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Autonomic heart rate modulation in patients with coronavirus disease 2019 in mechanical ventilation

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SUMMARY

BACKGROUND: Patients with coronavirus disease 2019 on automatic mechanical ventilation have greater heart rate modulation with greater parasympathetic modulation.

OBJECTIVE: To analyze the autonomic modulation of heart rate in critically ill patients with coronavirus disease 2019 on invasive mechanical ventilation.

METHODS: A cross-section study was carried out with 36 individuals divided into two groups. The control group included patients of both genders, in orotracheal intubation with invasive mechanical ventilation under controlled assisted mode, hospitalized in the intensive care unit for another 24 h. In the non-COVID group, patients diagnosed with coronavirus disease 2019 in the same condition mentioned in the control group.

RESULTS: There was a significant increase in heart rate variability (standard deviation of all normal RR intervals recorded at an interval of time; p=0.001; triangular interpolation histogram of RR intervals; p=0.048; and SD2; p=0.014) in the coronavirus disease group compared to the non-COVID group. Successively, the parameters that demonstrate parasympathetic modulation are shown to be higher in the group of patients with coronavirus disease 2019 (root mean square of the square of differences between adjacent normal RR intervals in an interval of time; p<0.001; pNN50; p<0.001; SD1; p=0.002; and high frequency; p=0.022).

CONCLUSIONS: There was a greater autonomic modulation of heart rate with a greater parasympathetic modulation in patients with coronavirus disease 2019 on mechanical ventilation.

KEYWORDS: Autonomic nervous system. Coronavirus. Artificial respiration.

INTRODUCTION

In December 2019, an outbreak of pneumonia caused by a new coronavirus, called coronavirus disease 2019 (COVID-19), occurred in Wuhan, Hubei Province, China. After the initial outbreak, it spread rapidly around the world in the following months, leading to more than millions of cases and hundreds of thousands of deaths. Although most patients seem to have a favorable prognosis, elderly people and those with chronic diseases may have an unfavorable prognosis, with a greater need for interventions such as endotracheal intubation and invasive mechanical ventilation. Recent research has shown that, similarly to SARS-CoV, this virus can invade various tissues by binding to the angiotensin-converting enzyme 2 receptor, expressed mainly in lung alveolar epithelial cells, small intestine enterocytes, vascular endothelial cells, and airway epithelial cells and renal cells[1,2].

Sympathetic hyperactivity and/or decreased parasympathetic activity are related to an increased risk of various cardiac outcomes[3,4]. Heart rate variability (HRV) is a technique used to noninvasively estimate the characteristics of the autonomic nervous system and analyze the modulation of sympathetic and parasympathetic inputs[1,5]. The use of mechanical ventilation can influence heart rate (HR) due to significant changes in alveolar and intrathoracic pressure and subsequent changes in cardiac output and mean arterial pressure (MAP). Ventilation can profoundly alter the functioning of the cardiovascular system through complex and opposing processes that reflect the interaction between myocardial and ventricular reserve, pump function, circulating blood volume, blood flow, distribution, autonomic tone, endocrinological responses, pulmonary volume, intrathoracic pressure, and the surrounding pressures for the rest of the circulation[6].

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Some of the critical patients with COVID-19 require invasive mechanical ventilation, and the effects of positive pressure on the autonomic nervous system have been less explored; hence, it is of paramount importance to obtain a more detailed understanding of the association between invasive mechanical ventilation and autonomic modulation of HR in these patients. Therefore, the aim of this study was to analyze the autonomic modulation of HR in critically ill patients with COVID-19 on invasive mechanical ventilation.

METHODS

The research project was approved by the Research Ethics Committee of the Universidade Municipal de São Caetano (#2.912.528) and was applied only after approval by the Committee and signature of the consent term by the legal guardian of each research subject. This research follows STROBE checklist.

A cross-sectional study was carried out from July 2020 to March 2021, in which 36 patients admitted to the intensive care unit (ICU) in Brazil were evaluated.

The subjects were divided into two groups. The control group (CNG) included patients of both genders, and for the COVID group (CG), all patients of both sexes under invasive mechanical ventilation in controlled assisted mode admitted to the ICU in orotracheal intubation and who had authorization from the guardians to participate in the study were considered eligible. Patients with artificial cardiac pacemakers were excluded.

Data on prognosis and mortality risk were quantified by the Simplified Acute Physiology Score (SAPS III).

Data collection instruments

A data collection form filled at the bedside and from the patient's medical record was used through the online platform. The measurements taken included cardiorespiratory and hemodynamic data, such as peripheral oxygen saturation (SpO_2), HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP), MAP, and ventilatory data. All patients were ventilated in the Newport E500® device. SpO_2 data were collected by viewing the DX 2010 multiparameter monitor from Dixtal®, and SBP, DBP, and MAP data were obtained by a single measurement provided by the same monitor. HR was recorded using a Polar® V800 HR monitor.

The recording strap was placed on the chest of the volunteers, and, on their wrist, the individuals were kept in the supine position in Fowler's position (semi-sitting, at 45°), with ventilatory parameters at the discretion of the physician on duty, and physiotherapist of the sector.

The Kubios HRV® software was used to obtain consecutive RR intervals and analyze HRV. Only sets with more than 95% sinus beats were included in the study; for this, a digital filtering was performed, followed by manual filtering, to eliminate premature ectopic beats and artifacts. The analysis of HRV was performed using linear methods, analyzed in the domains of time and frequency and through geometric índices[7].

Statistical analysis

Excel and SPSS (Statistical Package for Social Research) version 17.0 programs for statistics were used. Each variable was checked for normal distribution using the Shapiro-Wilk test. The comparison of the clinical profile and physiological parameters between positive and negative individuals for SARS-CoV-2 was performed using the independent Student's t-test and expressed as mean and standard deviation. The comparison between variables of HRV between groups was performed using the Mann-Whitney U test and expressed as median and percentiles. Descriptive statistics were used with mean values, and standard deviations of the differences were statistically significant when the probability of type I error was less than 5% ($p<0.05$). The sample was selected from a pilot test using the online software available at www.lee.dante.br, considering the root mean square of the square of differences between adjacent normal RR intervals in an interval of time (RMSSD) index as a variable. The sample size determined was a minimum of 13 individuals per group.

RESULTS

Thirty-six patients with a mean age of 70 years were analyzed. There were no statistical differences in the measurements of cardiorespiratory, hemodynamic data, and SAPS III severity score (Table 1).

Table 1. Comparison of the clinical profile and physiological parameters between positive and negative individuals for SARS-CoV-2 (COVID-19).

	COVID group	Non-COVID group	p-value*
	Mean±SD	Mean±SD	
Age, years	70±5	70±6	0.38
Predicted weight, kg	63±9	59±13	0.06
SBP, mmHg	121±17	127±25	0.25
DBP, mmHg	66±9	64±12	0.16
MAP, mmHg	84±9	80±13	0.26
SpO_2, %	96±1	96±2	0.07
SAPS III	66±14	70±18	0.51
Sex, male	61.1% (11)	72.2% (13)	0.48
Race, white	66.6% (12)	55.5% (10)	0.09
Use of vasoactive drugs	50.0% (9)	61.1% (11)	0.31

*Student's t-test. Data presented as mean±standard deviation (SD) and frequency {n (%)}. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; SpO_2: oxygen pulse saturation; SAPS III: Simplified Acute Physiology Score III.

The standard deviation of all normal RR intervals recorded at an interval of time (SDNN) (p=0.001), pNN50 (p<0.001), RMSSD (p<0.001; Figure 1), and triangular interpolation histogram of RR intervals (TINN) (p=0.048) indices were higher in the CG compared to the non-COVID group (NCG).

In the frequency-domain indices, lower values were recorded in the CG in the following parameters: LFms^2 (p=0.002), LFnu (p=0.001), and the LF/HF ratio (p<0.001) and higher in the HFms^2 indices (p=0.022; Figure 2) and HFnu (p<0.001). The SD1 (p=0.002), SD2 (p=0.014), and SD1/SD2 (p<0.001) indices were higher in the CG.

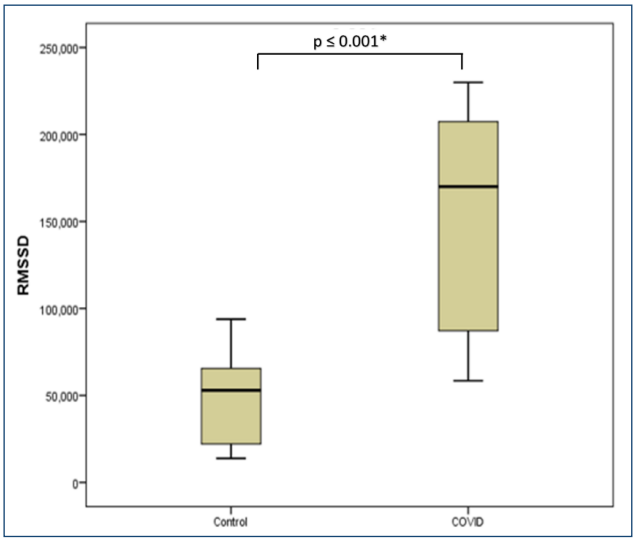

Figure 1. Comparison of RMSSD analysis indices in the time domains between individuals with SARS-CoV-2 and the control group. *Mann-Whitney test; RMSSD: square root of the mean square of the differences between successive normal RR intervals.

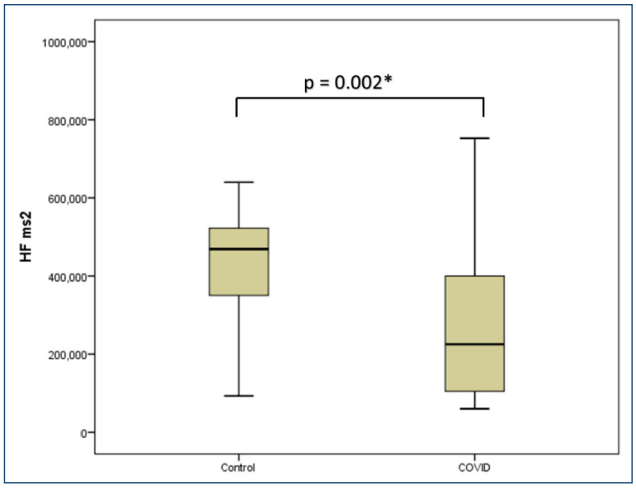

Figure 2. SARS-CoV-2. Comparison of HF between individuals with SARS-CoV-2 and the control group. *Mann-Whitney test; HF: high frequency; ms: milliseconds.

DISCUSSION

The study indicates the differences in HRV parameters in the COVID-19 group, which supports the hypothesis that infection influences HRV in patients undergoing invasive mechanical ventilation. The SDNN (p=0.001), TINN (p=0.048), and SD2 (p=0.014) were higher in the CG compared with the NCG. These parameters show a higher overall HRV in patients with COVID-19. Successively, the parameters that demonstrate parasympathetic modulation are shown to be higher in the group of patients with COVID-19 (RMSSD; p<0.001, pNN50; p<0.001, SD1; p=0.002; and HF; p=0.022).

Patients with COVID-19 are variably susceptible to the "pro-inflammatory cytokine storm" that simultaneously increases sympathetic noradrenergic system flows (SNS) and sympathetic adrenergic system[8]. Hyperactivation of the SNS, an important component of autonomic dysregulation in the setting of infections and hyperinflammatory release, together with attenuation of vagal activity caused by the vagus nerve injury produced by the virus, can lead to a serious autonomic imbalance in COVID-19 infection[9]. After an inflammatory response, afferent signals travel through the vagus nerve primary nerve of the parasympathetic nervous system to the nucleus of the solitary tract. A subsequent efferent signal via the vagus inhibits the synthesis of proinflammatory cytokines through the neurotransmitter acetylcholine. In short, a basic set of physiological structures involving the vagus nerve is responsible for a rapid reflex action in response to inflammation, known as the cholinergic anti-inflammatory pathway[8,9].

Few reports of autonomic dysfunction among patients with COVID-19 have been described. However, the relationship between HRV and inflammatory states has been widely studied. A meta-analysis demonstrated an inverse relationship between HRV and inflammation; this study examined the association of HRV with inflammation markers such as interleukins, C-reactive protein, interferon-gamma, and factor alpha tumor necrosis. This study showed a significant positive association with HR, and negative associations with SDNN, pNN50, RMSSD, and HF[9,10].

Haensel et al.[11] showed that SDNN was negatively correlated with markers of inflammation compared with HF and RMSSD. In summary, the results were particularly robust for SDNN and inflammatory markers compared with primarily SNP influence[12]. In contrast to the findings in our study, there was a significant increase in the values of SDNN, pNN50, and RMSSD in patients with COVID-19. In our study, we also evidenced an increase in sympathetic activity and a decrease in vagal tone, and a decrease in the LF/HF ratio, considered a marker of sympathovagal balance. This

is in spite of a previous study demonstrating that the RRtri geometric index was significantly lower in older women, with lower global HRV indices[13]. Age and gender can significantly contribute to the association between HRV and inflammatory states.

Monitoring of vagal tone in patients with COVID-19 may be a predictive marker of the course of the disease, with the idea that people with very low vagal tone at the onset of symptoms may be at high risk of developing an overstimulated dysregulated pro-inflammatory response during infection, leading to sudden death or transfer from the ICU. In the analysis of HRV, the RMSSD and HF indices are considered primary indices of HRV, mediated by the vagus nerve[14]. In our study, these variables had a positive correlation in patients with COVID-19 considered severe.

Several comorbidities are commonly associated with patients in the ICU, including systemic arterial hypertension, heart failure, type II diabetes mellitus and chronic kidney disease, and sympathetic hyperactivity, which in many cases contributes to disease progression[14,15]. These findings suggest that HRV analysis may have diagnostic value in intensive care. HRV is not only affected by pathophysiological conditions but also by treatments and events commonly performed in the ICU, such as sedation, mechanical ventilation, and stressful stimulation[16-20].

The analysis of the HRV is an important tool for evaluating the functioning of the organism under normal and pathological conditions, providing the development of actions aimed at the prevention, treatment, and/or detection of pathological conditions.

The data on the effect of positive pressure on the autonomic nervous system analyzed in our study are relevant to gain an understanding of the association between mechanical ventilation and autonomic modulation of HR in patients with COVID-19[17].

LIMITATIONS

This study has potential limitations. It is noteworthy that HRV analysis is a noninvasive tool and easy to apply at the bedside, which are its main advantages; however, the interpretation of results must be done carefully in the context of its limitations. The RR time series were measured under uncontrolled conditions; hence, the results may have been affected to some extent by unknown external factors. In addition, we did not measure recordings in the study group before SARS-CoV-2 infection; hence, a direct comparison of the results of HRV analysis before and after the advent of COVID-19 was not possible and their comparison was made with a control group without COVID-19 infection.

CONCLUSION

Our study demonstrated a greater autonomic modulation of HR with a greater parasympathetic modulation in patients with COVID-19 on mechanical ventilation.

AUTHORS' CONTRIBUTIONS

PJ: Conceptualization, Funding acquisition, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **JZ-R:** Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **JAM:** Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. **ICES:** Data curation, Formal Analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. **RDR:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.e8. Available from: https://www.sciencedirect.com/science/article/pii/S0092867420302294
2. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7. https://doi.org/10.1002/path.1570
3. Olsson G, Wikstrand J, Warnold I, Manger Cats V, McBoyle D, Herlitz J, et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. Eur Heart J. 1992;13(1):28-32. https://doi.org/10.1093/oxfordjournals.eurheartj.a060043
4. Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. Prog Cardiovasc Dis. 2008;50(6):404-19. https://doi.org/10.1016/j.pcad.2008.01.003
5. Morris JA Jr, Norris PR, Ozdas A, Waitman LR, Harrell FE Jr, Williams AE, et al. Reduced heart rate variability: an indicator of cardiac uncoupling and diminished physiologic reserve in 1,425 trauma patients. J Trauma. 2006;60(6):1165-73; discussion 1173-4. https://doi.org/10.1097/01.ta.0000220384.04978.3b
6. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(11):2850-5. https://doi.org/10.1161/01.cir.94.11.2850
7. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and

practical applications. Int J Cardiol. 2002;84(1):1-14. https://doi.org/10.1016/s0167-5273(02)00057-8

8. Manolis AS, Manolis AA, Manolis TA, Apostolopoulos EJ, Papatheou D, Melita H. COVID-19 infection and cardiac arrhythmias. Trends Cardiovasc Med. 2020;30(8):451-60. https://doi.org/10.1016/j.tcm.2020.08.002
9. Williams DP, Keonig J, Carnevali L, Sgoifo A, Jarczok MN, Sternberg EM, et al. Heart rate variability and inflammation: a meta-analysis of human studies. Brain Behav Immunol. 2019;80:219-26. https://doi.org/10.1016/j.bbi.2019.03.009
10. Psychari SN, Apostolou TS, Iliodromitis EK, Kourakos P, Liakos G, Kremastinos DT. Inverse relation of C-reactive protein levels to heart rate variability in patients after acute myocardial infarction. Hellenic J Cardiol. 2007;48(2):64-71. PMID: 17489343
11. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. A relação entre variabilidade da frequência cardíaca e marcadores inflamatórios em doenças cardiovasculares. Psiconeuroendicrinologia. 2008;33(10):1305-12. https://doi.org/10.1016/j.psyneuen.2008.08.007
12. Thayer JF, Fischer JE. Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults. J Intern Med. 2009;265(4):439-47. https://doi.org/10.1111/j.1365-2796.2008.02023.x
13. Carvalho TD, Norberto AR, Oliveira FR, Paiva LS, Baracat EC, Soares Júnior JM, et al. Do heart rate variability indices present potential to predict late postmenopausal? A retrospective study. Rev Assoc Med Bras (1992). 2022;68(6):853-9. https://doi.org/10.1590/1806-9282.20220219
14. Carnagarin R, Lambert GW, Kiuchi MG, Nolde JM, Matthews VB, Eikelis N, et al. Effects of sympathetic modulation in metabolic disease. Ann N Y Acad Sci. 2019;1454(1):80-9. https://doi.org/10.1111/nyas.14217
15. Díaz HS, Toledo C, Andrade DC, Marcus NJ, Del Rio R. Neuroinflammation in heart failure: new insights for an old disease. J Physiol. 2020;598(1):33-59. https://doi.org/10.1113/JP278864
16. Nishiyama T, Misawa K, Yokoyama T, Hanaoka K. Effects of combining midazolam and barbiturate on the response to tracheal intubation: changes in autonomic nervous system. J Clin Anesth. 2002;14(5):344-8. https://doi.org/10.1016/s0952-8180(02)00370-7
17. Shen H-N, Lin L-Y, Chen K-Y, Kuo P-H, Yu C-J, Wu H-D, et al. Changes of heart rate variability during ventilator weaning. Chest. 2003;123(4):1222-8. http://doi.org/10.1378/chest.123.4.1222
18. Guerra M, Zangirolami-Raimundo J, Sarmento GJV, Salatini R, Silva PJ, Raimundo RD. Cardiac autonomic modulation during different modes of weaning of mechanical ventilation. J Hum Growth Dev. 2019;29(2):232-40. http://doi.org/10.7322/jhgd.v29.9427
19. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. J Am Coll Cardiol. 2008;51(18):1725-33. https://doi.org/10.1016/j.jacc.2008.01.038
20. Unoki T, Grap MJ, Sessler CN, Best AM, Wetzel P, Hamilton A, et al. Autonomic nervous system function and depth of sedation in adults receiving mechanical ventilation. Am J Crit Care. 2009;18(1):42-51. https://doi.org/10.4037/ajcc2009509