



EFFECT OF VITAMIN D DEFICIENCY ON PULMONARY FUNCTION AND AUTONOMIC MODULATION IN OLDER COPD PATIENTS

EFEITO DA DEFICIÊNCIA DE VITAMINA D NA FUNÇÃO PULMONAR E NA MODULAÇÃO AUTONÔMICA EM PACIENTES IDOSOS COM DPOC

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ABSTRACT: The aim was to evaluate the effect of vitamin D deficiency on autonomic modulation and respiratory function in COPD patients. This was a cross-sectional study in which individuals with COPD were selected and divided into two groups: 1) with normal vitamin D levels (NorVD) (n=24), and 2) with vitamin D insufficiency (InsVD) (n=17), and cardiac autonomic modulation and respiratory function were assessed. InsVD individuals showed worse autonomic modulation compared to individuals with normal vitamin D levels, respectively evidenced by lower values in Sample's Entropy (1.53 ± 0.05 vs 1.21 ± 0.1 , $p=0.01$) and Shannon's Entropy (3.61 ± 0.13 vs 3.18 ± 0.13 , $p=0.01$), suggesting greater sympathetic modulation and less parasympathetic modulation. In the evaluation of the frequency and symbolic analysis domains, there was a predominance of sympathetic activity in the InsVD subjects compared to the NorVD subjects, shown, respectively, by the LF (ms²) indices (319 ± 304 vs 158 ± 217 , $p=0.05$), bare LF (58 ± 19 vs 44 ± 18 , $p=0.01$), bare HF (42.19 vs 56 ± 18 , $p=0.01$), LF/HF (1.9 ± 1.18 vs 1.01 ± 0.65 , $p=0.01$), and 2UV% (13 ± 7 vs 22 ± 11 , $p=0.01$). No changes were observed in hemodynamic variables or respiratory function. This suggests that insufficient vitamin D levels may negatively influence autonomic modulation in COPD patients.

KEYWORDS: COPD. Heart rate variability. Vitamin D.

RESUMO: O objetivo foi avaliar o efeito da deficiência de vitamina D na modulação autonômica e na função respiratória de doentes com DPOC. Trata-se de um estudo transversal que foram selecionados indivíduos com DPOC, e divididos em dois grupos: 1) com níveis normais de vitamina D (NorVD) (n=24), e 2) com insuficiência de vitamina D (InsVD) (n=17), tendo sido avaliadas a modulação autonômica cardíaca e a função respiratória. Os indivíduos InsVD apresentaram pior modulação autonômica em comparação aos indivíduos com níveis normais de vitamina D, respectivamente evidenciada por valores mais baixos na Entropia de Sample (1.53 ± 0.05 vs 1.21 ± 0.1 , $p=0.01$) e Entropia de Shannon (3.61 ± 0.13 vs 3.18 ± 0.13 , $p=0.01$), sugerindo uma maior modulação simpática e menor modulação parassimpática. Na avaliação dos domínios de frequência e análise simbólica houve predomínio da atividade simpática nos indivíduos InsVD em comparação os indivíduos NorVD, apresentados, respectivamente, pelos índices de LF (ms²) (319 ± 304 vs 158 ± 217 , $p=0.05$), LF nu (58 ± 19 vs 44 ± 18 , $p=0.01$), HF nu (42.19 vs 56 ± 18 , $p=0.01$), LF/HF (1.9 ± 1.18 vs 1.01 ± 0.65 , $p=0.01$), e de 2UV% (13 ± 7 vs 22 ± 11 , $p=0.01$). Não foram observadas alterações nas variáveis hemodinâmicas e nas funções respiratórias. Com isso, é sugestivo que níveis insuficientes de vitamina D podem influenciar negativamente a modulação autonômica em doentes com DPOC.

PALAVRAS-CHAVE: DPOC. Variabilidade da frequência cardíaca. Vitamina D.

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Received: 20 Sept. 2024

Accepted: 19 Jan. 2025

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INTRODUCTION

Vitamin D deficiency currently has a high prevalence in the general population, and has been associated with the worsening of autoimmune diseases, metabolic alterations, cardiovascular diseases and psychological disorders¹. In addition, vitamin D deficiency has been considered a risk factor for patients with chronic obstructive pulmonary disease (COPD), with estimates that 60% of individuals with severe COPD may be vitamin D deficient, and this may be related to the severity of the disease². Epidemiological studies indicate that decreased vitamin D levels are associated with an increased frequency of respiratory infections, not only in COPD patients but also in healthy people^{2,3}. This is probably due to the involvement of vitamin D in the regulation of innate and adaptive immunity^{4,5}.

In individuals with COPD, vitamin D deficiency often occurs due to smoking-induced skin aging, reduced outdoor activity and inadequate quality of food intake⁶. The hypothesis that vitamin D deficiency contributes to the worsening of COPD still needs to be discussed. However, epidemiological evidence associates vitamin D deficiency with an increased incidence of COPD and a faster decline in lung function in these individuals, and it has also been associated with cardiovascular complications⁷.

Cardiovascular diseases contribute as independent factors of greater morbidity and mortality in COPD patients. They may be responsible for the largest number of hospitalizations and 25% of deaths in these patients⁸. In addition, COPD is associated with many other complications that can contribute to unfavorable changes in cardiac autonomic modulation and decreased heart rate variability (HRV), which is an important marker of cardiac arrhythmias and sudden death⁹.

Although there is evidence of cardiovascular complications and Vitamin D deficiency in COPD patients, few studies have explored the impact of this clinical condition on cardiac autonomic modulation, hemodynamic variables and respiratory function. Therefore, this study investigates the effect of serum Vitamin D levels on respiratory function, blood pressure and autonomic modulation in COPD patients.

METHODOLOGY

COPD PARTICIPANTS

This is a cross-sectional study carried out jointly with patients with COPD, institutionalized in the COPD Outpatient Program at the Federal University Hospital of Maranhão. The sample consisted of 41 elderly people with COPD, GOLD 2 classification (FEV1- 50-79% of predicted) and former smokers. All patients were using long-acting bronchodilators (b2 adrenergic agonists) and inhaled corticosteroids.

The Vitamin D levels of the population included in the study were observed, and the patients were divided into two groups: Group with Insufficiency and Vitamin D deficiency (<20 ng/mL as deficient, 20 to 30 ng/mL as insufficient; InsVD, n=17), and Group with normal Vitamin D values (≥30 ng/mL) (NorVD, n=24).

A sampling error of 5% and a confidence interval of 95% were adopted.

Patients were excluded if they were under 60 years of age, had a history of hypercalcemia, used medication for depression, cancer, had pulmonary infection, tuberculosis, pleural effusion, congestive heart failure, primary pulmonary hypertension, pulmonary embolism, chronic kidney disease, diabetic neuropathy, restrictive airway disease, vitamin D supplementation, active smokers, orthopedic disorders that affected physical performance, and inability to walk.

SERUM VITAMIN D LEVEL

Serum vitamin D level was extracted from a small blood sample and assessed by measuring 25-hydroxyvitamin D (25-OH-D) by the chemiluminescence method according to the manufacturer's instructions. Serum levels of 25-OH-D in the amount of <20 ng/mL as deficient, 20 to 30 ng/mL as insufficient levels (InsVD), and ≥ 30 ng/mL as normal values (NorVD). The exam was carried out in the laboratory of the Federal University Hospital of Maranhão.

ANTHROPOMETRIC EVALUATION

Weight was measured using a digital scale on the kilogram scale (Balmak, BK – 50FAN, São Paulo). For height, the EST 23 Trena Compact stadiometer was used on the millimeter scale. In addition, the body mass index (BMI) identified in the formula weight (Kg)/height (m²) was calculated.

BLOOD PRESSURE MEASUREMENTS

The procedures for measuring Blood Pressure (BP) were carried out in accordance with the guidelines of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)¹⁰. Patients remained seated in a comfortable chair for 20 minutes, and with an automatic and non-invasive BP monitor (BP710, Omron, Tokyo, Japan) three BP measurements were taken on the right arm, with an interval of at least 2 minutes between each one.

PULMONARY FUNCTION

One morning was reserved for collecting data from spirometry exams (MicroLoop Spirometer, CareFusion, Yorba Linda, CA, USA) by a qualified technician.

The individuals underwent the spirometry test in the sitting position, using a nose clip, to obtain the parameters of Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 Second (FEV1), and the relationship between FEV1 and FVC (FEV1/FVC, expressed as a percentage), according to the American Thoracic Society (ATS)¹¹.

In addition to the automatic evaluation performed by the software, the quality of the spirometric tests was evaluated according to ATS criteria, including the number of acceptable maneuvers from 0 to 3, the highest maintained by the spirometry software, and reproducibility (FEV1 and FVC were considered reproducible according to ATS criteria when the two best values differed by no more than 200 mL).

CARDIAC AUTONOMIC MODULATION

The NN interval was recorded continuously for 20 minutes in the supine position, using a portable Wincardio (600 Hz) electrocardiogram (Micromed, Brazil) for spectral collection of Heart Rate Variability (HRV).

The variability of the N-N interval was evaluated in the Time Domain (Total Variability [ms²], SDNN [ms] and RMSSD [ms]), and Frequency Domain (LF [ms² and %], HF [ms² and %] and LF/ HF). Spectral power for low (LF: 0.03–0.15 Hz) and high (HF: 0.15–0.4 Hz) frequency bands was calculated employing integration of the power spectrum density within each frequency range. frequency band through Fast Fourier Transformation, using Kubios analysis software¹².

Nonlinear heart rate variability was assessed by Shanon, sample entropy and symbolic analysis. For this method, the same 5 minutes of the selected NN interval were used. A coarse-grained approach based on a uniform quantization procedure was used to transform the iNN series into a sequence of symbols. Length (L) was kept fixed in all analyses.

The full range of sequences was evenly distributed across six levels (from 0 to 5), and patterns of length $L = 3$ were constructed. Therefore, each subject and each experimental condition had its range of iNN intervals. Sample and Shannon entropy were calculated to provide a quantification of the complexity of the distribution. The sequence method was distributed across six levels, and all possible patterns were divided into four groups, consisting of patterns with 1 - no variations (0V, three identical symbols, associated with sympathetic modulation); 2 - one variation (1V, two identical symbols and one different, associated with sympathetic and parasympathetic modulation); 3 - two variations (2LV = with two similar variations and 2UV= with two different variations, associated with parasympathetic modulation).

STATISTICAL ANALYSIS

Data are presented as mean $\pm$ standard deviation. Data normality was tested using the Kolmogorov-Smirnov test. An unpaired t-test was used to compare parametric data. Chi-Square was used to compare groups when data were distributed in frequency. Differences were considered significant when $p \leq 0.05$.

Furthermore, effect size values greater than 0.8 were considered very strong; values ranging from 0.6 to 0.8 were considered strong; values ranging from 0.4 to 0.6 were considered moderate, and less than 0.4 were considered insignificant.

RESULTS

Table 1 shows that BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were similar between the groups. In addition, no differences were found between the groups in terms of medication use and smoking.

Table 1. Smoking load, Blood Pressure, Spirometry test, and Body composition variables in NorVD e InsVD COPD.

	NorVD (n=24)	InsVD (n=17)	<i>p</i>	<i>ES</i>
Body Composition				
Age (years)	72.43 $\pm$ 11.05	72.73 $\pm$ 10.43	0.94	0.09
Weight (Kg)	64.25 $\pm$ 16.20	56.33 $\pm$ 9.72	0.11	0.59
Height (m)	158.35 $\pm$ 7.58	156.22 $\pm$ 6.83	0.46	0.28
BMI (Kg/m ²)	25.44 $\pm$ 5.17	23.05 $\pm$ 3.41	0.15	0.46
Blood Pressure				
SBP (mmHg)	146.44 $\pm$ 23	148.57 $\pm$ 16.08	0.59	0.10
DBP (mmHg)	80.88 $\pm$ 12.17	79.64 $\pm$ 9.72	0.56	0.09
MBP (mmHg)	101.04 $\pm$ 15.81	102.09 $\pm$ 10.72	0.81	0.07
Drugs				
ARAI	8	7		

	NorVD (n=24)	InsVD (n=17)	<i>p</i>	<i>ES</i>
Metformin	3	2	0.10	
Simvastatin	2	1		
Smoking load (Pack Years)	21 ± 6	22 ± 5	0.55	0.18
Disease time (Years)	14 ± 3	13 ± 7	0.54	0.18
Vitamin D (ng/ml)	41 ± 7.9	26 ± 2.4	0.0001*	2.56
Spirometry test				
FVC (L)	2.02 ± 0.69	1.75 ± 0.62	0.31	0.41
FEV1 (L)	1.26 ± 0.53	1.16 ± 0.40	0.51	0.21
FEV1/FVC (%)	58 ± 20	49 ± 24	0.19	0.40
FEF 25-75%	0.73 ± 0.47	0.58 ± 0.35	0.27	0.36

Values are presented as mean ± standard deviation; Unpaired t-test; Effect size values higher than 0.8 were considered very strong; values ranging from 0.6-0.8 were considered strong; values ranging from 0.4-0.6 were considered moderate, and lower than 0.4 were considered negligible. *Statistical difference $p \leq 0.05$ vs NorVD.

In the assessment of lung function, the InsVD group showed similar values to the NorVD group in the variables of FVC (Forced Vital Capacity - Liters) and FEV1 (Forced Expiratory Volume - Liters). In addition, there was no significant difference in the FEV1/FVC and FEF 25-75% values.

Table 2 shows the results obtained in the assessments of autonomic modulation in COPD patients. There was greater vagal modulation (HF band) (44±18 vs 58±19) and less sympathetic modulation (LF band) (56±18 vs 42±19) in the NorVD group when compared to the InsVD group, respectively. In addition, the InsVD group had a higher sympathovagal balance (LF/HF ratio) compared to the NorVD group. However, in the time domain analysis, no difference was found between the groups.

Table 2. Symbolic analysis and Time and Frequency Domain Heart Rate Variability in NorVD and InsVD COPD patients.

	NorVD (n=24)	InsVD (n=17)	<i>P</i>	<i>ES</i>
Frequency Domain				
VAR-NN (ms ²)	981±1000	1184±643	0.70	0.24
LF (ms ²)	158±217	319±304	0.05	0.60
HF (ms ²)	294±471	230±213	0.60	0.17
LF nu	44±18	58±19	0.01	0.75
HF nu	56±18	42 ± 19	0.01	0.75
LF/HF	1.01±0.65	1.9±1.18	0.01	0.93
Time Domain				
NN (ms)	857±145	835±148	0.64	0.15
SDNN (ms)	32±31	44±25	0.18	0.42
RMSSD (ms)	24±19	29±18	0.43	0.27
Symbolic Analysis				
0V%	27±17	38±18	0.07	0.63
1V%	41±7	40±8	0.81	0.13
2LV%	9±7	6±6	0.34	0.46

	NorVD (n=24)	NorVD (n=24)	P	ES
2UV%	22±11	13±7	0.01	0.97
Nonlinear domain				
Sample entropy	1.53±0.05	1.21±0.1	0.01	4.04
Shannon entropy	3.61±0.13	3.18±0.13	0.01	3.30

Values are mean ± SD; NN= NN interval; RMSSD = Square root of the mean of successive squared differences between adjacent R-Rs; VAR-NN = total variance of indices N-N; LF = Low frequency spectral component; HF = High frequency spectral component; NU = standard units; LF/HF = Relationship between LF and HF components; OV= three symbols equal, associated with a sympathetic modulation ; 1V = with one variation ; 2LV = with two like variations and 2UV= with two unlike variations ; Unpaired t-test; *p<0.05 vs. NorVD. Effect size values higher than 0.8 were considered very strong; values ranging from 0.6-0.8 were considered strong; values ranging from 0.4-0.6 were considered moderate, and lower than 0.4 were considered negligible¹⁸.

The symbolic analysis of autonomic modulation also showed greater parasympathetic modulation, evidenced by a higher value of 2UV% in the NorVD group compared to the InsVD group (22 ± 11 vs 13 ± 7, respectively). In addition, HRV showed lower Shannon and sample entropy values in the InsVD group compared to the NorVD group.

The sympathetic modulation index (LF%) and the sympathovagal balance (LF/HF) were negatively associated with vitamin D levels (Figure 1). On the other hand, the parasympathetic indices (HF%) and 2UV% showed a positive association with vitamin D levels (Table 3).

Table 3. Pearson correlation between autonomic modulation, pulmonary function, and vitamin D levels.

	R-value	P-value	95% Confidence Interval
Vitamin D vs. Autonomic variables			
LF (nu)	-0.35	0.03*	-0.6106 to -0.0374
HF (nu)	0.35	0.03*	0.0099 to 0.5868
LF (ms ²)	-0.15	0.36	-0.2292 to 0.4129
HF (ms ²)	-0.21	0.21	-0.4970 to 0.1169
LF/HF	-0.42	0.008*	-0.6547 to -0.1201
OV (%)	-0.15	0.35	-0.3909 to 0.2361
2UV (%)	0.33	0.04*	0.0145 to 0.5897
Sample entropy	0.42	0.006*	0.1293 to 0.6496
Shannon entropy	0.42	0.008*	0.1155 to 0.6467

*Correlation is significant at the 0.05 level.

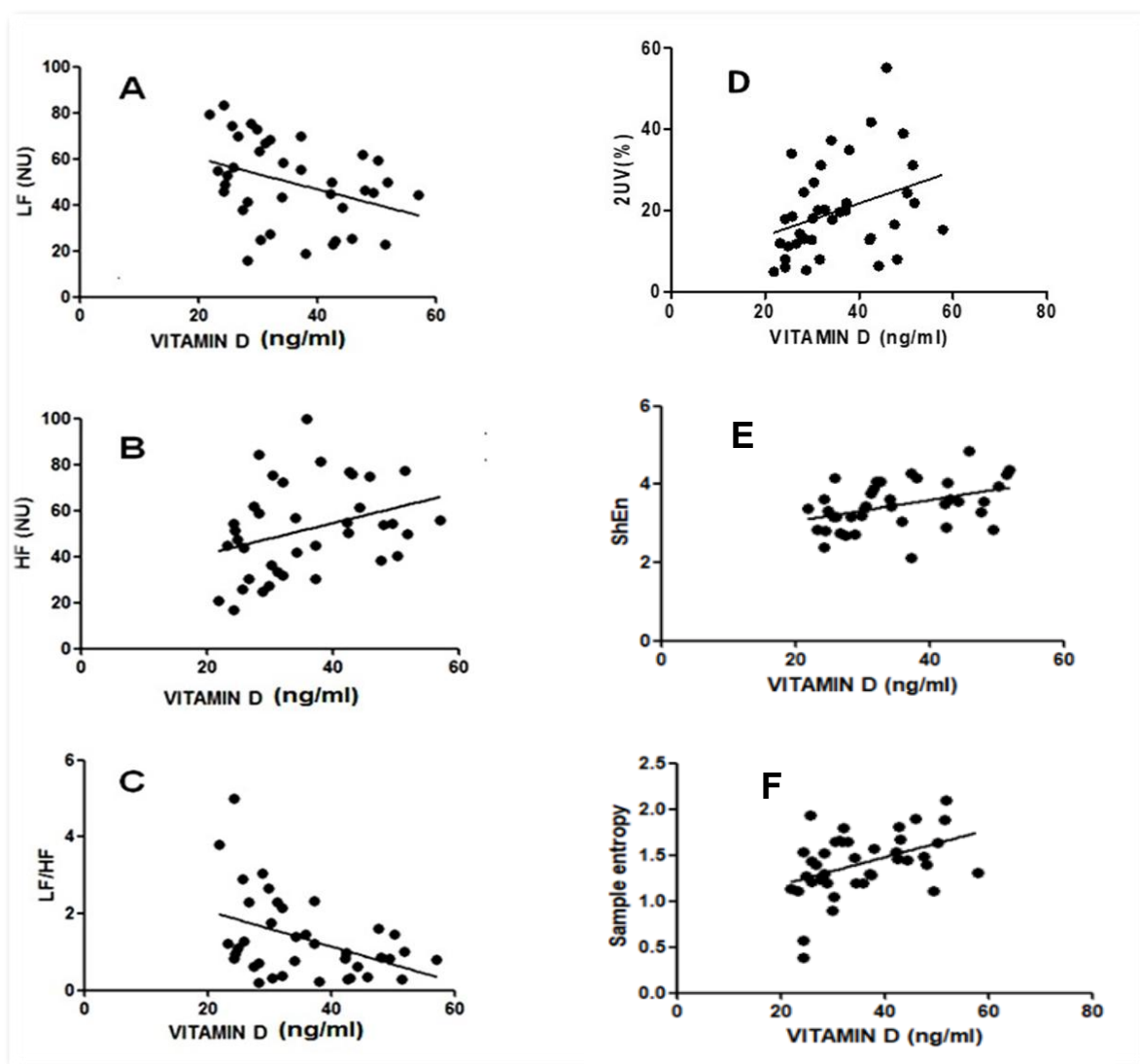


Figure 1. Correlation between Vitamin D and frequency domain autonomic modulation index and pulmonary function.

A- Negative association between sympathetic modulation and vitamin D; B- positive association between parasympathetic modulation and vitamin D; C- negative association between autonomic balance and vitamin D; D- positive association between vagal modulation index 2UV and vitamin D; E- positive association between Shannon Entropy and vitamin D; F- positive association Sample entropy modulation and vitamin D.

In addition, non-linear evaluation (sample and Shannon entropy) was positively associated with vitamin D levels (Figure 1). The autonomic variables did not show significant values when associated with lung function.

DISCUSSION

The main results of this study indicate that individuals with COPD who have vitamin D deficiency or insufficiency have worse autonomic modulation, with lower vagal modulation compared to individuals with normal vitamin D levels.

The literature refers to the clinical importance of how cardiac autonomic dysfunction may be associated with an increased incidence of cardiovascular disease in COPD patients¹³, specifically when alterations in autonomic modulation and respiratory function are associated with low vitamin D levels in this population.

Due to the situation of chronic coughing, poor airflow, incomplete or fragmented inhalation and exhalation cycles, the autonomic balance has been shown to be impaired, raising concerns about comorbidities and the sequential continuity of mortality from cardiac causes, since it is known that cardiac autonomic dysfunction encompasses several multiple disorders and may be associated with an increased incidence of cardiovascular diseases in patients with COPD¹⁴.

Studies have highlighted the role of autonomic function as an important physiological marker for prognosis and stratification in COPD patients^{13,15}, demonstrating that decreased HRV is associated with cardiovascular mortality in various conditions¹⁶, including cardiovascular diseases which are independent factors of increased morbidity and mortality in COPD individuals¹⁷, consequently increasing the number of hospitalizations⁸. In addition, vitamin D deficiency has been associated with autonomic dysfunction¹⁸, and autonomic modulation may be improved following vitamin D treatment in these individuals^{19,20,21}.

This study showed no association between respiratory capacity and low vitamin D levels, corroborating reports in the literature, in which authors found no association between vitamin D levels and the risk of acute respiratory exacerbations in a cohort of 973 COPD patients²².

However, there is still no consensus on the relationship between vitamin D deficits and lung capacity. COPD patients develop low levels of vitamin D as a result of the disease, which can be caused by physical disability caused by reduced daily activities and decreased cardiorespiratory fitness, as well as advanced age, induction of vitamin D catabolism by treatment with glucocorticoids, and malnutrition²³.

Corroborating our study, no relationship was found between vitamin D level in a prospective cohort study, reporting that vitamin D level in 462 COPD patients was not associated with mortality^{24,25}. Similarly, a study of 182 patients with moderate to very severe COPD showed that high-dose supplementation did not reduce the incidence of exacerbations, although it may reduce exacerbations in participants with severe vitamin D deficiency²⁶.

In addition, the literature reinforces that lung function (FVC, FEV1, FEV1/FVC, DLCO, TLC) was significantly lower in COPD patients with vitamin D deficiency compared to COPD patients without vitamin D deficiency²⁷.

Although this study showed no correlation with any other variable apart from the association between vitamin D levels and autonomic modulation, the mechanisms by which vitamin D deficiency can compromise autonomic function do not seem to be clear, so it is hypothesized that some factors, such as an increase in inflammatory mediators and the renin-angiotensin system, are influenced by vitamin D deficiency. These factors would affect autonomic function and increase the prevalence of cardiovascular diseases^{7,28,29}.

Despite some limitations, such as the small sample size, we believe that these initial results encourage other researchers to study the relationship between vitamin D lung capacity and autonomic modulation in individuals with COPD. Although factors such as medication use and smoking may have interfered with autonomic modulation, we found no differences in smoking load or between the classes of medication used. Furthermore, in this study, although all the patients had a history of smoking, only COPD patients who had stopped smoking were included.

PRACTICAL IMPLICATIONS

A worsening of cardiac autonomic modulation has been observed in elderly patients with low levels of Vitamin D, which can worsen cardiovascular control and cause exacerbations of the disease.

Therefore, through the results of this study, we hope to demonstrate the importance of investigating vitamin D levels in this population, and to emphasize the supervision of cardiac autonomic modulation in making strategic intervention decisions in this population.

More research is needed to understand all the interactions involved in the cardiorespiratory system between the pathophysiology of COPD and vitamin D, so that clinical recommendations can be more assertive and more individualized, improving the treatment of these patients.

CONCLUSION

It is suggestive that COPD patients with low vitamin D levels have impaired cardiac autonomic modulation, with a predominance of sympathetic activity and vagal withdrawal, due to the direct interference of pro-inflammatory factors that obstruct the passage of airflow, which has impaired baroreflex sensitivity, decreased HRV, reduced respiratory sinus arrhythmia and increased muscle sympathetic nerve activity.

ACKNOWLEDGMENTS

We would like to thank Fundação de Amparo à Pesquisa e ao Desenvolvimento Científico e Tecnológico do Maranhão - FAPEMA, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES).

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