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Impaired heart rate variability, Valsalva and 30:15 ratio indexes are associated with reduced submaximal exercise capacity in subjects with diabetes mellitus

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ABSTRACT

Aims: To assess cardiac autonomic control and its association with submaximal exercise measured using the 6-minute walk test (6MWT) in subjects with type-2 diabetes mellitus (DM2).

Methods: Cardiac autonomic control was assessed using Ewing's tests and heart rate variability (HRV) in DM2 volunteers (DG, n = 22) and sex-, age- and body mass index-matched non-diabetic controls (CG, n = 22) before, during and after 6MWT.

Results: Before the 6MWT, DG presented lower HRV represented by reduced SDNN [median 28.9 ms^2 (IQR:18.6–35.4) vs. 45.1 (IQR:39.2–62.67), $p < 0.001$] and Total Power [median 785 ms^2 (IQR:256–1264) vs. 1757 ms^2 (IQR:1006–2912), $p = 0.004$]. Exercise capacity was reduced in DG [maximal predicted distance (%) = 88.4 ± 6.4 vs. 95.2 ± 11.0%, $p = 0.018$]. DG demonstrated lower global HRV during recovery and lower parasympathetic drive, represented by reduced RMSSD, during all phases of the 6MWT. Moreover, supine HR ($r = -0.32$), HR orthostatism ($\rho = -0.40$), SDNN pre-6MWT ($\rho = 0.39$), TP pre-6MWT ($\rho = 0.38$), Valsalva ratio ($\rho = 0.39$) and 30:15 ratio ($\rho = 0.38$) were all correlated with maximal walked distance.

Conclusions: DM2 subjects presented abnormal HRV during and after submaximal exercise. Furthermore, autonomic control impairment in orthostatism, represented by lower global HRV (SDNN, Total power) and lower Ewing's indexes (Valsalva and 30:15 ratios), was associated with lower exercise capacity.

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1. Introduction

Diabetes mellitus (DM) is a highly prevalent disease nowadays [1] and its most frequently associated complications are neuropathies [2,3]. Even though diabetic peripheral sensorimotor polyneuropathy is the most frequent neuropathy, autonomic neuropathies including cardiac autonomic neuropathy (CAN) can affect patients with diabetes and are associated with increased risk of sudden death, silent myocardial ischemia [2] and overall mortality rates [4].

The impairment in exercise capacity in subjects with diabetes, mainly demonstrated in maximal exercise tests [5–7] has been described before, and symptoms such as early fatigue and exhaustion during exercise [8] are common. However, this level of activity, i.e. high intensity aerobic exercise, is not always recommended or prescribed for patients with diabetes.

Thus, it is necessary to provide detailed information regarding cardiac autonomic control in submaximal activities, such as walking, which are part of regular activities of the daily routine. Therefore, this study aimed to assess the association of autonomic control at rest and during six-minute walk test in subjects with diabetes.

2. Subjects

This is a case-controlled study comparing a group of Type 2 diabetes mellitus patients and a control group of volunteers without diabetes matched by sex, age and BMI. The study enrolled volunteers under treatment for DM2 at the Endocrinology Outpatient Clinic at Onofre Lopes University Hospital (HUOL-UFRN) in Natal, Brazil. DM was diagnosed by the endocrinologist of the hospital, following the Brazilian Diabetic Society diagnostic criteria, which are similar to the criteria proposed by the American Diabetes Association [9]. Individuals without DM2 had DM excluded based on an oral glucose tolerance test. The study was approved by the Ethics Committee (421/10 CEP-HUOL) following the Declaration of Helsinki and Brazilian guidelines for studies involving humans. All patients participated voluntarily and gave their written consent as required.

The sample was composed of 22 volunteers with DM2 in the Diabetes Group (DG) (n = 22) and 22 subjects without diabetes in the Control Group (CG) (n = 22).

For inclusion, subjects should have had no prior diagnosis of peripheral artery disease; advanced heart disease such as chronic heart failure; diabetic neuropathy previously diagnosed; neuromuscular disease or rheumatic or metabolic diseases (except DM), which could influence the exercise capacity assessment. Subjects with previous amputations, subjects who had undergone coronary revascularization or had revascularization in the peripheral arterial beds were excluded. Medications that volunteers were currently using to treat DM, dyslipidemia or hypertension were not withdrawn for the study.

3. Materials and methods

A sequence of tests was established, as following: anthropometric assessment, ankle-brachial index (ABI) assessment, electrocardiography and assessment of Ewing's battery tests, which encompass HRV at rest in the supine position and HRV during submaximal exercise (6MWT).

3.1. *Anthropometric assessment and screening for peripheral arterial disease*

Weight, height and body mass index (BMI) were measured according to the World Health Organization (2000) [10]. Peripheral Arterial Disease (PAD) was assessed using the ankle-brachial Index, following the American College of Cardiology/American Heart Association (ACC/AHA) guideline, which considers ABI < 0.9 abnormal and therefore the diagnostic of PAD [11,12]. Subjects with abnormal ABI were excluded due to possible interference in the maximal walking distance during the 6MWT.

3.2. *Autonomic cardiac neuropathy assessment - Ewing's tests*

Previous to HRV and Ewing's tests, subjects were informed to refrain from caffeinated beverages on the day of the exam and to avoid exhaustive physical exercises on the day before. All data were collected in the morning (7:30 to 12am), considering the effect that the circadian rhythm could have on HRV.

After a resting period of 10 min, the blood pressure was measured with the subject in the lying position. Afterwards, a 12-lead Electrocardiogram (ECG) was performed at the same position (ECG-PC, TEB, Brazil), which allowed for the identification of electrocardiographic alterations that could interfere on exercise or HRV analysis, thus leading to exclusion.

After the resting period, HRV was monitored in supine position, by a frequency meter (RS800CX, Polar Electro Inc, USA) using skin surface electrodes, as previously described [13].

Ewing's tests were performed as recommended by the American Diabetes Association [14], including deep breathing, orthostatic test and Valsalva maneuver, represented by the indexes: E:I ratio, 30:15 ratio and Valsalva ratio, respectively [2,15]. The cut-off value was 1.03 for 30:15 ratio and 1.12 for Valsalva ratio [15]. E:I ratio cut-off point was adopted according to age, ranging from 1.17 (20–24 years) to 1.02 (70–75 years) [2]. Orthostatic hypotension was tested adopting a cut-off value of 30 mmHg for systolic pressure decrease [2]. CAN was classified as follows: early involvement of CAN (one abnormal test), definite involvement of CAN (two or more abnormal test) and severe involvement of CAN (two or more abnormal test and abnormal orthostatic hypotension) [2].

After basal ECG and HRV in the supine position were collected, the sequence of Ewing's tests started. First, the subject was instructed to stand up, for the orthostatic test. Afterwards, the subject returned to the lying position for a 5-

minute rest, and then was instructed to perform the deep breathing, which consists of controlled breathing (5 s of inspiration and expiration) during one minute. Finally, the Valsalva maneuver was performed, using a breathing tube connected to a manometer, where the subject blew until a steady state pressure of 40 mmHg and 15 s were reached [2,15].

3.3. *Assessment of heart rate variability*

HRV was measured by acquiring R-R intervals within one millisecond resolution and posterior data analysis was done using the Kubius HRV Software (Kuopio, Finland). HRV was analyzed in the time and frequency domains using the area of greatest stability in the R-R intervals, corresponding to 5 min of recordings (containing at least 256 consecutive beats) during spontaneous breathing. Frequency domains were analyzed by Fast Fourier Transform after subtracting the linear tendency using automatic filters. The domains were studied using low-frequency (LF: 0.04 to 0.15 Hz) and high-frequency (HF: 0.15 to 0.4 Hz) ranges in spectral density (ms^2) and normalized units (n.u.), Total Power (TP) (ms^2) and the LF/HF ratio. Time domain parameters were calculated as follows: SDNN (Standard deviation of all R-R intervals) and RMSSD (Square root of the mean of the squares of the successive R-R interval differences) [16,17].

HRV was analyzed in the lying position (Supine position), then for 5 more minutes in the standing position just before starting the 6MWT (Before), during the last 5 min of the 6MWT (During) and then 5 min after the 6MWT, during recover (After).

3.4. *Assessment of exercise capacity*

The exercise capacity was assessed by the 6MWT, according to the American Thoracic Society Guidelines [18,19] in a 30.5 m (100 ft.) corridor. The maximal HR achieved during the test was normalized to the estimated maximum heart rate by age (220-age (years)).

The walked distance was recorded and the percentage of the predicted distance was calculated according to age and sex using equations for the Brazilian population, published by Iwama et al. (2009) [20], as follows: $622.461 - (1.846 \times \text{age (years)}) + (61.503 \times \text{gender})$, in which the multiplication factor was 1 for men and 0 for women.

3.5. *Statistical analysis*

The normality of data was verified by the Shapiro-Wilk Test.

For mean comparison between groups, the unpaired T-test, in case of parametric data, or the Mann-Whitney test, in case of non-parametric data, was applied. Chi-squared test was used to compare the frequency of medication use. A Friedman test followed by a Dunn's multiple comparisons test were performed to analyze the behavior of the spectral components of HRV.

For the correlation test, Pearson Correlation Coefficient was calculated in case of parametric data and Spearman Correlation Coefficient in case of non-parametric data. A p-value lower than 0.05 was considered a criterion for statistical significance.

The effect size was calculated using coefficient d of Cohen, using the GPower 3.1 software, which was stablished as small if $0.2 \leq d < 0.5$, medium if $0.5 \leq d < 0.8$ and large if $d \geq 0.8$ (Cohen, 1988) [21].

4. Results

The cardiac autonomic control was assessed using Ewing's battery of tests. HRV was assessed at rest and during submaximal exercise (6MWT) in subjects with DM2 (DG) and controls, matched by sex, age and BMI (n = 22 each group, 15 women, 7 men). The groups were homogeneous regarding age (DG 52.31 ± 9.17 vs. CG 53.22 ± 9.34, p = 0.74), BMI (DG 27.90 ± 4.24 vs. CG 28.83 ± 4.19, p = 0.52) and Waist-Hip Index (DG 0.90 ± 0.08 vs. CG 0.90 ± 0.07, p = 0.90). The mean duration of DM was 9.95 ± 6.46 years. DG presented higher values for fasting glucose (DG 193.50 ± 116.20 vs. CG 86.10 ± 8.7, p < 0.001), 50% were using insulin and 77.3% were using hypoglycemic drugs. There was no statistic difference between groups regarding antihypertensive drugs use (DG = 59% vs. CG = 36%, p = 0.13), but the use of hypolipidemic drugs was more prevalent in subjects with DM2 (DG 50% vs. CG 4%, p = 0.001). None of the subjects were diagnosed with PAD assessed using the ABI (DG 1.08 ± 0.08 vs. CG 1.04 ± 0.08, p = 0.20).

The results from the Ewing's tests and the HRV assessed at baseline and during orthostatism tests are presented in Table 1. The supine rest HR was significantly higher (d = 1.67; power = 0.99), while Valsalva (d = 0.91; power = 0.84) and 30:15 ratios (d = 0.99; power = 0.88) from Ewing's test were lower in the DG. All HRV variables measured, except LF/HF and normalized LF values, were lower in the DG (d values from 0.88 to 1.24 and power from 0.80 to 0.87). Classification of cardiac autonomic neuropathy based on Ewing's test was as follows: early involvement of CAN and definite CAN was present in 59.1% and 9.1%, respectively, and 31.8% had no CAN. There were no subjects with severe CAN. Only 2 subjects had a borderline decrease in arterial pressure at the orthostatic hypotension test.

The results from the HR, blood pressure and 6MWT distance are summarized in Table 2. The HR Before, at standing position, was higher in the DG (d = 0.88; power = 0.82). Subjects with diabetes demonstrated impaired submaximal exercise capacity represented by a reduced maximal walking distance (% Predicted Maximal Distance) (d = 0.75; power = 0.68). The maximal HR and Blood Pressure were not different between groups.

Analysis of HRV before, during and after the 6MWT is summarized in Table 3. At standing position, 5 min before the 6MWT, all variables were lower in the DG, mainly SDNN (d = 0.99; power = 0.88) and RMSSD (d = 0.88; power = 0.74), except for LF/HF that was higher compared to controls (d = 0.39; power = 0.24). During the last 5 min of the 6MWT, SDNN, RMSSD, HF and TP remained lower in the DG. Finally, at the first 5 min of recovering after exercise, all HRV variables were lower in the DG (effect size ranging from 0.37 to 0.60), except for LF/HF that was not different between groups.

Fig. 1 represents telemetry data in a control subject (A) and a subject with DM2 (B) before, during and after the 6MWT. A qualitative assessment demonstrates a slower reduction in

Table 1 – Heart rate at supine position, Ewing's tests, and heart rate variability domains in volunteers with DM2 compared to controls.

	Diabetes Group (n = 22)	Control Group (n = 22)	p value
Supine HR (bpm)	77.10 ± 10.40	61.70 ± 7.90	<0.001
E:I Ratio	1.33 (1.29–1.45)	1.43 (1.37–1.59)	0.15
30:15 Ratio	0.98 (0.94–1.10)	1.22 (1.11–1.25)	0.002
Valsalva	1.46 ± 0.18	1.71 ± 0.34	0.004
Supine SDNN	23.40 (15.22–30.20)	40.20 (30.67–51.27)	<0.001
Supine RMSSD	13.20 (8.50–20.17)	27.90 (20.80–42.60)	<0.001
Supine LF (ms^2)	96.50 (46.50–163.50)	273.00 (170.50–593.50)	<0.001
Supine LF (nu)	60.41 ± 18.10	53.60 ± 24.50	0.30
Supine HF (ms^2)	51.50 (17.70–115)	317.00 (116.5–538)	0.001
Supine HF (nu)	39.56 ± 18.18	46.32 ± 24.54	0.30
Supine LF/HF	1.95 (1.07–2.64)	1.17 (0.45–3.25)	0.30
Supine Total Power (ms^2)	400.50 (162.20–846.00)	1159.00 (758.70–2142.20)	<0.001

HR - Heart Rate, LF/HF – Ratio between LF and HF, LF – Low frequency, HF – High frequency, SDNN - Standard deviation of all R-R intervals, RMSSD - Square root of the mean of the squares of successive R-R interval differences - Data are presented as mean ± SD for parametric variables and as median (interquartile range) for nonparametric variables.

Table 2 – Heart rate, blood pressure and maximal distance during the 6MWT in volunteers with DM2 and controls.

Variable	Diabetes Group	Control Group	p-value
HR Before 6MWT (bpm)	80.00 ± 10.06	70.68 ± 10.39	0.004
Max HR (bpm)	124.50 ± 23.30	112.70 ± 17.70	0.067
% Max Walked Distance	88.40 ± 6.40	95.20 ± 11.00	0.018
Initial SBP (mmHg)	130.00 (120.00–130.00)	125.00 (10.00–140.00)	0.884
Initial DBP (mmHg)	80 (80.00–90.00)	90.00 (80.00–92.5)	0.070

HR – heart rate, 6MWT – six-minute walking test, Max HR - Maximal Heart Rate reached in the 6MWT, % Max Walked Distance – percentage of the maximal predicted distance for age and sex, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure. Data are presented as mean ± SD for parametric variables and as median (interquartile range) for nonparametric variables.

R-R duration and also slower change in HRV in the volunteer with DM2, compared to a control matched by age, sex and BMI, when exercise was initiated, in addition to a slower recovery from exercise until baseline values were reached. A Friedman test followed by a Dunn's multiple comparisons test was performed to analyze the behavior of the spectral components of HRV. In the control group, LFnu increased during exercise ($p = 0.02$) and demonstrated no differences between pre-test and post-test. No statistical difference was found for normalized LF in the DG.

The HF component decreased with exercise ($p=<0.001$) as well as HFnu ($p = 0.02$) in CG. In DG, HF decreased during exercise ($p = 0.04$) but statistical changes were not observed when normalized units were used.

Correlation of variables representing cardiac autonomic control and percentage of maximal predicted distance (PMPD) was assessed. The HR ($\rho = -0.40$; $p = 0.006$) and LF (ms^2) ($\rho = 0.30$; $p = 0.04$) at supine position were significantly correlated with PMPD. HRV variables analyzed at the standing position, just before 6MWT, such as LF (ms^2) ($\rho = 0.33$; $p = 0.027$), TP ($\rho = 0.38$; $p = 0.01$) and SDNN ($\rho = 0.39$; $p = 0.009$) were also correlated with PMPD. The same was observed for Valsalva ($\rho = 0.39$; $p = 0.007$) and 30:15 ratios ($\rho = 0.38$; $p = 0.025$).

5. Discussion

In this case-controlled study, cardiac autonomic control was assessed during rest and submaximal exercise in subjects with DM2 and controls. Considering previous research, this is the first study to systematically assess HRV during a functional test (6MWT) in DM2 volunteers. Altered autonomic control in orthostatism and abnormal behavior of HRV during submaximal exercise in DM2 was observed. HRV parameters such as SDNN, TP and LF (ms^2), and Valsalva and 30:15 ratios correlated with maximal predicted distance in 6MWT and should be further investigated as possible predictors of submaximal exercise limitation.

When HRV was measured at lying position, SDNN, RMSSD, LF, HF and TP were lower in the DG, which demonstrate a decrease in global HRV. These findings corroborate with previous studies [22–26]. An abnormally higher resting HR was also observed in DG as consequence of a reduction in parasympathetic drive in DM2 volunteers, as indicated previously by other authors [2,7,27–30].

Early involvement of CAN was present in the majority (59.1%) of DM2 subjects. Ewing's tests assessment demonstrated an abnormal adaptation to autonomic challenges in DM2 subjects represented by decreased Valsalva and 30:15 ratios. Abnormal adaptation to autonomic challenges and high resting HR are indications of dysfunction in the autonomic system, characterizing CAN [2,3,15,29].

HRV in standing position before submaximal exercise was also assessed because the aim was to assess HRV variations during the 6MWT; therefore, the baseline was registered in the same position in which the exercise test was performed. Impaired HRV became evident in orthostatism. All time and

Table 3 – Heart rate variability assessed before, during and after the 6-minute walk test in volunteers with DM2 and controls.

HRV Variables	Diabetes Group (n = 22)	Control Group (n = 22)	P Value
SDNN			
Before 6MWT	28.90 (18.62–35.45)	45.10 (39.15–62.67)	<0.001
During 6MWT	18.50 (12.47–31.00)	28.50 (18.57–49.62)	0.028
After 6MWT	40.40 (31.37–55.55)	68.45 (53.47–82.07)	0.001
RMSSD			
Before 6MWT	13.35 (7.70–18.22)	25.90 (16.72–37.10)	0.001
During 6MWT	8.30 (5.77–11.70)	11.55 (7.70–22.30)	0.032
After 6MWT	9.90 (5.45–13.67)	21.05 (13.67–26.12)	0.001
LF (ms^2)			
Before 6MWT	209.50 (76.75–429.25)	417.50 (227.50–955.50)	0.026
During 6MWT	79.00 (22.00–171.00)	255.00 (56.25–560.25)	0.08
After 6MWT	132.50 (33.50–371.75)	424.50 (214.25–773)	0.006
LF (nu)			
Before 6MWT	76.30 (69.25–84.10)	67.20 (53.38–78.15)	0.042
During 6MWT	86.05 (78.37–88.50)	80.25 (75.90–87.82)	0.252
After 6MWT	76.60 (70.95–87.72)	76.95 (62.72–84.47)	0.467
HF (ms^2)			
Before 6MWT	52.00 (14.75–120.75)	190.50 (84.75–459.50)	0.003
During 6MWT	13.50 (3.25–54.75)	47.50 (10.75–135.50)	0.038
After 6MWT	42.00 (11.75–76)	147.50 (59.50–232.25)	0.001
HF (nu)			
Before 6MWT	23.70 (15.90–30.75)	32,70 (21.77–46.75)	0.043
During 6MWT	13.95 (11.50–21.62)	19.75 (12.17–24.10)	0.252
After 6MWT	23.40 (12.27–29.05)	23.05 (15.50–37.17)	0.467
LF/HF			
Before 6MWT	3.22 (2.25–5.29)	2.06 (1.15–3.59)	0.034
During 6MWT	6.15 (3.63–7.69)	4.06 (3.14–7.21)	0.247
After 6MWT	3.27 (2.44–7.14)	3.34 (1.69–5.46)	0.467
Total Power (ms^2)			
Before 6MWT	785.00 (256.50–1264.25)	1757.00 (1006.25–2912.25)	0.004
During 6MWT	177.50 (71.25–696.25)	623.00 (207.75–2077.75)	0.027
After 6MWT	586.50 (389.75–1676.75)	1910.50 (1290–4102.25)	0.001

SDNN - Standard deviation of all R-R intervals, RMSSD - Square root of the mean of the squares of successive R-R interval differences, LF – Low frequency, HF – High frequency, LF/HF – Ratio between LF and HF. Data are presented as mean ± SD for parametric variables and as median (interquartile range) for nonparametric variables.

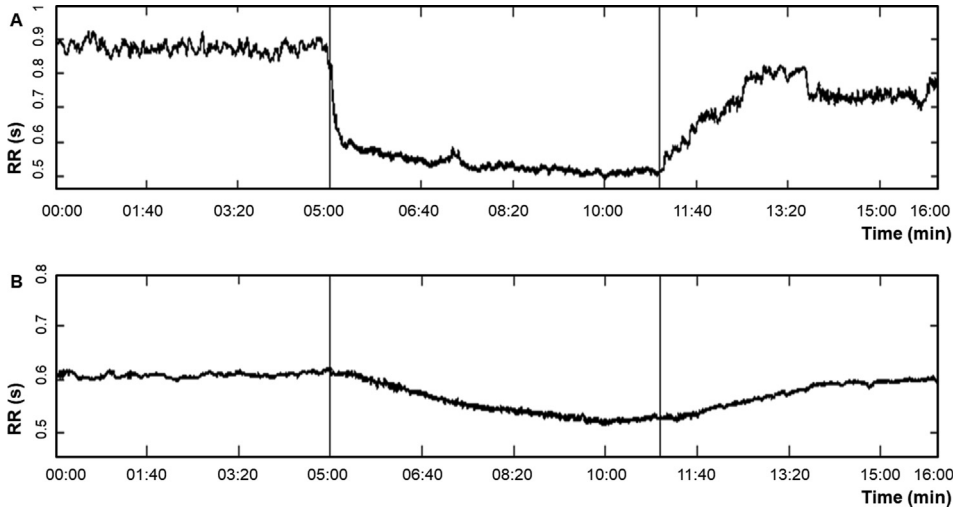

Fig. 1 – Telemetry data of R-R intervals before, during and after the 6-minute walk test in non-diabetic (A) and diabetic volunteer (B). RR- RR interval; minutes 1–5 correspond to rest period before walking, minutes 5–11 correspond to exercise (walking) period and minutes 11–16 correspond to recovering period.

frequency domains variables were different in DG, mainly SDNN and RMSSD. Furthermore, the increase in LFnu, decrease in HFnu and a higher LF/HF denotes an increased sympathetic drive at rest in orthostatism. The consequence was a higher HR previous to exercise in DG that may diminish cardiac reserve and contribute to impaired submaximal exercise performance. Wilson *et al.* (2017) [7] also described higher resting HR and lower reserve HR in subjects with type 1 diabetes and with DM2 (Wilson et al., 2017-b) [31], demonstrated by lower increase in cardiac output, stroke volume and ejection fraction during submaximal exercise echocardiography.

There is no study comparing HRV between subjects with and without DM2 at standing position to contrast the findings of this study; however, Ewing et al. (1985) [15] have demonstrated in the past that almost 40% of the subjects with DM2 presented an altered adaptation of HR to changes in body position from lying to standing, reflecting an acute dysfunction in cardiac autonomic control. The present data demonstrate a persistent altered autonomic control at rest in standing position with a predominance of sympathetic drive. It is believed that enhanced sympathetic drive and impaired vagal efferent function contributes to various comorbidities and complications related to diabetes, including increased cardiovascular mortality [28,32].

Functional walk tests measure functional status or exercise capacity, employing demanding activities that individuals perform daily (i.e. walking) and can better assess functional capacity [33]. Impairment in submaximal exercise capacity (6MWT) was found in DG, represented by reduced PMPD. It was established that none of the patients had PAD by ABI ratio. This is important, especially in older individuals, who have a higher PAD incidence. This also differentiates the present study from others that use 6MWT to assess functional capacity without checking for lower limbs blood flow.

Alterations in HRV compared to controls were persistent in DG during exercise (Table 3). Overall HRV (SDNN and TP) and indexes representing the parasympathetic branch (RMSSD and HF (ms^2)) were lower in DG during exercise and maintained lower after recovery.

Regarding the spectral analysis of HRV, it is expected that all the spectral components had decreased values due the parasympathetic withdrawal during exercise [34]. Corroborating with this study, the investigation of HRV dynamics on incremental intensity exercise [5,6] and on cycle ergometer [35] also demonstrated that absolute values of HF and LF components are expected to decrease progressively, depending on the intensity, or the parasympathetic index. However, sympathetic predominance (associated with increase in blood catecholamines) is apparent after 50–60% VO_{2peak} [5,6]. Analyzing changes within the group during 6MWT, there was an expected increase in LFnu and decrease in HFnu in CG; however, the same analysis did not demonstrate significant alterations in these variables in DG, demonstrating an impaired autonomic adaptation in DG group.

During the recovery period, the HR and HRV of both groups returned to pre-test level. This was also found by Arai et al. (1989) [35]. In the present study, both rate of R-R changes, during the start of exercise and during the transition to recovery were slower in DG (Fig. 1), demonstrating slower recovery of SDNN and RMSSD indexes, which were also observed by Anaruma et al (2016) [30] in Type 1 DM subjects during moderate intensity aerobic exercise.

The impaired autonomic adaptation assessed during the change to orthostatic position and the forced expiration measured by the 30:15 ratio and Valsalva Index, respectively, seems to impact the performance on submaximal exercise. It must be noted that correlation is moderate and further investigation is needed to establish this ratio as a predictor of submaximal exercise capacity. SDNN, TP and HR in standing position were positively correlated with PMD which corroborates the hypothesis that the better the HR adaptation in standing position the better the performance during submaximal exercise. Similar observation was found in studies in subjects with heart failure [36], subjects with chronic liver disease [37] and with type 1 diabetes [7].

Further research should focus on investigation of the best variable representing autonomic control that predicts exercise capacity in DM2 subjects. If it derives from HRV, it will be a good instrument to assess DM subjects because it is non-invasive, easy to perform and allows serial evaluations at different time points.

Limitations of this study were the wide age range of DM2 subjects and consequently matched controls, due to the selection of subjects, which was convenience sampling. Future studies should attempt to analyze and compare subjects in different age groups and consider the statistical correction for the diabetes duration.

6. Conclusions

In summary, there is an impaired autonomic control in DM2 subjects, that is in part responsible for limitation in submaximal exercise capacity, which is associated with higher HR at rest, global HRV indexes in standing position and lower Valsalva and 30:15 ratio indexes.

Declaration of Competing Interest

No conflicts of interest declared concerning the publication of this article.

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