POOR GLYCEMIC CONTROL IMPACTS LINEAR AND NON-LINEAR DYNAMICS OF HEART RATE IN DM TYPE 2

POBRE CONTROLE GlicêmICO IMPACTA A DinÂMICa LINEAR E NÃO LINEAR DA FRECUÊNCIA CARDÍACA NO DM2

CONTROL GLUCÉMICO DEFICIENTE IMPACTA LA DÍNAMICA LINEAL Y NO LINEAL DE LA FRECUENCIA CARDIACa EN EL DM2

Daniela Bassi¹ (Physiotherapist)
Vivian Maria Arakelian¹ (Physiotherapist)
Renata Gonçalves Mendes¹ (Physiotherapist)
Flávia Cristina Rossi Caruso¹ (Physiotherapist)
José Carlos Bonjorno Júnior² (Physician)
Katany Thays Lopes Zangrado¹ (Physiotherapist)
Cláudio Ricardo de Oliveira³ (Physician)
Jacob Haus⁴,⁵ (Exercise Science)
Ross Arena⁶ (Physiotherapist)
Audrey Borghi-Silva¹ (Physiotherapist)

1. Universidade Federal de São Carlos (UFSCar), Laboratório Cardiopulmonar, São Carlos, Brasil.
2. Universidade de São Paulo, Departamento de Intenunidades de Bioengenharia, São Paulo, Brasil.
3. Universidade Federal de São Carlos (UFSCar), Departamento de Medicina, São Carlos, Brasil.
4. University of Illinois Chicago, Department of Kinesiology and Nutrition 6, College of Applied Health Sciences, Chicago, USA.
5. University of Illinois Chicago, College of Applied Health Sciences, Integrative Physiology Laboratory, Chicago, USA.
6. University of Illinois Chicago, Department of Physical Therapy and Integrative Physiology Laboratory, College of Applied Health Sciences, Chicago, USA.

Correspondence:
Audrey Borghi Silva
Rod. Washington Luis Km 235.
Laboratório de Fisioterapia Cardiopulmonar, Departamento de Fisioterapia, Universidade Federal de São Carlos, São Carlos, SP, Brasil. audrey@ufscar.br

ABSTRACT

Introduction: It is well known that type 2 diabetes mellitus (T2DM) produces cardiovascular autonomic neuropathy (CAN), which may affect the cardiac autonomic modulation. However, it is unclear whether the lack of glycemic control in T2DM without CAN could impact negatively on cardiac autonomic modulation. Objective: To evaluate the relationship between glycemic control and cardiac autonomic modulation in individuals with T2DM without CAN. Descriptive, prospective and cross sectional study. Methods: Forty-nine patients with T2DM (51±7 years) were divided into two groups according to glycosylated hemoglobin (HbA1c): G1≤7% and G2>7.0%. Resting heart rate (HR) and RR interval (RRi) were obtained and calculated by linear (Mean iRR; Mean HR; rMSSD; SD RR; LF; HF; LF/HF, TINN and RR Tri) and non-linear (SD1; SD2; DFA1; DFA2, Shannon entropy; ApEn; SampEn and CD) methods of heart rate variability (HRV). Insulin, HOMA-IR, fasting glucose and HbA1c were obtained by blood tests. Results: G2 (HbA1c<7%) showed lower values for the mean of iRR; STD RR; RR Tri, TINN, SD2, CD and higher mean HR when compared with G1 (HbA1c > 7%). Additionally, HbA1c correlated negatively with mean RRi (r=0.28, p=0.044); STD RR (r=0.33, p=0.017); RR Tri (r=0.35, p=0.013), SD2 (r=0.39, p=0.004) and positively with mean HR (r=0.28, p=0.045). Finally, fasting glucose correlated negatively with STD RR (r=-0.36, p=0.010); RR Tri (r=-0.36, p=0.010); TINN (r=-0.33, p=0.019) and SD2 (r=-0.42, p=0.002). Conclusion: We concluded that poor glycemic control is related to cardiac autonomic modulation indices in individuals with T2DM even if they do not present cardiovascular autonomic neuropathy.

Keywords: diabetes mellitus, type 2; blood glucose; heart rate; autonomic nervous system; hemoglobin A, glycosylated.

RESUMO

Introdução: É de conhecimento geral que o diabetes mellitus tipo 2 (DM2) produz neuropatia autonômica cardiovascular (NAC), que pode afetar a modulação autonômica cardíaca. Entretanto, não é claro se a falta de controle glícêmico em diabéticos tipo 2 sem NAC, poderia impactar negativamente na modulação autonômica cardíaca. Objetivo: Avaliar a relação entre controle glícêmico e modulação autonômica cardíaca em indivíduos com DM2 sem neuropatia autonômica cardiovascular. Estudo descritivo, prospectivo e transversal. Métodos: Quarenta e nove pacientes com DM2 (51±7 anos) foram divididos em dois grupos de acordo com a hemoglobina glicosilada (HbA1c): G1≤7% e G2>7.0%. A frequência cardíaca de repouso (Fc) e intervalo rr (irr) foram obtidos e calculados por métodos lineares (média irr; média Fc; r mSSD; StD rr; lF; HF; lF/HF , tinn e rr tri) e non-lineares (SD1; SD2; DFA1; DFA2, entropia de Shannon; ApEn; SampEn e CD) de variabilidade de frequência cardíaca. Insulina, HOMA-IR, glicemia de jejum e HbA1c foram obtidas por análiases sanguíneas. Resultados: G2 (HbA1c<7%) mostrou valores menores para média de irr; STD RR; RR Tri, TINN, SD2, CD e maiores para média de FR quando comparado com G1 (HbA1c > 7%). Adicionalmente, HbA1c correlacionou-se negativamente com media irr (r=0.28, p=0.044); STD RR (r=0.33, p=0.017); RR Tri (r=0.35, p=0.013), SD2 (r=0.39, p=0.004) e positivamente com média FC (r=0.28, p=0.045). Finalmente, a glicemia de jejum correlacionou-se negativamente com STD RR (r=-0.36, p=0.010); RR Tri (r=-0.36, p=0.010); TINN (r=-0.33, p=0.019) e SD2 (r=-0.42, p=0.002). Conclusão: Concluímos que o controle glicêmico deficiente relaciona-se com índices de modulação autonômica cardíaca em indivíduos com DM2, ainda que não apresentem neuropatia autonômica cardiovascular.

Palavras-chave: diabetes mellitus tipo 2, glicemia, frequência cardíaca, sistema nervoso autônomo, hemoglobina A glicosilada.

RESUMEN

Introducción: Es de conocimiento general que la diabetes mellitus tipo 2 (DM2) produce neuropatía autonómica cardiovascular (NAC), que puede afectar la modulación autonómica cardiaca. Entretanto, no es claro si la falta de control glucémico en diabéticos tipo 2 sin NAC, podría impactar negativamente en la modulación autonómica cardiaca. Objetivo: Evaluar la relación entre control glucémico y modulación autonómica cardiaca en individuos con DM2 sin neuropatía autonómica cardiovascular. Estudio descriptivo, prospectivo y transversal. Métodos: Cuarenta y
INTRODUCTION

Diabetes mellitus (DM) is one of the most common metabolic disorders in the world, in which more than 90% of the cases are type 2 DM (T2DM)\(^1\). Moreover, it is well known that T2DM is an important independent risk factor for cardiovascular mortality and morbidity\(^2\). Most patients with DM develop autonomic neuropathy, which is one of the more common complications in this population\(^1\). Damage to autonomic nerve fibers that innervate the heart and blood vessels consequently lead to abnormalities in heart rate (HR) control and vascular dynamics\(^3\). Comparatively, the mortality of DM patients manifesting an autonomic neuropathy is markedly higher\(^6,7\) than DM patients without autonomic neuropathy. Thus, early diagnosis of cardiac autonomic dysregulation is of great clinical importance in patients with DM\(^8\).

In 2007, Vinik and Dan Ziegler showed that heart rate variability (HRV) can accurately detect the presence of a cardiac autonomic neuropathy\(^9\). In fact, reduced HRV has been recognized as an early hallmark of cardiac autonomic neuropathy and it predicts mortality in patients with ischemic heart disease and DM\(^10,11\). Heart rate variability was first analyzed using linear models, such as spectral analysis\(^12\), however, nonlinear modeling has been recently proposed as a superior method to analyze the complexities of HR dynamics\(^4,5\). Comparatively, the mortality of DM patients manifesting an autonomic neuropathy is markedly higher\(^6,7\) than DM patients without autonomic neuropathy. Thus, early diagnosis of cardiac autonomic dysregulation is of great clinical importance in patients with DM\(^8\).

The study followed the Declaration of Helsinki guidelines and was approved by the Human Research Ethics Committee of our Institution (protocol number 1318/1). The procedure was explained to each subject separately and all signed written informed consent.

All subjects were investigated in a quiet room from 7:30 to 12:00am. All subjects were instructed to avoid caffeinated and alcoholic beverages 12 hours before the test and not to perform activities requiring moderate-to-heavy physical exertion.

HR and RR interval (RRi) recording

The HR and RRi were recorded continuously using a Polar S810i telemetry system (Polar Electro Oy, Kempele, Finland) and these data were used to quantify HRV. Each subject rested for 10 min before the initiation of data collection to ensure HR stabilization. Heart rate was then continuously recorded during a 10 min period of supine rest period.

HRV analysis

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The nonlinear dynamic properties of HRV were analyzed using measures such as approximate entropy (ApEn)\(^21\), correlation dimension (CD)\(^22\) and Poincaré plot\(^23\). ApEn quantifies the regularity of time series data and is represented as a simple index for the overall complexity and predictability of each time series. Large values of ApEn indicate high irregularity and smaller values of ApEn indicate a more regular signal. Thus, higher ApEn value reflects better health and function\(^21\). The nonlinear analysis of the Poincare plot of RRi was applied and the following two descriptors of the Poincare plot were used in the study: (i) SD1 – the standard deviation measuring the dispersion of points in the plot perpendicular to the line-of-identity. This parameter is usually interpreted as a measure of short-term HRV, which is caused mainly by respiratory sinus arrhythmia (parasympathetic modulation); and (ii) SD2 – the standard deviation measuring the dispersion of points along the identity line, which is interpreted as a measure of both short and long-term HRV (overall HRV)\(^23\).

Linear traditional measures in the time domain HRV analysis were evaluated by calculating the following, widely accepted, parameters: (i) mean of RR and its standard deviation (STD RR), also called SDNN, in ms; (ii) square root of the mean squared differences of successive RRi (rMSSD) in ms; and (iii) geometrical forms as the integral of the Poincare plot23. ApEn value reflects better health and function21. The nonlinear analysis of the Poincare plot of RRi was applied and the following two descriptors of the Poincare plot were used in the study: (i) SD1 – the standard deviation measuring the dispersion of points in the plot perpendicular to the line-of-identity. This parameter is usually interpreted as a measure of short-term HRV, which is caused mainly by respiratory sinus arrhythmia (parasympathetic modulation); and (ii) SD2 – the standard deviation measuring the dispersion of points along the identity line, which is interpreted as a measure of both short and long-term HRV (overall HRV)\(^23\).

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MATERIAL AND METHODS

Descriptive, prospective and cross sectional study. A total of 49 male and female (34 male and 15 female), participants diagnosed with type 2 DM (T2DM), aged 51.8 ± 6 years, were divided into two groups according to glycosylated hemoglobin (HbA1c): 1) G1: ≤7.0% (n=10) and 2) G2: >7.0%, (n=39)\(^9\), with or without additional coronary heart disease risk factors including hypertension (≥130 mmHg systolic or ≥80 mmHg diastolic) and dyslipidemia. Duration of diabetes was based on a self-reported date of diagnosis. Exclusion criteria consisted of a history consistent with heart disease, uncontrolled hypertension, musculoskeletal disorders, and other concomitant respiratory diseases.
Laboratory analysis

Blood specimens were obtained after an overnight fast for all measurements. HbA1c was measured in a central laboratory by anion-exchange high-performance liquid chromatography (Variant II, Bio Rad, Berkeley, California), coupled with a fluorescence detector method certified by the National Glycohemoglobin Standardization Program. Insulin resistance was evaluated by the Homeostatic model (HOMA–IR) which is calculated by the following formula: (fasting plasma glucose (mg/dl) x fasting plasma insulin (µU/ml)/22.5). Fasting plasma glucose was measured by an enzymatic method using an AU 680® (Beckman Couter, Suerlée (NAMUR) Belgium) and fasting plasma insulin was measured by a chemiluminescent assay (Unicel® Dxl 800, Pasadena, California). Total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured by an enzymatic method AU 680® (Beckman Couter, Suerlée (NAMUR) Belgium).

Statistical analysis

Data are reported as mean ± SD, unless otherwise specified. All data were verified for the assumptions of normality and comparisons of data were performed using unpaired T-Tests. Correlation of key variables was assessed using Spearman's correlation coefficients. Tests with a p-value < 0.05 were considered statistically significant. Statistical analyses were carried using Statistica 5.5 (StatSoft Inc., Tulsa, USA).

RESULTS

A total of 49 patients were evaluated over a 1-year period. Table 1 describes the clinical characteristics of all subjects and compares them according to an HbA1C threshold (G1 and G2). There were no significant differences in baseline characteristics: age, height, weight and BMI. Fasting plasma glucose was significantly higher in G2 and duration of diabetes was significant higher in G1 when compared to G2. Additionally, there were no significant differences regarding risk factors for cardiovascular disease and oral hypoglycemic medications.

The results of HRV indices are presented in table 2. Linear indices (Mean RR, STR RR, RR Tri and TINN) were significantly lower in G2 when compared to G1, with the exception of mean HR, which was significantly higher in the G2 when compared to G1. Non-linear dynamics of HR indices (SD2 and CD) demonstrated significantly lower values in G2 when compared to G1.

Table 3 lists Spearman correlation coefficient (r) results, demonstrating a negative and significant association between HRV linear indices and both HbA1c and FPG values. In addition, a negative relationship between SD2 and CD were observed with HbA1c and FPG. Duration of DM was not correlated with any HRV indices.

Table 1. Patient characteristics, stratified by assessment of glycosylated hemoglobin (HbA1c).

<table>
<thead>
<tr>
<th>HbA1c ≤ 7% (n=10)</th>
<th>HbA1c &gt; 7% (n=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>6 male/4 female</td>
<td>28 male/11 female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.2 ± 7.7</td>
<td>51.2 ± 7.2</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>82.7 ± 17.6</td>
<td>82.9 ± 17.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 1.0</td>
<td>170 ± 1.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7 ± 5.2</td>
<td>29.4 ± 5.3</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>6.4 ± 0.4</td>
<td>9.2 ± 1.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>125 ± 50.3</td>
<td>168.9 ± 59.7</td>
</tr>
<tr>
<td>Duration DM (years)</td>
<td>1.9 ± 1.0</td>
<td>6.5 ± 4.1</td>
</tr>
</tbody>
</table>

Risk factors CVD

- SAH: 6 (50%)
- Otw/Ob: 8 (80%)
- Dyslipidemia: 8 (80%)
- Biguanide: 6 (60%)
- Sulfonurea: 4 (40%)
- DPP4 inhibitor: 1 (10%)
- Combination: 3 (30%)

Indices of heart rate variability: Mean RR, mean of R-R intervals; Mean HR: mean heart rate; rMSSD: square root of the mean squared differences of successive RR; STD RR: standard deviation of RR; SD2 (ms) r = -0.39 0.004; STD RR r = -0.36 0.010; RR Tri r = -0.36 0.010; TINN r = -0.33 0.019; FPG (mg/dL) r = -0.39 0.004.

Indices of heart rate variability: Mean RR, mean of R-R intervals; Mean HR: mean heart rate; STD RR: standard deviation of RR; RR Tri: integral of the RR histogram divided by the height of the histogram; SD: standard deviation of instantaneous R-R interval variability; CD: short-term correlation properties of RRi; SE: Shannon Entropy; ApEn: approximate entropy; SampEn: sample entropy; CD: correlation dimension.
DISCUSSION

The main findings of the present study are: (i) individuals with T2DM with poor glycemic control presented with a greater impairment in linear and nonlinear HR dynamics compared to those with better glycemic control; and (ii) poor glycemic control negatively affects HRV dynamics, confirming our hypothesis. To our knowledge, this is the first study to address these relationships. The findings of the present study stress the clinical importance of early and ongoing strategies to manage blood glucose levels in T2DM in order to deter the numerous physiologic consequences of this condition, including a negative effect on HRV.

Negative effects of poor glycemic control on cardiac autonomic control

A reduction in HRV is common in patients with DM and it is also associated with adverse poor cardiovascular prognosis and stroke. The current study demonstrated that poor metabolic control negatively affects cardiac autonomic modulation in these patients, as observed by reduced HRV values. Therefore, in subjects with T2DM who are already prone to cardiac autonomic dysfunction, lack of glycemic control further compounds poor autonomic control of HR. Reduced HR variability is the earliest indicator of cardiovascular autonomic neuropathy and is thus important to prevent.

An interesting finding of the present study was the majority of subjects analyzed presented with poor glycemic control (79.6%). We expected the converse to be observed since all subjects were in treatment, receiving frequent medical follow-up. However, in the context of poor glycemic control, our study is consistent with Viana et al., in 2013, which described the clinical profile of Brazilian patients with T2DM managed by the public healthcare system.

Linear analysis on HRV and glycemic control

Specifically, in the present study, we observed that the time domain of HRV indicated that patients who presented with a HbA1c >7 had a lower Mean RRI, STD RRI, RR Tri and TINN. In 2005, Faulkner et al. compared autonomic control of HR in adolescents with T2DM, which had been diagnosed for at least a year, to those with T1DM; finding significantly lower levels of HRV time domain indices in the former group.

CAN in DM is the result of complex interactions between the degree of glycemic and disease duration. It has been shown that chronic hyperglycemia promotes progressive autonomic neural dysfunction in a manner that parallels the development of peripheral neuropathy. In this way, Matsushita et al., using a cut-off for HbA1c of 5.5 – 6.0%, showed a higher incidence of heart failure in a middle-aged population without DM, suggesting that chronic hyperglycemia may contribute to the development of heart failure.

HRV is commonly analyzed using linear models such as spectral analysis. Nonlinear analysis differs from traditional approaches because it considers qualitative properties of HR time series and could provide early and additional information of HR dynamics. Therefore, in this study, subjects with a HbA1c >7% showed reduced cardiovascular complexity, which is considered to be an early marker of risk for cardiovascular disease.

A recent study evaluated HRV in individuals with T2DM, without CAN, in response to an active postural maneuver and they showed that this cohort presented with higher cardiac sympathetic modulation. However, the complexity of HRV was not influenced by the imbalance of autonomic modulation in individuals with T2DM. In parallel, the current study was the first to show higher HbA1c in other words, uncontrolled and persistent hyperglycemia affects non-linear dynamics of HR, which has been considered an important early marker of abnormal cardiac modulation damage. The current study corroborates with Nayak et al., who observed that subjects with DM undergoing regular treatment with insulin and oral hypoglycemic agents did not demonstrate a correlation between CAN score and duration of diabetes. However, Nolan et al., found that duration of DM was independently and inversely associated with HRV markers of vagal HR modulation (HF power and rMSSD) and total R-R variability (SDNN) among male subjects. Taken together, these data suggest that the glycemic control may be time-dependent with duration of DM.

CONCLUSION

In conclusion, the findings of the current study suggest that patients with T2DM with poor glycemic control, as demonstrated by higher HbA1c values above the recommended target, are more susceptible to poor autonomic nervous control of HR. In this way, new
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