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ABSTRACT:

Background: At the end of 2019, a hitherto unknown coronavirus was identified in Wuhan (China) it was called SARS CoV-2 and the disease caused by it was named COVID-19. With the increase in cases an unusual manifestation for this type of virus began to appear: anosmia and dysgeusia, of uncertain etiology, which it could be an autonomic alteration, more precisely in the baroreflex. In this context, it seems likely that subclinical manifestations of baroreflex involvement occur. The regulation of the baroreflex is carried out by the vegetative nervous system through the balance between sympathetic and parasympathetic activity. The objective of this study is to verify whether patients with COVID-19 present alteration of this mechanism by means of ECG Holter recording

Material and methods: the study design was cross-sectional, observational, descriptive, prospective inclusion and the sampling was non-probabilistic of convenience. Patients were included if they had a confirmed diagnosis of COVID-19 admitted to the Internal Medicine Service of JB Iturraspe Hospital in Santa Fe city, Argentina, in the period from May 10 to July 20, 2021. An ECG Holter recording was performed at rest for 5 minutes, determining the variables of the frequency domain using Fourier transform analysis through Kubios. Data are presented for frequency measures of HRV: low-frequency power (LF), and high-frequency power (HF) and normalized unit LFnu, HFnu. Were excluded patients with a diagnosis of diabetes mellitus of more than 5 years of evolution, medicated with beta-blockers or with a history of irradiation in the neck

Results: 68 patients were studied. 62% were men 38% were women. The mean age was 48.9 ± 13.3 years. The median systolic blood pressure (SBP) was 120 mmHg (95 to 170) and the diastolic blood pressure (DBP) 80 mmHg (60 -110). The heart rate was 76 ± 13 beats per minute and the respiratory rate was 24 (16 to 40). Anosmia was observed in 22% (n = 15) and dysgeusia in 19% (n = 13). The variables of the analysis in the frequency domain were: LF 135.8 ms² (13.7 - 2861.7); HF, 89.04 ms² (4.14-5234.4), LFnu 57.57 ± 22.39 , HFnu 43.18 ± 22.64 . LF / HF ratio $2.1 \text{ ms}^2 \pm 2.09$. 41.2% (n = 28) of the patients had a high LF / HF ratio (> 2).

Discussion: The high and low frequency components known as HF (High Frequency) representing predominantly parasympathetic function, and LF (Low Frequency) which is both sympathetic and parasympathetic activity; can be obtained through the analysis in the frequency domain. The relationship between these two elements would thus represent the sympatho-vagal balance and is expressed as the LF / HF ratio. We observed that 41.2% of the studied patients showed elevated LF / HF ratio

Conclusion: The 41.2% of the patients hospitalized with COVID-19 presented with an increase in the LF / HF ratio and this result could be interpreted as an alteration in autonomic function.

BACKGROUND:

At the end of 2019, a hitherto unknown coronavirus was identified in Wuhan (China), which showed unusual characteristics and spread to the entire planet. Due to the predominantly pulmonary involvement in its severe forms and its similarities with the microorganism that caused the pandemic in 2003, it was called SARS CoV-2 (severe acute respiratory syndrome coronavirus-2) and the disease caused by it was named COVID-19.

Already in the early days of the pandemic, increasingly frequent reports of an unusual manifestation for this type of virus began to appear: anosmia and dysgeusia. (1) Although the mechanism of production of both symptoms is not exactly known, it has been postulated that they are due to neurological involvement. There have been also some communications that describe the possible alteration of the autonomic nervous system, with various manifestations such as postural tachycardia syndrome with dysautonomia (POTS) (2) orthostatic hypotension, bradycardia and syncope (3)

In this context, it seems likely that subclinical manifestations of baroreflex involvement occur, a mechanism responsible for 90% of the short-term variability in blood pressure and heart rate. The regulation of the baroreflex is carried out by the vegetative nervous system through the balance between sympathetic and parasympathetic activity.

If there is an alteration of the baroreflex with a decrease in its sensitivity, this could cause difficulties in the diagnosis and treatment of arterial hypertension. Likewise, and if it persists over time, it could constitute a cardiovascular risk factor of unknown importance.

Baroreflex can be evaluated by analysis in the time domain: mean of RR intervals, standard deviation, RMSSD, etc. Likewise, the analysis of heart rate variability in the frequency domain using the Fourier transform is of immense value. In this way, the LF and HF indices are obtained, the quotient of which represents the sympathetic vagal equilibrium.

The evaluation of the LF / HF (low frequency / high frequency) ratio in the spectral analysis of the heart rate variability is a simple method for the evaluation of the baroreflex mechanism. The objective of this study is to verify whether patients with COVID-19 present alteration of this mechanism by means of Holter recording.

keywords: baroreflex, dysautonomia, covid-19, heart rate.

MATERIALS AND METHODS:

The study design was cross-sectional, observational, descriptive, prospective inclusion and the sampling was non-probabilistic of convenience.

Patients were included if they had a confirmed diagnosis of COVID-19 according to the clinical, epidemiological and laboratory criteria established by the Argentine Health Ministry (4), admitted to the Internal Medicine Service of JB Iturraspe Hospital in Santa Fe city, Argentina, in the period from May 10 to July 20, 2021.

Verbal informed consent was obtained to avoid potential exposure to contaminated material by the infected patient. Prior authorization was obtained from the hospital Teaching and Research Committee. At all times, the research was governed by the guidelines of good clinical practice, following the Declaration of Helsinki principles.

An ECG Holter recording was performed at rest for 5 minutes, determining the variables of the frequency domain using Fourier transform analysis through Kubios (v.3.0.0 [free version], HRV analysis, University of Eastern Finland).

Data are presented for frequency measures of HRV: low-frequency power (LF), and high-frequency power (HF) in both ms² and normalized units and the ratio of LF power to HF

power (LF:HF). The normalized (or normalized unit) spectral indices are defined as $LFnu = LF / (LF + HF)$ and $HFnu = HF / (LF + HF)$.

Patients with a diagnosis of diabetes mellitus of more than 5 years of evolution, medicated with beta-blockers or with a history of irradiation in the neck were excluded.

The analysis of the results was carried out with the statistical package IBM® SPSS® (23rd version). Normality in the distribution of continuous variables was determined using the Kolmogorov-Smirnov test. Quantitative variables of parametric distribution were described by means and standard deviation and those non-parametric by means of the median and range. Qualitative variables were expressed in percentages.

Reference values from the normal population published in the literature were used, with a cut-off point greater than 2 considered an alteration in the LF / HF ratio. (5.6)

RESULTS:

68 patients were studied. 62% were men and 38% women. The mean age was 48.9 ± 13.3 years. The median systolic blood pressure (SBP) was 120 mmHg (95 to 170) and the diastolic blood pressure (DBP) 80 mmHg (60 -110). The heart rate was 76 ± 13 beats per minute and the respiratory rate was 24 (16 to 40). Anosmia was observed in 22% (n = 15) and dysgeusia in 19% (n = 13).

The variables of the analysis in the frequency domain were: LF 135.8 ms² (13.7 - 2861.7); HF, 89.04 ms² (4.14-5234.4), LFnu 57.57 ± 22.39 , HFnu 43.18 ± 22.64 . LF / HF ratio $2.1 \text{ ms}^2 \pm 2.09$. 41.2% (n = 28) of the patients had a high LF / HF ratio (> 2).

Variable	Mean	SD
LFnu	57,57	22,39
HFnu	43,18	22,64
LF/HF(ms ²)	2,1	2,09

Variable	Median	Range
LF(ms ²)	135,8	13,7 – 2861,7
HF(ms ²)	89,04	4,14 – 5234,4

DISCUSSION:

The theory that has been proposed to explain the development of neurological symptoms in SARS CoV-2 infection is that, due to the action of the virus, an internalization of angiotensin II receptors would occur in the solitary tract nucleus, altering baroreflex response.

The high and low frequency components known as HF (High Frequency) representing predominantly parasympathetic function, and LF (Low Frequency) which is both sympathetic and parasympathetic activity; can be obtained through the analysis in the frequency domain. The relationship between these two elements would thus represent the sympatho-vagal balance and is expressed as the LF / HF ratio.

We observed that 41.2% of the studied patients showed elevated LF / HF ratio, so we interpret that this was due to an imbalance of autonomic function due to increased sympathetic activity. We do not know the clinical significance of this finding in the evolution of the disease.

We have not found previous publications that demonstrate the presence of dysautonomia through an objective measurement such as that obtained by Holter in this type of patient.

Limitations of this work include the lack of knowledge of LF/HF values prior to infection and the absence of controls. In addition, no follow-up has been carried out to know the permanence of this alteration over time.

CONCLUSION:

Through the analysis of a 5-minute Holter recording, it was found that 41.2% of the patients hospitalized with COVID-19 presented with an increase in the LF / HF ratio, and this result could be interpreted as an alteration in autonomic function.

DECLARATION OF CONFLICTS OF INTEREST:

The authors indicate that they have no conflict of interest for this article.

AUTHORS CONTRIBUTIONS:

Hector Mario Musacchio: Conceptualization, methodology, formal analysis, investigation, resources, writing original draft preparation, supervision, project administration.

Delfina Godano: conceptualization, investigation, resources, writing original draft preparation, supervision, project administration

Federico Barbone: Formal analysis, investigation, writing review and editing.

Florencia Debona: Investigation, visualization.

Hugo Miño: Investigation, visualization.

María Florencia Cogliano: Investigation.

Gonzalo Romagnoli: Investigation.

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