Promoção da Saúde
DOI: 10.17765/2176-9206.2025v18e12855

Repeated diagnosis of covid-19: influence on autonomic modulation and functional capacity in older people

Diagnóstico repetido de covid-19: influência na modulação autonômica e capacidade funcional de pessoas idosas

Thamyres da Cruz Miranda[1,2], Leonardo Hesley Ferraz Durans[1,3], Kamilla de Jesus Reis Cruz[1], Helen Nara da Silva e Silva[1,3], Cristiano Teixeira Mostarda[1,4], Flávio de Oliveira Pires[1,4]

[1]Laboratory of Cardiovascular Adaptations to Exercise - LACORE, Federal University of Maranhão (UFMA), São Luís (MA), Brazil; [2]Postgraduate Program in Physical Education, Federal University of Maranhão (PPGEF/UFMA), São Luís (MA), Brazil; [3]Master's Degree in Adult Health, Federal University of Maranhão, São Luís (MA), Brazil; [4]Faculty Member, Federal University of Maranhão, São Luís (MA), Brazil.

***Corresponding author**: Cristiano Teixeira Mostarda – *Email*: cristiano.mostarda@gmail.com

ABSTRACT
Aim: To analyze the influence of the number of times of diagnosis of covid-19 on autonomic modulation and functional capacity in the older people. Methodology: This is a quantitative cross-sectional study, which included 38 without covid-19 (Control), 25 who had covid-19 once (C1), and 16 infected with covid-19 two or more times (C2+). Anamnesis, anthropometry, blood pressure collection, 6-minute walk test, Time Up and Go and resting electrocardiogram were performed. Data were analyzed by Kolmogorov-Smirnov, followed by 1-way ANOVA and Tukey-Kramer Multiple Comparisons Test, with significance for $p \leq 0.05$. Results: No differences were found between age, Body Mass Index, systolic and diastolic blood pressure. In terms of autonomic variables, there was a reduction in NN intervals ($p=0.04$) when comparing C1 and C2+, an increase in LF/HF when comparing C2+ to the control group and C1 ($p=0.02$), a reduction in SD2 ($p=0.01$) between C1 and C2+ when compared to the control group, and a reduction in Alpha 1 when comparing the control group to the C1 and C2+ groups ($p=0.001$). Conclusion: It is suggestive that individuals with a higher number of reinfections may be subject to reduced Heart Rate Variability and increased cardiac autonomic dysfunction.

Keywords: Covid-19. Functionality. Older people. Reinfection. Heart rate variability.

RESUMO
Objetivo: Analisar a influência do número de vezes de diagnóstico de covid-19 sobre a modulação autonômica e capacidade funcional de idosos. Metodologia: Trata-se de uma estudo transversal quantitativo, que foram incluídos 38 sem covid-19 (Controle), 25 que tiveram covid-19 uma vez (C1), e 16 infectados por covid-19 duas ou mais vezes (C2+). Foi realizado anamnese, antropometria, coleta de pressão arterial, Teste de caminhada de 6 minutos, *Time Up and Go* eletrocardiograma de repouso. Os dados foram analisados por Kolmogorov-Smirnov, seguido de ANOVA 1 via e Tukey-Kramer Multiple Comparisons Test, com significância para $p \leq 0.05$. Resultados: Não foram encontradas diferenças entre idade, Índice de massa corporal, pressão arterial sistólica e diastólica. Nas variáveis autonômicas, houve redução dos intervalos RR ($p=0.04$) comparando C1 e C2+, aumento de LF/HF comparando C2+ ao grupo controle e C1 ($p=0.02$), redução de SD2 ($p=0.01$) entre C1 e C2+ quando comparados ao grupo controle, e diminuição de Alpha 1 quando comparado grupo controle aos grupos C1 e C2+ ($p=0.001$). Conclusão: É sugestivo que indivíduos com maior número de reinfecções podem estar sujeitos a redução da Variabilidade da Frequência Cardíaca e aumento de disfunção autonômica cardíaca.

Palavras-chave: Covid-19. Funcionalidade. Idosos. Reinfecção. Variabilidade da frequência cardíaca.

INTRODUCTION

Coronavirus is a rapidly transmissible virus that causes respiratory infections with a very broad clinical aspect, and can vary from cases with mild to severe symptoms[1,2]. Covid-19 infection can cause prolonged complications that generate sequelae lasting approximately three months after the initial recovery, which has come to be called long covid or post covid-19 syndrome[3]. Post-covid 19 syndrome is a condition with multiple subsequent symptoms, with persistent coughing, fatigue and dyspnea, and may be related to dysregulation of the autonomic nervous system[4], the mechanism of which implies a worse prognosis[5], especially in the older people.

Although a first contact with the virus that causes covid-19 generates a number of alterations in various body systems, reinfection with the disease has been a cause for concern due to the supposed exacerbation of symptoms, due to an increase in antibodies or exposure to greater amounts of the virus, and may be the reason for an increase in the number of systemic alterations due to a repeat diagnosis of covid-19, generating permanent humoral, cardiac and neurological alterations due to the process of new infection[6,7].

Studies of the body components of these cases of reinfection may make it possible to identify increased changes that generate worse consequences in the elderly population. Identifying such factors can be of great importance, given that recent reinfection can evolve in a more serious way compared to the first infection[8].

In this context, the observation of autonomic modulation, indicated by Heart Rate Variability (HRV), stands out as it shows that a reduction in its values in the baseline condition can be an indication of abnormal and ineffective adaptation of the autonomic physiology of the nervous system, and is a predictive method for identifying and preventing diseases[9], as in cases of long covid-19, which can be altered in the event of reinfection.

HRV is a method increasingly used to assess the modulation of the autonomic nervous system on the heart. Studies show that a reduction in HRV has been associated with an increased risk of developing cardiovascular diseases and mortality in the older people, and may be able to identify alterations caused by covid-19, such as in cases of residual sequelae[10].

In addition, in this post-process phase of the first covid-19 infection, it is possible to identify some degree of physical and functional implications, capable of impairing the ability to carry out activities of daily living by impairing the functionality of individuals over 60 years of age who have had covid-19, interfering with professional performance and hindering social interaction[11].

Assessing the functional capacity of this elderly population infected and reinfected by covid-19 through, for example, the 6-minute Walk Test (6MWT) and the Time Up and Go (TUG), which are tests carried out to assess the individual's development during exercise, can enable an analysis of physical fitness and cardiorespiratory functionality, through signs presented during the test, applied to individuals with pre-existing diseases[12,13].

Covid-19 has represented a huge challenge for health systems around the world. However, organizations all over the world have been concerned with dealing with the physical and psychological sequelae left by the pandemic, and various changes that are not yet specific about the remaining effects of the disease after infection[14].

Few studies have investigated autonomic and functional capacity variables in the older people after repeated infection with covid-19. In this context, it is relevant to analyze the HRV and functionality of this population of older people who have had covid-19, stratified by the number of times infected, in order to identify possible autonomic and functional changes in these individuals according to the number of infections.

METHODOLOGY

STUDY DESIGN AND ETHICAL ASPECTS

This is a cross-sectional, quantitative and analytical study, approved by the Human Research Ethics Committee of the University Hospital of the Federal University of Maranhão (HU/UFMA), CAAE nº. 57650022.6.0000.5086. This study was carried out in accordance with all the recommendations of the 1964 Declaration of Helsinki.

The individuals were informed about the risks and benefits of the research, and those who agreed to take part signed an informed consent form.

PARTICIPANTS AND STUDY SETTING

The study was carried out between May 2022 and July 2023, at the Center for Comprehensive Health Care for the Elderly, São Luís, Brazil. A non-probabilistic convenience sample included older people of both sexes, aged between 60 and 80, who had or had not been diagnosed with covid-19 once or more, divided into three groups: a group without covid-19 (Control), a group who had Covid-19 only once (C1), and a group infected with covid-19 twice or more (C2+).

Eligible individuals were older people who had tested positive for covid-19 in a retrospective window of no more than one year from the time of the interview, with no history of hospitalizations and no pulmonary impairment as a result of the disease, both sexes, aged between 60 and 80 years, hemodynamically stable, cooperative with the practice adopted, and who did not have psychiatric disorders or decompensated hypertension. Individuals who met any of these criteria were not included in the study, or were excluded if identified during data collection.

The control group included older people with no previous diagnosis of covid-19, both sexes, aged between 60 and 80, who met the criteria described above.

ANAMNESIS

Data was collected from the individuals, such as: name, gender, date of birth, age, telephone number, address, occupation, marital status, diagnosis of other diseases. All procedures took place on the same day.

ANTHROPOMETRIC ASSESSMENT

Weight was measured using a digital scale in kilograms (Balmak, BK - 50FAN, São Paulo). Height was measured using a Trena Compact EST 23 stadiometer in millimeters. The participants were instructed to remain in an orthostatic position to measure the data. In addition, the Body Mass Index (BMI) was calculated using the formula weight (kg)/height (m^2).

BLOOD PRESSURE

Systolic and diastolic blood pressure were measured using the auscultatory method (Sphygmomanometer with a precision of 1 mmHg and stethoscope, both Premium brand), and classified according to the Brazilian Guidelines for Hypertension[15]. These blood pressure values were measured after anamnesis, with the elderly at rest.

FUNCTIONAL TESTS

Patients' gait was assessed using the TUG test, and participants were initially instructed on how to perform the test. The test began when the volunteer stood up from a chair, walked 3 meters forward, and returned to the chair in their starting position, and the time taken to complete the test was timed. The classification is based on the time taken, with <10 seconds being a low risk of falling, 11 to 20 seconds a moderate risk of falling, 21 to 29 seconds a high risk of falling, and ≥ 30 seconds a high risk of falling[13].

A 6MWT was also carried out, which is a standardized measure of functional capacity, capable of reflecting activities of daily living, where participants walked on a flat surface for 6 minutes, at a predetermined distance of 30

meters demarcated at the ends by signal cones. Participants were warned to discontinue the test if they presented any limiting symptoms[12,16,17].

HEART RATE VARIABILITY

HRV was obtained continuously and non-invasively, beat by beat, using a 12-lead electrocardiogram developed for HRV data collection (Micromed Biotecnologia, Wincardio). The data was collected with the subjects in the supine position for a period of 10 minutes. After data collection, the NN intervals were analyzed using the Kubios HRV 3.5.0 software (Kuopio, Finland).

HRV was analyzed using linear and non-linear methods, respectively: NN variance (NN), the square root of the mean of the square of the differences between adjacent normal NN intervals (RMSSD), the standard deviation of normal NN time series interval (SDNN), Low Frequency (LF), High Frequency (HF), and sympathovagal balance (LF/HF); standard deviation of instantaneous beat-to-beat variability (SD1), long-term standard deviation of continuous NN intervals (SD2), short-term fractal scale exponent (Alpha) 1 and long-term exponent (Alpha 2).

STATISTICAL ANALYSIS

The data was analyzed using the Kolmogorov-Smirnov test to assess the normality of its distribution. Next, analysis was carried out using the One-way Analysis of Variance test, followed by the Tukey-Kramer Multiple Comparisons Test, and the results were considered statistically significant for $p \leq 0.05$. The figures were made using GraphPad Prism 6.01 statistical software (GraphPad, San Diego, California, USA).

RESULTS

The results presented in mean ± standard deviation in Table 1 show the characterization of the sample and anthropometric and physiological variables between the groups. 79 older people of both sexes were included, divided into three groups: 38 in the Control group, 25 in the C1 group, and 16 in the C2+ group. There were no significant differences between the groups in terms of age, BMI, systolic blood pressure and diastolic blood pressure. However, there was a significant difference in body measurements between the groups, with an increase in weight in the C1 and C2+ groups ($p = 0.02$).

With regard to the medications used by the older people (Table 1), we did not observe any influence of the use of statins between the groups ($p = 0.93$); and it is important to note that some older people were taking polypharmacological treatment to treat comorbidities.

Table 1. Characterization of the sample and anthropometric, physiological and medication variables between the groups.

Variables	Control (N = 38)	C1 (N = 25)	C2+ (N = 16)	p
Age (years)	67.81 ± 3.14	68.25 ± 5.89	68.81 ± 4.76	0.78
Weight (kg)	61.97 ± 13.47	65.74 ± 8.6	71.96 ± 12.25*	**0.02**
BMI (kg/m²)	26.47 ± 5.39	27.18 ± 3.82	29.46 ± 4.38	0.11
DBP (mmHg)	76.56 ± 9.68	76.37 ± 8.69	74 ± 8.81	0.62
SBP (mmHg)	130.62 ± 17.55	125.46 ± 13.6	128.31 ± 15.33	0.42
Medication				
Statins	17	13	9	x^2
Antidiabetic	21	25	15	
ACEI	4	1	1	0,93
Diuretic	1	1	1	
Beta blocker	4	1	2	

ARA2	1	1	1
BCC	2	1	2

Control: group without covid-19; C1: group that had covid-19 only once; C2+: group infected with covid-19 two or more times; BMI: Body Mass Index; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure. *p≤0.05. ACEI: Angiotensin Converting Enzyme Inhibitors; ARA2: Angiotensin 2 Receptor Antagonist; BCC: Calcium Channel Blocker. Data presented in absolute values; chi-squared test *p≤0.05.

The HRV data is shown in Table 2. In the time domain, there was a reduction in NN intervals between heartbeats when comparing the control group to C1 and C2+ ($p = 0.04$). In the frequency domain, there was an increase in LF/HF when comparing the C2+ group to the control group and C1 ($p = 0.02$). Among the non-linear methods, a significant difference was observed for the SD2 index ($p = 0.01$) between the C1 and C2+ groups when compared to the control group, representing a decrease in global modulation; and Alpha 1 showing a decrease in parasympathetic modulation when comparing the control group to the C1 and C2+ groups ($p = 0.001$).

Table 2. HRV analysis between the Control, C1 and C2+ groups.

Variables	Control (N = 38)	C1 (N = 25)	C2+ (N = 16)	p
		Linear methods		
		Time domain		
NN (ms²)	927.76 ± 124.42	907.34 ± 98.71	840.64 ± 106.98$^{\mu}$	**0.04**
RMSSD (ms)	25.42 ± 14.28	24.45 ± 14.64	20.21 ± 15.2	0.51
SDNN (ms)	23.62 ± 14.56	21.74 ± 13.38	14.66 ± 5.85	0.06
		Frequency domain		
HF (ms²)	312.71 ± 376.88	183.36 ± 166.17	116.25 ± 153.83$^{\#\mu}$	**0.04**
LF (ms²)	313.2 ± 500.25	164.85 ± 184.19	106.85 ± 94.95	0.08
LF/HF	0.89 ± 0.73	0.81 ± 0.49	1.39 ± 0.87$^{\#\mu}$	**0.02**
		Non-linear methods		
SD1 (ms)	18.07 ± 12.26	16.5 ± 5.87	15.15 ± 7.4	0.76
SD2 (ms)	31.97 ± 21.16	19.53 ± 6.3*	18.34 ± 4.59$^{\mu}$	**0.01**
Alfa 1	1.08 ± 0.23	0.75 ± 0.23*	0.79 ± 0.25$^{\mu}$	**0.001**
Alfa 2	0.4 ± 0.1	0.41 ± 0.07	0.47 ± 0.15	0.33

Control: group without covid-19; C1: group that had covid-19 only once; C2+: group infected with covid-19 two or more times; NN: NN variance; RMSSD: square root of the mean square of the differences between adjacent normal NN intervals; SDNN: standard deviation of the interval of normal NN time series, LF: Low Frequency; HF: High Frequency; LF/HF: sympathovagal balance; SD1: standard deviation of instantaneous beat-to-beat variability; SD2: long-term standard deviation of continuous NN intervals; Alpha 1: Short-term fractal scale exponent; Alpha 2: Long-term exponent. *control vs C1; $^{\#}$C1 vs C2+; $^{\mu}$control vs C2+, $^{*\#\mu}$p≤0.05.

Figure 1 shows the mean ± standard deviation of the functional tests assessed. There was no statistical difference between the groups for the 6MWT ($p=0.1$) and TUG ($p=0.24$).

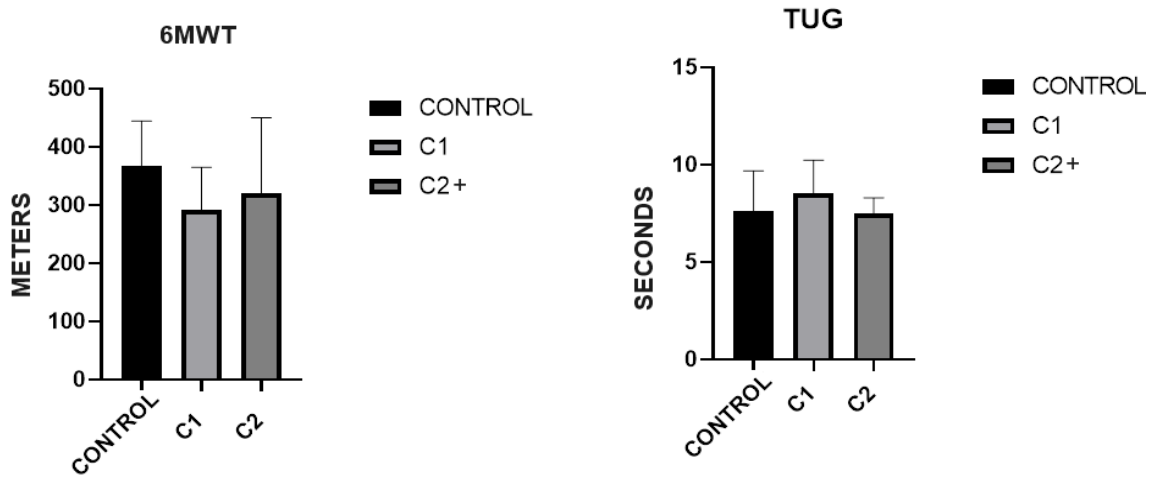

Figure 1. Analysis of functional capacity between groups.
Control: group without covid-19; C1: group that had covid-19 only once; C2+: group infected with covid-19 two or more times; 6MWT: 6-minute walk test; TUG: Time Up and Go. *p≤0,05.

DISCUSSION

This study analyzed the influence of the number of times of diagnosis of covid-19 on cardiac autonomic modulation and functional capacity in the older people. The main findings of this study suggest that older people infected with covid-19 may show a decrease in global HRV and parasympathetic activity, as well as an autonomic imbalance, demonstrating that the greater the number of times the disease is diagnosed, the more the cardiac autonomic function of these individuals is altered. In addition, weight gain was seen in the groups affected one or more times by the disease.

In post-covid 19 syndrome, a significant number of symptoms described in case reports, population studies and meta-analyses show that infection with the disease can substantially affect the autonomic nervous system[18]. High levels of catecholamines in prolonged orthostasis can trigger the vasovagal reflex, with suppression of sympathetic activity and parasympathetic activation, causing paradoxical vasodilation, hypotension and, consequently, syncope[18].

Corroborating our findings, studies such as Durans et al.[10], when analyzing the cardiac autonomic modulation of elderly diabetic women in the post-covid 19 syndrome, showed a reduction in the autonomic indices of NN (ms²), HF-log (ms²), LF-log (ms²), and SD2 (ms), suggesting that elderly women who have had covid-19 have interference in HRV with a decrease in parasympathetic autonomic modulation.

Cardiovascular dysautonomia often occurs in patients recovering from covid-19 and, associated with our findings, studies such as Marques et al.[19] show that linear and non-linear methods have shown good accuracy in verifying changes in HRV, suggesting that they are capable of identifying changes in the autonomic control of cardiac function in elderly individuals who have had covid-19, showing lower parasympathetic activity and sympathovagal imbalance.

Our findings showed a decrease in parasympathetic modulation, as seen by Alpha 1, when comparing the control group to the C1 and C2+ groups, which may represent non-linear methods as a good indicator for identifying changes in autonomic modulation, and quantifying or stratifying morbidity and mortality in individuals with chronic diseases who are in the long covid phase[20].

According to Vanderlei et al.[21], non-linear systems have been applied to interpret, explain and predict the behavior of biological phenomena, and these parameters have been shown to be good predictors of morbidity and mortality in the clinical field, and corroborate the findings of Huikuri et al.[22] where they show that the use of non-linear methods in HRV can be more powerful in terms of risk stratification to predict sudden death.

Reinforcing our findings, seen by the increase in weight in the groups affected one or more times by covid-19, Jesus et al.[23] and Garcia and Miranda[24] concluded that covid-19 can generate an impact that contributes to increased body weight and overweight in this elderly population, and that high weight would be related to a reduction in HRV, and would worsen in association with covid-19.

Although we didn't see any significant correlations in the functional capacity assessments, in contrast to our findings, Badal et al.[25] and Cunha et al.[26] showed that there can be a reduction in the distance covered assessed by the 6MWT, revealing impaired functionality.

Costa et al.[27], corroborating our study, used TUG to assess the functional status of post-covid 19 patients and found no significant difference in this test. In contrast, Kowal et al.[28], in order to determine the long-term effects of covid-19 on gait, showed a significant correlation for changes in range of motion in relation to the TUG.

With regard to the main medications used by the older people evaluated in our study, Italia et al.[29] and Maciel et al.[30], suggest that although statins have known anti-inflammatory effects and provide protection against cardiovascular outcomes, the lack of protection against infections and the potential promotion of cardiac and skeletal muscle impairment can worsen the results of covid-19, thus generating significant concerns regarding the use of statins associated with this disease, as aging can predispose to arterial stiffening and metabolic changes, which can culminate in cases of diabetes and hypertension.

According to Ferrari and Santos[31], their findings hypothesize that statins could worsen covid-19 infection, although the literature does not yet confirm that the use of statins worsens the prognosis of covid-19.

Although there are some limitations, such as not checking nutritional and biochemical factors, physical exercise practices, and levels of anxiety and depression, which are factors that can often be linked to this elderly population, in addition to anthropometric and sociodemographic data retrospective to covid-19 infection, this study makes an important contribution to understanding the changes caused by covid-19 in cardiac autonomic modulation in the older people, being one of the first to work with the study of reinfection of the disease associated with autonomic variables.

PRACTICAL IMPLICATIONS

These findings are important because many older people diagnosed with covid-19 continue to suffer from autonomic dysfunction, which can be aggravated if there are periods of reinfection with the covid-19 virus, which could be an important risk factor for cardiovascular disease in this population.

In view of this, the inclusion of risk stratification plans for the cardiorespiratory and autonomic components in order to take intervention measures is necessary to reduce the worsening of morbidity and mortality due to the reinfection of covid-19 in elderly individuals.

CONCLUSION

The findings show that older people who have had covid-19 one or more times, when compared to older people who have not had covid-19, may be predisposed to weight gain, and have interference with the autonomic nervous system, with reduced HRV, leading to cardiac autonomic dysfunction, with decreased parasympathetic modulation.

ACKNOWLEDGEMENTS

We would like to thank the Graduate Program in Physical Education (PPGEF/UFMA); Foundation for Research Support and Scientific and Technological Development of Maranhão (FAPEMA) (Universal - 01293/16); FAPEMA (BEPP-01404/21, universal 00919/17); and Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Finance Code 001.

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Received: 07 june. 2024
Accepted: 18 july. 2024