DOI: 10.4149/BLL_2022_146

CLINICAL STUDY

Complexity and heart rate adjustments of diabetic people during isometric contraction

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ABSTRACT
INTRODUCTION: Type 2 Diabetes Mellitus (DM2) can lead to autonomic nervous system dysfunction and heart rate variability (HRV) is often used to assess this system both during rest and during physical exercise.
OBJECTIVE: To evaluate the autonomic modulation at rest and the responses of heart rate and parasympathetic indices of individuals with DM2 to isometric handgrip exercise.
METHOD: The sample consisted of individuals of both sexes; over 40 years, divided into groups, with and without DM2 diagnosis. The collection of resting HRV was performed for 20 minutes in the supine position, and 256 points were selected for symbolic and linear analysis. The individuals performed isometric contraction for one minute with intensities of 10, 20, 30, 40 and 50 % of the maximum contraction, using the parasympathetic indexes RMSSD and SD1 for analysis.
RESULTS: Linear and symbolic indices of HRV at rest and those obtained during exercise were similar (p-value>0.05). No association was found between the indices at rest and the responses to exercise, with a slight delay in the response of diabetics in HR and parasympathetic indices being identified.
CONCLUSION: There was no difference between the groups in the modulation of rest or in the parasympathetic adjustments of the exercise *(Tab. 4, Ref. 32)*. Text in PDF *www.elis.sk*
KEY WORDS: diabetes mellitus, autonomic nervous system, heart rate, exercise, parasympathetic nervous system.

Introduction

Diabetes *Mellitus* (DM2) is caused by resistance to insulin action, which leads to a sustained increase in blood glucose. In the long term, it can cause micro and macrovascular changes that lead to autonomic nervous system (ANS) dysfunctions, especially in the parasympathetic branches (1, 2, 3).

One of the methods that has been widely used to investigate the ANS is the analysis of heart rate variability (HRV) by linear and non-linear methods (4). More recently, non-linear analyzes have been proposed that consider the predictability of the system, such as symbolic indices (5).

Predictability analyzes have been gaining strength precisely because they consider that organic systems are organized in a complex way, the cardiocirculatory system, for example, is controlled by several other subsystems that communicate with the central nervous system (CNS) by reflex and humoral mechanisms, making the necessary adjustments to maintain homeostasis. Therefore, the decrease in the complexity of the cardiocirculatory system indicates some type of impairment in the organic function itself or in the adequate communication between the subsystems involved, thus, this measure is an important instrument to guide conducts that facilitate a diagnosis (6).

Under normal conditions, in the initial ten seconds of muscle contraction, a rapid initial heart rate (HR) response is observed, attributed to the inhibition of vagal modulation on the sinus node, after vagal resumption, if the exercise is of low intensity, HR stabilizes, at moderate or high intensity there are adjustments dependent on the sympathetic SNA (7, 8, 9, 10, 11, 12, 13). Thus, it has been observed that during physical exercise there is an increase in HR and a decrease in HRV, especially in the indices related to parasympathetic modulation, as the intensity of the effort increases (10).

It is known that during isometric contraction, the increase in HR is dependent on the size of the muscle mass involved, the strength performed and the duration of the contraction (10, 14, 15, 16.) It has been reported that DM2 have deficits in HR responses during isometric exercise because the damage caused by hyperglycemia in the parasympathetic branches reduces the speed of vagal withdrawal (17).

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Based on what has been presented, the objective of this research was to evaluate the autonomic modulation at rest and the responses of HR and parasympathetic indices of individuals with DM2 to progressive isometric handgrip exercise, as well as the association of these indices with resting HRV.

Considering all the aspects mentioned above, the hypothesis is that diabetics present lower autonomic modulation during rest, that they have an attenuated parasympathetic response during submaximal isometric exercise and, in addition, that the resting indices are associated with the adjustments found during exercise.

Materials and methods

General procedures

Study approved by the Research Ethics Committee Involving Humans (CEP: 2485118/2018). All volunteers signed an informed consent form.

The diabetic group (DG) was composed of individuals of both sexes; over 40 years; with laboratory diagnosis of pre-diabetes or DM2 after 30 years of age, non-gestational, and non-insulin dependent.

Those with heart, lung and neurological diseases, with thyroid disorders, smokers, alcoholics, with motor impairment, pregnant women and regular exercisers in the last 6 months were not included in the groups. Those who dropped out or had data with less than 95 % of artifact-free signal were excluded.

The experiments were carried out between 2 pm and 6 pm with a temperature of 23 ± 2 °C and a relative humidity of 50 ± 10 %. All subjects underwent prior familiarization. On the day before and on the day of the evaluation, the volunteers did not ingest alcoholic beverages and/or stimulants, did not perform strenuous physical activities 24 hours before and had a light meal at least 2 hours before the tests.

Initially, patient history was taken, application of the habitual physical activity questionnaire (Baecke) (18) and a request for blood collection after 12 hours of fasting. The anthropometric assessment consisted of measuring height, body weight, waist circumference and calculating BMI. Percentage of fat and lean mass were collected by tetrapolar bioimpedance (*Biodynamics*, 450, *Shoreline*, USA).

Recording of RR intervals and analysis of cardiac autonomic modulation at rest

HR and instantaneous RR intervals (iRR) were recorded with a heart rate monitor (*Polar* RS800Cx). The recording lasted 20 minutes, with the volunteer at rest, supine and breathing spontaneously. 256 more stable points were analyzed, after digital filtering of a maximum of 5%, performed, when necessary, to remove very noticeable artifacts in the visual analysis of the selected section (*Kubios HRV*, version 2.0, *University of Kuopio, Finland*).

In the time domain, the parasympathetic indexes RMSSD (ms), pNN50 (%) and SD2 (ms), the sympathetic index SD1 (ms) and the SD1/SD2 ratio (ms) (19, 20) were used.

For the analysis in the frequency domain, the HF index (ms^2) was used, representative of the parasympathetic system, LF in normalized units (un), which reflects the sympathetic system, and the LF/HF ratio (ms^2) that analyzes the sympatho-vagal balance. All indices were decomposed by the Fast Fourier Transform (FFT) (19, 20).

The Symbolic Analysis was carried out through the program developed by Professor Alberto Porta and collaborators (5). The indices 0V (sympathetic), 1V (sympathetic and parasympathetic modulation), 2LV (parasympathetic) and 2UV (parasympathetic) were used, in addition to Shannon‘s Entropy (SE) (21).

Maximum voluntary isometric contraction test and exercise with submaximal loads

The maximum voluntary isometric contraction (MVIC) test and submaximal exercise were performed in the sitting posture, during spontaneous breathing, with the dominant upper limb resting on the adjustable chair support throughout the test, using an analog handgrip dynamometer (*North Coast* ^{tm} *Hydraulic Hand Dynamometer*).

To determine the MVIC, three maximum attempts of 10 seconds each were performed, considering the highest load obtained. After 10 minutes, the individuals performed sets of one minute of exercise, with submaximal intensities of 10, 20, 30, 40 and 50 % of MVIC.

The most stable 30-second stretches of the pre-exercise rest minute and the final 30 seconds of the exercise were selected for analysis (21). The variables analyzed were HR and the parasympathetic indices RMSSD and SD1. A maximum of 5 % digital filtering of the sections was used, performed, when necessary, to remove very noticeable artifacts in visual analysis.

Statistical analysis

Quantitative data were presented as mean and standard deviation (Dp), while qualitative data in absolute (f) and relative (%) frequency distribution. The Shapiro–Wilk test was performed to verify the normality distribution of the variables studied and the Spearman (non-parametric) and Pearson (parametric) correlation.

Tab. 1. Results for age, anthropometric measurements and laboratory tests.

Variable	GC (n=12)		DG (n=14)		p
	Average	PD	Average	PD	
Age (years)	56.9	7.7	60.0	9.4	0.367
Blood glucose (mg/dL)	91.5	8.6	116.2	21.8	0.001*
TC (mg/dL)	212.9	22.3	188.7	35.3	0.045*
LDL-C (mg/dL)	136.3	18.8	106.4	30.3	0.006*
HDL-C (mg/dL)	54.4	9.6	43.6	7.7	0.005*
TG (mg/dL)	107.7	33.5	193.4	78.5	0.003*
BMI (Kg/m2)	27.9	4.4	28.5	4.4	0.722
Fat (%)	34.1	6.5	36.6	9.2	0.662
Lean Mass (kg)	46.3	8.1	45.8	8.9	0.896
CC (cm)	93.1	10.2	94.6	15.1	0.759
Baecke	7.7	1.2	7.8	1.2	0.945

CT = total cholesterol; LDL-C = low-density lipoprotein; HDL-C = high density lipoprotein; TG = triglycerides; BMI = body mass index; WC = waist circumference. *$p \leq 0.05$ significant difference between groups by independent t-test or Mann–Whitney

Tab. 2. Distribution of frequency of medication use.

Medication	CG (n=12)		DG (n=14)	
	f	%	f	%
Antacid	1	8.3	1	7.1
Hormone Replacement	1	8.3	1	7.1
Cholesterol Reducer	1	8.3	3	21.4
hypoglycemic	0	0	12	85.7
Angiotensin II blocker	0	0	1	7.1
Diuretic	0	0	3	21.4
Beta Blocker	0	0	2	14.3
calcium channel blocker	0	0	3	21.4
ACE inhibitor	0	0	7	50.0
Platelet aggregation inhibitor	0	0	4	28.6
Anti-inflammatory	1	8.3	1	7.1
contraceptive	0	0	1	7.1
antiarthritic	0	0	1	7.1

ACE = angiotensin converting enzyme; *p≤0.05 significant difference in frequency distribution between groups by Fisher‘s Exact test

Tab. 3. Resting heart rate variability indices.

Variable	CG (n=12)		DG (n=14)		
	Average	PD	Average	PD	p-value
RMSSD (ms)	18.2	7.0	16.9	6.5	0.631
pNN50 (ms)	1.8	2.2	1.4	2.1	0.388
HF (n,u)	47.4	21.7	54.4	21.5	0.382
LF (ms2)	165.7	129.4	101.9	75.1	0.165
LF/HF (ms2)	1.6	1.2	1.2	1.1	0.537
SD1 (ms)	12.9	5.0	12.0	4.6	0.625
SD2 (ms)	31.4	10.3	27.1	7.3	0.238
SD1/SD2 (ms)	0.4	0.1	0.4	0.1	0.628
0V (%)	19.4	9.9	19.8	11.3	0.911
1V (%)	50.5	5.4	49.8	4.4	0.716
2LV (%)	12.8	6.6	12.4	8.8	0.905
2UV (%)	17.3	7.7	17.9	6.1	0.824
IF	3.6	0.3	3.4	0.4	0.719

RMSSD = square of the differences between adjacent normal RR intervals, in a time interval; pNN50 = percentage of adjacent RR intervals with a duration difference greater than 50 ms; HF = high frequency; LF = low frequency; SD1 = standard deviation of the perpendicular points of the Poncaré plot; SD2 = standard deviation of points along the identity line of the Poncaré plot; 0V = standard without variation; 1V = standard with one variation; 2LV = standard with two equal variations; 2UV = standard with two different variations; SE = Shennon entropy , *p ≤ 0.05 significant difference between groups by independent t test or Mann–Whitey

The T-Student test for repeated samples (parametric) and Mann–Whitney (non-parametric) were used to compare the HRV of the groups during rest. Levene ‚s test was used to test the homogeneity of variances. Fisher ‚s exact test was used to test the association of qualitative variables. For the analysis of the exercise, the ANOVA test of repeated measures was used to evaluate the effects of the group (control and diabetic), of the moments (rest and exercise) and of the interaction (time and group). Box ‚s M test was used to verify if the covariance matrices of the observed dependent variables are the same for both groups and Mauchly‘s test was used to test the hypothesis of sphericity. In case of rejection of the sphericity hypothesis, the analyzes were based on the Greenhouse–Geisser multivariate test. When there was a significant effect of the interaction, the Bonferroni multiple comparison test was performed to find out which moments there was a difference. The confidence level adopted was 5 %. Data were analyzed using SPSS software version 24.0 for Windows.

Results

A total of 140 volunteers over 40 years of age were screened, 98 were not included in the study, 16 were excluded (6 were on continuous high-dose psychotropic medication, 1 was on a bronchodilator and 9 had motor limitations). 26 volunteers were selected to compose the samples, being 12 individuals in the CG and 14 in the DG.

There was no significant difference in the frequency of gender distribution between the groups (p = 0.248), so that the CG was composed of 3 male and 9 female volunteers, while the DG was composed of 7 of each of the sexes.

Table 1 shows age, results of laboratory tests and anthropometric measurements.

Table 2 illustrates the absolute frequency (*f*) and percentage (%) of continuous medication use during the evaluation period.

Table 3 shows the results of autonomic modulation and HR complexity during rest in the supine position.

Table 4 presents the results referring to the analysis of the exercise in each of the intensities used.

Discussion

In the present study, the T2DM group that was medicated had higher blood glucose, TC, LDL-c and TG values and lower HDL-c values. However, the temporal, spectral and symbolic indices of the resting HRV were similar to the control group. Likewise, the adjustments of HR and SD1 and RMSSD parasympathetic indices to isometric exercise were similar between the two groups, but the DM2 group showed some delay in these adjustments.

The results found do not support the hypothesis, as the literature indicates that individuals with DM2 have reduced HRV during rest, a factor that may explain this are the medications used daily by the DG (2, 23), since some of these drugs have a positive effect on HRV (24). Symbolic indices and HRV complexity were also the same between groups (25).

Metformin was ingested daily by 85.7 % of the DG, it is known that this drug has a direct ANS depressant effect, reducing BP, HR and consequently improving the sympathovagal balance (26, 27).

Previous studies also demonstrate that the angiotensin II-converting enzyme contributes to the decrease in vagal activity, leading to a decrease in the baroreflex response (24, 28, 29), thus, the inhibition of this enzyme can cause the opposite effect. Taking into account that 50 % of the sample of diabetics used this class of medication daily, this may have contributed to the improvement in the autonomic modulation of these individuals.

The results regarding the exercise adjustments also do not corroborate the hypothesis, since the two groups were the same, when a lower response from the DG (17) was expected.

It is known that during isometric contraction, the increase in HR is dependent on the size of the muscle mass involved, the strength performed and the duration of the contraction (14, 15, 16). When considering the physiological response of isometric handgrip exercise, a contraction of up to 30 % of maximum strength does not promote a very important vagal withdrawal, causing HR to be very close to baseline, as well as VE and DC (30).

Tab. 4. Responses of hemodynamic variables and parasympathetic heart rate indices during progressive isometric exercise.

		loads												The new		
		Rest		10%		20%		30%		40%		50%		Group	Charge	Interaction
Time	Group	Average	dp	Average	dp	Average	dp	Average	dp	Average	dp	Average	dp	p-value	p-value	P-value
FC	GC	70.3	10.9	71.3	9.7	75.7†	8.8	75.7†	8.8	79.5†	9.5	83.4†	11.7	0.998	0.001*	0.241
	GD	71.9	8.8	73.2	8.7	73.6	7.7	74.9	9.0	78.2†	8.3	81.9†	9.3			
RMSSD	GC	23.8	14.9	16.6	7.2	17.7	11.7	14.9†	7.9	11.8†	5.9	10.1†	3.9	0.567	0.001*	0.408
	GD	19.8	10.4	15.5	8.8	13.9	6.4	13.6	6.3	11.6	5.1	11.1	6.1			
SD1	GC	17.1	10.7	11.9	5.2	12.7	8.4	10.6†	5.5	8.0†	3.6	7.7†	3.4	0.571	0.001*	0.412
	GD	14.2	7.5	11.1	6.3	10.0	4.6	9.8	4.5	8.4	3.6	8.0	4.4			

HR = heart rate; RMSSD = square of the differences between adjacent normal RR intervals, in a time interval; SD1 = standard deviation of the perpendicular points of the Poncaré plot; CG = control group; GD = diabetic group.* p ≤ 0.05 significant difference between loads by ANOVA test; † p ≤ 0.05 significant difference in relation to rest within the group by the Post-Hoc Bonferroni test

Thus, we can observe that, although there was no statistical difference between the groups, the individuals in the DG only presented HR different from rest with 40 % of MVIC, while the CG with 20 %, showing a certain delay in the response of diabetics, a fact which can also be explained by the high levels of glucose that damage peripheral nerve fibers, causing changes in the autonomic nervous system of these individuals (31, 32).

During exercise, a decrease in HRV is expected, especially in the indices related to parasympathetic modulation, as the intensity of the effort increases (10) and only the CG showed a significant reduction in relation to rest in the parasympathetic indices RMSSD and SD1, from 30 % MVIC, which is expected because, according to Ziegler et al (2005), about 34.3 % of people with DM2 have abnormal HRV results.

The fact that the muscles used to perform the exercise are small and the intensity used of up to 50 % may have contributed to the result not indicating a difference between diabetics and controls, as the tendency of lower response in the DG is clear.

Highlights and limitations of the study

- Resting autonomic modulation was similar between groups.
- Responses to the exercise were similar between the groups.
- There was a delay in the HR, RMSSD and SD1 responses of diabetics.
- No association was found between HRV and exercise indices.

The number of diseases present and the respective drugs that the sample used is a limitation that should be reported in this study. Although other pathologies are associated and are part of the clinical reality of these patients, the subgroups by diseases are less representative and may have influenced, even in a small way, the results obtained.

Conclusion

Thus, we conclude that in the studied population there was no difference between the groups in the autonomic modulation at rest or in the parasympathetic adjustments during isometric exercise. It is safe to prescribe isometric handgrip exercise with up to 50 % of MVIC in the population studied, due to the homogeneous response of the groups.

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Received June 17, 2022.
Accepted August 15, 2022.