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## Circadian Rhythm of Heart Rate in Myotonic Dystrophy

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This study investigates the heart rate circadian rhythm (CR) in patients affected by myotonic dystrophy. The purpose was to detect whether or not the heart rate CR is preserved until the last stage of the disease. The study was performed in 53 myotonic dystrophy patients (29 men and 24 women, age: 14–62 yrs) without apparent signs of cardiac involvement, subdivided into four groups according to the severity of their neuromuscular impairment. The control group was constituted by 10 sedentary clinically healthy subjects (5 men and 5 women, age: 23–30 yrs). Each participant underwent a 24-hour Holter electrocardiogram. Heart rate was measured for each minute using the sinusal R-R intervals. The heart rate in beats per minute was averaged for each hour of the day-night span. The Cosinor method was applied to verify and quantify the heart rate CR. A diurnal sinusal tachycardia was detected in myotonic dystrophy patients at the initial stage of their disease. No evident sinusal bradycardia was observed in that the day-night variability of heart rate was seen to decrease during the process of the disease. The heart rate CR was seen to be preserved in all the stages of the disease. Myotonic dystrophy, that evolves without the involvement of the cardiac apparatus, allows the heart rate to maintain its CR even in advanced cases. The preservation of the heart rate CR suggests that the disease may leave intact the pacemakers which control the heart rate rhythmicity such as the sine node as well as the suprachiasmatic nuclei. *J Clin Basic Cardiol 2000; 3: 181–6.* 

Key words: chronobiology, circadian rhythm, electrocardiography, heart rate, myotonic dystrophy

Myotonic dystrophy (Steinert's disease) is a neuromuscular disease that is said to be frequently associated with bradycardia [1]. The low heart rate is said to be due not only to sinusal bradycardia, but also to defects of the atrioventricular conduction [2–9]. The present study is devoted to investigating how sinusal heart rate changes in myotonic dystrophy patients (MDP) who show differing grades of severity in their disease. The study takes into consideration that human sinusal heart rate is said to show a well established circadian rhythm (CR) in its physiological variability along the 24-h scale [10–14].

#### Methods

#### Subjects and protocol

The study was performed in 53 MDP (29 men and 24 women, ranging in age from 14 to 62 years). The diagnosis of Steinert's disease was performed via clinical examination and genetic findings. The control group was constituted by 10 sedentary clinically healthy subjects (CHS, 5 men and 5 women, ranging in age from 23 to 30 years) whose health status was established via clinical examination and laboratory data.

All the participants volunteered with informed consent to the study. The study was performed in conformity to the principles outlined in the Declaration of Helsinki.

Heart rate was investigated by means of a dynamic Holter ECG (see later), which was performed in all the participants on an ordinary day of the week, recommending them to follow a common protocol concerning the sleep-wake alternation, meal timing schedule and diurnal activity. More exactly, all the investigated subjects were requested to wake up between 06:00 and 08:00, to go to sleep between 21:00 and 23:00, to have their breakfast, lunch and dinner, respectively, between 06:30 and 08:30, between 12:00 and 14:00, between 19:30 and 21:00. As further recommendations, they were requested not to do extraordinary physical and mental activity, not to abuse food, alcohol, coffee, caffeinated beverages, mineral water and

dietary salt. Heavy drinkers and smokers were *a priori* excluded from the protocol. Criteria for exclusion were also abnormal anxiety, depression, insomnia (see later for the cardiac criteria of exclusion).

The investigated MDP were classified into 4 severity grades based on the patient's ability to perform daily activities that can be limited by neuromuscular disablement, ie, grade 0 (4 cases): no appreciable neuromuscular deficit but genetics and CTG trinucleotide repeat expansion positive for Steinert's disease; grade 1 (28 cases): disease mildly severe; grade 2 (13 cases): disease moderately severe but patients still able to do light work; grade 3 (8 cases): patients severely incapacitated but neither bedridden nor institutionalized. Regardless of the severity, all the investigated MDP did not have cardiac conduction defects (ie, atrioventricular and/or intraventricular conduction delay), cardiac rhythm disturbances (ie, supraventricular and/or ventricular arrhythmias), cardiac muscle involvement (ie, cardiomyopathy with or without heart failure), otherwise they were excluded from the protocol.

#### **Dynamic ECG monitoring**

The dynamic ECG monitoring was performed by means of a 3-channel Holter recorder, manufactured by Rozinn (Glendale, NY11385, USA). The ECG Holter was applied to each subject at the same hour of the day, ie, at 11:00, and removed twenty-four hours later. The monitored data were transferred to and stored on an IBM-compatible microcomputer for further analysis. The microcomputer was complemented by a computerized analysing system, provided by the manufacturer, for measuring the R-R interval ocurring between two normal consecutive QRS templates (sinusal R-R intervals). The scrutiny of the ECG was performed at every time by the same member of our staff, in order to avoid inter-observer errors. The person dedicated to the interpretation of the 24-h ECG was, however, not involved in data analysis (see ahead), and vice versa, in order to operate in a double blind protocol.

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Heart rate was estimated in beats per minute (bpm), which were averaged for each hour of the day-night span, in order to obtain the hourly-qualified mean values of heart rate, in bpm, for each investigated subject (individual chronogram).

#### Data analysis

In a first biometric approach (conventional biometry), the individual hourly-qualified mean values of heart rate were used to build a matrix, the columns of which represented the hours of the day, while the rows corresponded to the mean heart rate (in bpm) of that given hour. Five matrices were constructed in this way, each one corresponding to an investigated group, ie, CHS, group 0 MDP (G0), group 1 MDP (G1), group 2 MDP (G2), group 3 MDP (G3).

The columns of each matrix were analyzed for their central location and dispersion (standard deviation, SD) in order to obtain the time-qualified mean ( $\pm$  SD) of heart rate, in bpm, in each hour of the day-night period for each group. The 24 mean values, with their SD, constituted the hourlyqualified profile of mean heart rate (in bpm) in each investigated group (mean chronogram).

Importantly, each matrix served also to compute the mean heart rate (in bpm) for the temporal intervals going from 00:00 to 24:00 (daily mean heart rate), from 07:00 to 23:00 (diurnal mean heart rate), from 23:00 to 07:00 (nocturnal mean heart rate). Each one of these mean values was computed with its SD.

In a second approach (rhythmic biometry), the individual hourly-qualified values of heart rate were analysed for their CR by means of the single-cosinor method [15], a procedure of periodic regression analysis which fits a cosine function

$$Y_t = M + A\cos\left(\frac{2\pi}{\tau}\right)t + \phi$$

to the experimental time-qualified series. In the formula, M (mesor, acronym of *m*idline *e*stimating *s*tatistic *of r*hythm) is the mean oscillatory level, A (amplitude) is the extent of the fluctuation from M,  $\tau$  is the fitted period (that is equal to 24-h when dealing with a CR), t is a progressive given time of the entire period,  $\phi$  (acrophase) is the time in which the oscillatory crest reaches its maximum with respect to the local midnight.

The cosinor-derived rhythmometric parameters of each investigated subject were summarized for each group by means of the population-mean cosinor [16]. In so doing it has been possible to obtain, for each investigated group, the mean values with their dispersion, respectively, for M ( $\pm$  standard error, SE), A and  $\phi$  (with their 95 % confidence limits, 95 % CL). The values M and A were expressed in bpm, while the parameter  $\phi$  was expressed in negative sexagesimal degrees (°), which were transformed into hours and minutes, considering that 360° are equal to 24-h, 15° are equal to 1-h and 1° is, hence, equal to 4 min. From the rhythmic mean values, the mean oscillatory curve optimally fitting the hourly-qualified mean values of heart rate for each investigated group (mean cosinorgram) was obtained.

The statistical comparisons among the groups, for each estimate, were performed by means of the Student-Newman-Keuls test, a comparative statistical test adjusted for multiple contrasts.

#### Results

#### **Conventional biometry**

Figure 1 displays the mean chronograms of sinusal heart rate in each investigated group. A clear within-day variability is detectable in each profile. However, the mean level around



**Figure 1.** Group-related chronograms of hourly-qualified mean heart rate ( $\pm$  SD) in 10 clinically healthy subjects and 53 myotonic dystrophy patients, subdivided into four groups (from G0 to G3) according the severity of their neuromuscular inability

which each profile changes its time-qualified pattern appears to be distinct, demonstrating that the values of the hourly-qualified mean heart rate show a group specific daily variability.

Table 1 illustrates the conventional biometric estimates concerning the within-day variability of heart rate in each investigated group. Table 2 displays the statistical contrasts among the groups for the above-cited estimates.

From the estimates and the statistical contrasts, it is possible to derive that the G0 MDP, as compared to the CHS, show a significant increase in both the daily mean and diurnal mean of their sinusal heart rate. Such a significant increase, however, is no longer appreciable in the corresponding contrasts respectively of the G1 MDP, the G2 MDP, and the G3 MDP *versus* the controls.

From the estimates, it is possible to see that the MDP show a progressive decrease in the daily, diurnal and nocturnal mean of their sinusal heart rate, in relation to the severity of the disease. From the statistical contrasts, it is possible to derive that both the G2 MDP and G3 MDP, as compared to the G0 MDP, show a significant decrease in both the daily mean and diurnal mean of their sinusal heart rate. Such a significant decrease, however, is not detectable in the corresponding contrasts respectively of the G1 MDP *versus* the G0 MDP, of the G2 MDP and the G3 MDP *versus* the G1 MDP, of the G3 MDP *versus* the G2 MDP.

From the estimates and the statistical contrasts, it is possible to see that the G0 MDP, the G1 MDP and the G3 MDP, as compared to the CHS, show a significantly larger difference between the diurnal and nocturnal mean values of their sinusal heart rate. Such a wider nychtohemeral difference decreases gradually, as it is demonstrated by the significant contrasts of the G1 MDP, the G2 MDP and the G3 MDP *versus* the G0 MDP, as well as of the G2 MDP and the G3 MDP *versus* the G1 MDP.

From the estimates and the statistical contrasts, it is possible to deduce that, despite the progressive decrease of the daily mean heart rate in MDP, the lowest (trough) values of the daily heart rate remain, on average, significantly unchanged during the course of the disease. This phenomenon is explainable with the progressive reduction of the heart rate day-night variability, which is observable in MDP more advanced in their stage of the disease.

#### **Rhythmic biometry**

Figure 2 displays the mean cosinorgrams of sinusal heart rate in each investigated group. A clear sinusoidal oscillation is detectable in each profile. However, not only the mean level

Table 1. Conventional analysis of 24-h heart rate in 10 clinically healthy subjects (CHS) and 53 myotonic dystrophy patients (MDP), subdivided into four groups (from G0 to G3) according to the severity of their neuromuscular inability

| Groups        | Estimates                      |                                  |   |  |                                |  |  |
|---------------|--------------------------------|----------------------------------|---|--|--------------------------------|--|--|
| ·             | Daily mean<br>heart rate (bpm) | Diurnal mean<br>heart rate (bpm) | Nocturnal mean<br>heart rate (bpm)<br>Mean heart rate (bpm) | Difference between<br>diurnal and nocturnal<br>(bpm) | Daily lower<br>mean heart rate |  |  |
| CHS           | 75 ± 5                         | 79 ± 2                           | 70 ± 4  | 9 ± 1  | 50 ± 5                         |  |  |
| MDP: G0       | $89 \pm 14$                    | 96 ± 11                          | 76 ± 13   | 20 ± 4   | 59 ± 8                         |  |  |
| G1            | 79 ± 10                        | 86 ± 12                          | 70 ± 10   | $16 \pm 3$   | 49 ± 6                         |  |  |
| G2            | 74 ± 10                        | 79 ± 11                          | 68 ± 10   | $11 \pm 3$   | 49 ± 6                         |  |  |
| G3            | $72\pm 6$                      | $78 \pm 5$                       | $65 \pm 7$  | $13 \pm 3$   | $59 \pm 7$                     |  |  |
| Values rounde | d to the nearest unit: $\pm$ s | tandard deviation                |   |  |                                |  |  |

Table 2. P-values from statistical contrasts by Student's t test between the conventional estimates of 24-h heart rate in clinically healthy subjects (CHS) and myotonic dystrophy patients (MDP), subdivided into four groups (from G0 to G3) according to the severity of their neuromuscular inability

| Groups  | Estimates  | p-values of MDP groups                    |                           |   |  |  |
|---------|--|---|---------------------------|---|--|--|
| •       |  | G0  | G1                        | Ğ2  | G3                                       |  |
| CHS     | Daily mean<br>Diurnal mean<br>Nocturnal mean<br>Diurnal-nocturnal mean difference<br>Daily lower mean heart rate   | = 0.014<br>< 0.001<br>ns<br>< 0.001<br>ns | ns<br>ns<br>< 0.001<br>ns | ns<br>ns<br>ns<br>ns<br>ns                | ns<br>ns<br>ns<br>< 0.05<br>ns           |  |
| MDP: GC | ) Daily mean<br>Diurnal mean<br>Nocturnal mean<br>Diurnal-nocturnal mean difference<br>Daily lower mean heart rate | -<br>-<br>-                               | ns<br>ns<br>= 0.023<br>ns | = 0.030<br>= 0.016<br>ns<br>< 0.001<br>ns | -0.013<br>= 0.002<br>ns<br>= 0.002<br>ns |  |
| G1      | Daily mean<br>Diurnal mean<br>Nocturnal mean<br>Diurnal-nocturnal mean difference<br>Daily lower mean heart rate   | -<br>-<br>-<br>-                          | -<br>-<br>-<br>-          | ns<br>ns<br>< 0.05<br>ns                  | ns<br>ns<br>< 0.05<br>ns                 |  |
| G2      | P Daily mean<br>Diurnal mean<br>Nocturnal mean<br>Diurnal-nocturnal mean difference<br>Daily lower mean heart rate | -<br>-<br>-<br>-                          | -<br>-<br>-<br>-          | -<br>-<br>-<br>-                          | ns<br>ns<br>ns<br>ns<br>ns               |  |

ns = not significant

![](_page_4_Figure_3.jpeg)

**Figure 2.** Group-related cosinorgrams of hourly-qualified mean heart rate in 10 clinically healthy subjects (CHS) and 53 myotonic dystrophy patients (MDP), subdivided into four groups (from G0 to G3) according the severity of their neuromuscular inability

around which each profile fluctuates, but also the amplitude with which the profile fluctuates, appear to be particular, demonstrating that there is a group-specific oscillation in the within-day variability of heart rate.

Table 3 illustrates the rhythmometric estimates concerning the 24-h oscillation of heart rate in each group. Table 4 lists the statistical contrasts between the rhythmometric estimates in each group.

From the estimates, it is possible to derive that the values of the hourly mean heart rate in each investigated group can be fitted by a waveform profile whose rhythm detection level shows a significant p level of probability. This means that the within-day variability of heart rate in each investigated group is structured as a significant CR.

From the estimates and the statistical contrasts, it is possible to derive that the G0 MDP, as compared to the CHS, show a significant increase in mesor of their heart rate CR. Such a significant increase, however, is no longer appreciable in the contrasts of the G1 MDP, the G2 MDP and the G3 MDP *versus* the CHS.

From the estimates, it is possible to derive that the MDP show a progressive decrease in mesor of their heart rate CR, in relation to the progression of the disease. From the statisti-

**Table 3.** Rhythm analysis of 24-h heart rate in 10 clinically healthy subjects (CHS) and 53 myotonic dystrophy patients (MDP), subdivided into four groups (from G0 to G3) according to the severity of their neuromuscular inability

| Groups |    | Estimates                           |                     |                                 |                                   |  |  |
|--------|----|-------------------------------------|---------------------|---------------------------------|-----------------------------------|--|--|
|        |    | Rhythm<br>detection<br>level<br>(p) | Mesor ± SE<br>(bpm) | Amplitude<br>(95 % CL)<br>(bpm) | Acrophase<br>(95 % CL)<br>(h:min) |  |  |
| CHS    |    | < 0.001                             | $73\pm3$            | 7                               | 15:04                             |  |  |
|        | _  |                                     |                     | (4;10)                          | (13:47; 16:2 1)                   |  |  |
| MDP:   | G0 | 0.043                               | $88 \pm 6$          | 15                              | 14:44                             |  |  |
|        |    |                                     |                     | (1;30)                          | (09:48;19:08)                     |  |  |
|        | G1 | < 0.001                             | 79 ± 2              | 11                              | 13:48                             |  |  |
|        |    |                                     |                     | (8; 14)                         | (12:36;14:52)                     |  |  |
|        | G2 | < 0.001                             | $74 \pm 3$          | 8                               | 14:24                             |  |  |
|        |    |                                     |                     | (4; 12)                         | (12:36;16:24)                     |  |  |
|        | G3 | < 0.010                             | 72 ± 2              | 10                              | 14:36                             |  |  |
|        |    |                                     |                     | (4;16)                          | (11:32;16:52)                     |  |  |
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Values rounded to the nearest unit; ± standard deviation

Table 4. P-values from statistical contrasts by Student-Newman-Keuls test between the rhythmic estimates of 24-h heart rate in clinically healthy subjects (CHS) and myotonic dystrophy patients (MDP), subdivided into four groups (from G0 to G3) according to the severity of their neuromuscular inability

| Groups              | Estimates   | Groups<br>MDP            |                                    |  |  |  |
|---------------------|---|--------------------------|------------------------------------|--|--|--|
|                     |   | G0                       | G1                                 | G2   | G3   |  |
| CHS                 | Mesor<br>Amplitude<br>Acrophase   | = 0.050<br>= 0.009<br>ns | ns<br>< 0.001<br>ns                | ns<br>ns<br>ns                                 | ns<br>ns<br>ns                                   |  |
| MDP: G0<br>G1<br>G2 | Mesor<br>Amplitude<br>Acrophase<br>Mesor<br>Amplitude<br>Acrophase<br>Mesor |                          | ns<br>= 0.015<br>ns<br>-<br>-<br>- | = 0.043<br>= 0.004<br>ns<br>< 0.001<br>ns<br>- | = 0.013<br>= 0.002<br>ns<br>ns<br>ns<br>ns<br>ns |  |
| 62                  | Amplitude<br>Acrophase  | _<br>_<br>_              | -                                  | -  | ns<br>ns   |  |

cal contrasts, it is possible to see that the G2 MDP and the G3 MDP, as compared to the G0 MDP, show a significant decrease in their heart rate mesor. Such a significant decrease, however, is not detectable in the contrasts of the G1 MDP *versus* the G0 MDP, the G2 MDP and the G3 MDP *versus* the G1 MDP, the G3 MDP *versus* the G2 MDP.

From the estimates and the statistical contrasts, it is possible to derive that the G0 and the G1 MDP, as compared to the CHS, show a significantly larger amplitude of their heart rate CR. Such a wider nychtohemeral difference in heart rate decreases gradually, as is demonstrated by the not significant contrasts between the G2 MDP and the G3 MDP *versus* the CHS, as well as the significant contrasts between the G3 MDP *versus* the G0 MDP, the G2 MDP and the G3 MDP *versus* the G0 MDP.

Finally, from the estimates and the statistical contrasts, it possible to derive that the G0 MDP, the G1 MDP, the G2 MDP and the G3 MDP, as compared to the CHS, shows an acrophase timing which is not statistically different.

#### Discussion

The present study provided evidence that the MDP show a significant increase of the daily mean of their sinusal heart rate at the early stage of their disease. Such a light tachycardia is mostly due to an increase of heart rate during the diurnal hours of the day. The diurnal tachycardia, however, tends to progressively disappear, so that the MDP at the stages 2 and 3 show both a daily mean and diurnal mean of their sinusal heart rate that are comparable to the corresponding values in CHS.

Importantly, the present study has shown that the MDP exhibit a higher difference between the diurnal and nocturnal mean values of their heart rate as compared to CHS. Such an amplified day-night variability, however, tends to progressively decrease, causing the MDP at the stages 2 and 3 to show a diurnal-nocturnal difference in their heart rate that is substantially comparable to that estimated in CHS.

Interestingly, the present study has demonstrated that a progressive sinusal bradycardia does not characterize the investigated MDP in relation to the stage of their disease. As a matter of fact, the daily trough values of heart rate were seen to remain, on average, almost unchanged in each group of MDP, despite the different severities of their disease. With this respect, it must be remarked that the MDP investigated in the present study were all selected as individuals who were not affected by cardiac conduction defects, hyperkinetic and hypokinetic arrhythmias, cardiac muscle hypocontractility. This means that the MDP are not obligatorily prone to develop a sinusal bradycardia when the disease does not involve the sinusal control of heart rate, during the negative course of its clinical history, by altering the symphatetic innervation of the heart [17]. The lack of a progressive sinusal bradycardia can be explained by the fact that the reduction to normalization of the daily mean heart rate, which characterizes the MDP in a more advanced stage of the disease, is accompanied by a contemporary coarctation of the day-night heart rate variability. This combination of events prevents the MDP herein investigated from showing a progressive negative trend for the lower values of their daily heart rate.

It must be remarked that the present study provided evidence that the MDP show a significant CR in their heart rate at every stage of their disease. Such a preserved CR, however, is characterized by a mesor increase in MDP at the initial stage of the disease. The higher mesor of heart rate, however, tends to progressively decrease, so that the MDP at the stages 2 and 3 show this rhythmic property to be comparable to that found in CHS. Additionally, the present study provided evidence that the MDP show a wider oscillation in their heart rate CR at the initial stage of their disease. Such an amplified periodic variability, however, tends to progressively disappear, causing the MDP at the stages 2 and 3 to show an amplitude of their heart rate CR that is substantially comparable to that estimated in CHS.

A particular comment has to be made on the meaning of the sinusal heart rate CR in MDP. Its persistence until the last stages of the disease is the demonstration that Steinert's disease does not obligatorily involve the sinusal rhythmic control of heart rate. In addition, it means that Steinert's disease, which is responsible for lesions of the adrenergic neurons in the medullary reticular formation [18], may leave undamaged that neural area of the anterior hypothalamus which contains the suprachiasmatic nuclei, a magnicellular structure that is said to be a central pacemaker for the circadian periodicity of sinusal heart rate [19]. Notwithstanding that, the changes in mesor and amplitude of heart rate CR allow us to hypothesize that Steinert's disease is in some way responsible for a modulation of the above-cited neural pacemaker. Because of the progressive changes in mesor and amplitude, it can be argued that the neural pacemaker undergoes a tonic as well as an amplitude modulation, which can explain the initial higher rate of the sine node at the beginning of the disease. Such a neural interference could be realized via neurovegetative and humoral mechanisms, it being well known that Steinert's disease is accompanied by changes in sympathetic and vagal modulation of heart rate [20] as well as by increased levels of circulating catecholamines [21] and atrial natriuretic peptide [22].

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