Ann Allergy Asthma Immunol 000 (2024) 1–7

Contents lists available at ScienceDirect

Original Article

Parasympathetic nervous system: A key role in control and mood disorders in patients with asthma

Lorena Soto-Retes, MD[*,†]; Javier Milagro, PhD[‡,§]; Astrid Crespo-Lessmann, PhD[*,†]; Elena Curto, PhD[‖]; Éder F. Mateus Medina, PhD[*,†]; Raquel Bailón, PhD[‡,§]; Eduardo Gil, PhD[‡,§]; Pablo Laguna, PhD[‡,§]; Vicente Plaza, PhD[*,†]

[*] *Pneumology and Allergy Department, Hospital de la Santa Creu i Sant Pau and Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain*
[†] *Institut de Investigació Biomédica Sant Pau, Barcelona, Spain*
[‡] *Biomedical Signal Interpretation and Computational Simulation Group, Aragón Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain*
[§] *Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Zaragoza, Spain*
[‖] *Pneumology Department, Salamanca University Hospital, Salamanca, Spain*

ARTICLE INFO

Article history:
Received for publication January 23, 2024.
Received in revised form July 4, 2024.
Accepted for publication July 22, 2024.

ABSTRACT

Background: Patients with severe asthma often have uncontrolled disease and experience mood disorders, particularly anxiety and depression. The autonomic nervous system (ANS) plays an important role in asthma, mainly through the parasympathetic ANS system (PANS), which favors bronchoconstriction and mental health status.
Objective: To evaluate the role of the activation of the PANS in uncontrolled asthma and related mood disorders.
Methods: This was a proof-of-concept cross-sectional study that analyzed demographic and clinical variables reflecting asthma severity and control, lung function, inflammation (from induced sputum), evaluation of quality of life, and the risk for anxiety and depression according to validated questionnaires. The PANS analysis was conducted based on heart rate variability: SD of the difference between consecutive normal-to-normal (NN) intervals (SDNN), root mean square of the successive differences (RMSSD), percentage of consecutive NN intervals (pNN50), total power (TP), and respiratory-related power (Pr).
Results: A total of 30 patients with asthma were grouped according to asthma control and the risk for anxiety and depression; 10 patients with uncontrolled asthma compared with the patients with controlled asthma showed significant differences ($P < .05$) in SDNN (26.5 [8.2] vs 42.7 [29.7]), RMSSD (14.1 [6.5] vs 24 [20]), pNN50 (0.6 [1.5] vs 6.2 [11.8]), TP (0.0005 [0.00046] vs 0.0014 [0.00085]), and Pr (0.0003 [0.00025] vs 0.0007 [0.00060]) respectively. A total of 13 patients at risk for anxiety and depression compared with the patients without showed reduced values ($P < .05$) for SDNN (26.5 [7.9] vs 45.6 [31.3]), pNN50 (0.75 [1.4] to 7.12 [12.6]), TP (0.0005 [0.00048] to 0.0012 [0.0008]), and Pr (0.0003 [0.00027] to 0.0008 [0.00062]).
Conclusion: Our results suggest that PANS activity is depressed in patients with uncontrolled asthma and common mood disorders such as depression and anxiety, and the evaluation of heart rate variability may be a useful means for follow-up of asthma control and related mood disorders.

Introduction

The important role played by the autonomic nervous system (ANS) in asthma pathophysiology and symptomatology has long been known.[1] In addition to regulating important airway functions, such as bronchial smooth muscle tone, secretions, blood flow, and microvascular permeability, the ANS also intervenes in the migration and release of inflammatory mediators.[2–5] Inflammatory phenotypes in asthma can usually be distinguished based on the presence of eosinophils or neutrophils, using non-invasive procedures such as exhaled nitric oxide and induced sputum.[6] However, bronchoconstriction is not always mediated by bronchial inflammation, as evidenced by a significant proportion of patients with asthma (40%) in whom bronchial inflammation is not detected.[7,8] However, it is suspected that bronchoconstriction may be caused by strictly airway diameter-related mechanical mechanisms induced by nerve stimulation (the cholinergic reflex).[9] This complex interaction between inflammation and neuronal airway control, with effects on inflammatory mediators in neurotransmitters, modulates the inflammatory response (hypersecretion, edema, and the release of pro-inflammatory mediators such as mast cells)[3] by activating the cholinergic reflex.[4,5]

Address correspondence to: Lorena Soto-Retes, MD, Pneumology and Allergy Department, Hospital de la Santa Creu i Sant Pau and Department of Medicine, 08025 Sant Antoni Maria Claret 167, Barcelona, Spain. E-mail: lsoto@santpau.cat.

https://doi.org/10.1016/j.anai.2024.07.022

Evidence-based literature refers specifically to mental and emotional health in people with severe asthma.[10] Anxiety and depression are 1.5 to 2.4 times more common in people with asthma than in people without asthma,[11,12] and the impact is even greater in people with severe or uncontrolled asthma.[13,14] Anxiety and depression, which often occur together, affect a person's ability to function and are associated with various behavioral, cognitive, and physiological changes.[15] There is growing awareness of the shared relationship between mental health and asthma course, as both interact directly with the pathogenic mechanisms of the respiratory tract and affect the appearance and evolution of asthma.[10,15] Although the relationship is not fully understood, anxiety and depression can negatively affect the asthma course, which could be related to the overlap in autonomic mechanisms that appear to play a role in asthma and are also involved in the activation and regulation of the physiological response to emotional disorders related to asthma.[16,17]

Decreased heart rate variability (HRV), a neurobiologic marker of the ANS, is associated with a variety of negative physical and psychological outcomes.[18] Given that individuals with asthma tend to have a dysregulated heart rate compared with individuals without asthma, some authors suggest that autonomic control of airway caliber in asthma may be accompanied by a change in heart rhythm, suggesting altered activity of the parasympathetic ANS (PANS).[19–21] In fact, variations in PANS activity and HRV have been observed in children with asthma and allergy, with the baseline parasympathetic tone associated with altered HRV.[22]

Mood disorders, including depression and anxiety, are prevalent psychiatric disorders and common comorbidities in people with asthma,[15] and their impact on psychophysiological markers of health and wellbeing, such as HRV, has been documented.[23] The mechanism underlying the relationship between physical and mental health may, in part, be related to impaired vagus nerve activity, leading to dysregulation of inflammatory processes.[24]

Non-invasive PANS are evaluated via HRV according to measurement, physiological interpretation, and clinical use standards as described in guidelines of the working group of the European and American Society of Cardiology and Electrophysiology, which recommends measuring HRV with the electrocardiogram (ECG) as a means for non-invasively evaluating the PANS.[18]

Because publications are few and yield different results, we aimed to comprehensively evaluate the role played by activation of the PANS in uncontrolled asthma and related mood disorders (specifically anxiety and depression). We hypothesized that ANS dysregulation, particularly PANS dysregulation, plays a role in both uncontrolled asthma and mood disorders. Although studies have evaluated the association of both disorders separately, to our knowledge, no study has comprehensively related whether greater anxiety and depression lead to worse asthma control or vice versa objectively by analyzing the PANS.

Methods

Study Population

A proof-of-concept cross-sectional study was conducted to assess the PANS in relation to uncontrolled asthma, anxiety, and depression.

A total of 42 patients diagnosed with asthma were recruited from the pneumology and allergy outpatient clinic at the Hospital Santa Creu i Sant Pau (Barcelona, Spain). However, 12 declined to participate, and 30 agreed to be included. All 30 patients complied with the inclusion and exclusion criteria. Inclusion criteria were as follows: age ≥ 18 years and an asthma diagnosis based on Spanish Asthma Guidelines[25] and Global Initiative for Asthma criteria.[26] Exclusion criteria were as follows: upper respiratory tract infection or asthma exacerbation within the previous 4 weeks, concomitant respiratory disease (bronchiectasis, fibrosis, etc.), and any other major comorbidity (according to investigator criteria), such as diabetes, psychiatric or neurological disease, and systemic inflammatory or immunologic disease.

The research complied with the principles of the Declaration of Helsinki (18th World Medical Assembly, 1964) and was approved by the Hospital Santa Creu i Sant Pau Hospital Clinical Research Ethics Committee (NTC02836691).

Clinical Assessment

Patients were informed about the purposes of the study and signed their informed consent before inclusion. The 30 patients meeting the inclusion criteria attended a single visit for ECG measurement of HRV. All asthma medications could be used, but short acting β2 agonist (SABA) use had to be avoided at least 6 hours before. Patients completed specific asthma and anxiety-depression questionnaires, and demographic and clinical data collected included data on asthma severity, asthma control, lung function, inflammatory cells in induced sputum, and mental and emotional health (specifically depression and anxiety).

Heart Rate Variability Measurement

The HRV analysis has been widely used for non-invasive ANS characterization.[18] Traditionally, a distinction has been made between analysis in the time and frequency domains, each with advantages and disadvantages. In this study, both domain types were considered.[27] Measurements were conducted with participants seated and motionless; they were asked to breathe naturally and avoid talking during recording, and after a 2-minute stabilization period, they were recorded for 10 minutes. Time-domain analysis was based on calculating different statistics from the HRV signal, which, in our study, were the following: the normal-to-normal (NN) interval; the time between consecutive beats (a measure of the average heart rate); SD of the difference between consecutive NN intervals (SDNN; a global measure of HRV); root mean square of successive differences (RMSSD; a measure of short-term variability reflecting parasympathetic regulation); and the percentage of consecutive NN intervals that differ by more than 50 milliseconds (ms) (pNN50; a widely used HRV measure).[18]

The resting HRV spectrum is characterized by 2 main components: a high-frequency (HF) component in the 0.15 to 0.4 Hz band, and a low-frequency (LF) component in the 0.04 to 0.15 Hz band. Although the HF band has been related to parasympathetic activity, the LF band has been related to both sympathetic and parasympathetic activity, so the power in each of the bands is related to different ANS branches. The following parameters were considered: LF power (PLF), HF power, and total power (TP); that is, LF power, related to both sympathetic and parasympathetic activity, HF power, mainly related to parasympathetic activity, and TP (ie, PLF and HF power summed), respectively.[21,28]

In the frequency domain, when the respiratory rate (RR) is low, HRV analysis is compromised. This is because the information contained in the HF band is mainly related to respiration, so if the RR is so low as to be contained within the limits of the LF band, the HF band ends up empty, and consequently, physiological interpretation according to traditional measures is not feasible. One way to overcome this problem is to use orthogonal sub-space projection,[27] which combines respiratory signal and HRV information and separates the HRV part due to respiration from that due to other effects. From this decomposition, we obtained the following indices: non-respiratory-related HRV power (PLFnr) and respiratory-related HRV power (Pr.)[28]

Generated through the ECG, those signals distinguish between the influence of the sympathetic ANS and the PANS.[18] This method, previously developed and studied by our team, has been adapted to

patients with asthma using 12 leads, a respiratory band, and a pulse oximeter. Encephalan-EEGR-19/26 (Medicom MTD Ltd, Russia) software was used for recording over 10 minutes and registration.[28]

Clinical Variables, Atopic Status, Lung Function, and Inflammatory Tests

Collected data were as follows: demographic and anthropometric data; smoking status; forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC),[29,30] asthma severity (according to the Spanish Asthma Guidelines[25] and the Global Initiative for Asthma[26]); and fraction of exhaled nitric oxide (FeNO) (chemiluminescence sensor SIR System N6008, SIR, Madrid, Spain).[31,32] Atopic status was determined using skin prick tests for common aeroallergens such as dust mites, grass pollen, animal dander, and common fungi (Leti Pharma, Madrid, Spain),[33] with positivity defined as the presence of at least 1 weal more than or equal to 3 mm.

Induced Sputum

Cell count was analyzed by microscopy following the method described by Belda et al[34] and Pin et al.[35] Patients were classified by bronchial inflammatory phenotype according to European Respiratory Society recommendations, as follows: paucigranulocytic (eosinophils < 3%, neutrophils < 65%), neutrophilic (eosinophils < 3%, neutrophils ≥ 65%), eosinophilic (eosinophils ≥ 3%, neutrophils < 65%), and mixed (eosinophils ≥ 3%, neutrophils ≥ 65%).[36]

Questionnaires

To establish clinical asthma control level, a validated Spanish version of the Asthma Control Test (ACT) questionnaire was administered.[37] Patients completed the ACT, which comprises 5 questions to assess activity limitation, shortness of breath, nighttime symptoms, use of rescue medication, and patient overall rating of asthma control over the previous 4 weeks. The questions are scored from 1 (worst) to 5 (best), and the ACT score is the sum of the responses, giving a maximum best score of 25. An ACT score of 19 or less is the cutoff point defining uncontrolled asthma. To evaluate the quality of life (QoL), a validated Spanish version of the short version of the Asthma Quality of Life Questionnaire (MiniAQLQ) was administered.[38,39] It includes 15 items divided into 4 dimensions: symptoms (5 items), activity limitation (4 items), emotional function (3 items), and environmental stimuli (3 items). The 15 items are scored on a 7-point Likert scale, with scores 1 to 7 corresponding to maximum limitation and absence of limitation (worst and best possible QoL), respectively. Finally, administered to asses anxiety-depression was the Hospital Anxiety and Depression Scale (HADS),[40] a 14-point self-assessment scale used to screen for clinically significant anxiety and depression (7 points each). Each item is rated on a 4-point scale: 0 indicating not at all; 1, sometimes; 2, often; and 3, all the time. This gives a maximum subscale score of 21 for anxiety and depression, respectively. We considered the HADS questionnaire because it is very simple and explores both anxiety and depression. In the validation of the questionnaire, a score greater than 7 (in the 2 subscales) has been found to define anxiety or depression.

Peripheral Blood Test

Biologic samples were collected (using BD-Vacutainer, United Kingdom) to determine complete blood count and total IgE by enzyme-linked immunosorbent assay (UNICAP, Pharmacia, Uppsala, Sweden).

Statistical Analysis

Descriptive baseline values were reported as percentages and frequencies for qualitative data and as mean and SD values for quantitative data. Severity groups were compared using analysis of variance. The non-parametric Kruskal–Wallis test was used for non-normally distributed quantitative variables, yielding median, minimum, and maximum values for each group. Multivariate analysis included possible confounding and/or interaction variables. Statistical significance was set to 5% ($\alpha = 0.05$) and SPSS (version 22.0) for Windows (SPSS, Inc, Chicago, Illinois) was used for the statistical analysis.

Results

Demographic and Disease Characteristics

The study included 30 patients with asthma (53.3% women; mean [SD] age, 49.4 [12.8]; 80% atopic; and 6.7% active smokers). Most had elevated type-2 biomarkers at baseline, and mean eosinophils and FeNO were 311 cells/mL and 45 parts per billion (ppb). Baseline demographics and disease characteristics are reported in Table 1.

Asthma Control and Heart Rate Variability

A total of 10 patients with uncontrolled asthma (ACT ≤ 19) were predominantly female (70%) and had overweight (mean [SD] body mass index [BMI], 30 [4.6] vs 26 [3], $P = .02$), and all required combination inhalers with a long-acting β2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and SABAs ($P < .05$). Compared with patients with controlled asthma, these 10 patients also had poorer lung function (FEV_1 1.9 L [0.4 L] vs 3 L [0.8 L]; FEV_1 72% [18%] vs 92% [8.5%]; FEV_1/FVC 60.3% [13%] vs 69.9% [9.5%]), poorer QoL (MiniAQLQ 4.4 [1.2] vs 6.2 [0.8]), and experienced greater mood disorders (HADS 14.4 [7.8] vs 7.5 [9.1]) ($P < .05$) (Table 2). The 10 patients with uncontrolled asthma also had significantly lower scores for SDNN (26.5 [8.2] vs 42.7 [29.7], $P = .03$), RMSSD (14 [6] vs 24 [20], $P = .05$), pNN50 (0.6 [1.5] vs 6.2 [11.8], $P = .05$), TP (0.0005 vs 0.0014, $P = .02$), and Pr (0.0003 vs 0.0007, $P = .01$) (Table 3).

Asthma, Mood Disorders, and Heart Rate Variability

Regarding the classification according to mood disorder severity, 13 patients had borderline or clinically problematic HADS ≥ 8 (Table 4). Compared with patients without depression-anxiety, patients at risk for depression-anxiety predominantly had overweight (BMI, 29.6 [4.8] vs 25.9 [2.4], $P = .02$). These patients needed combination inhalers with LABA (100%) ($P < .05$); differences due to LAMA and SABA use were non-significant (76.9% vs 52.9%, $P = .1$; 84.6% vs 41.1%, $P = .1$). These patients also presented greater airway obstruction (FEV_1 2.2 L [0.79 L] vs 3.09 L [0.79 L], $P = .001$; FEV_1 77.6% [19%] vs 91.8% [6.5%], $P = .02$; FEV_1/FVC 60% [13%] vs 71% [7%], $P = .01$), lower ACT scores (18 [3.8] vs 23 [2], $P = .001$), and lower MiniAQLQ scores (4.8 [1.3] vs 6.3 [0.9], $P = .002$). Finally, they also had reduced SDNN (26.5 [7.9] vs 45.6 [31.3], $P = .04$), RMSSD (13.4 [6.5] vs 26 [20], $P < .05$), pNN50 (0.75 [1.4] vs 7.12 [12.6], $P = .05$), TP (0.0005 vs 0.0012, $P = .02$), and Pr (0.0008 vs 0.0003, $P = .01$) (Table 5). Only 2 patients with severe uncontrolled asthma were out of risk of mood disorders with the following clinical features, mean (SD): age 59 (10.6), 1 male; BMI 28 (2.8); both no smoker; both required combined LABA and LAMA treatment, and SABA use; FEV_1 2.03 L (0.24 L); FEV_1 89% (2.5); FEV_1/FVC 65% (9.5); FeNO 100 ppb (78.5); blood eosinophils 280 mm^3 (84); total IgE 336 UI/ml (132), eosinophils and neutrophils in induced sputum 17.5% (15.5) and 69 (10), respectively; ACT score 18.5 (0.5); MiniAQLQ score 4.1 (1); HADS 3 (1); SDNN and RMSSD 16.8 (20.8), pNN50 0.27 (0.39), TP 0.0007 (0.003), and Pr 0.0001 (0.0007).

Table 1
Baseline Demographics Asthma Characteristics

Variables	All sample, n = 30	Mild and moderate asthma, n = 10	Severe asthma, n = 20	*P*
Demographic/clinical data				
- Age, mean (SD), y	49.4 (12.8)	48 (10)	49.70 (14)	.9
- Body mass index, mean (SD), kg/m^2	27.5 (4)	27.2 (2.7)	30.2 (4.6)	**.01**
- Female (%)	53.3	40	60	.4
- Atopy (%)	80	90	75	.5
- Active smoker (%)	6.7	10	5	.6
- SABA use/wk (%)	60	30	75	**.002**
- Combined LABA treatment (%)	86.7	60	100	**.007**
- Combined LAMA treatment (%)	66.7	0	100	**.000**
- Asthma control test, mean (SD)	20.8 (3.9)	23 (1.7)	19.70 (4.2)	**.000**
- MiniAQLQ, mean (SD)	5.6 (1.3)	6.6 (0.2)	5.1 (1.4)	**.001**
- HADS, mean (SD)	9.83 (9.2)	7.8 (11.2)	10.8 (8.1)	.1
Pulmonary function				
- FEV_1, mean (SD), L	2.7 (0.8)	3.2 (0.83)	2.4 (0.8)	**.001**
- Reference FEV_1 (%)	85.7 (15)	95.6 (9.7)	80.7 (15.4)	**.001**
- FEV_1/FVC (%)	66.7 (11.6)	74.7 (6.3)	62.7 (11.7)	**.01**
- FeNO, mean (SD), ppb	45.8 (49.1)	26.3 (13.3)	55.6 (57.4)	.1
Laboratory				
- Blood eosinophils, mean (SD) mm^3	311 (171)	289 (95.9)	232 (200.2)	.8
- Total IgE, mean (SD), UI/mL	309 (419)	283.9 (385.2)	323.2 (446.3)	.1
Induced sputum (%)				
- Eosinophils	4.9 (7)	3.5 (4.6)	5.7 (7.9)	.6
- Neutrophils	54.3 (19)	56.7 (21.3)	53.2 (18.3)	.8
- Macrophages	34.5 (19)	37.5 (19.7)	33 (19.4)	.5
- Lymphocytes	1.4 (0.8)	1.2 (0.74)	1.5 (0.8)	.3

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonists; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; ppb, parts per billion; SABA, short acting β2 agonists.
NOTE: Bold values in *P* column means are statistically different ($p<0.05$).

Discussion

Our main finding is that, compared with patients with controlled asthma, patients with poorly controlled asthma had poorer lung function, overweight, a poorer QoL, and more depressed PANS.

We demonstrated that objective data obtained from HRV measurement could be a non-invasive means of discriminating uncontrolled from controlled asthma. We also found that depression-anxiety was associated with reduced HRV parameters in patients with poorer lung function. Our results suggest that the PANS pathway could play a role in asthma pathogenesis, given the alteration in PANS activity in patients with asthma, most especially in patients with uncontrolled asthma and depression-anxiety.

A strength of the study is that we used an algorithm to stratify patients with asthma (as described in our recent study[28]) that, in other studies, has performed well in analyzing HRV.[41–43] The most

Table 2
Demographic and Clinical Characteristics for Patients With Controlled and Uncontrolled Asthma

Variables	Controlled asthma, n = 20	Uncontrolled asthma, n = 10	*P*
Demographic/clinical data			
- Age, mean (SD), y	49 (12)	49 (13)	.9
- Body mass index, mean (SD), kg/m2	26 (3)	30 (4.6)	**.02**
- Female (%)	30	70	.1
- Atopy (%)	85	70	.8
- Active smoker (%)	5	10	.3
- SABA use/wk (%)	40	100	**.000**
- Combined LABA treatment (%)	80	100	**.000**
- Combined LAMA treatment (%)	50	100	**.000**
- Asthma Control Test, mean (SD)	23 (2.1)	16 (2.8)	**.001**
- MiniAQLQ, mean (SD)	6.2 (0.8)	4.4 (1.2)	**.001**
- HADS, mean (SD)	7.5 (9.1)	14.4 (7.8)	**.04**
Pulmonary function			
- FEV_1, mean (SD), L	3.09 (0.8)	1.9 (0.4)	**.001**
- Reference FEV_1 (%)	92.2 (8.5)	72.7 (18)	**.001**
- FEV_1/FVC (%)	69.9 (9.5)	60.3 (13.3)	**.03**
- FeNO, mean (SD), ppb	34.3 (37)	68.9 (63)	.06
Laboratory			
- Blood eosinophils, mean (SD) mm^3	303 (190)	328 (132)	.6
- Total IgE, mean (SD), UI/mL	219 (298)	510 (582)	.08
Induced sputum (%)			
- Eosinophils	4.2 (4.7)	6.5 (10.4)	.4
- Neutrophils	54 (18)	54 (21)	.9
- Macrophages	37 (17)	28 (21)	.2
- Lymphocytes	1.3 (0.6)	1.7 (1.06)	.1

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; LABA, LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonists; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; ppb, parts per billion; SABA, short acting β2 agonists.
NOTE: Bold values in *P* column means are statistically different ($p<0.05$).

Table 3
Heart Rate Variability Indices in Studied Patients With Controlled and Uncontrolled Asthma

Variables	Controlled asthma, n = 20	Uncontrolled asthma, n = 10	*P*
HRV parameters (PANS-related)			
- SDNN, mean (SD)	42.7 (29.7)	26.5 (8.2)	**.03**
- RMSSD, mean (SD)	24 (20)	14.1 (6.5)	**.05**
- pNN50, mean (SD)	6.2 (11.8)	0.6 (1.5)	**.05**
HRV frequency domain			
- TP, mean (SD)	0.0014 (0.00085)	0.0005 (0.00046)	**.02**
HRV respiratory component			
- Pr, mean (SD)	0.0007 (0.00060)	0.0003 (0.00025)	**.01**
- PLFnr, mean (SD)	0.0001 (0.00014)	0.0001 (0.00022)	.5

Abbreviations: HRV, heart rate variability; PLFnr, non-respiratory-related HRV power; pNN50, percentage of consecutive normal-to-normal intervals that differ by more than 50 ms; Pr, respiratory-related HRV power; RMSSD, root mean square of the successive differences; SDNN, SD of the difference between normal-to-normal intervals; TP, total power (PLFnr and Pr summed).
NOTE: Bold values in *P* column means are statistically different ($p<0.05$).

important result was, for the uncontrolled asthma group compared with the controlled asthma group, a reduction was detected in vagal components; that is, in RMSSD, pNN50, Pr, and TP. This finding contributes to pediatric findings by Lufti et al,[44,45] who reported that poor asthma control in children and adolescents was associated with depressed HRV modulations and that patients with better ventilatory functions had better HRV than patients with uncontrolled severe asthma.

The reduction in HRV vagal components observed in patients with uncontrolled asthma would suggest that there is a complex relationship between inflammation and neural airway control. Regarding impaired autonomic control, it is known that changes in bronchomotor tone in asthma occur rapidly. Decades ago, it was suggested that people with asthma may have abnormal autonomic neural airway control, with an imbalance between the excitatory and inhibitory pathways, resulting in overly reactive airways.[2] However, other studies of severe asthma pointed to increased vagal dominance in response to autonomic challenge (deep breathing, the Valsalva maneuver, and standing up from the recumbent position) and during sleep.[19,20,46] Hence, it is possible that the PANS in patients with severe asthma may become depressed during inactivity or relaxation, with bronchoconstriction occurring when the vagal pathways are activated or over-respond to stimuli.[47]

Our patients with controlled asthma obtained better results for all PANS parameters, although statistically non-significant differences were found for PLFnr, which reflects the sympathetic branch. Likewise, patients at risk for depression-anxiety showed depressed PANS for all parameters, whereas no differences were found for PLFnr. Compared with patients with controlled asthma, patients with poor asthma control and obstructive spirometry ($FEV_1 \leq 70\%$ predicted) showed more depressed HRV, independently of inflammation as measured by FeNO, induced sputum, peripheral blood eosinophilia, or total IgE (Table 1). Notably, although mood disorders such as depression-anxiety are inherent to patients with severe asthma,[10,11,14–17] a strength of our study is that the ANS results were objective, and so can complement information obtained from self-administered questionnaires that are subjective and difficult to interpret.[37–40]

We found significant differences between the groups in terms of mood disorders as measured by the HADS questionnaire: patients

Table 4
Clinical Characteristics of Patients With Asthma With and Without Risk of Clinical Stress and Anxiety

Variables	HADS ≤ 7, n = 17	HADS ≥ 8, n = 13	*P*
Demographic/clinical data			
- Age, mean (SD), y	50 (10)	48 (15)	.7
- Body mass index, mean (SD), kg/m2	25.9 (2.4)	29.6 (4.8)	**.02**
- Female (%)	23	76	.1
- Atopy (%)	85	84	.2
- Active smoker (%)	0	15	**.001**
- SABA use/week (%)	41.1	84.6	.1
- Combined LABA treatment (%)	76.5	100	**.000**
- Combined LAMA treatment (%)	52.9	76.9	.1
- Asthma Control Test, mean (SD)	23 (2.4)	18 (3.8)	**.001**
- MiniAQLQ, mean (SD)	6.3 (0.9)	4.8 (1.3)	**.002**
- HADS, mean (SD)	2.94 (1.9)	18.85 (6.7)	**.001**
Pulmonary function			
- FEV_1, mean (SD), L	3.09 (0.79)	2.2 (0.79)	**.001**
- Reference FEV_1 (%)	91.8 (6.5)	77.6 (19.7)	**.02**
- FEV_1/FVC (%)	71.7 (7)	60 (13.3)	**.01**
- FeNO, mean (SD), ppb	44 (53.1)	48.3 (45.3)	.8
Laboratory			
- Blood eosinophils, mean (SD) mm3	292 (184)	336 (155)	.4
- Total IgE, mean (SD), UI/mL	206 (246)	455 (566)	.1
Induced sputum (%)			
- Eosinophils	5.7 (8)	3.9 (5.5)	.4
- Neutrophils	56.7 (17.6)	51.3 (21)	.4
- Macrophages	34.1 (17.6)	35 (21.9)	.9
- Lymphocytes	1.5 (0.67)	1.3 (0.9)	.5

Abbreviations: FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonists; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; ppb, parts per billion; SABA, short acting β2 agonists.
NOTE: Bold values in *P* column means are statistically different ($p<0.05$).

Table 5
Heart Rate Variability Indices in Studied Patients With Asthma With and Without Risk of Clinical Stress and Anxiety

Variables	HADS ≤ 7, n = 17	HADS ≥ 8, n = 13	*P*
HRV parameters (PANS-related)			
- SDNN, mean (SD)	**45.6 (31.3)**	**26.5 (7.9)**	**.04**
- RMSSD, mean (SD)	**26.4 (20.8)**	**13.4 (6.5)**	**.03**
- pNN50, mean (SD)	**7.12 (12.6)**	**0.75 (1.4)**	**.05**
HRV frequency domain			
- TP, mean (SD)	**0.0012 (0.00087)**	**0.0005 (0.00048)**	**.02**
HRV respiratory component			
- Pr, mean (SD)	**0.0008 (0.00062)**	**0.0003 (0.00027)**	**.01**
- PLFnr, mean (SD)	**0.0002 (0.00014)**	**0.0001 (0.0019)**	**.3**

Abbreviations: HRV, heart rate variability; PLFnr, non-respiratory-related HRV power; pNN50, percentage of consecutive normal-to-normal intervals that differ by more than 50 ms; Pr, respiratory-related HRV power; RMSSD, root mean square of the successive differences; SDNN, SD of the difference between normal-to-normal intervals; TP, total power (PLFnr and Pr summed).
NOTE: Bold values in *P* column means are statistically different ($p<0.05$).

with severe asthma with depression-anxiety had poorer lung function, poorer asthma control, poorer QoL, and a depressed PANS compared with patients not experiencing mood disorders. Although patients with uncontrolled asthma are known to experience mood disorders,[48] in our study, depression-anxiety was related to PANS alteration, so the question remains as to whether depression-anxiety is a consequence or an independent comorbidity of severe uncontrolled asthma.

To date, several studies have been published on HRV and anxiety or depression disorders.[23,24,48] The reasons given for altered HRV in mood disorders, according to a model of neurovisceral integration, nerve fibers that moderate parasympathetic activity and inhibition of the vagus nerve, a dysregulation is related to pathologies such as diabetes type II, cardiac and neurodegenerative diseases, and depression.[49–52] This model of neurovisceral integration is also characterized by specific neural structures that allow people to respond adaptively to physiological, environmental, cognitive, and emotional influences. Therefore, a healthy cardiorespiratory system is characterized, in the cardiac period, by oscillations (high HRV), whereas an unhealthy cardiorespiratory system shows a few oscillations (low HRV),[24] which is related to our findings in this study.

All patients were on asthma medication, especially the patients with uncontrolled asthma that was so severe as to require more than 1 inhaler. Patients with asthma were being treated with LABAs in combination with inhaled corticosteroids and with LAMAs; those with mild and moderate asthma were only on inhaled corticosteroids, without LABAs or LAMAs. However, SABAs were avoided in the hours before recording. Although LABA or LAMA use suggests that our results might have been influenced by those medications, the literature is not entirely clear as to LABA's or LAMA's influence on HRV, as contradictory results are reported. An HRV study of patients on LABA found that its use was associated with sympathetic nervous system (SNS) dominance,[53] whereas another study demonstrated that salbutamol was associated with decreased PANS and increased SNS activity.[54] Although the underlying mechanism is not entirely clear, it is possible that LABAs bind to β2 adrenoceptors at efferent sites in the cardiac SNS, or that the peripheral vasculature may directly stimulate SNS activity. Another more direct study of the potential effect of LABAs on HRV reported that there was no change in time-domain parameters (mean RR and standard deviation of all the R-R intervals, SDRR) when fenoterol was administered immediately before and immediately after HRV analysis, which would suggest sympathetic activation.[55] However, studies in patients with asthma show that different LABAs have different effects on cardiac autonomic control. Thus, Eryonucu et al[56] reported that fenoterol inhalation had no effect on sympathetic activation (mean RR and SDRR) in regularly treated patients, whereas Zahorska-Markiewicz et al[46] showed that salbutamol and terbutaline tended to increase SNS parameters. Yao-Kuang Wu et al,[57] who studied the effects of LAMA on HRV in patients with stable chronic obstructive pulmonary disease, found no significant change in HRV parameters other than a significant decrease in the HF component and an increase in the LF component after 1 month of continued LAMA treatment, but not after 3 months. Overall, they found no change in HRV parameters that was of sufficient magnitude to explain the increased HRV. However, since we found significant differences between patients with severe controlled asthma treated with LABAs or LAMAs and patients with uncontrolled asthma, we do not believe that LABAs or LAMAs had a direct effect on HRV results. Given the lack of clarity, nonetheless, further studies are needed on the pharmacological effects of LABAs or LAMAs and their influence on HRV outcomes in asthma.

The main limitations of our study are the small number of subjects and the lack of a control group, both typical features of proof-of-concept studies. Necessary to confirm our results is an extended study that includes more subjects, other physiological factors, and a control group. However, the study's strength is that our asthma population is very well characterized, with objective evidence of asthma status (such as bronchodilator reversibility, lung function, inflammation biomarkers, and allergy status).

This study points to the potential role that the PANS may play in asthma control and its relationship with depression-anxiety. No study, as far as we are aware, has focused on the role of the PANS, despite the existence of studies addressing the ANS response to pharmacological intervention and bronchial provocation. In this sense, and if confirmed with other studies, it could underscore the pathophysiological role of the PANS in the control of asthma associated with depression-anxiety, justifying the development of future research to identify new pharmacological therapeutic targets in the PANS, even for the development of a potential complementary clinical tool, objective and non-invasive in specialist consultations focused on severe asthma, which could contribute to remote or continuous monitoring with wireless devices or mobile applications, providing a comprehensive approach to the current ones for the evaluation of asthma control and mood disorders.

In conclusion, variables derived from the PANS showed depressed HRV in patients with uncontrolled asthma and depression-anxiety, as compared with patients with controlled asthma and without mood disorders. PANS evaluation by analyzing non-invasive cardiorespiratory parameters may be a useful means for, and contribute to, follow-up of asthma control and associated depression-anxiety. Further studies using HRV analysis are needed to be able to comprehensively evaluate the PANS in patients with uncontrolled asthma and depression-anxiety.

Acknowledgments

The authors thank the patients who generously contributed to this study. They also thank Jordi Giner for her unwavering support and assistance throughout the project; their guidance and insights were instrumental in the successful completion of this project.

Disclosures

The authors have no conflict of interest to report.

Funding

This study was funded by Proyectos Integrados de Investigación de Asma through Sociedad Española de Neumología y Cirugía Torácica.

References

1. Kaliner M, Shelhamer JH, Davis PB, Smith LJ, Venter JC. Autonomic nervous system abnormalities and allergy. *Ann Intern Med*. 1982;96(3):349–357.
2. Barnes PJ. Neuroeffector mechanisms: the interface between inflammation and neuronal responses. *J Allergy Clin Immunol*. 1996;98(5 Pt 2):S73–S81. discussion S81-S83.
3. Barnes PJ. Neural mechanisms in asthma. *Br Med Bull*. 1992;48(1):149–168.
4. Gosens R, Bos IST, Zaagsma J, Meurs H. Protective effects of tiotropium bromide in the progression of airway smooth muscle remodeling. *Am J Respir Crit Care Med*. 2005;171(10):1096–1102.
5. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med*. 2010;363(18):1715–1726.
6. Malerba M, Ragnoli B, Radaeli A, Tantucci C. Usefulness of exhaled nitric oxide and sputum eosinophils in the long-term control of eosinophilic asthma. *Chest*. 2008;134(4):733–739.
7. Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. *BMC Pulm Med*. 2013;13:11.
8. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms. *Thorax*. 2002;57(7):643–648.
9. Haldar P, Pavord ID. Noneosinophilic asthma: A distinct clinical and pathologic phenotype. *J Allergy Clin Immunol*. 2007;119(5):1043–1052.
10. Wright RJ. Exploring biopsychosocial influences on asthma expression in both the family and community context. *Am J Respir Crit Care Med*. 2008;177(2):129–130.
11. Scott KM, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, Alonso J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry*. 2007;29(2):123–133.
12. Strine TW, Mokdad AH, Balluz LS, Gonzalez O, Crider R, Berry JT, et al. Depression and anxiety in the United States: findings from the 2006 Behavioral Risk Factor Surveillance System. *Psychiatr Serv*. 2008;59(12):1383–1390.
13. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015;46(5):1308–1321.
14. Amelink M, Hashimoto S, Spinhoven P, Pasma HR, Sterk PJ, Bel EH, et al. Anxiety, depression and personality traits in severe, prednisone-dependent asthma. *Respir Med*. 2014;108(3):438–444.
15. Kewalramani A, Bollinger ME, Postolache TT. Asthma and mood disorders. *Int J Child Health Hum Dev*. 2008;1(2):115–123.
16. Lehrer PM, Isenberg S, Hochron SM. Asthma and emotion: a review. *J Asthma*. 1993;30(1):5–21.
17. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax*. 1998;53(12):1066–1074.
18. Camm AJ, Malik M, Bigger JT, et al. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93(5):1043–1065.
19. Kallenbach JM, Webster T, Dowdeswell R, Reinach SG, Millar RN, Zwi S. Reflex heart rate control in asthma. Evidence of parasympathetic overactivity. *Chest*. 1985;87(5):644–648.
20. Shah PK, Lakhotia M, Mehta S, Jain SK, Gupta GL. Clinical dysautonomia in patients with bronchial asthma. Study with seven autonomic function tests. *Chest*. 1990;98(6):1408–1413.
21. Garrard CS, Seidler A, McKibben A, McAlpine LE, Gordon D. Spectral analysis of heart rate variability in bronchial asthma. *Clin Auton Res*. 1992;2(2):105–111.
22. Tokuyama K, Morikawa A, Mitsuhashi M, Mochizuki H, Tajima K, Kuroume T. Beat-to-beat variation of the heart rate in children with allergic asthma. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1987;22(2):222–228.
23. Blase K, Vermetten E, Lehrer P, Gevirtz R. Neurophysiological approach by self-control of your stress-related autonomic nervous system with depression, stress and anxiety patients. *Int J Environ Res Public Health*. 2021;18(7):3329.
24. Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front Psychiatry*. 2014;5:80.
25. GEMA. Guía Española Para el Manejo del Asma. Available at: http://www.gemasma.com/. Accessed August 16, 2024.
26. GINA. Global Strategy for Asthma Management and Prevention. Available at: http://www.ginasthma.org. Accessed August 16, 2024.
27. Varon C, Lázaro J, Bolea J, Hernando A, Aguiló J, Gil E, et al. Unconstrained estimation of HRV indices after removing respiratory influences from heart rate. *IEEE J Biomed Health Inform*. 2019;23(6):2386–2397.
28. Milagro J, Soto-Retes L, Giner J, Varon C, Laguna P, Bailón R, et al. Asthmatic subjects stratification using autonomic nervous system information. *Biomed Signal Process Control*. 2021;69: 102802.
29. Aldás JS, Clarà PC, Gómez JC, Mangado NH, Ballesteros LP, Torrent JR. Normativa para la práctica de la espirometría forzada. *Arch Bronconeumol*. 1989;25(4):132–142.
30. Roca J, Sanchis J, Agusti-Vidal A, Segarra F, Navajas D, Rodriguez-Roisin R, et al. Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir*. 1986;22(3):217–224.
31. Silkoff PE. Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children-1999. *Am J Respir Crit Care Med*. 1999;160(6):2104–2117.
32. Fortuna AM, Feixas T, Casan P. Measurement of fraction of exhaled nitric oxide with the portable NIOX-MINO monitor in healthy adults. *Arch Bronconeumol*. 2007;43(3):176–179.
33. Report on Skin Test Standardization. The Committee on Skin Test Standardization of The Netherlands Society of Allergology. *Clin Allergy*. 1988;18(3):305–310.
34. Belda J, Leigh R, Parameswaran K, O'Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):475–478.
35. Pin I, Gibson PG, Kolendowicz R, Girgis-Gabardo A, Denburg JA, Hargreave FE, et al. Use of induced sputum cell counts to investigate airway inflammation in asthma. *Thorax*. 1992;47(1):25–29.
36. Djukanović R, Sterk PJ, Fahy JV, Hargreave FE. Standardised methodology of sputum induction and processing. *Eur Respir J Suppl*. 2002;37:1s–2s.
37. Vega JM, Badia X, Badiola C, López-Viña A, Olaguíbel JM, Picado C, et al. Validation of the Spanish version of the Asthma Control Test (ACT). *J Asthma*. 2007;44(10):867–872.
38. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. 1999;14(1):32–38.
39. Sanjuàs C, Alonso J, Sanchís J, Casan P, Broquetas JM, Ferrie PJ, et al. [The quality-of-life questionnaire with asthma patients: the Spanish version of the Asthma Quality of Life Questionnaire]. *Arch Bronconeumol*. 1995;31(5):219–226.
40. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
41. Milagro J, Gil E, Lazaro J, Seppa VP, Malmberg LP, Pelkonen AS, et al. Nocturnal heart rate variability spectrum characterization in preschool children with asthmatic symptoms. *IEEE J Biomed Health Inform*. 2018;22(5):1332–1340.
42. Milagro J, Gracia-Tabuenca J, Seppa VP, Karjalainen J, Paassilta M, Orini M, et al. Noninvasive cardiorespiratory signals analysis for asthma evolution monitoring in preschool children. *IEEE Trans Bio Med Eng*. 2020;67(7):1863–1871.
43. Bailón R, Laguna P, Mainardi L, Sörnmo L. Analysis of heart rate variability using time-varying frequency bands based on respiratory frequency. *Annu Int Conf IEEE Eng Med Biol Proc*. 2007;2007:6674–6677.
44. Lutfi M. Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability. *Lung India*. 2012;29(3):254–258.
45. Lutfi MF. Patterns of heart rate variability and cardiac autonomic modulations in controlled and uncontrolled asthmatic patients. *BMC Pulm Med*. 2015;15(1):119.
46. Zahorska-Markiewicz B, Tkacz E, Kossmann S, Konieczny B, Hefczyc J. Circadian heart rate variability in asthma. *Med Sci Monit*. 1997;3(1):52–56.
47. Ritz T, Simon E, Trueba AF. Stress-induced respiratory pattern changes in asthma. *Psychosom Med*. 2011;73(6):514–521.
48. Caulfield JI. Anxiety, depression, and asthma: new perspectives and approaches for psychoneuroimmunology research. *Brain Behav Immun Health*. 2021;18: 100360.
49. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52(7):1799–1805.
50. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ*. 2000;321(7255):199–204.
51. Gao HM, Hong JS. Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression. *Trends Immunol*. 2008;29(8):357–365.
52. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65(9):732–741.
53. Ali H, Brooks C, Tzeng YC, Crane J, Beasley R, Gibson P, et al. Heart rate variability as a marker of autonomic nervous system activity in young people with eosinophilic and non-eosinophilic asthma. *J Asthma*. 2023;60(3):534–542.
54. Jartti TT, Kaila TJ, Tahvanainen KU, Kuusela TA, Vanto TT, Valimaki IA. Altered cardiovascular autonomic regulation after 2-week inhaled salbutamol treatment in asthmatic children. *Eur J Pediatr*. 1997;156(11):883–888.
55. Tsou CH, Pon LS, Liang JZ, Chan YH, Chen KJ, Cheng FS, et al. Response of heart rate variability and cardiorespiratory phase synchronization to routine bronchodilator test in patients with asthma. *Chin J Physiol*. 2021;64(4):177–185.
56. Eryonucu B, Uzun K, Güler N, Bilge M. Comparison of the acute effects of salbutamol and terbutaline on heart rate variability in adult asthmatic patients. *Eur Respir J*. 2001;17(5):863–867.
57. Wu YK, Huang CY, Yang MC, Huang GL, Chen SY, Lan CC. Effect of tiotropium on heart rate variability in stable chronic obstructive pulmonary disease patients. *J Aerosol Med Pulm Drug Deliv*. 2015;28(2):100–105.