

## AUTONOMIC MODULATION AND FUNCTIONAL CAPACITY IN DIABETES MELLITUS TYPE 1 AND 2 SUBJECTS

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### ABSTRACT:

**Objectives:** Evaluation of heart rate variability (HRV) during cardiovascular autonomic tests and functional capacity of patients with type 1 and type 2 DM. **Methods:** Fifteen individuals with DM and twelve healthy ones were evaluated during cardiovascular autonomic tests of maneuver enhancement of respiratory sinus arrhythmia (RSA), handgrip and Valsalva. In addition, the Paschoal test was applied to evaluate submaximal functional capacity. During the tests, autonomic heart rate variability (HRV) was collected by recording the RR intervals, considering the rates in the time domain (RMSSD and pNN50) and frequency domain, as low and high frequency (LF and HF) and the relationship between them (LF / HF). Besides the analysis of HRV and capillary glucose, the distance traveled during Paschoal test was also recorded. Results: The values related to blood glucose levels were significantly higher ( $p < 0.05$ ) in DM1 and DM2 groups compared to controls. PNN50 values for DM1 in all tests were lower compared to CDM1. No statistical difference was found when compared DM2 with CDM2. The distance of Paschoal test was similar between groups of individuals with diabetes and their respective controls. **Conclusion:** The variable pNN50 was lower in individuals with DM1, suggesting reduced of the parasympathetic activity in these individuals, but no change in functional capacity, as measured by Paschoal test when compared to the control group.

**Key words:** diabetes mellitus; autonomic nervous system; heart rate; functional capacity.

### INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic disease characterized by hyperglycemia resulting from defects secretion or insulin action, or both. The disease is associated to increased mortality and high risk development of complications micro- and macrovascular complications, as well as neuropathies, blindness, kidney failure and limb amputations<sup>1,3</sup>. It is responsible by expenditures in health and substantial reduction in the ability to work and the expectation of life<sup>1,2,3</sup>.

Cardiovascular autonomic neuropathy is a common dysfunction autonomic found in DM

patients DM, causing abnormalities in heart rate control, and dynamic vascular<sup>4</sup>.

Autonomic dysfunction may be evaluated by the heart rate variability (HRV), which reflects the periodic fluctuations in heart rate instantaneous and the duration of intervals between R waves (R-Ri) consecutive electrocardiogram, and is therefore depending on the activity of sympathetic and parasympathetic nervous system<sup>5,6</sup>.

For this evaluation, some tests have been used since the invasive through block pharmacological (single or double lock of the cardiac sympathetic and parasympathetic)<sup>7,8</sup>, even by physiological maneuvers not invasive as Valsalva<sup>9</sup>

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maneuver, active<sup>10,11</sup> or passive<sup>12</sup> postural maneuver, realization of respiratory sinus arrhythmia<sup>13</sup>, immersion of the face or hand in cold water test<sup>14</sup> or change in altitude<sup>15</sup>. However, it is noteworthy that they are few studies have analyzed HRV during not invasive autonomic maneuvers in individuals with DM.

Through of the evaluation for HRV autonomic maneuvers can identify objectively cardiovascular autonomic neuropathy early stages and provide treatment options that based on control of symptoms and prevention of disease progression. Thus, it is possible to prevent cardiac events arising from complications of autonomic neuropathy, such as resting tachycardia and silent myocardial infarction, among others<sup>16</sup>.

Another important aspect for understanding of clinical diabetes Mellitus the functional capacity of affected individuals is research. Was published in Brazil, the Paschoal Test suggests that the prediction of physical capacity from an effort protocol performed on a cycle ergometer, similar Six-Minute Walk Test (6MWT)<sup>17</sup>. This test differs from the 6MWT for proposing a graduate of the physical capacity from the distance reached by the person while performing the same. Furthermore, connotes biomechanics differently due to the fact that person doing it in a sitting position which may reveal functional capacity different aspects and heart and breathing response.

Thus, the objective is to evaluate the heart rate variability (HRV) during cardiovascular autonomic tests and functional capacity in DM types 1 and 2 subjects.

## METHODS

### *Casuistry*

In the period between September 2008 and March 2009, 145 DM patients registered in Strategies Family Health (SFH) of Diamantina - MG were tried based on their records and notes of the register in the basic unit of health, 37 were pre-selected to participate in this study because at this point satisfies the inclusion criteria.

Pre-selected individuals were submitted to initial assessment, which consisted of anamnesis and verification of the medication at the time. Of these 37 subjects, 15 accepted or met the inclusion criteria, and others being excluded they were using beta-blocker or channel blocker calcium medication (16), presenting difficulties to perform the tests as osteoarthritis affecting the gait or other orthopedic conditions (1), physiological and/or neurological conditions as stroke (2), or by incompatibility between days and times assessments of the availability of volunteers (3).

### *Inclusion Criteria*

Inclusion criteria consisted in: to be eighteen years or when smaller, have the consent free and

informed consent signed by parents or responsible, have a diagnosis of DM type 1 and 2, with blood glucose levels greater than the 126mg/dL<sup>18</sup>.

### *Exclusion criteria*

The exclusion criteria adopted in this study were normal values of glucose, arterial hypertension in stage 2 and 3<sup>19</sup>, cardiopathies or pneumopathies confirmed or instability clinical, neuropathy unrelated the DM, regular physical activity more than one month, drugs beta-blockers, calcium channel blockers and beta-adrenergic agonists or the inability to understand and perform the tests.

### *Ethical aspects of research*

The 27 individuals who agreed participate in the study were explained about the procedures which would be submitted and signed an informed consent, approved by the Ethics Committee of Federal University of the Vales do Jequitinhonha and Mucuri under resolution number 008/09.

### *Experimental protocol*

The volunteers were divided into two groups which are: individuals with diagnosis of DM type 2 (DM 2, n = 10) and individuals diagnosed with DM type 1 (DM1, n = 5). The control groups consisted of individuals registered in the SFH or members of the University invited by the researchers, they should also meet the same inclusion criteria, except for the diagnosis of DM 1 or 2. The sample selected for the control totalized 12 individuals, distributed in two groups according to age should be similar to the experimental group: the control group for diabetes mellitus 1 (CDM1, n = 6) and the control group for diabetes mellitus 2 (CDM2, n = 6).

### *Autonomic tests and Paschoal Test*

Autonomic cardiovascular tests adopted were Valsalva maneuver, maneuver enhancement of Respiratory Sinus Arrhythmia and Handgrip addition of a submaximal Paschoal test. They were held in sequence presented with a range rest for the variables cardiovascular return to values baseline.

The protocols were performed with the individual in the sitting position, always controlling the temperature (20°C and 25°C) and relative humidity (between 40% and 60%).

For each protocol performed was registered a file hrn on the heart rate monitor, comprising the periods initial and final rest and the period of the maneuver.

#### *1. Valsalva maneuver<sup>12,20</sup>*

The Valsalva maneuver was performed while seated, this being told to keep the forced expiration against a closed glottis for 15 seconds with an expiratory pressure of 40 mmHg measured by manometer, observing two minutes of rest before performing of the maneuver and two minutes later to complete the same.

## 2. **Maneuver enhancement of Respiratory Sinus Arrhythmia**<sup>13,20</sup>

During the maneuver accentuation of respiratory sinus arrhythmia (RSA), with the subject sitting the same was asked to inhale and exhale deeply and slowly, and is also instructed to monitor the respiratory rate according to the verbal command of the evaluator, allowing themselves to 5-6 breaths per minute in a collect of about 6 minutes, the first two minutes of spontaneous breathing, 3rd and 4th minutes of RSA and 5th and 6<sup>th</sup> minutes with return to spontaneous breathing.

## 3. **Handgrip**<sup>20</sup>

Also known as static exercise, was the measure of grip strength, three maximal contractions, whichever is the greater of the same. We used 30% of this intensity in an isometric contraction sustained for at least 2 minutes with the patient in the sitting position, observing the periods of two minutes of rest before and after the maneuver. Both the measurement of force, and monitoring for its sustained isometric contraction was performed with the aid of a dynamometer.

## 4. **Paschoal Test**<sup>17</sup>

Finally we performed the Paschoal test, used in protocols of evaluation of the cardiac functional capacity. The volunteers were instructed to pedal on a cycle ergometer horizontal (Movement<sup>®</sup>H3), the highest possible speed for six minutes without resistance. The speed minimum average for validation was 20 km/h, and at the end of the test, the total distance traveled was recorded.

Between each autonomic maneuver performed inserted itself a period of rest for the HR returned to baseline, but was considered for HRV analysis only the period of the maneuvers.

## **HRV Analysis**

In all protocols of modulation autonomic evaluation was monitored and data recording of the HR beat to beat by Polar<sup>®</sup> frequencimeter (model S810i, 2001, Finland). Such equipment is validated in the literature to evaluate the autonomic modulation of HR<sup>21</sup> and, because of its low cost is available to clinical practice.

Data analysis was performed later to the transfer thereof to a computer using an infrared interface compatible with the frequencimeter model using the software Polar Precision Performance<sup>®</sup>.

After the transfer of data, HR graphics were analyzed visually and if necessary a digital filter was applied by their own analysis software. Furthermore, it was observed that each signal collected had a minimum of 256 points necessary to sustain the data analysis.

HRV was analyzed considering the indices in the time domain, using simple statistics and frequency domain, which by means of spectral analysis allows to decompose the HRV into its

components, defining them by their frequency and amplitude.

### **In the time domain the indices were used:**

RMSSD: represents the square root of the sum of the square of the differences between the iR-R in the registry divided by the number of iR-R at a given time minus one iR-R<sup>22</sup>. It is able to provide an indirect measure of parasympathetic activity specifically active in the sino atrial node<sup>23</sup>.

pNN50: which represents the percentage of the total number of iR-R that have a difference of more than 50 milliseconds relative to the previous R-Ri, also reflecting an indirect measure of parasympathetic tone<sup>24</sup>.

### **In the frequency domain were used the indices:**

Low frequency (LF): with variation range from 0.04 to 0.15 Hz, which is due to the joint action of vagal and sympathetic components of the heart, being that the sympathetic action is predominant. Therefore, this frequency band has been used as a marker of the sympathetic modulation on heart<sup>5,6</sup>.

High frequency (HF): with a variation range of 0.15 to 0.4 Hz, which corresponds to the respiratory modulation and is an indicator of the vago action in the heart<sup>5,6</sup>.

LF / HF ratio: ratio that reflects the absolute and relative interactions between the sympathetic and parasympathetic components of autonomic nervous system in heart<sup>25,26</sup>.

### **Statistical Analysis**

We used the Kolmogorov-Smirnov test, though there is the normal distribution of variables analyzed.

We compared the data of age, anthropometric characteristics, resting heart rate, systolic and diastolic blood pressure at rest and glucose between groups of volunteers with diabetes and their control groups using the unpaired t test.

The indices obtained by applying the experimental protocols (RMSSD, pNN50, LF, HF, LF/HF) were compared between groups of individuals with diabetes and their respective control groups using the unpaired t test. All statistical tests used in this study had a significance level set at 5%.

## **RESULT**

The results of this study are presented in Tables 1 and 2, on average and standard deviation. It is noted in Table 1 that the group of individuals with DM had higher blood glucose levels ( $p < 0.05$ ) when compared to their respective control groups. In addition, body weight and body mass index (BMI) were lower in DM1 patients group when compared to CDM1.

**Table 1:** Characteristics of individuals studied

	DM1 (n = 5)	CDM1 (n = 6)	p	DM2 (n = 10)	CDM2 (n = 6)	p
<b>Sex</b>	1Masc./4Fem.	3Masc./3Fem.	-	2Masc./8Fem.	3Masc./3Fem.	-
<b>Age (years)</b>	17.6±1.94	21.17±3.19	0.0577	56.9±10.59	66.67±16.51	0.1683
<b>Body Mass (kg)</b>	56.52±5.76	71.7±8.04	0.0065*	73.86±13.93	73.67±19.12	0.9816
<b>Heith (meters)</b>	1.62±0.09	1.72±0.07	0.0715	1.57±0.12	1.61±0.07	0.4623
<b>BMI (kg/m<sup>2</sup>)</b>	21.4±1.57	24.01±1.19	0.0121*	29.61±1.69	28.13±5.71	0.4481
<b>SBP (mmHg)</b>	122±19.24	102,67±10.63	0.0633	131,2±20.55	129,67±12.09	0.8713
<b>DBP (mmHg)</b>	78±10.95	71,33±7.23	0.2560	81,4±13.13	77,67±4.27	0.5155
<b>HR rest (bpm)</b>	95.2±23.56	77.7±9.33	0.1262	88.9±17.0	77.67±11.62	0.1769
<b>Glucose (mg/dL)</b>	429.2±79.69	94.5±10.78	< 0.0001*	211.1±89.63	101.67±15.80	0.0111*
<b>Number of hypertensive individuals</b>	0	0	-	4	1	-

\*  $p < 0.05$  - unpaired t test

HR rest (heart rate at rest) assessed by the radial pulse, BMI (body mass index), SBP (systolic blood pressure - mmHg), DBP (diastolic blood pressure - mmHg).

In Table 2, of the variables considered during the cardiac autonomic tests, the variable pNN50 was lower in DM1 compared to the group CDM1 in all maneuvers. Furthermore, the variable LF was lower in DM1 group compared to the CDM1 during ASR.

There were no statistical differences in the comparisons of the indices in the time and frequency domain when compared the DM2 and CDM2 groups.

We also found no statistically significant differences when comparing the distances traveled during the Paschoal test.

**Table 2:** Variables RMSSD, pNN50, LF, HF, LF / HF during cardiovascular autonomic tests and distance traveled on the test of Paschoal in individuals with diabetes and their respective controls

Maneuvers	Variables	DM1 (n = 5)	CDM1 (n = 6)	p	DM2 (n = 10)	CDM2 (n = 6)	p
<b>RSA</b>	RMSSD	69,86±41,27	147,52±70,40	0.0586	112,84±142,42	113,35±68,53	0.9936
	pNN50	4,2±5,78	18,72±9,47	0.0154*	4,72±5,56	4,48±3,34	0.9266
	BF	1843,54±1711,65	7749,37±4591,09	0.0242*	9450,13±22953,84	2460,63±1318,27	0.4746
	AF	1574,87±1594,83	7287,50±5459,19	0.0516	8411,20±21853,22	4351,28±5455,78	0.6659
	BF/AF	153,2±72,46	145,07±76,39	0.8612	216,09±181,48	101,47±58,10	0.1600
<b>Valsalva</b>	RMSSD	108,54±60,33	195,62±112,88	0.1574	95,29±56,45	136,52±92,05	0.2813
	pNN50	5,94±7,25	17,82±9,32	0.0456*	2,36±3,09	3,75±2,83	0.3842
	BF	2589,58±2629,90	11275,78±8376,80	0.0543	3025,91±2511,51	4487,23±5029,52	0.4471
	AF	3638,85±4442,97	14089,61±13012,15	0.1230	3323,90±3959,08	6134,53±8376,75	0.3741
	BF/AF	68,8±18,57	104,8±46,90	0.1434	153,54±140,87	130,57±132,54	0.7519
<b>Handgrip</b>	RMSSD	65,86±46,12	78,53±38,09	0.6290	109,23±51,53	139,92±81,83	0.3690
	pNN50	2,08±1,82	9,78±4,94	0.0095*	2,25±2,41	2,55±2,81	0.8240
	BF	2584,07±1799,32	3432,93±1601,58	0.4289	2173,19±1691,87	8711,84±14531,25	0.1717
	AF	1893,31±2825,76	2256,68±2479,30	0.8252	3687,09±3361,50	5757,14±5630,91	0.3682
	BF/AF	253,44±183,83	271,92±276,44	0.9015	66,91±20,14	141,27±154,25	0.1462
<b>Paschoal</b>	Distance (Km)	3,08±0,54	3,17±0,34	0.7406	2,65±0,43	2,60±0,58	0.8681

## DISCUSSION

In the present study, we used HRV to evaluate autonomic modulation of heart rate, because it is a noninvasive method, effective and low cost.

Studies report significant changes in HRV as a function of age, fitness level<sup>27</sup> and the presence of risk factors for coronary artery disease (CAD)<sup>28</sup> or established CAD<sup>29</sup>.

Besides these factors, the literature also shows that heart rate (HR) and systolic blood pressure (SBP) and diastolic (DBP) at rest is influenced by: genetic characteristics,

anthropometric measurements (weight and height), gender, hormonal and emotional factors, body position, environmental influences, level of physical fitness, clinical condition, among others<sup>9</sup>.

In this study, the values related to body mass and BMI were significantly lower in DM1 compared to CDM1. However, for both groups the values were situated in the normal range<sup>18</sup>. HR, SBP and DBP at rest showed no significant difference between groups. As expected, blood glucose levels in groups with a diagnosis of diabetes mellitus was higher when compared to their respective controls, confirming the presence of a primary disorder, either in liberation

or capture of insulin or both mechanisms, leading to high blood glucose levels found .

In relation to the indices in time domain, the values of RMSSD showed no statistically significant differences in comparisons between the groups with diabetes and their respective controls. However, the DM1 group had significantly lower pNN50 variable when compared to the control group CDM1 in all autonomic maneuvers performed, thus suggesting lower vagal activity in DM1 group.

According to the data of pNN50 variable, the results of this study are consistent with previous studies that found a reduction in vagal activity in patients with diagnosis of DM1<sup>30,31</sup>.

Considering the RMSSD values obtained in this study, lower mean values are observed in individuals with DM1 although not statistically significant. But it may be noted that there is great dispersion of data, observed by the high standard deviation in all maneuvers used, may explain the absence of statistical difference.

In relation to results obtained in the frequency domain, were found significantly higher values of the BF band for the individuals of the group CDM1 during the maneuver of accentuation of the respiratory sinus arrhythmia. However, these individuals also tended to have larger values of the AF band, even if no present statistically significant difference, so that there was no significant difference in LF / HF ratio, but with a tendency to lower values in CDM1.

Some studies have shown that a better way to characterize the sympathetic-vagal balance is the use of LF/HF ratio, which reflects the absolute and relative interactions between the sympathetic and parasympathetic components of autonomic nervous system in the heart<sup>5</sup>.

The results for the frequency domain, in DM1 group, are discordant from other previous studies that found a statistically significant difference, showing a diabetic autonomic neuropathy in the early stage of onset of the disease<sup>28,31,32</sup>.

The possible explanation for the absence of significant differences in the present work is the time of diagnosis of disease. As was not standardized the time of diagnostic of DM1 for inclusion of individuals in the study, this data was heterogeneous and may be the reason for the large dispersion of data and lack of significant difference.

In relation to subjects with DM2 were not statistically significant differences in any of the indices evaluated for autonomic maneuvers.

This result is similar to the results of previous studies that assessed HRV during autonomic maneuvers. In a recent study of HRV tests were used as the Valsalva maneuver and deep breathing and are not statistically significant differences

between healthy subjects and those with early diagnosis of diabetes<sup>33</sup>. Another study in 2008 evaluated healthy and obese women with and without DM2 during Handgrip maneuver, finding no statistically significant differences between groups<sup>34</sup>.

The results of this study differ from others found in the literature, where individuals with T2DM have increased sympathetic tone compared to healthy subjects<sup>35,36,37</sup>.

The values of the distance traveled during the performance of Paschoal test showed no statistically significant difference. This test offers a graduation of the physical capacity from the distance traveled on a cycle ergometer<sup>17</sup> in submaximal intensity (level of activity of daily living).

According to the literature it is expected under aerobic capacity in individuals diagnosed with diabetes mellitus<sup>38,39</sup>. One possible explanation for the results of this study in relation to functional capacity, is that the assessment protocol applied, using submaximal intensity of effort. Therefore, it is possible that the functional limitations resulting from the DM occurs in levels of physical exercise levels higher, not limiting the activities of daily living of individuals with DM.

The sample size and the lack of records regarding the duration of the disease can be identified as limiting factors in this study. We can still consider the difficulty of selecting a sample that fully meets the criteria inclusion, taking into consideration the high percentage of subjects with DM in association with other diseases such as hypertension and concomitant use of drugs, such as channel blockers calcium or beta-blockers, which greatly affect the autonomic modulation.

The variable pNN50 was significantly lower in subjects with diabetes mellitus type 1 in all cardiovascular autonomic tests performed, showing a reduction of parasympathetic activity in these individuals when compared to the control group. Already, the functional capacity assessed at submaximal levels were similar between subjects with and without Diabetes Mellitus, thereby inferring that the activity limitations due to the change in HRV found, occurs at higher levels of physical activity in the sample considered.

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