsy samples. None of the study patients were taking drugs that directly affect the autonomic system.

All patients underwent three-channel 24 h Holter ambulatory ECG monitoring during eight years of follow up. Holter recordings were analysed by a blinded observer with a Elatec Holter System (ELA Medical).

For each patient we recorded the average 24 h RR interval and the number of extrasystoles, couplets of extrasystoles and episodes of non-sustained ventricular tachycardia (defined as three extrasystoles at a rate of 100 beats/min).

HRV was analysed and mean heart rate was measured after all artefacts, arrhythmias, sinus pauses and atrioventricular conduction disturbances were eliminated. Periods during which arrhythmias or artefacts constituted more than 10% of the recording were not included in the analysis. HRV was evaluated in both the time domain and the frequency domain by using a software provided by ELA Medical (HRV module for Elatec 1.0). Frequency domain HRV was assessed in the range of frequencies from 0 to 0.5 Hz by a fast Fourier transform spectral analysis algorithm, with a spectral resolution of 0.0005 Hz. Low frequency (LF; 0.04–0.15 Hz, ms) and high frequency (HF; 0.15–0.40 Hz, ms) amplitudes were obtained, and the LF:HF ratio, which was considered an index of sympathovagal balance,¹⁰ was calculated. For

Table 1 Electrocardiographic and echocardiographic parameters in 30 men with BMD and in 30 age- and sex-matched male controls

	Patients with BMD	Control group	p Value
Age (years)	44.2 (12)	39 (3.2)	0.05
Ejection fraction (%)	53.0 (9.98)	61.8 (3.08)	0.0001
Fibre shortening (%)	27.23 (5.92)	32.28 (2.09)	0.0001
RR interval (ms)	799.10 (121.86)	864.24 (97.78)	NS
QRS interval (ms)	108.81 (15.98)	96.10 (9.64)	0.003
mHR (beats/min)	85.55 (13.4)	75 (9.3)	0.03
QTc (ms)	436 (32.3)	393 (13.48)	0.0001

Data are mean (SD).

BMD, Becker's muscular dystrophy; mHR, mean heart rate.

long-term time domain variables we obtained the standard deviation of all RR intervals (SDNN).

Among the study population with BMD, patients with non-sustained ventricular tachycardia or with extrasystoles > 30/h constituted a high arrhythmic risk group. Eight patients with BMD died from sudden cardiac death during eight years of follow up.

The Mann–Whitney non-parametric test and Student's *t* test for unpaired data were chosen to compare the 24 h Holter data from the two groups. The same statistical tests were used to compare the Holter data obtained from the eight patients with BMD who died suddenly with those from the remaining BMD population. All data are expressed as mean (SD). Difference were considered to be significant at a *p* < 0.05 for both the Mann–Whitney non-parametric test and Student's *t* test for unpaired data.

RESULTS

Table 2 presents Holter parameters for patients with BMD and controls. The two groups differed significantly in heart rate, SDNN and LF:HF. A significant increase in mean heart rate (*p* < 0.03) and a significant difference in SDNN (*p* < 0.05) and in LF:HF (*p* < 0.03) were observed in patients with BMD compared with the control group.

In the BMD study population, the high arrhythmic risk group had significantly different mean heart rate, SDNN and LF:HF from the remaining patients with BMD (table 3).

Eight patients with BMD who died suddenly during this study had significantly lower SDNN (82 (13.5) ms *v* 122.2 (20) ms, *p* < 0.02) and significantly higher mean heart rate (99.7 (5.4) ms *v* 71.8 (12.6) ms, *p* < 0.002) and LF:HF (4.3 (3.7) *v* 2.2 (1.1), *p* < 0.001) than the patients who survived. Figure 1 shows raw SDNN values for the BMD patients who died.

Abbreviations: BMD, Becker's muscular dystrophy; HF, high frequency; HRV, heart rate variability; LF, low frequency; SDNN, standard deviation of all RR intervals

Table 2 Holter parameters in patients with BMD and in the control group

	Patients with BMD	Control group	p Value
mHR (beats/m)	85.55 (13.4)	75 (9.3)	<0.03
SDNN (ms)	120.5 (47.3)	135 (37)	<0.05
LF:HF (ms)	2.4 (1.6)	1.1 (0.9)	<0.03

Data are mean (SD).

BMD, Becker's muscular dystrophy; HF, high frequency; mHR, mean heart rate; LF, low frequency; SDNN, standard deviation of all RR intervals.

Table 3 Difference in Holter parameters between patients with BMD with and without high arrhythmic risk

	High arrhythmia risk	No high risk	p Value
mHR (beats/m)	93.4 (10.7)	79.5 (12.5)	<0.03
SDNN (ms)	108.9 (15.6)	125.5 (26.7)	<0.05
LF:HF (ms)	2.4 (1.6)	1.1 (0.9)	<0.03

Data are mean (SD).

BMD, Becker's muscular dystrophy; HF, high frequency; mHR, mean heart rate; LF, low frequency; SDNN, standard deviation of all RR intervals.

DISCUSSION

Our study suggests that the autonomic nervous system has an important role in BMD. Our data showed an increment of sympathetic tone in patients with BMD, characterised by a lower HRV in the frequency and time domains and a higher mean heart rate than in the control group. HRV was lower in the high arrhythmic risk group than in the remaining patients with BMD. All patients who died had lower HRV than the minimum HRV recorded in the survivor and none of them had an SDNN > 100 ms and LF:HF < 2. This shows the need for careful monitoring of the high arrhythmic risk group. Our present findings in patients with BMD agree with previous studies of patients with congestive heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy that found SDNN < 100 ms to be a significant predictor of cardiac death, independent of clinical variables.⁹ Further studies are needed to evaluate the role of automatic implantable cardioverter defibrillators in the primary prevention of sudden cardiac death in patients with BMD. In conclusion, HRV is a reliable index to assess sympathovagal balance and can be used to stratify arrhythmic risk in patients with BMD.

Figure 1 Raw standard deviation of all RR intervals (SDNN) values in patients with Becker's muscular dystrophy (BMD) who died compared with those who survived.

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