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Stratification of the Type 2 Diabetes Mellitus Based on Heart Rate Variability Parameters in Elderly Women at Rest

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ABSTRACT

Cardiac autonomic neuropathy in type 2 diabetes mellitus (T2DM) patients is frequent and associated with high cardiovascular mortality. The purpose of the present study was to stratify the T2DM using a logistic model based on parameters derived from heart rate variability (HRV). This study was designed as a cross-sectional study of consisted of thirty elderly women subjects 60 to 70 yrs of age with diagnosed with T2DM (N = 15) and healthy (N = 15). All subjects were instructed to lie in the supine position for 5 min at rest while breathing normally with a heart rate monitor Polar RS810 working at a sampling rate of 1000 Hz was used to record RR intervals (RRi). The HRV analysis in the time domain was performed to obtain the classical parameters pNN50, SDNN, RMSSD and MeanRRi and, subsequently, re-sampling procedure to bootstrapping based on 1000 samples. The model for predicting T2DM was obtained by backward stepwise multivariate logistic regression assuming as independent variable MeanRRi. This model presented 0.80 positive predictive value, 0.73 negative predictive value and 0.76 total accuracy. In conclusion, the use of the proposed MeanRRi parameter measured at rest seems to be able to stratify the T2DM in elderly women. The benefits of HRV monitoring the severity of T2DM should be potential as a reliable and non-invasive.

Keywords: Diabetes; Elderly; Heart rate variability; Cardiac autonomic neuropathy; Logistic regression

1 Introduction

Aging, an inevitable and extremely complex, multifactorial process, is characterised by the progressive degeneration of organ systems and tissues [1]. Many neurological diseases of in the elderly such as Parkinson's disease [2], Alzheimer's disease [3] and especially in those with diabetes [4] have been reported to be caused by age-related cholinergic dysfunction.

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycemia which results from defects in insulin secretion, insulin action or both. [5]. DM is associated with increased risk of multiple coexisting medical conditions in older adults, such as whether stringent glycemic control would be of net benefit [6].

In the sense, type 2 DM (T2DM) is increasingly frequent in the world in association with the increase of sedentary behaviors, unhealthy diet, obesity and metabolic syndrome [7-8] and a public health concern [9]. Cardiac autonomic neuropathy in type 2 diabetes mellitus (T2DM) patients with metabolic disease are at a high risk of cardiovascular complications ranging from microvascular dysfunction [10] to

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cardiometabolic syndromes including heart failure [11] and associated with high cardiovascular mortality [12].

Heart rate variability (HRV) is defined as variations in instantaneous heart rate and RR intervals measured using electrocardiography (ECG) and highly influenced by the Autonomic Nervous System [13]. The HRV assessment has been used as the gold standard to measure cardiac autonomic neuropathy [14]. T2DM was associated with an overall decrease in the HRV [12, 15, 16], but both sympathetic and parasympathetic activities were decreased, which can be explained by the deleterious effects of altered glucose metabolism on HRV, leading to cardiac autonomic neuropathy [17].

Recent studies have identified a possible link between HRV and T2DM or glucose intolerance [17-19]. In other words, loss of autonomic function resulting in a reduction in HRV may also have negative effects on the body's ability to process and store glucose [17]. Therefore, impaired parasympathetic regulation increases risk for chronic hyperglycemia also known as insulin resistance, which is a pre-cursor for diabetes mellitus [19]. However, until the present study it has not been investigated a simple, safe and accurate procedure for stratification of T2DM, only based on the resting parameters derived from HRV through the development of a mathematical model. Therefore, the purpose of the present study was to stratify the T2DM using a logistic model based on parameters derived from HRV.

2 Research Methods

The study protocol was approved by a local Ethical Human Research Committee of Universidade Federal do Amapá (protocol: 1230.276.2007), and an informed written consent was obtained from all subjects. This study was conducted in accordance with the instructions of the Helsinki Declaration of 2008 and in accordance with Resolution 466/2012 of the National Health Council.

2.1 Subjects

This study was designed as a cross-sectional and thirty elderly women, 60–70 years old, were divided into two groups, fifteen subjects each: control group (CG) and pathological group (PG) with a diagnosis of type 2 diabetes mellitus selected at random from the Project of the Health Promotion Program for People with Diabetes Mellitus (AMAP/UNIFAP) from the Federal University of Amapá located northwest of the North Region of Brazil, also known as the Amazon Region. In addition, no patient had severe or unstable cardiac disease, or any underlying comorbidity which could directly interfere with the performance of the tests. None of the recruited patients were involved in regular physical activity before participating in study. All subjects were nonsmokers, with no history of cardiopulmonary disease, and none were taking any medication or using home oxygen therapy.

2.2 Anthropometric Measurements

During an orientation session, the testing procedures and time commitment required for participation in this study were verbally explained to the potential volunteers. The data collection and the anthropometric variables were performed by the same and experienced evaluator throughout the study. For measuring both body weight and height participants were kept barefoot, wearing light clothes and not carrying any object. The height was measured in centimeters and the body mass was measured in kilogram with certified and calibrated mechanics scale (Filizola, Brazil). Body mass index (BMI) was calculated as the quocient ratio of weight over squared height (kg/m^2).

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2.3 Experimental procedures

The tests were conducted in a quiet room with temperature maintained at 22ºC. All subjects were instructed to avoid strenuous activity in the 24 hrs prior to each testing session and to avoid alcohol, caffeine, and the consumption of large meals for at least 3 hrs prior to testing.

In the visit to the lab, all subjects were instructed to lie in the supine position for 5 min at rest while breathing normally. A heart rate monitor Polar RS810 (Polar, Finland) working at a sampling rate of 1000 Hz was used to record RR intervals (RRi) during this period. The tachograms of RRi were transferred using an infrared interface device to the Polar Precision Performance SW software v. 3.0 (Polar, Finland), which automatically corrects RRi based on moving average filter. All records of sample data showed less than 2% error, and were then saved to ".txt" files.

2.4 Data Analysis

The HRV analysis in the time domain was performed by the SinusCor Matlab package software [20] to obtain the classical parameters: (a) pNN50 - the percentage of times in which the change in consecutive normal sinus (NN) intervals exceeded 50 ms; (b) SDNN - the standard deviation (SD) of all NN intervals (SDNN); (c) RMSSD - the root mean square of SD between adjacent NN intervals; and (d) MeanRRi - the mean of NN intervals. All parameters were computed as recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [21]. All signal analysis procedures were performed with programs written in Matlab version 2019.b (The MathWorks, USA).

2.5 Statistical Analysis

Descriptive statistical analyses of the data were expressed as mean ± standard deviation or standard error. The Kolmogorov-Smirnov test confirmed the normality of distributions. The bootstrap was used to estimate statistics of the HRV parameters on a population based on 1000 samples defined in terms of bias and confidence intervals [22]. The between groups difference in anthropometric characteristics was tested by Student's t-test for independent variables. The model for predicting the T2DM values through the logistic distribution function are probabilities where 1 corresponds to control and 0 to diabetes. A multivariate logistic regression (*stepwise*) was applied, assuming as independent variables the HRV parameters. The adjustment was selected by the least squared error, and the Wald test results were examined for individual parameters [23]. Thus, it was obtained a confusion matrix for plotting ROC curve with better sensitivity, specificity and global accuracy corresponding to a particular threshold, and the area under the curve (AUC) with standard error was used for expressing the overall discriminatory power [24]. All procedures assumed $p \leq 0.05$ for statistical significance and were processed in Matlab version 2019.b (The MathWorks, USA).

3. Results

Anthropometric characteristic of the subjects were similar between groups with low values of standard deviation (Table 1), values are mean ± standard deviation, showing no significant differences, which made it possible to two groups with homogeneous anthropometric characteristics. The actual power (1 - beta error level) was estimated as 0.99.

Table 1. Physical and anthropometric characteristics of each group

Variables	CG	PG	P-value
Age (years)	65.2 ± 2.1	64.0 ± 3.7	0.26
Height (cm)	150.5 ± 4.8	151.4 ± 7.3	0.71
Body Mass (kg)	64.5 ± 8.5	65.5 ± 10.7	0.78
BMI (kg/m^2)	28.4 ± 3.6	28.8 ± 4.9	0.83

Values are mean ± standard deviation (SD); *Significant difference in t-test

The bootstrap was used to estimate statistics of the HRV parameters on a population based on 1000 samples defined low bias and confidence intervals within the sample mean for both groups are showed in Table 2.

Table 2. The bootstrap of hate rate variability parameters of each group

Variables	CG	Bootstrapping		PG	Bootstrapping	
	Mean ± SE	Bias	CI95%	Mean ± SE	Bias	CI95%
MeanRRi (ms)	864.7 ± 17.5	0.06	829.4 – 899.7	767.3 ± 17.7	0.38	732.8 – 801.0
SDNN (ms)	29.5 ± 5.8	-0.18	19.0 – 41.7	29.0 ± 5.8	0.17	19.1 – 42.3
RMSSD (ms)	37.8 ± 8.9	-0.26	21.6 – 55.8	35.6 ± 7.7	0.22	21.9 – 52.6
pNN50 (%)	8.5 ± 4.1	-0.10	2.6 – 18.7	6.7 ± 2.8	0.12	2.3 – 12.8

Values are mean ± standard error (SE) and CI95% is confidence intervals 95%.

The HRV parameters were estimated in both groups and respective inter-group, however, alone the MeanRRi of PG was significantly less than those from CG ($p < 0.001$).

Considering this model logistic regression, all the added variables have few additional contributions (Table 3), thus a simple model maintain the quality of the adjustments in the predictive power of the model, according to equation for predicting probability of patients with T2DM resulting in values near zero:

$$PND = \frac{e^{-25.524+0.0313*MeanRRi}}{1+e^{-25.524+0.0313*MeanRRi}}$$

Where MeanRRi is the mean of normal sinus intervals.

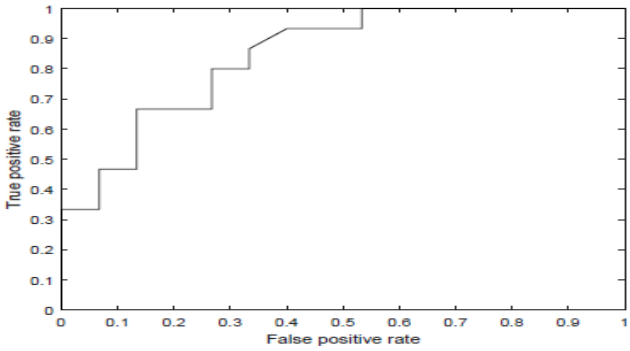

Figure 1. ROC for Classification by Logistic Regression to detect patients with T2DM.

Afterwards, the model showed 0.80 sensitivity, 0.73 specificity and 0.76 global accuracy with standard errors of 0.01 (p= 0.02) and the AUC was obtained in 0.84 (figure 1), which corresponded to a cut-off value of ≤ 817 ms to detect patients with T2DM.

3 Discussion

This study aimed to identify subjects with T2DM using the logistic regression model based on resting HRV analysis. This represented an important step for stratifying the degree of T2DM and extends the HRV applicability in the evaluation of the diabetes mellitus.

The number of people with T2DM is predicted to double within the next three decades [25]. Besides macrovascular and microvascular complications [10], the leading cause of death in T2DM is cardiovascular mortality [12]. The individuals at high risk for T2DM have lower heart rate variability, consequently, both parasympathetic and sympathetic activities were decreased [26, 27], which can be explained by the deleterious effects of altered glucose metabolism on HRV [18] and contribute to the development of diabetic cardiovascular autonomic neuropathy [28].

HRV analysis is a noninvasive method of assessing ANS activity and is related to variations between heartbeats due to sympathetic and parasympathetic innervations [13]. Thus, low HRV values indicate ANS deficiency [26, 27]. As the PG subjects presented lower values of SDNN, RMSSD and pNN50 when compared to CG, however, no significant difference (p = 0.73-0.95). The result supported the hypothesis that the decline is independent of cardiac autonomic function assessed by HRV, but declines most with aging, mainly, 65-70 years old [29] and that during stress, women had lower HRV than men [30].

Comparison with similar ECG changes in other diseases suggests that the electrocardiographic changes in DM patients are not specific and that they are particularly caused by an increased tone of the sympathetic nervous system and reduction in vagal tone [31] what was indirectly confirmed by the heart rate variability findings in these patients [32] and most heart rate variability parameters were lower in diabetes patients with chronic complications than in those without chronic complications [33].

The impact of T2DM on the electrical conduction of the heart and development of tachycardia is becoming increasingly apparent, but correlations between increased blood glucose levels, glucose fluctuation and hypoglycemia, and the heart beats too fast have been observed and are a likely initiator of the disease [34, 35]. Therefore, the result of the logistic regression model supported the hypothesis that lower values of MeanRRi adequately represents as a marker sympathetic control of the heart rate, decreasing the RR interval and thus it could be applicable to stratify TMD2 [26, 27, 32, 33], as observed in present study.

To the extent of our knowledge, the presented model is the first to stratify the T2DM from parameters derived only from heart rate variability at rest. It was applied with a homogeneous sample of elderly (60-70 years) women in healthy and with T2DM subjects. The bootstrap was used to estimate statistics of the HRV parameters on a population based on 1000 samples defined low bias and confidence intervals within the sample mean for both groups.

4 Conclusion

In conclusion, the use of the proposed MeanRRi parameter with cut-off value of ≤ 817 ms measured at rest seems to be able to stratify the T2DM in elderly women. The benefits of HRV evaluation in assessing

and monitoring the severity of T2DM should be potential as a non-invasive, reliable and pain-free measurement.

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DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relations hips that could be construed as a potential conflict of interest.

REFERENCES

[1] Nigam Y, Knight J, Bhattacharya S, Bayer A. Physiological changes associated with aging and immobility. J Aging Res. 2010;2012:468469. doi: 10.1155/2012/468469.

[2] Zucca FA, Segura-Aguilar J, Ferrari E, Muñoz P, Paris I, Sulzer D, et al. Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. Prog Neurobiol. 2017; 155:96-119. doi: 10.1016/j.pneurobio.2015.09.012.

[3] Pini L, Pievani M, Bocchetta M, Altomare D, Bosco P, Cavedo E, et al. Brain atrophy in Alzheimer's disease and aging. Ageing Res Rev. 2016;30:25-48. doi: 10.1016/j.arr.2016.01.002.

[4] Pintana H, Lietzau G, Augestad IL, Chiazza F, Nyström T, Patrome C, et al. Obesity-induced type 2 diabetes impairs neurological recovery after stroke in correlation with decreased neurogenesis and persistent atrophy of parvalbumin-positive interneurons. Clin Sci (Lond). 2019;133(13):1367-1386. doi: 10.1042/CS20190180.

[5] International Diabetes Federation. IDF diabetes atlas. 6th Brussels: International Diabetes Federation, 2013.

[6] Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. Diabetes care. 2006;29(3), 725-731. doi.org/10.2337/diacare.29.03.06.dc05-2078

[7] Jaacks LM, Siegel KR, Gujral UP, Narayan KMV. Type 2 diabetes: A 21st century epidemic. Best Pract Res Clin Endocrinol Metab. 2016;30: 331–343

[8] Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care. 2010;33: e147–e167. doi.org/10.2337/dc10-9990

[9] Da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, Guariguata L, Seuring T, Zhang P, et al. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. Diabetes Res Clin Pract. 2016;117:48–54. doi.org/10.1016/j.diabres.2016.04.016

[10] Rafeh R, Viveiros A, Oudit GY, El-Yarzi AF. (2020). Targeting perivascular and epicardial adipose tissue inflammation: therapeutic opportunities for cardiovascular disease. Clin Sci (Lond). 2020;134(7):827-851. doi: 10.1042/CS20190227.

[11] Bhaskar, S. Impact of obesity-induced type 2 diabetes on long-term outcomes following stroke. Clin Sci (Lond). 2019;133(14):1603-1607. doi: 10.1042/CS20190492.

[12] Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuiji H, Lloyd-Jones DM, et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol. 2000;86:309–312

[13] Albarado-Ibañez A, Arroyo-Carmona, RE, Sánchez-Hernández R, Wilson PF, Tsuiji H, Lloyd-Jones DM, et al. The Role of the Autonomic Nervous System on Cardiac Rhythm during the Evolution of Diabetes Mellitus Using Heart Rate Variability as a Biomarker. J Diabetes Res. 2019;2019:5157024. doi: 10.1155/2019/5157024.

[14] Arroyo-Carmona RE, López-Serrano AL, Albarado-Ibañez A, Mendoza-Lucero FMF, Medel-Cajica D, Lópesz-Mayirga RM, et al. Heart rate variability as early biomarker for the evaluation of diabetes mellitus progress. J Diabetes Res. 2016;2016:8483537. doi: 10.1155/2016/8483537

[15] Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Magdasy S, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta–analysis. PloS one. 2018;13(4):e0195166. doi: 10.1371/journal.pone.0195166

[16] Javorka M, Javorková J, Tonhajzerová I, Calkovska A, Javorka K, et al. Heart rate variability in young patients with diabetes mellitus and healthy subjects explored by Poincare and sequence plots. Clin Physiol Funct Imaging. 2005; 25:119–127.

[17] Schroeder E, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, et al. Diabetes, Glucose, Insulin, and Heart Rate Variability. Diabetes Care, 2005; 28:668-674.

[18] Bahremand M, Shahebrahimi K, Seyedi F, Montazeri, N. Relationship between changes in heart rate variability indices and blood glucose control in Type 2 Diabetes Mellitus. Revista Latinoamericana de Hipertension. 2019;14(3), 328-331.

[19] Zaidi AS, Singh PN, Gupta M, Siddiqi SS. Effect of Duration of Diabetes on Heart Rate Variability in Type 2 Diabetes Mellitus. Int J Cur Res Rev. 2018;10(6): 37-42.

[20] Bartels R, Neumamm L, Peçanha T, Carvalho ARS. SinusCor: An advanced tool for heart rate variability analysis. Biomedical Engineering Online. 2017;16(1):110.

[21] Task Force of the European society of cardiology and the North American society of pacing and electrophysiology. Heart rate variability-standards of measurement, physiological interpretation and clinical use. European Heart Journal. 1996;93:1043-65.

[22] DiCiccio TJ, Efron B. Bootstrap confidence intervals. Statistical Science, 189-212, 1996.

[23] Hanley JA, Mcneil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983;148(3), 839-43.

[24] Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: Wiley, 2000.

[25] Ginter E, Simko V. Type 2 diabetes mellitus, pandemic in 21st century. In Diabetes (pp. 42-50). Springer, New York, NY, 2013.

[26] Ribeiro ÍJS, Pereira RF, Valença Neto P, Freire IV, Casotti CA, Reis MGD. Relationship between diabetes mellitus and heart rate variability in community-dwelling elders. Medicina. 2017;53(6):375-379.

[27] Cha SA, Park YM, Yun, JS, Seung-Hwan Lee, Yu-Bae Ahn, Sung-Rae Kim, et al. Time-and frequency-domain measures of heart rate variability predict cardiovascular outcome in patients with type 2 diabetes. Diabetes Res Clin Pract. 2018;143:159-169.

[28] Liu Y, Jansen HJ, Rose RA. Impaired parasympathetic nervous system regulation of heart rate and sinoatrial node function in type 2 diabetes mellitus. Biophysical Journal. 2020;118(3):102a.

[29] Stein PK, Barzilay JI, Chaves PH, Domitrovich PP, Gottdiener JS. Heart rate variability and its changes over 5 years in older adults. Age and ageing, 38(2):212-218. doi: 10.1093/ageing/afn292.

[30] Hamidovic A, Van Hedger K, Choi SH, Flowers S, Wardle M, Childs E. Quantitative meta-analysis of heart rate variability finds reduced parasympathetic cardiac tone in women compared to men during laboratory-based social stress. Neurosci Biobehav Rev. 2020;S0149-7634(19)31029-2. doi: 10.1016/j.neubiorev.2020.04.005.

[31] Mba, C. M., Nganou-Gnindjio, C. N., Azabji-Kenfack, M. et al. (2019). Short term optimization of glycaemic control using insulin improves sympatho-vagal tone activities in patients with type 2 diabetes. Diabetes Res Clin Pract, 157:107875. doi: 10.1016/j.diabres.2019.107875.

[32] Kittnar O. Electrocardiographic changes in diabetes mellitus. Physiological Research. 2015;64:S559.

[33] Bassi D, Cabiddu R, Mendes RG, Tossini N, Arakelin VM, Caruso FCR, et al. Effects of coexistence hypertension and type II diabetes on heart rate variability and cardiorespiratory fitness. Arq Bras de Cardiol. 2018;111(1):64-72.

[34] Agarwal G, Singh SK. Arrhythmias in type 2 diabetes mellitus. Indian Journal of Endocrinology and Metabolism. 2017;21(5):715.

[35] Ziegler D, Strom A, Bönhof G, Püttgen S, Bódis K, Burkart V, et al. Differential associations of lower cardiac vagal tone with insulin resistance and insulin secretion in recently diagnosed type 1 and type 2 diabetes. Metabolism. 2018;79:1-9. doi: 10.1016/j.metabol.2017.10.013.

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