UAB
Universitat Autònoma de Barcelona

Papel del sistema nervioso autónomo determinado mediante la variabilidad del ritmo cardiaco y de los intervalos cardiacos del electrocardiograma en el asma grave no controlada

Lorena Soto Retes

Universitat Autònoma de Barcelona

Tesis Doctoral

Papel del sistema nervioso autónomo determinado mediante la variabilidad del ritmo cardiaco y de los intervalos cardiacos del electrocardiograma en el asma grave no controlada

Doctoranda

Lorena Soto Retes

Director y Tutor

Dr. Vicente Plaza Moral

Programa de Doctorado en Medicina

Departamento de Medicina

Universitat Autònoma de Barcelona

Barcelona, 2025

Agradecimientos

A mis padres, Eduardo y Rosa, y a mi esposo Héctor e hija Aina, les debo la inspiración para esta bella vida que hemos construido juntos. Son un ejemplo de cariño, fortaleza, resiliencia, generosidad y, sobre todo, de amor y buen humor, cualidades que nos definen como familia.

A todos mis mentores y compañeros en el campo de la medicina, especialmente a las especialidades de alergología y neumología; a la Sociedad Española de Alergia e Inmunología Clínica (SEAIC) y a la Sociedad Española de Neumología y Cirugía Torácica (SEPAR), instituciones que siempre serán mis referentes por su solidez y compromiso con la enfermedad asmática.

A la Universidad de Monterrey (UDEM), donde me formé como médica y obtuve la beca que me permitió iniciar mi camino en la investigación; a mis compañeros y amigos de biotecnología del Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM) en México; y a mis compañeros de residencia y adjuntos del servicio de alergología del Hospital Universitari Vall d'Hebron: gracias a todos, ustedes marcaron el comienzo de mi trayectoria en la investigación científica.

A mis coautores y colaboradores de esta Tesis Doctoral, muchas gracias por el recorrido, el aprendizaje y el apoyo que me han permitido aportar nuestro granito de arena a la ciencia. Asimismo, agradezco profundamente a todos los pacientes que, de forma desinteresada, han participado en nuestros estudios para impulsar el avance científico.

A la institución a la que pertenezco —el Servicio de Neumología y Alergia del Hospital de la Santa Creu i Sant Pau y el Institut de Recerca del Hospital de Sant Pau (IIB Sant Pau)—, gracias por recibirme desde el primer día como parte del equipo; y a todos mis

compañeros, tanto médicos de otras especialidades como el equipo de enfermería, por su cariño, apoyo y excelente trabajo en esta gran institución, fuente constante de inspiración.

A mis compañeros de la Unidad de Asma, especialmente a Jordi, Montse, Astrid, Elena y Teresa, y a mis colegas alergólogos, Ana y Gustavo.

Finalmente, a mi Director y Tutor, Vicente Plaza, por su apoyo, inspiración y por guiarme en la docencia, organización, gestión y liderazgo, contribuyendo a que la alergología sea un referente en el Hospital de la Santa Creu i Sant Pau.

Abreviaturas

ACh. Receptores muscarínicos de acetilcolina

ACQ. Cuestionario de Control del Asma

ACT. Test de Control del Asma

AGNC. Asma grave no controlada

ApEn. Entropía aproximada

D2. Dimensión de correlación

DE. Desviación Estándar

ECG. Electrocardiograma

FC. Frecuencia cardíaca

FeNO. Fracción del óxido nítrico exhalado

FEV1 /FVC. Relación volumen espiratorio forzado en el primer segundo/capacidad vital forzada

FEV_1. Volumen espiratorio forzado en el primer segundo

FVC. Capacidad vital forzada

GCI/LABA. Glucocorticoides inhalados/agonista β2 adrenérgico de acción prolongada

GCS. Glucocorticoides sistémicos

GEMA. Guía Española para el Manejo del Asma

GINA. Global Initiative for Asthma

HADS. Hospital Anxiety and Depression Scale

HF. Banda de alta frecuencia

HRB. Hiperreactividad bronquial

IgE. Inmunoglobulina IgE

IMC. Índice de masa corporal

IP. Impedancia

LAMA. Antimuscarínico de acción prolongada

LF. Banda de baja frecuencia

MiniAQLQ. Mini Asthma Quality of Life Questionnaire

NANC. Vía no adrenérgica no colinérgica

NN. Normal-normal

OMS. Organización Mundial de la Salud

PBD. Prueba broncodilatadora

PHF. Contenido de potencia en la banda HF

PLF. Contenido de la banda LF

PLFn. Non-respiratory-related HRV power

pNN50. Porcentaje de diferencias sucesivas de intervalos NN que difieren en más de 50 ms

PPB. Partículas por mil millones

Pr. Respiratory-related HRV power

PVLF. Potencia en la banda VLF

RMSSD. La raíz cuadrada de la media de la diferencia

SA. Sinoauricular

SABA. Agonista b2 adrenérgico de acción corta

SampEn. Entropía de muestra

SDNN. Desviación típica de las series de intervalos

SDSD. Desviación típica de la media de la diferencia entre intervalos NN

SNA. Sistema nervioso autónomo

SNP. Sistema nervioso parasimpático

SNS. Sistema nervioso simpático

TP. Potencia espectral total

VLF. Banda de muy baja frecuencia

VRC. Variabilidad del ritmo cardiaco

Índice de Figuras

Índice de Tablas

Índice

Resumen

El sistema nervioso autónomo (SNA) desempeña un papel crucial en el asma, principalmente a través del sistema nervioso parasimpático (SNP). Este último no solo regula funciones esenciales de las vías respiratorias, como el tono muscular bronquial, las secreciones, el flujo sanguíneo y la permeabilidad microvascular, sino que también participa en la migración y liberación de mediadores inflamatorios. Estos mediadores definen distintos fenotipos inflamatorios en el asma, caracterizados generalmente por la presencia de eosinófilos o neutrófilos, y cuya identificación se realiza mediante procedimientos no invasivos como esputo inducido.

Sin embargo, la broncoconstricción, una característica distintiva del asma, no siempre está mediada por la inflamación bronquial. De hecho, en una proporción significativa de pacientes asmáticos (aproximadamente el 40%), no se detecta inflamación bronquial. En estos casos, se sospecha que la broncoconstricción puede originarse por mecanismos mecánicos estrictamente ligados al diámetro de las vías respiratorias, inducidos por la estimulación nerviosa, específicamente el reflejo colinérgico.

Esta compleja interacción entre la inflamación y el control neuronal de las vías respiratorias modula la respuesta inflamatoria (hipersecreción, edema y liberación de mediadores proinflamatorios como los mastocitos) a través de la activación del reflejo colinérgico, con efectos recíprocos entre mediadores inflamatorios y neurotransmisores.

La variabilidad del ritmo cardíaco (VRC) es un marcador neurobiológico del SNA que, cuando se encuentra desregulada, se asocia con diversos resultados físicos y psicológicos negativos. Se ha observado que las personas con asma tienden a presentar una VRC alterada en comparación con individuos sanos, lo que sugiere una actividad desregulada

del SNA, particularmente del SNP. Diversos hallazgos indican que la VRC podría estar especialmente alterada en pacientes con asma grave, lo que señalaría un desequilibrio autonómico con una menor actividad parasimpática. Esta desregulación podría contribuir a la inflamación sistémica, a la pérdida de control y, por consiguiente, aumentar la susceptibilidad a las exacerbaciones.

Además, la ansiedad y la depresión, trastornos con alta prevalencia en pacientes asmáticos, también se han relacionado con un desequilibrio de la VRC. Se ha propuesto que la disfunción autonómica, caracterizada por una disminución del tono vagal, podría ser un mecanismo subyacente común que conecta estos trastornos psicológicos con el asma grave. Esta disfunción no solo afectaría la regulación cardiovascular, sino también la percepción de los síntomas respiratorios, lo que podría agravar el curso de la enfermedad y complicar su manejo clínico.

Por todo lo anterior, profundizar en el conocimiento de las diversas utilidades de la evaluación no invasiva del SNA en la enfermedad asmática, especialmente en el asma grave no controlada, podría aportar información neurobiológica valiosa y permitiría identificar características específicas dentro de cada perfil de pacientes. Esto podría facilitar un apoyo diagnóstico y una monitorización individualizada (medicina personalizada) del control de la enfermedad, proporcionando información objetiva para guiar las decisiones terapéuticas y complementar las herramientas validadas que se utilizan habitualmente en el manejo del asma.

El objetivo de esta Tesis es profundizar en la comprensión del papel del SNA en el asma grave no controlada (AGNC), utilizando la VRC como método de evaluación no invasivo a través de los intervalos cardiacos utilizando el electrocardiograma (ECG).

Para demostrar este concepto, se llevaron a cabo dos estudios. El primero analizó la potencial contribución de la evaluación del SNA a través de métodos no invasivos en población asmática. Y el segundo estudio, se centró en analizar a los pacientes asmáticos en función de su nivel de control y gravedad de la enfermedad y su estado emocional. En ambos se recopilaron los siguientes datos de los participantes: sociodemográficos, antropométricos, clínicos, funcionales respiratorios e inflamatorios. Además, se administraron cuestionarios validados para evaluar el control y la calidad de vida en el asma, así como cuestionarios específicos para identificar el riesgo de trastornos emocionales comúnmente asociados al asma, como son la ansiedad y la depresión. También se recogieron biomarcadores en sangre periférica, información sobre la medicación para el asma y marcadores neurobiológicos del SNA a través de la VRC, obtenida mediante los intervalos cardiacos del ECG.

Los resultados obtenidos fueron:

Estudio 1: Prueba de concepto que demuestra que la evaluación no invasiva del SNA mediante la VRC es una herramienta objetiva potencial para discriminar entre sujetos asmáticos según el control de sus síntomas, utilizando únicamente señales electrocardiográficas y respiratorias registradas durante 10 minutos. Revelamos una variabilidad de la frecuencia cardíaca significativamente más deprimida o desregulada en pacientes asmáticos no controladas en comparación con aquellos con asma controlada. La integración de la información obtenida del SNA de manera estratificada en los pacientes asmáticos, mostró un rendimiento similar al obtenido utilizando únicamente características clínicas, así como a las pruebas de control del asma empleadas en la práctica clínica habitual.

Estudio 2: Se encontraron diferencias significativas en los asmáticos graves no controlados en comparación con los sujetos con asma controlada independientemente de la gravedad ($P < .05$) al evaluar los parámetros más comúnmente empleados en la medición de la VRC analizados a través del ECG. También se evaluó el riesgo de ansiedad y depresión en los sujetos con asma estudiados, ya que son trastornos emocionales frecuentemente vinculados en la enfermedad asmática. Se analizaron los mismos parámetros estandarizados del SNA demostrando diferencias significativas ($P < .05$) en los sujetos asmáticos con riesgo de ansiedad y depresión mostrando valores reducidos o alterados del SNA, en comparación con los sujetos asmáticos sin riesgo de ansiedad y depresión. La evaluación de la VRC, puede ser un medio útil para el seguimiento del control del asma y ayudar a discriminar los trastornos del estado de ánimo más comúnmente relacionados (ansiedad y depresión).

Las conclusiones más relevantes de esta Tesis Doctoral son: la evaluación no invasiva del SNA mediante la medición de la VRC permite diferenciar entre sujetos asmáticos controlados y no controlados, especialmente en casos de asma grave no controlada. En esta Tesis también pudimos reconocer otros trastornos que están asociados a la desregulación del SNA como son la depresión y la ansiedad, comorbilidades habituales en la enfermedad asmática no controlada.

Palabras clave: asma grave, control del asma, sistema nervioso autónomo, variabilidad del ritmo cardíaco, depresión, ansiedad.

Abstract

The autonomic nervous system (ANS) plays a crucial role in asthma, primarily through the parasympathetic nervous system (PNS). The latter not only regulates essential airway functions, such as bronchial muscle tone, secretions, blood flow, and microvascular permeability, but is also involved in the migration and release of inflammatory mediators. These mediators define distinct inflammatory phenotypes in asthma, generally characterized by the presence of eosinophils or neutrophils, and whose identification is performed through noninvasive procedures such as induced sputum.

However, bronchoconstriction, a hallmark of asthma, is not always mediated by bronchial inflammation. In fact, in a significant proportion of asthmatic patients (approximately 40%), bronchial inflammation is not detected. In these cases, it is suspected that bronchoconstriction may be caused by mechanical mechanisms strictly linked to airway diameter, induced by nerve stimulation, specifically the cholinergic reflex.

This complex interaction between inflammation and neuronal control of the airways modulates the inflammatory response (hypersecretion, edema, and release of proinflammatory mediators such as mast cells) through the activation of the cholinergic reflex, with reciprocal effects between inflammatory mediators and neurotransmitters.

Heart rate variability (HRV) is a neurobiological marker of the ANS that, when dysregulated, is associated with various negative physical and psychological outcomes. It has been observed that people with asthma tend to have altered HRV compared to healthy individuals, suggesting dysregulated activity of the ANS, particularly the PNS. Several findings indicate that HRV may be especially altered in patients with severe asthma, indicating an autonomic imbalance with decreased parasympathetic activity. This

dysregulation could contribute to systemic inflammation, loss of control, and consequently, increased susceptibility to exacerbations.

Furthermore, anxiety and depression, disorders with a high prevalence in asthma patients, have also been linked to an imbalance in HRV. It has been proposed that autonomic dysfunction, characterized by decreased vagal tone, could be a common underlying mechanism linking these psychological disorders to severe asthma. This dysfunction would not only affect cardiovascular regulation but also the perception of respiratory symptoms, which could worsen the course of the disease and complicate its clinical management.

Therefore, further understanding the diverse uses of noninvasive ANS assessment in asthma, especially in severe uncontrolled asthma, could provide valuable neurobiological information and allow for the identification of specific characteristics within each patient profile. This could facilitate diagnostic support and individualized monitoring (personalized medicine) of disease control, providing objective information to guide therapeutic decisions and complementing the validated tools commonly used in asthma management.

The objective of this thesis is to deepen our understanding of the role of the ANS in severe uncontrolled asthma, using HRV as a noninvasive assessment method using cardiac intervals using the electrocardiogram (ECG).

To demonstrate this concept, two studies were conducted. The first analyzed the potential contribution of ANS assessment through noninvasive methods in the asthma population. The second study focused on analyzing asthma patients based on their level of disease control and severity, and their emotional state. In both, the following data were collected from the participants: sociodemographic, anthropometric, clinical, respiratory function,

and inflammatory data. In addition, validated questionnaires were administered to assess asthma control and quality of life, as well as specific questionnaires to identify the risk of emotional disorders commonly associated with asthma, such as anxiety and depression. Peripheral blood biomarkers, information on asthma medication, and neurobiological markers of the ANS were also collected through HRV, obtained from the cardiac intervals of the ECG.

The first study analyzed the potential contribution of noninvasive ANS assessment in an asthma population. The second study focused on analyzing asthma patients based on their level of control, disease severity, and emotional status.

The results obtained were:

Study 1: Proof of concept demonstrating that noninvasive ANS assessment using HRV is a potential objective tool for discriminating between asthmatic subjects based on symptom control, using only electrocardiographic and respiratory signals recorded over 10 minutes. We revealed significantly more depressed or dysregulated heart rate variability in uncontrolled asthmatic patients compared to those with controlled asthma. Integrating this autonomic information into patient stratification showed similar performance to that obtained using clinical characteristics alone in several tested approaches, as well as to asthma control tests used in routine clinical practice.

Study 2: Significant differences were found in the ANS between patients with severe uncontrolled asthma and controlled asthmatics ($p<0.05$), as well as in mood disorders common in asthma, such as depression and anxiety. HRV assessment may be a useful tool for monitoring asthma control and helping to distinguish the most associated mood disorders (anxiety and depression).

The most relevant conclusions of this doctoral thesis are the following: noninvasive assessment of the ANS through HRV measurement allows differentiation between controlled and uncontrolled asthma patients, especially in cases of severe uncontrolled asthma. In this study, we were also able to identify patients at risk for ANS-related mood disorders, such as depression and anxiety, significant comorbidities in uncontrolled asthma.

Keywords: severe asthma, asthma control, autonomic nervous system, heart rate variability, depression, anxiety.

1. Introducción

1.1 El Asma bronquial

1.1.1 Definición y epidemiología.

La definición del asma ha evolucionado significativamente a lo largo del tiempo. Actualmente, entidades reconocidas internacionalmente —como la Global Initiative for Asthma (GINA) y la Organización Mundial de la Salud (OMS)—, junto con la Guía Española para el Manejo del Asma (GEMA) a nivel nacional, lo definen como un síndrome heterogéneo que engloba diversos fenotipos clínicos. Aunque estos fenotipos presentan manifestaciones similares, se considera que sus etiologías pueden ser distintas (1-3). En términos pragmáticos, el asma se caracteriza por ser una enfermedad inflamatoria crónica de las vías respiratorias, en la que intervienen múltiples células y mediadores inflamatorios, modulada en parte por factores genéticos, y que se manifiesta mediante hiperreactividad bronquial y una obstrucción variable del flujo aéreo (3).

El asma es un problema de salud global que afecta a millones de personas, sin distinción de edad, género o condición socioeconómica. La OMS estima que más de 300 millones de personas padecen asma en todo el mundo (2). Por su parte, la GINA señala que la prevalencia global varía ampliamente, situándose entre el 1% y el 18% de la población, tanto en niños como en adultos (1). Esta enfermedad no solo deteriora significativamente la calidad de vida de quienes la sufren, sino que también tiene un impacto negativo considerable en el bienestar socioeconómico de la sociedad (4).

1.1.2 Etiopatogenia y fisiopatología.

En el asma se identifican como características patogénicas fundamentales la inflamación, la hiperreactividad bronquial (HRB), la obstrucción reversible del flujo respiratorio y el remodelado de las vías aéreas (5). Durante mucho tiempo, la obstrucción bronquial —y, por ende, la contracción del músculo liso— se consideró el rasgo patogénico más

relevante, hasta que se consolidó el paradigma que define al asma como un fenómeno inflamatorio. Aunque inicialmente se pensaba que la inflamación y la obstrucción eran elementos irreconciliables en la etiopatogenia del asma, se ha ido demostrando que el músculo liso bronquial no es simplemente un efector pasivo de la broncoconstricción, sino que desempeña un papel crucial en el desarrollo de la hiperreactividad, el remodelado y, en cierta medida, en la inflamación de las vías respiratorias (5).

La HRB es un rasgo distintivo del asma, aunque no exclusiva, ya que también puede manifestarse en otras patologías respiratorias e incluso en individuos aparentemente sanos. Además, la HRB puede presentarse de forma transitoria ante respuesta a irritantes ambientales, contaminación o infecciones del tracto respiratorio en personas sin enfermedad respiratoria (6).

En los pacientes asmáticos se distinguen dos tipos de HRB:

1. HRB basal o fija:

   Este tipo refleja los cambios estructurales en los bronquios de los asmáticos y suele ser parcial o totalmente irreversible, incluso tras el tratamiento antiinflamatorio. Aunque el mecanismo subyacente no se conoce completamente, se sugiere que está relacionado con la reducción del calibre de la luz bronquial, debido a la hipertrofia o hiperplasia del músculo liso bronquial, así como al engrosamiento de la matriz extracelular y de la membrana basal del epitelio bronquial (7,8).

2. HRB variable o episódica:

Se asocia con exposiciones agudas a agentes capaces de inducir broncoconstricción, como los alérgenos. Este tipo, es consecuencia de la inflamación de la vía respiratoria. Aunque, el mecanismo exacto que vincula la inflamación con la HRB aún no está completamente definido, se postula que el aumento de la permeabilidad de la mucosa respiratoria y el reclutamiento local de células inflamatorias podrían tener un efecto directo sobre las células del músculo liso bronquial (Figura 1) o sobre el sistema nervioso autónomo (SNA), potenciando la broncoconstricción (7,9,10).

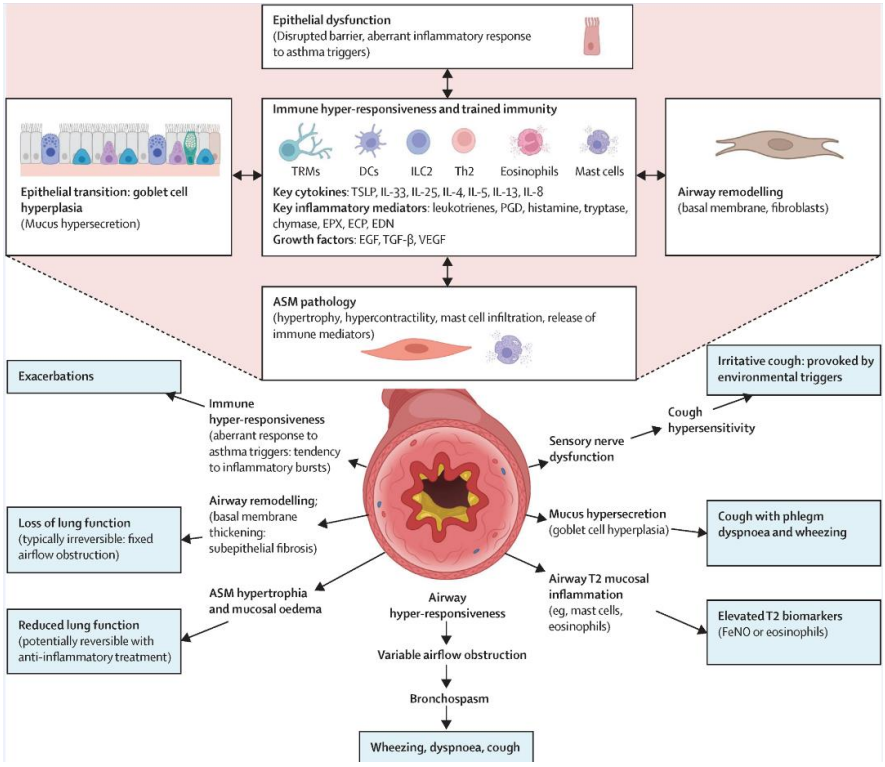

Figura 1. Unidad trófica epitelial-mesenquimal en el asma (11).

1.1.3 Diagnóstico y clasificación de la gravedad

El diagnóstico de asma debe considerarse en pacientes que presentan síntomas y signos clínicos sugestivos —como sibilancias, disnea, tos y opresión torácica— y se confirma mediante pruebas diagnósticas objetivas, siendo la espirometría la prueba de función pulmonar preferida para demostrar alteraciones compatibles (véase Figura 2).

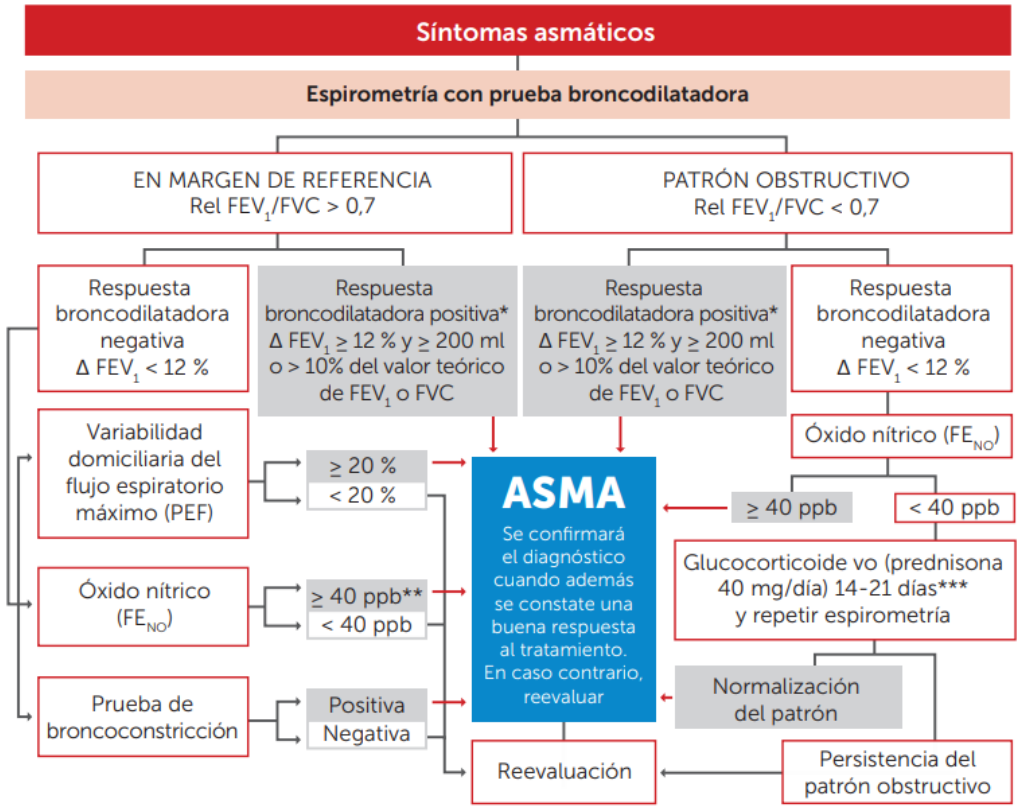

Figura 2. Algoritmo diagnóstico del asma GEMA (3).

*En niños un incremento del 12% es suficiente para considerarla positiva aunque éste sea < 200 ml. **En los casos en los que la prueba de broncoconstricción sea negativa debe considerarse el diagnóstico de bronquitis eosinofílica. ***Como alternativa pueden utilizarse glucocorticoides inhalados a dosis muy altas, 1.500 - 2.000 µg de propionato de fluticasona, en 3 o 4 tomas diarias, durante 2-8 semanas.

La definición de la gravedad en la enfermedad asmática ha evolucionado a lo largo del tiempo. Convencionalmente se ha fundamentado en criterios clínicos y funcionales: intermitente, persistente leve, persistente moderada y persistente grave. Es crucial resaltar que la gravedad comprende tanto la intensidad del proceso patológico como la respuesta al tratamiento del asma para alcanzar el control de los síntomas y prevenir exacerbaciones (2, 12,13) (Figura 3).

Gravedad	Intermitente	Persistente		
		Leve	Moderada	Grave
Necesidades mínimas de tratamiento para mantener el control	Escalón 1	Escalón 2	Escalón 3 o Escalón 4	Escalón 5 o Escalón 6

Figura 3. Clasificación de la gravedad del asma cuando está bien controlada con tratamiento, GEMA (3).

1.1.4 Control y métodos de medición.

El control del asma se define como el grado en que las manifestaciones clínicas de la enfermedad son eliminadas o reducidas significativamente mediante intervenciones terapéuticas, permitiendo alcanzar los objetivos del tratamiento y demostrando la eficacia del manejo (12,14). El control puede clasificarse en distintos niveles, desde buen hasta mal control, según los criterios establecidos en la GEMA (ver Figura 4).

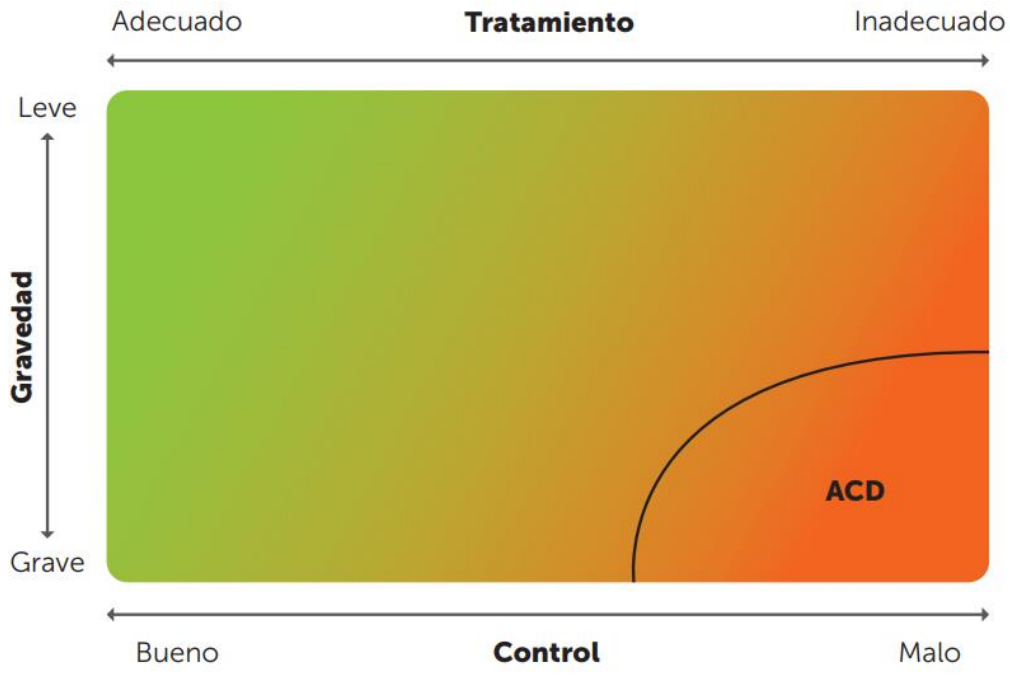

Figura 4. Relación entre la gravedad y el control en el asma. El nivel de control refleja en gran medida la adecuación del tratamiento. Algunos pacientes tienen un asma grave de control difícil (ACD) GEMA (3)

Sin embargo, el grado de control del asma no siempre coincide con lo que dictan las guías, ya que algunos pacientes pueden presentar un control adecuado de los síntomas diarios y de la función pulmonar, pero aun así sufrir exacerbaciones frecuentes; en contraste, otros pueden presentar síntomas persistentes sin llegar a experimentar crisis graves (17), además de no poder identificar si el paciente padece de otras comorbilidades —entre otros, los trastornos emocionales— que podrían aumentar el riesgo de un mal control del asma. Este aspecto se abordará en el punto 1.1.6.

Tal como se define el control, las guías nacionales e internacionales recomiendan una serie de procedimientos para evaluarlo (15). El elemento fundamental es la consulta médica periódica, en la que se examinan tanto el control actual como el riesgo futuro de exacerbaciones, la posible presencia de obstrucción fija del flujo aéreo y los efectos adversos asociados al tratamiento. Para estandarizar la evaluación del control actual, se han desarrollado diversos cuestionarios validados y adaptados culturalmente que el paciente autocumplimenta. Uno de los más ampliamente utilizados es el Test de Control del Asma (ACT) (16). Este test establece los siguientes puntos de corte: una puntuación igual o superior a 20 indica asma bien controlada, mientras que una puntuación igual o inferior a 19 señala asma no bien controlada. No obstante, la capacidad de estos cuestionarios para detectar asma mal controlada es limitada (17), por lo que no deben emplearse como única herramienta de valoración.

1.1.5 Asma grave no controlada.

En el asma grave, el tratamiento exige el empleo de múltiples fármacos a altas dosis, correspondiente a los escalones 5-6 de la GEMA (3) y el escalón 5 de la GINA (1). Este subtipo abarca tanto en sujetos controlados como a aquellos que permanecen sin control,

y se asocia con un mayor consumo de recursos económicos en comparación con el asma moderada o leve (4).

El asma grave no controlada (AGNC) ha sido denominada de diversas maneras, sin existir un consenso unánime. Una de las más aceptadas en la GEMA (3), la define cuando la enfermedad persiste mal controlada pese a recibir tratamiento en el último año con una combinación de glucocorticoides inhalados a dosis elevada/ agonista β2 adrenérgico de acción prolongada (GCI/LABA) y antimuscarínicos de acción prolongada (LAMA) o requiera glucocorticoides (GCS) de mantenimiento (tratamiento con duración de 6 meses al año independientemente de la dosis, o dosis acumulada > 1 g de prednisona o equivalente, independientemente de la duración). El no control del asma, se objetiva mediante cualquiera de las siguientes características:

- Test de Control del Asma (ACT) inferior a 20 o Cuestionario de Control del Asma (ACQ) superior a 1,5.
- Dos o más exacerbaciones graves o haber recibido al menos dos ciclos de glucocorticoides orales (cada uno con una duración mínima de 3 días) durante el año previo.
- Al menos una hospitalización por exacerbación grave en el año previo.
- Limitación crónica del flujo aéreo, definida como una relación FEV1/FVC inferior a 0,7 o un FEV1 menor al 80 % del valor predicho, después de haber administrado un tratamiento adecuado.

1.1.6 Asma grave y trastornos emocionales.

Además de evaluar el control del asma, es crucial identificar la presencia de comorbilidades que puedan aumentar el riesgo de resultados adversos relacionados con la enfermedad (véase Figura 5). Se reconoce que las comorbilidades psiquiátricas se asocian con un manejo deficiente de los síntomas asmáticos, especialmente por su elevada frecuencia. Entre los trastornos emocionales, la ansiedad y la depresión son los más comunes en personas con asma, ya que se ha vinculado a un incremento en las exacerbaciones y a un mayor número de visitas a urgencias (18).

La literatura evidencia una estrecha relación entre la salud mental y el asma grave. Se ha comprobado que la ansiedad y la depresión son de 1,5 a 2,4 veces más frecuentes en personas con asma que en aquellas sin la enfermedad, siendo el impacto aún mayor en individuos con asma grave o no controlada. Ambos trastornos, que a menudo se presentan conjuntamente, afectan la capacidad funcional de la persona y se asocian con diversos cambios conductuales, cognitivos y fisiológicos (19).

A pesar de contar con diversas herramientas para detectar sintomatología ansiosa y depresiva en atención primaria, la mayoría no ha sido validada en pacientes con asma. Es fundamental estar alerta ante la presencia de depresión y/o ansiedad en personas asmáticas, especialmente cuando existe un historial previo de estos trastornos. Cuando sea pertinente, se debe evaluar al paciente, derivarlo a un especialista en psiquiatría o utilizar un instrumento diagnóstico psiquiátrico específico, ya que estas afecciones tienen importantes implicaciones pronósticas en el manejo del asma.

Comorbilidad	Pruebas diagnósticas	Tratamiento
Enfermedad nasosinusal	Rinoscopia/endoscopia nasal Estudio de imagen de senos (TC/RM)	Glucocorticoides intranasales Lavados nasales/antileucotrienos Cirugía endonasal
Reflujo gastroesofágico	pH-metría/manometría esofágica Ensayo terapéutico con IBP EDA (endoscopia digestiva alta)	Consejos higiénico-dietéticos Inhibidores de la bomba de protones Intervención quirúrgica
Obesidad	IMC	Pérdida de peso Cirugía bariátrica
Síndrome de apnea del sueño (SAHS)	Polisomnografía	CPAP Pérdida de peso si procede
Psicopatología (ansiedad, depresión)	Evaluación por psicólogo/psiquiatra	Psicoterapia/tratamiento específico
Fibromialgia	Valoración reumatológica	
Disnea funcional	Cuestionarios específicos (Cuestionario de Nijmegen)	Psicoterapia Reeducación respiratoria
Obstrucción laríngea inducible (OLI)	Laringoscopia en la crisis o provocación con: metacolina/ejercicio	Rehabilitación logofoniátrica Tratamiento de comorbilidades: reflujo
Fármacos: AINE, β-bloqueantes no selectivos, IECA	Historia clínica	Sustitución
Tabaco y otros tóxicos inhalados	Interrogatorio	Deshabituación

AINE: antinflamatorio no esteroideo; IECA: inhibidor de la enzima convertidora de angiotensina; TC: tomografía computarizada; RM: resonancia magnética; IBP: inhibidores de la bomba de protones; IMC: índice de masa corporal.

Figura 5. Comorbilidades y agravantes más comunes en asma, sus correspondientes pruebas diagnósticas y su tratamiento GEMA (3)

Una revisión sistemática sobre la evaluación integral del asma, evidenció que el bienestar psicológico solo se valoró en dos tercios de los pacientes (20). En la práctica clínica, la ansiedad y la depresión se determina habitualmente mediante cuestionarios autoadministrados. Las respuestas obtenidas con estos instrumentos validados posibilitan describir la intensidad de los síntomas, optimizar la identificación de problemas de salud mental e incluso orientar y valorar la intervención terapéutica (21). Sin embargo, en individuos con enfermedades respiratorias, la ansiedad y la depresión tienden a estar infradiagnosticadas e insuficientemente tratadas. Considerando la recomendación de cribar la ansiedad y la depresión en personas con asma grave, y dado que existen herramientas de sencilla aplicación en el contexto clínico, una de las escalas más empleadas para estimar el riesgo de estos trastornos es la Escala Hospitalaria de Ansiedad y Depresión (HADS). Este instrumento se centra en las manifestaciones emocionales y

cognitivas, evitando la interferencia de los síntomas físicos, y ha sido validado y traducido a múltiples lenguas para su uso en entornos hospitalarios no psiquiátricos (22).

La HADS se compone de 14 preguntas, divididas en dos subescalas de 7 ítems cada una (una para ansiedad y otra para depresión). Cada ítem se puntúa en una escala de 0 a 3, donde 0 representa "ausencia total", 1 "ocasionalmente", 2 "frecuentemente" y 3 "constantemente". Esto resulta en una puntuación máxima de 21 en cada subescala, y se ha establecido que una puntuación mayor de 7 en cualquiera de ellas sugiere la existencia de ansiedad o depresión (22).

1.2 El Sistema nervioso autónomo

1.2.1 El sistema nervioso simpático y parasimpático.

El sistema nervioso autónomo (SNA) es la rama del sistema nervioso periférico encargada de regular de manera involuntaria el funcionamiento de múltiples órganos y tejidos. Desempeña un papel fundamental en el mantenimiento de la homeostasis al supervisar y modular diversas variables fisiológicas, como la frecuencia cardíaca (FC), la presión arterial, la actividad respiratoria, la temperatura corporal y el peristaltismo gastrointestinal. Para ello, las fibras aferentes de los nervios craneales transmiten información sensorial al tronco encefálico y al hipotálamo, donde se procesa e integra. Posteriormente, estas estructuras, junto con áreas superiores del cerebro, envían señales a través de fibras eferentes para regular la función de los órganos (23).

El SNA se compone de tres vías: el sistema nervioso simpático (SNS), el sistema nervioso parasimpático (SNP) y el sistema nervioso entérico. Este último, encargado del control del tracto gastrointestinal, no se abordará en esta Tesis. La actividad del SNS, está relacionada con el aumento de la frecuencia cardíaca y de la fuerza de contracción, mayor frecuencia respiratoria, vasoconstricción, broncodilatación, fortalecimiento del tono

muscular esquelético y dilatación pupilar. Por el contrario, la actividad del SNP induce una disminución de la frecuencia cardíaca y respiratoria, promoviendo la vasodilatación, broncoconstricción y constricción pupilar (23).

Dado que la mayoría de los tejidos reciben inervación tanto del SNS como del SNP, cuyos efectos son opuestos, el SNA proporciona un control ágil y eficiente de la función orgánica. Es importante señalar que ambos sistemas presentan tasas de descarga basal, denominadas tono simpático y parasimpático (o vagal), lo que permite modular su actividad a través de variaciones en la frecuencia de las señales eferentes (24) (ver figura 6).

Esta Tesis se enfocará en el SNA, específicamente en el sistema nervioso parasimpático (SNP). Este último es el responsable fisiológico de la broncoconstricción (24) y la regulación del tono bronquial (25).

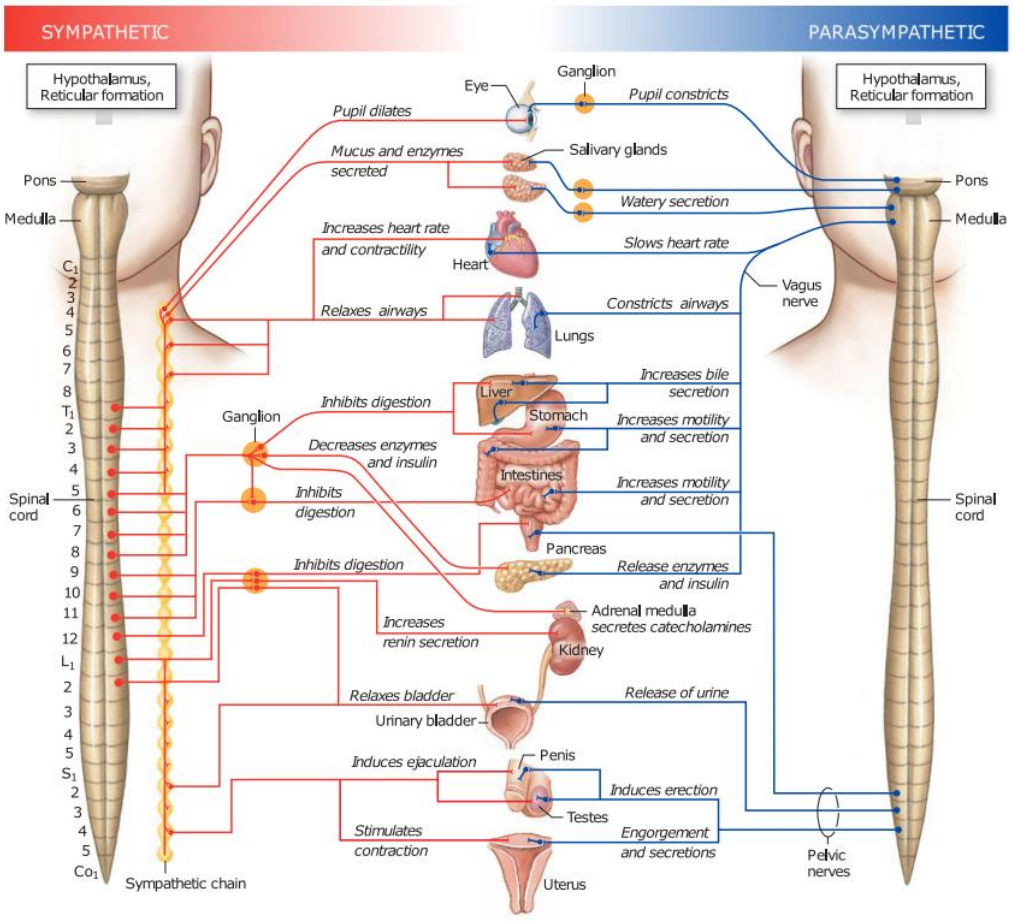

Figura 6. Anatomía de las ramas simpática (izquierda) y parasimpática (derecha) del sistema nervioso autónomo. Se indica el efecto que ejerce cada rama sobre los diferentes órganos que inervan. Reproducido y modificado Silverthorn (24).

1.2.2 El Sistema nervioso parasimpático y el asma.

El SNA regula el tono del músculo liso en las vías respiratorias mediante tres mecanismos: adrenérgico, colinérgico y no adrenérgico no colinérgico (NANC). La vía colinérgica es de particular interés debido a la presencia de dos tipos de receptores muscarínicos para la acetilcolina (ACh): los receptores M2, que no participan directamente en la contracción muscular lisa, pero restringen la liberación excesiva de ACh por el nervio vago, y los receptores M3, que inducen la contracción del músculo liso. Aunque no se han hallado alteraciones en la cantidad o función de los receptores M3

en asmáticos en comparación con individuos no asmáticos (26,27), el análisis del rol de los receptores M2 en asmáticos ha revelado una alteración consistente (27,28). Una posible causa de esta disfunción es la presencia de eosinófilos, ya que liberan diversas proteínas con carga positiva durante la respuesta inflamatoria (27). Dado que los receptores M2 son especialmente susceptibles al bloqueo por proteínas con carga positiva, la presencia de proteínas eosinofílicas provoca una disfunción de estos receptores, impidiendo la retroalimentación negativa que normalmente ejercen tras la liberación de ACh, lo que conlleva una secreción excesiva e incontrolada de ACh (27). Por consiguiente, la disfunción de los receptores M2 aparenta ser un elemento clave en la hiperreactividad de las vías respiratorias. No obstante, la existencia de un considerable grupo de asmáticos no eosinofílicos (29) sugiere la participación de otros mecanismos que podrían influir en el funcionamiento anómalo de los receptores M2. La suposición de que el SNA desempeña un papel significativo en el desarrollo del asma, junto con las dificultades en el diagnóstico (especialmente en los casos graves de control difícil) y el monitoreo continuo de esta enfermedad, ha impulsado estudios dirigidos a evaluar la actividad del SNA en individuos con asma. Partiendo de la premisa de que la regulación alterada del calibre de las vías respiratorias podría reflejarse en modificaciones paralelas en el control de la frecuencia cardíaca o de los intervalos cardiacos, se ha considerado el análisis de la variabilidad del ritmo cardiaco, para la caracterización de la actividad autónoma tanto en adultos (30-33) como en niños (34,35) con asma.

Diversos autores han informado sobre alteraciones del tono vagal (33,35) o un predominio vagal (30) en individuos con asma en comparación con sujetos sanos. En contraste, otros estudios revelan modificaciones en la actividad parasimpática mediante pruebas de evaluación del SNA (31,32,34), analizando la respuesta de la frecuencia cardíaca a la respiración profunda o a la maniobra de Valsalva. Adicionalmente, se

encontró una correlación positiva entre la alteración de la actividad vagal medida y la gravedad del asma en la población infantil (31). En consecuencia, considerando la implicación del SNP en la broncoconstricción (24) y la regulación del tono broncomotor (25), se ha postulado una actividad disfuncional del SNP como un posible factor fundamental en la patogénesis del asma. Esta idea se alinea con la hipótesis que señala la disfunción de los receptores M2 como la causa principal de la hiperreactividad de las vías respiratorias. Así, la visión convencional de la inflamación como el principal desencadenante de la hiperreactividad de las vías respiratorias podría transformarse hacia una comprensión más compleja, donde la disfunción del SNA se presenta como un factor clave, que podría ser tanto una consecuencia de la inflamación como de otros mecanismos. Dicho de otra manera, una alteración o depresión del SNP puede conducir a una disfunción en la regulación del tono muscular de las vías respiratorias, lo que puede acarrear un incremento de la broncoconstricción. Esto ocurre porque la inhibición del sistema parasimpático puede perturbar el equilibrio entre los efectos constrictores (ejercidos por el sistema parasimpático) y relajantes (ejercidos por el sistema simpático) en las vías aéreas.

A modo de ejemplo, situaciones que disminuyen la función parasimpática, tales como el estrés crónico, ciertas afecciones autoinmunes o desórdenes en el equilibrio del sistema nervioso autónomo, podrían potencialmente originar una broncoconstricción más pronunciada o recurrente. Esto reviste importancia en patologías respiratorias como el asma, donde la broncoconstricción constituye una manifestación clínica esencial (Figura 7).

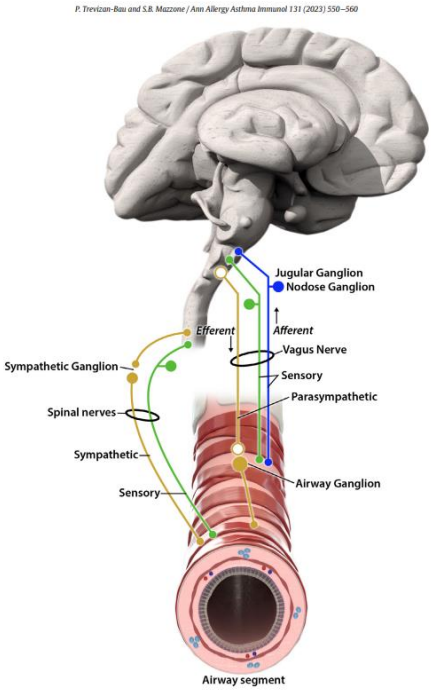

Figura 7. Inervación neural de las vías respiratorias.

1.2.3 El sistema nervioso parasimpático y los trastornos emocionales.

Existen varios trastornos del estado de ánimo, pero en esta Tesis nos centraremos en dos de los más comunes: la depresión y la ansiedad. Estos trastornos, que constituyen comorbilidades frecuentes en personas con asma (18,19), han sido ampliamente estudiados por su impacto en los marcadores psicofisiológicos de la salud y el bienestar. Esta evidencia ha aumentado la conciencia sobre la relación bidireccional entre estos trastornos y el asma, ya que, en esta enfermedad, interactúan directamente con los mecanismos patogénicos del tracto respiratorio, influyendo en su aparición y evolución (19,36). No solo se ha demostrado que la ansiedad y la depresión son altamente frecuentes en individuos asmáticos en comparación con aquellos sin asma, (37,38), si no que su impacto es aún mayor en pacientes con asma grave o no controlada (39,40). Más allá de los estudios del asma y su vinculación con la depresión y la ansiedad, dentro del campo de la neurociencia, existen estudios que demuestran que una actividad vagal cardíaca

disfuncional se vincula cada vez más con la depresión y con la ansiedad, lo que corrobora la idea de que una dinámica del SNA comprometida, y que puede contribuir a los trastornos del estado de ánimo (41,42). La reducción del control vagal cardíaco, analizada mediante la VRC, se asocia con síntomas depresivos y ansiosos. Incluso, la alteración o la reducción de la actividad vagal en la depresión mayor no solo se asoció con la gravedad de la depresión, sino que también predijo la persistencia de los síntomas depresivos (47). Además, la actividad vagal disfuncional en la depresión a menudo puede resultar en enfermedades cardíacas. Un metaanálisis mostró que la depresión aumentó el riesgo de todos los accidentes cerebrovasculares (50). Sin embargo, no se ha hallado literatura disponible de la relación de la alteración del SNA observado en la ansiedad y la depresión, y que pueda afectar negativamente el curso del asma. Pero, podría estar relacionado con la superposición de mecanismos autonómicos, que intervienen en la activación y regulación de funciones fisiológicas, como la variabilidad del ritmo cardíaco, ya documentada tanto para el asma como para la ansiedad y depresión (41,42) (Figura 8).

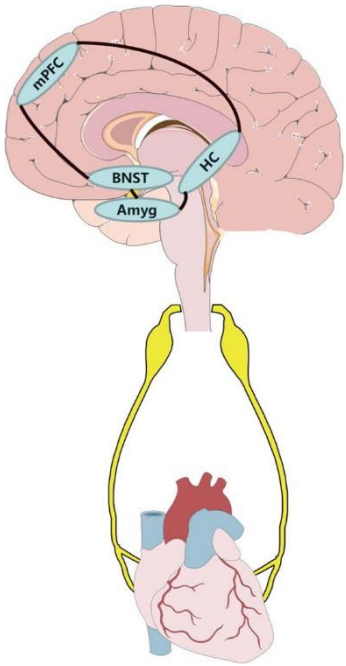

Figura 8. Los circuitos neuronales relacionados con los trastornos emocionales que influyen en el sistema cardiovascular a través del SNA.

Se sugiere que el vínculo entre la salud física y mental podría estar, en parte, asociado a un deterioro en la actividad del nervio vago, lo que conduce a una desregulación de los procesos inflamatorios (42) (Figura 9).

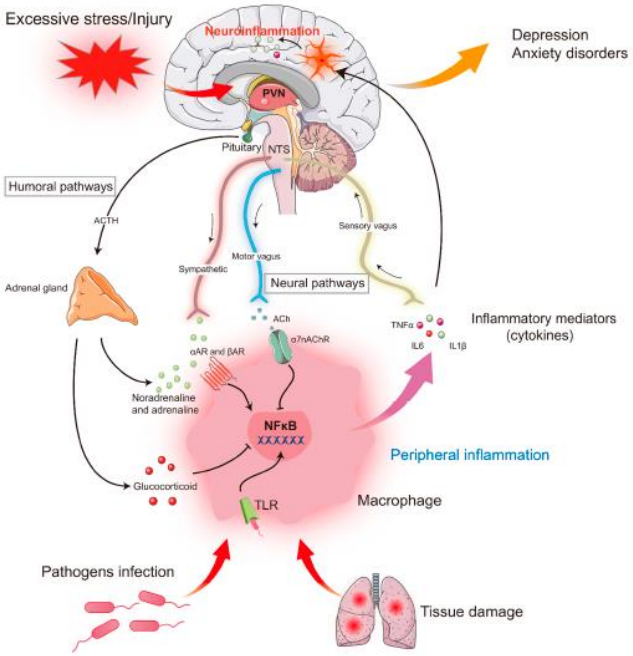

Figura 9. Inflamación periférica inducida por estrés y neuroinflamación en trastornos relacionados con el estrés. Adaptación (42)

1.3 La Variabilidad del ritmo cardiaco

1.3.1 La variabilidad del ritmo cardiaco y el asma bronquial.

Algunos autores sugieren que la alteración del control autonómico del diámetro de las vías respiratorias en el asma podría manifestarse con cambios paralelos en el ritmo cardíaco (31,32). Esta hipótesis se basa en la observación de que las personas con asma suelen presentar una frecuencia cardíaca en reposo más elevada que quienes no padecen la enfermedad (30-35).

En consecuencia, diversas investigaciones se han enfocado en desarrollar métodos no invasivos para evaluar la actividad del SNA en personas con asma. Se ha prestado especial atención a la rama parasimpática ya que participa en la broncoconstricción y el control broncomotor como se expuso en el apartado 1.2.1, y la escasa inervación simpática en las vías respiratorias pequeñas (24), ha señalado que el SNP está fuertemente relacionado con la alteración del tono de las vías respiratorias en asmáticos.

Dado que el SNA también modula la función cardíaca, el análisis de la VRC se ha propuesto como una herramienta útil para caracterizar la actividad autonómica (32,33). Este enfoque ha revelado un predominio de la actividad vagal en respuesta a pruebas autonómicas (31,32) o durante el sueño (35). En pacientes asmáticos y alérgicos, esta condición se ha asociado a un aumento en la actividad del SNP, y se ha sugerido que el asma modifica la VRC, evaluada a través del tono parasimpático basal. De hecho, estudios también relacionan la gravedad del asma con una mayor desregulación de la VRC (33).

Por otro lado, otros trabajos se han centrado en la actividad respiratoria, igualmente influenciada por el control neural. Se ha descrito una disminución más rápida de la actividad muscular inspiratoria en sujetos con obstrucción de las vías respiratorias en comparación con controles sanos (43), lo que indica que el análisis de la dinámica inspiratoria podría ofrecer información sobre el estado subyacente del SNA en el asma. En contraste, la actividad espiratoria se relaciona más con las propiedades mecánicas del sistema respiratorio, observándose una reducción en la compliancia en sujetos con obstrucción de las vías respiratorias (44). Además, se ha sugerido que la dinámica respiratoria se altera en sujetos asmáticos

en respuesta al estrés (45), lo que, junto con el predominio vagal detectado en pruebas autonómicas (31,32), podría indicar una respuesta autonómica desequilibrada ante situaciones exigentes.

Dado que la valoración directa del sistema nervioso parasimpático resulta inviable o poco práctica en el contexto clínico, se propone su evaluación no invasiva mediante la medición de los intervalos cardiacos de la VRC, utilizando los estándares de medición, interpretación fisiológica y aplicación clínica establecidos por las guías de las Sociedades Europea y Americana de Cardiología y Electrofisiología (46), los cuales se obtienen a través del electrocardiograma (ECG).

1.3.2 La variabilidad del ritmo cardiaco en la depresión y la ansiedad.

Diversos estudios han abordado la VRC en la ansiedad y los trastornos depresivos hasta el momento (42,47,48). La explicación para la alteración de la VRC en los trastornos del estado de ánimo se fundamenta en un modelo de integración neurovisceral, que postula la intervención de fibras nerviosas en la modulación de la actividad y la inhibición parasimpática del nervio vago. Esta desregulación se ha vinculado también con otras afecciones como la diabetes mellitus tipo 2, las enfermedades cardiovasculares y neurodegenerativas, entre otras (49-52). El modelo de integración neurovisceral se define asimismo por estructuras neuronales específicas que capacitan a las personas para responder de forma adaptativa a las condiciones fisiológicas, ambientales, cognitivas y emocionales. En consecuencia, un sistema cardiorrespiratorio sano se distingue por oscilaciones "altas" de la VRC en el intervalo cardíaco, mientras que un sistema no saludable exhibe oscilaciones "bajas" (42).

La actividad vagal cardíaca disfuncional se ha asociado crecientemente con la depresión y la ansiedad, lo que refuerza la noción de que una dinámica comprometida del SNA puede contribuir a los trastornos del estado de ánimo. Un control vagal cardíaco reducido, cuantificado mediante series de la VRC (53), se relaciona con síntomas depresivos y ansiosos.

Incluso, en consonancia a la mención anterior, la estimulación del nervio vago se está investigando como potencial vía de tratamiento, para la depresión refractaria al tratamiento, sustentada por datos alentadores (41). Adicionalmente, la estimulación no invasiva del nervio vago potencia la regulación emocional, lo cual ratifica la participación causal del nervio vago en el procesamiento de las emociones.

1.3.3 Métodos no invasivos para la evaluación del SNA a través de la variabilidad del ritmo cardiaco y su análisis.

La variabilidad del ritmo cardíaco (VRC) se define como las fluctuaciones en el intervalo cardiaco entre latidos a lo largo del tiempo y se evalúa comúnmente mediante un electrocardiograma (ECG). El ECG registra la actividad eléctrica del músculo cardíaco a través de electrodos adheridos a la piel. Esta señal resulta de la suma espacio-temporal de los potenciales de acción generados por todas las células del tejido cardíaco, produciendo ondas características cuya morfología y duración contienen información crucial para el diagnóstico de patologías cardíacas. Así, cada ciclo cardíaco se refleja en el ECG mediante deflexiones consecutivas positivas y negativas, que corresponden a la despolarización y repolarización de los cardiomiocitos en las distintas regiones del corazón.

Dentro del registro del ciclo cardíaco reflejado en el ECG—que incluye elementos como el complejo QRS, la onda Q y la onda T—se pueden identificar intervalos temporales relevantes. Uno de ellos es el intervalo RR, definido como el tiempo entre dos ondas R consecutivas. Este intervalo, que se considera el período entre latidos sucesivos, se utiliza para caracterizar arritmias y también para el análisis de la VRC, objetivo de esta Tesis (54).

En condiciones normales, la frecuencia cardíaca está controlada por el nodo sinoauricular, cuya periodicidad de despolarización depende tanto del SNS como del SNP. Lejos de ser constante, la frecuencia cardíaca varía latido a latido, y esta variación, conocida como la VRC, está sujeta a los efectos opuestos de la actividad simpática y vagal, que tienen como objetivo satisfacer las demandas homeostáticas del cuerpo. Mientras que el aumento de la actividad simpática o la retirada parasimpática dan lugar a un aumento de la frecuencia cardíaca, un aumento vagal o una reducción de la actividad simpática conducen a una desaceleración de la frecuencia cardíaca.

Este parámetro es un marcador esencial del bienestar psicológico y de la salud cardiovascular general, además de representar un predictor significativo de mortalidad (55,56). Se ha propuesto que la relación entre la salud mental y física podría estar, en parte, con el deterioro de la actividad del nervio vago, lo que ocasiona una desregulación de los procesos inflamatorios (57). En particular, las reducciones en la VRC en condiciones de reposo reflejan una disminución en el gasto vagal.

El análisis de la VRC puede abordarse a partir de diversas representaciones del ritmo cardíaco, utilizando distintas estrategias analíticas. Entre las metodologías

más extendidas se encuentran aquellas basadas en los dominios del tiempo y la frecuencia, así como el análisis no lineal. Cada enfoque posee particularidades que lo hacen más adecuado según la estrategia a investigar. A continuación, se presenta tres aproximaciones de los parámetros más comúnmente utilizados:

1. Análisis en el dominio del tiempo: Este método se basa en el estudio de los momentos de primer orden y las propiedades geométricas de las series de intervalos normal-normal (NN). Entre los índices más utilizados se encuentran (46,58):

- Media y desviación estándar de los intervalos NN (NN y SDNN, respectivamente): reflejan la variabilidad cardíaca global.
- Desviación estándar y raíz cuadrada de la media de las diferencias entre intervalos NN adyacentes (SDSD y RMSSD, respectivamente): indican variaciones a corto plazo.
- Porcentaje de diferencias sucesivas de intervalos NN mayores de 50 ms (pNN50).

Además, dentro del dominio del tiempo se identifican las medidas geométricas, que se obtienen a partir del histograma del intervalo RR, el cual suele presentar una forma triangular. En este sentido:

- El índice triangular de la VRC se calcula dividiendo la integral del histograma del intervalo RR por su altura.
- La interpolación triangular del histograma de intervalos NN se determina a partir del ancho de la línea base del histograma.

2. Análisis en el dominio de la frecuencia: Este análisis se centra en examinar la distribución de la potencia en los distintos componentes de frecuencia presentes en la VRC. En estudios a corto plazo se han definido tres bandas de interés:

- Banda de muy baja frecuencia (VLF): 0 a 0,04 Hz.
- Banda de baja frecuencia (LF): 0,04 a 0,15 Hz.
- Banda de alta frecuencia (HF): 0,15 a 0,4 Hz.

Basándose en investigaciones que utilizan inhibidores farmacológicos del SNS y SNP, así como en la aplicación de estresores, se ha establecido que el contenido de potencia en la banda HF (PHF) se asocia con la actividad parasimpática. En contraste, el contenido de la banda LF (PLF) refleja tanto la modulación simpática como la parasimpática y se cree que está influenciado, principalmente, por la actividad barorrefleja (59,60). Por otro lado, la interpretación fisiológica de la potencia en la banda VLF (PVLF) es menos directa, y se ha vinculado a procesos de termorregulación y al sistema renina-angiotensina (61).

Además de estos índices, se emplea ampliamente la potencia espectral total (TP), calculada como la suma de PLF y PHF, junto con la relación de potencia LF a HF (RLF/HF = PLF/PHF) y la potencia LF normalizada (PLFn = PLF/(PLF + PHF)). Mientras que la TP se asocia con la variación total de la actividad del SNS y el SNP, la RLF/HF y la PLFn se interpretan comúnmente como indicadores del equilibrio simpático-vagal, ofreciendo una representación cuantitativa de la interacción entre ambas vías del SNA (59,60).

3. Análisis no lineal: Este enfoque se basa en la cuantificación de la complejidad o regularidad de la VRC, utilizando parámetros como la dimensión de correlación (D2), la entropía aproximada (ApEn) y la entropía de muestra (SampEn) (62). Otro método no lineal ampliamente utilizado es el diagrama de Poincaré, que consiste en reconstruir el espacio de fases a partir de la serie de intervalos RR. A partir de este diagrama, se pueden extraer diversos parámetros que representan la VRC a corto plazo (SD1) o de forma global (SD2, S) (61).

Existen otras estrategias para el análisis de la VRC, en las denominadas basadas en la dinámica de la información (58), pero para la siguiente Tesis Doctoral, se realizaron análisis de la VRC en los 3 dominios descritos que son los más empleados y recomendados a partir de la serie de intervalos cardiacos RR, tras la corrección de latidos ectópicos, siguiendo las recomendaciones del Grupo de Trabajo (46).

2. Hipótesis y justificación

Hipótesis y justificación

Dado el conocimiento actual sobre la desregulación del sistema nervioso autónomo (SNA), en particular del sistema nervioso parasimpático (SNP), en población asmática, y considerando que puede evaluarse de forma objetiva mediante métodos no invasivos, se plantea que su análisis podría contribuir a una mejor comprensión de la fisiopatología del asma, concretamente en las formas más graves. Aunque se ha avanzado en la comprensión de los mecanismos inmunológicos subyacentes en el asma, estos no explican completamente la broncoconstricción, ya que, en una proporción significativa de pacientes, esta no está mediada por la inflamación bronquial. Se sospecha, en cambio, que la broncoconstricción podría deberse a mecanismos mecánicos estrictamente relacionados con el diámetro de las vías respiratorias, inducidos por la estimulación nerviosa a través del reflejo colinérgico.

En este contexto, nos propusimos investigar marcadores neurobiológicos no inflamatorios con potencial implicación en la broncoconstricción asmática, como por ejemplo el SNA. Diversos estudios han explorado enfoques no invasivos para evaluar la actividad del SNA en asmáticos, dado que la broncoconstricción y el control del tono broncomotor están mediados principalmente por la vía vagal del SNA. Además, el control neural desempeña un papel clave como modulador de la inflamación de las vías respiratorias, lo que sugiere que una disfunción del SNP podría ser un factor determinante en la patogénesis del asma. En este sentido, el análisis de la variabilidad del ritmo cardíaco (VRC) o de los intervalos cardiacos del ECG, ha surgido como una herramienta viable para caracterizar la actividad autonómica en asmáticos, evidenciando un desequilibrio o desregulación de predominio vagal en respuesta a pruebas autonómicas (respiración profunda, maniobra de Valsalva y ortostatismo) e incluso durante el sueño en sujetos asmáticos.

Sin embargo, dado el número limitado de estudios y la variabilidad de sus hallazgos, nos propusimos evaluar exhaustivamente el papel del SNA en el AGNC y también su relación con los trastornos del estado de ánimo más frecuentemente asociados al asma, como son la ansiedad y la depresión, ya que hay estudios donde se analizan independientemente y están asociados a trastornos de la VRC, pero hasta donde sabemos, ningún estudio ha abordado de forma integral, mediante un enfoque objetivo basado en el análisis del SNA tanto para el AGNC y su relación con los trastornos emocionales.

Para esta Tesis se plantean las dos siguientes hipótesis:

1. Es posible a través de métodos no invasivos evaluar la actividad del sistema nervioso autónomo en pacientes con asma.
2. La desregulación del sistema nervioso autónomo desempeña un papel fundamental en el asma grave no controlada y en la aparición de trastornos del estado de ánimo, como la ansiedad y la depresión

3. Objetivos

3.1 Objetivo Principal

El objetivo principal de esta tesis es determinar el papel del sistema nervioso autónomo en la patogénesis del asma grave no controlada.

3.2 Objetivos secundarios

1. Evaluar de forma no invasiva la actividad del sistema nervioso autónomo como una posible herramienta para la estratificación de pacientes asmáticos según el nivel de control de sus síntomas, utilizando únicamente señales electrocardiográficas y respiratorias.

2. Evaluar el sistema nervioso autónomo en pacientes con asma grave en relación con el nivel de control de la enfermedad y la relación de trastornos emocionales frecuentes asociados, como la depresión y la ansiedad.

4. Compendio de Publicaciones

4.1 Artículo 1

Asthmatic subjects stratification using autonomic nervous system information

*Javier Milagro, **Lorena Soto-Retes**, Jordi Giner, Carolina Varón, Pablo Laguna, Raquel Bailón, Vicente Plaza, Eduardo Gil*

Biomed Signal Process Control. 2021; 69: 102802. 29.

https://doi.org/10.1016/j.bspc.2021.102802

IF: 5.076

Biomedical Signal Processing and Control 69 (2021) 102802

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Asthmatic subjects stratification using autonomic nervous system information

Javier Milagro [a,b,*], Lorena Soto-Retes [c], Jordi Giner [c], Carolina Varon [d,e], Pablo Laguna [a,b], Raquel Bailón [a,b], Vicente Plaza [c], Eduardo Gil [a,b]

[a] Biomedical Signal Interpretation & Computational Simulation (BSICoS) Group, Aragón Institute of Engineering Research (I3A), IIS Aragón, University of Zaragoza, Spain
[b] Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Spain
[c] Pneumology and Allergy Department, Santa Creu i Sant Pau Hospital, IIB Sant Pau, Departament de Medicina de la Universitat Autònoma de Barcelona, Spain
[d] Department of Electrical Engineering-ESAT, STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, Belgium
[e] Circuits and Systems (CAS) group, Delft University of Technology, The Netherlands

ARTICLE INFO

Keywords:
Asthma
Autonomic nervous system
Heart rate variability
Asthma control
Machine learning

ABSTRACT

Objective: the aim of this study is to evaluate whether noninvasive autonomic activity assessment could represent a potential tool for the stratification of asthmatic subjects based on symptoms control, using only 10-min electrocardiographic and respiratory signals.
Methods: several heart rate variability (HRV) derived indexes, which are regarded as surrogates of autonomic activity, were evaluated in a group of asthmatic patients classified based on their symptomatology control. The effect of respiration on HRV was mitigated by means of orthogonal subspace projection. The most relevant features were used for training different classifiers.
Results: similar classification performance was obtained when using HRV or clinical features, with just a 10% decrease in accuracy when using the HRV features (80% vs. 70%). This classification performance is equivalent to that achieved in new patients using the current asthma control tests.
Conclusion: results suggest that the noninvasive assessment of autonomic activity could represent an added value for the monitoring of asthmatic subjects outside the clinic, using less cumbersome equipment, and therefore being suitable for an objective asthma self-monitoring.
Significance:: This study provides evidence on the usefulness of noninvasive autonomic activity assessment for asthma control stratification, supporting it as a potential complement to the current clinical practice.

1. Introduction

Diagnosis of asthma in adults is performed following a well-established clinical routine, and it is based on the identification of characteristic symptom patterns and evidence of variable airflow limitation assessed through functional respiratory tests [1,2]. Since asthma is an heterogeneous disease with different underlying pathological processes, additional strategies may be needed to monitor the disease or to classify the subjects in recognizable clusters of demographic, clinical and/or pathophysiological characteristics, often referred to as asthma phenotypes [3]. For this purpose, several inflammatory biomarkers are usually quantified, being the most common the inflammatory cells count in the induced sputum, the amount of serum immunoglobulin E (IgE) and the levels of exhaled nitric oxide (FeNO) [1,2].

Apart from the severity of the disease, there is a high clinical interest in stratifying the level of control of the symptomatology, since a poor symptoms control has been associated with an increased risk of exacerbations [4], and might require additional treatment. The assessment of asthma control is generally based on self-applied questionnaires, although their reliability is lower than that of clinical diagnosis [5] and might be hampered in the absence of asthma self-management training [6]. Therefore, an accurate diagnosis and monitoring of asthma requires continuous visits to the hospital, very specific equipment and personnel, and is highly time consuming. This, together with the current growth of telematic and mobile healthcare, has led to the development of hundreds of mobile apps aiming to improve asthma self-management [7]. In

* Corresponding author at: María de Luna, 1, Edif. Ada Byron, DIEC, L.3.07, 50018, Zaragoza, Spain.
E-mail address: milagro@unizar.es (J. Milagro).

https://doi.org/10.1016/j.bspc.2021.102802
Received 29 December 2020; Received in revised form 3 May 2021; Accepted 15 May 2021
Available online 6 July 2021
1746-8094/

a recent study investigating the requirements these apps should meet from the point of view of patients and healthcare professionals, the former were interested in the monitoring of asthma over time and the collection of data to present to healthcare teams, whereas the latter were concerned about the assessment of deteriorating asthma control, so that patients can be advised to seek medical attention when required [8]. Additionally, some of the participants pointed to the measurement of physiological markers such as breathing rate, heart rate, stress levels or quality of sleep as useful for the monitoring of asthma control [8]. The exponential growth of the market of wearable devices for physiological monitoring [9] also motivates research on noninvasive biomarkers that can aid in the continuous screening of chronic disorders such as asthma, an even anticipate the occurrence of exacerbations.

Regarding previous efforts for the non-invasive assessment of respiratory disorders, two main groups of studies can be found in the literature. On one hand, those focusing on the analysis of respiration, either by means of respiratory activity measurement [10] or focusing on respiratory sounds [11,12]. Although these approaches present very good performance in asthma stratification, measurement of respiratory activity requires from specific equipment (e.g. respiratory belts or impedance pneumography acquisition systems), whereas the recording of respiratory sounds cannot be performed in a continuous-time basis, thus limiting their usefulness for symptoms evolution monitoring.

On the other hand, several authors have focused on the development of noninvasive approaches for the study of autonomic nervous system (ANS) activity in asthmatics. Since broncho-constriction and bronchomotor tone control are mainly mediated by the vagal pathway of the ANS [13,14], and given the role of the neural control as a modulator of airway inflammation [15], the suspicion that an altered ANS functioning could be an important factor in the pathogenesis of asthma has received widespread research attention for decades. In this context, heart rate variability (HRV) analysis has raised as a feasible option, and has been employed for the characterization of ANS activity in asthmatic children [16–18] and adults [19–21], revealing an increased vagal dominance in response to autonomic tests [16,19,21] or during sleep [17,18,20]. Moreover, the study of asthmatic subjects classified based on their asthma control suggests a decreased HRV in subjects with uncontrolled asthma [22,23]. Despite the promising results highlighted by the aforementioned studies, they do not address the potential of the proposed methodologies in comparison with clinical features, and they are limited to statistical analysis, not providing a classification framework for patient stratification. Therefore, no ANS information is currently employed in the diagnosis or phenotyping of asthma [1,2], neither for asthma control monitoring.

Nevertheless, during last years' pandemic the need of a reduction in the technological gap and the development of cost-efficient tools for patient monitoring has been further emphasized. In the case of asthmatic patients, agglomerations in health services centers could be reduced if a non-invasive monitoring tool was available to warn the patients when their symptoms have worsened and hence they should visit a clinician. The main contribution of the present work is the study of the potential of ANS assessment through HRV for the monitoring of asthma control. Results reveal that the performance achieved with the proposed non-invasive methodology is similar to that of clinical features which require specialized equipment and a visit to the hospital, and also to that of the widely employed asthma control tests (ACT). Additionally, combination of ANS-derived and clinical features resulted in an improved performance with respect to using only clinical features in some classification schemes. Therefore, results suggest that non-invasive ANS assessment could have an added value for the clinical management of asthmatic patients.

2. Materials and methods

2.1. Study population

Thirty adults with persistent asthma were recruited for this study. The diagnosis was performed according to the clinical criteria established in the Spanish guidelines for the management of asthma [2]. The patients were classified into controlled asthma (19 subjects) and uncontrolled asthma (11 subjects), following the results of the self-applied ACT (uncontrolled asthma if the score of the test was $\leq$ 19 and controlled asthma otherwise) [24]. All the subjects were requested to remain seated and without talking for a period of 10 min, during which multi-lead ECG (Frank's lead configuration) and respiratory effort (using a respiratory band) were acquired and sampled at 1000 and 250 Hz, respectively. Afterwards, they underwent spirometric, skin prick and induced sputum tests, in order to assess airway obstruction, their atopic status and the existence of airway inflammation (when the count of either eosinophils or neutrophils was higher than the reference levels established by Pin et al. [25]). Airway obstruction was assessed through the forced expiratory volume in one second (FEV_1), the percentage of FEV_1 with respect to a normalized population ($FEV_{1,\%}$) and the FEV_1 with respect to the forced vital capacity (FEV_1/FVC). Moreover, the fraction of FeNO was assessed, and saliva and blood tests were performed to account for the levels of cortisol and IgE respectively, as well as the existence of peripheral eosinophilia (considered as positive when the blood eosinophils count was higher than 300 per mm^3). Finally, they filled a questionnaire aiming to assess their perceived quality of life (mini asthma quality of life questionnaire, MiniAQLQ [26]). The demographics and clinical parameters of the subjects in the different groups are displayed in Table 1. The data acquisition was

Table 1
Demographics and clinical features of the subjects classified based on their asthma control. The values are displayed as median [25th, 75th percentiles] for the continuous variables (* indicates $p < 0.05$. BMI: body mass index, Eos: eosinophilia, Inflam: airway inflammation.)

	Controlled	Uncontrolled
N (#)	19	11
Age (years)	50.00 [39.50, 58.50]	49.00 [42.75, 63.25]
Sex (Male/Female)	11/8	2/9*
BMI (kg/m^2)	26.40 [23.85, 27.75]	30.00 [25.25, 33.50]
Atopy (Yes/No)	16/3	8/3
FEV_1 (liters)	3.20 [2.40, 3.63]	2.00* [1.72, 2.29]
$FEV_{1,\%}$ (%)	91.00 [84.25, 96.50]	87.00* [57.50, 91.25]
FEV_1/FVC (%)	73.00 [65.50, 76.00]	56.00* [50.75, 74.00]
FeNO (ppb)	27.00 [20.75, 34.50]	41.00 [22.25, 87.88]
ACT	24.00 [21.00, 25.00]	18.00* [14.50, 19.00]
MiniAQLQ	6.60 [6.40, 6.80]	5.20* [3.43, 5.45]
Peripheral Eos (Yes/No)	7/12	6/5
IgE (UI/ml)	131.00 [59.50, 209.00]	204.00 [28.83, 478.75]
Inflam (Yes/No)	4/15	3/8
Cortisol (pg/ml)	860.00 [522.50, 1212.50]	655.00 [491.30, 1670.00]

performed in accordance with the Declaration of Helsinki, being approved by the Ethic Committee of Clinical Investigation of the Santa Creu i Sant Pau Hospital (NCT02836691, Barcelona, Spain). All the subjects provided a signed written informed consent prior to their inclusion in the study, and none of them presented cardiac, neurological or endocrine disease, nor other obstructive disease different from asthma at the time of the study.

2.2. Signal preprocessing

Baseline wander were estimated from the ECG signals using low-pass (3rd order Butterworth filter with 0.5 Hz cut-off frequency) forward-backward filtering, to have zero-phase response in order to preserve the morphology of the signal. Baseline was further subtracted from the original signals.

Afterwards, the wavelet-based approach described by Martínez et al. [27] was applied for the R-peaks detection, and ectopic and misdetected beats correction was performed according to the method proposed by *Mateo and Laguna* [28] (the number of corrected beats represented a 0.13% of the total number of beats).

Regarding the respiratory effort signals, they were band-pass filtered (3rd order Butterworth filter with 0.05–1 Hz cut-off frequencies) in order to discard the baseline and those components that are not expected to be related with respiration. Forward-backward filtering was employed as for the ECG signals.

The respiratory effort signals were downsampled at 4 Hz.

2.3. Time-domain HRV analysis

Mean and standard deviation of the normal-to-normal (NN) intervals ($\overline{NN}$ and SDNN, respectively), standard deviation and root mean square of the successive differences (SDSD and RMSSD, respectively), and the percentaje of NN intervals greater than 50 ms (pNN50), were computed from the RR interval series following ectopic correction (Table 2), according to the *Task Force* [29]. The analysis was performed in 5-min windows, with 4-min overlap, and each subject was characterized by the median value of each parameter in the resulting six time windows.

Table 2
Definition of the considered time-domain HRV parameters. In the table, t_k represents the time occurrence of the kth beat, following ectopic correction, and K accounts for the total number of beats. More information regarding the indexes on this table can be found at [29].

Parameter	Definition
NN:normal-to-normal intervals.	$NN(k) = t_k - t_{k-1}$
$\overline{NN}$: mean of NN intervals.	$\overline{NN} = \frac{1}{K}\sum_k (t_k - t_{k-1})$
SDNN: standard deviation of NN intervals.	$SDNN = \frac{1}{K}\sum_k (NN(k) - \overline{NN})^2$
SD: successive differences.	$SD(k) = NN(k) - NN(k-1)$
SDSD: standard deviation of successive differences.	$SDSD = \frac{1}{K}\sum_k (SD(k) - \overline{SD})^2$
RMSSD: root mean square of successive differences.	$RMSSD = \sqrt{\frac{1}{K}\sum_k SD(k)^2}$
pNN50: percentage of NN intervals greater than 50 ms.	$pNN50 = 100 \times \frac{\sum NN > 50\,ms}{K}$

2.4. Frequency-domain HRV analysis

ANS modulation was estimated by means of the modulating signal, $m(t)$, using a method based on the time-varying integral pulse frequency modulation (TVIPFM) [30]. Such model relates autonomic modulation to instantaneous HR, where the presence of ectopic beats [30] is assumed to be accounted for, before the model is used. The model is expressed as:

$$k = \int_0^{t_k} \frac{1 + m(t)}{T(t)} dt, \tag{1}$$

being k and t_k the index and occurrence time of the kth beat, respectively, and $T(t)$ a term accounting for the time-varying mean heart period. In Eq. (1), the term:

$$d_{HR}(t) = \frac{1 + m(t)}{T(t)} = \frac{1}{T(t)} + \frac{m(t)}{T(t)}, \tag{2}$$

accounts for the instantaneous HR, and is composed by two terms: the HRV signal, $m(t)/T(t)$, and the time-varying mean HR, $1/T(t)$. Under the assumption that the variations in mean HR are much slower than the variations in HRV, the latter term can be easily obtained by low-pass filtering $d_{HR}(t)$ derived from the QRS detection marks. Defining the resulting components as $d_{HRM}(t) = 1/T(t)$, and then $m(t)$ can be estimated as:

$$m(t) = \frac{d_{HR}(t) - d_{HRM}(t)}{d_{HRM}(t)}. \tag{3}$$

Finally, an evenly-sampled discrete-time version of the modulating signal, $m(n)$, was obtained by resampling $m(t)$ at 4 Hz. For simplicity, $m(n)$ can be also expressed in vector notation as $\mathbf{m} = [m(0), m(1), \ldots, m(N-1)]^T$ (being N the total number of samples in the 10-min recordings).

An *a priori* analysis of the respiratory rate revealed that it was lower than or just above 0.15 Hz in a 13% of the subjects. In frequency-domain HRV analysis, the lower limit of the high frequency (HF) band (which is assumed to be related to vagal activity) has been traditionally set at 0.15 Hz [29]. However, in those cases in which the main components of the respiratory modulation of the HR fall below this limit, there is an overestimation of the low-frequency (LF, related to both sympathetic and vagal activity [29]) and an underestimation of the HF contributions of HRV. Moreover, the power content in the HF band is assumed to quantify the respiratory modulation of the HR, so that the interpretation of the frequency components within this band, when the respiratory contribution lays outside it, remains an open debate [31]. Therefore, several authors have developed methodologies for the decomposition of the HRV signals into respiratory-related and -unrelated components irrespective of their frequency band. As a result, the frequency-domain HRV analysis can be applied even in the presence of low respiratory rates [32]. In this work, an orthogonal subspace decomposition (OSP) approach was employed [33]. Essentially, it consists in projecting the HRV signal onto a subspace defined by respiration. For this purpose, an orthogonal projection matrix, P, is defined as:

$$\mathbf{P} = \mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T, \tag{4}$$

where X is a matrix whose columns are one sample incremental delayed versions of the respiratory effort signal, $x_r(n)$, up to 2 seconds [33]:

$$\mathrm{X} = \begin{pmatrix} x_r(0) & x_r(1) & \cdots & x_r(D-1) \\ x_r(1) & x_r(2) & \cdots & x_r(D) \\ \vdots & \vdots & \ddots & \vdots \\ x_r(N-D-1) & x_r(N-D) & \cdots & x_r(N-1) \end{pmatrix} \quad (5)$$

where N is the total number of samples in the 10-min recordings and D is a 2-s delay.

Then, the respiratory-related and -unrelated components of m (m_r and $\mathrm{m}_{r^\perp}$ respectively) can be obtained as:

$$\begin{aligned} \mathrm{m}_r &= \mathrm{P}\mathrm{m}, \\ \mathrm{m}_{r^\perp} &= \mathrm{m} - \mathrm{m}_r. \end{aligned} \quad (6)$$

The estimated spectra of both components, $\widehat{S}_r(F)$ and $\widehat{S}_{r^\perp}(F)$, were calculated in 5-min windows with 4-min overlap, using the Welch's periodogram (50 s windows, 50% overlap). An example of an spectrum before and after the OSP decomposition is displayed in Fig. 1. Afterwards, the non-respiratory related HRV power, $\mathrm{P}_{r^\perp}^{\mathrm{LF}}$, and the respiratory-related power, P_r, were obtained as:

$$\begin{aligned} \mathrm{P}_{r^\perp}^{\mathrm{LF}} &= \int_{0.04}^{0.15} \widehat{S}_{r^\perp}(F)\mathrm{dF}, \\ \mathrm{P}_r &= \int_{0.04}^{\overline{\mathrm{HR}}/2} \widehat{S}_r(F)\mathrm{dF}, \end{aligned} \quad (7)$$

where $\overline{\mathrm{HR}}$ represents the mean HR expressed in Hz. Finally, the ratio $\mathrm{SB}_{\mathrm{n}} = \mathrm{P}_{r^\perp}^{\mathrm{LF}}/\mathrm{P}_r$ was calculated as an unconstrained measurement of the sympathovagal balance [33], whereas the total power (TP) was computed as the power of $m(n)$ within the [0.04, 0.4] Hz band [29]:

$$\mathrm{TP} = \int_{0.04}^{0.4} \widehat{S}_m(F)\mathrm{dF}. \quad (8)$$

2.5. Statistical analysis

The temporal median of all the time and frequency domain HRV parameters was obtained for each subject. Normality of the data was assessed using a Kolmogorov–Smirnov test, so that two-sample t-tests were applied in order to assess the differences between groups. The statistical significance threshold was set to $p = 0.05$. Those features showing statistical differences among groups were tested in several machine learning algorithms, in order to explore their potential to stratify the patients in controlled and uncontrolled asthma. The feature selection and classification approaches used for this purpose are described below.

2.6. Automatic stratification

First, feature importance was computed with the out-of-bag permuted predictor importance algorithm [34], using a random forest with 400 decision trees. After training each tree using a random subset of patients (bagging), feature importance was computed as follows:

1. For each tree i, $i = 1,\ldots,I$, estimate the out-of-bag error ϵ_i (prediction error in the out-of-bag examples, i.e., the data which was not used for training the tree i).
2. For each predictor variable θ_j, randomly permute the observations of θ_j, and estimate a new out-of-bag error, ϵ_{ij}, using the permuted observations. Subindex j indicates permutation of the jth predictor variable.
3. Compute the error difference as $d_{ij} = \epsilon_{ij} - \epsilon_i$.
4. For each predictor variable, compute the mean and standard deviation ($\overline{d}_j$ and σ_j) of the differences d_{ij}.
5. Finally, obtain the out-of-bag permuted predictor importance for each θ_j as $\overline{d}_j/\sigma_j$.

Those features with an almost negligible importance (< 0.025) were discarded, and the remaining were considered as candidates for building a classification model. When two features were highly correlated (Pearson correlation coefficient higher than 0.75) the one with lower feature importance was discarded. Six different approaches were tested, namely logistic regression (LR), k nearest neighbors (kNN) and support vector machines (SVM), the latter with four different kernels: linear, quadratic, cubic and radial basis function (RBF). For each of the six types of classifiers, feature selection was addressed using a greedy forward algorithm, maximizing the F1 score of the minority class, since the groups are unbalanced. This feature selection process is dependent on the classifier type, and only the relevant features selected in the previous step were considered. In order to avoid overfitting, leave-one-patient-

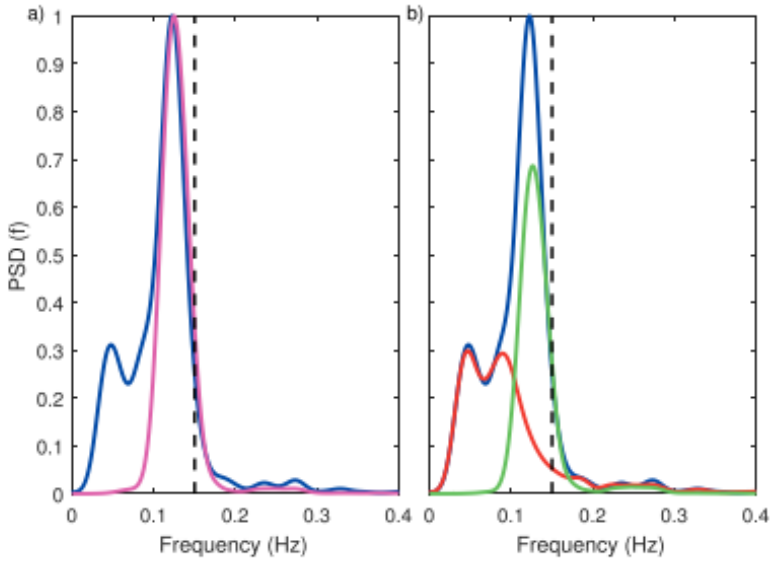

Fig. 1. (a) Normalized power spectral density of the modulating signal (blue) and the respiratory effort (pink) in a 5-min segment. Note that the respiratory activity lays below 0.15 Hz (black dashed line). (b) Orthogonal subspace projection was applied to separate the respiratory-related (green) and -unrelated (red) components of the modulating signal.

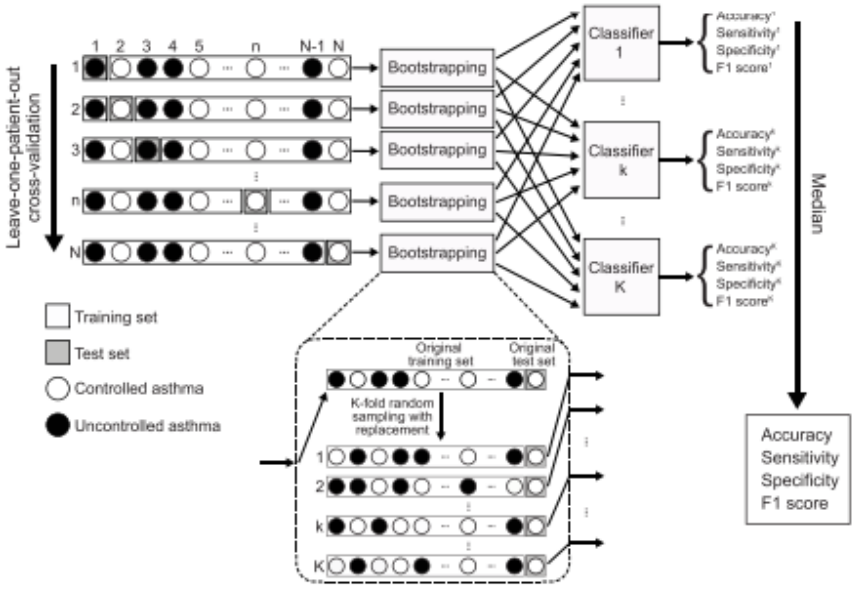

Fig. 2. A schematic of the combination of the leave-one-patient-out cross-validation with bootstrapping is displayed. White and black circles represent the subjects with controlled and uncontrolled asthma, respectively. After defining a training (white rectangle) and a test (gray square) set, bootstrapping is applied K times to obtain K different training sets. Then, the median of the performance of the K classifiers is used as a robust measure of the performance of the tested classification model.

out cross-validation was combined with bootstrapping [35], following the methodology in [36], as depicted in Fig. 2 ($K_{train} = 10,000$ was employed, being K_{train} the number of folds used in the bootstrapping, which is different from the number of folds of the leave-one-patient-out cross-validation). Also the maximum number of features was restricted to the square root of the number of subjects in the minority group (i.e., to 3). Afterwards, the leave-one-patient-out cross-validation and bootstrapping were repeated for constructing a model and testing the performance of the features selected for each classifier (with $K_{test} = 100$ in this case).

This process was repeated considering the clinical and the HRV features separately, so that the performance of both approaches can be compared. Additionally, we also considered the possibility that the ANS information represents an added value to the clinical routine, so that we repeated the classification process a third time, combining both sets of features.

2.7. Hyperparameter selection

Given the reduced number of subjects and the preliminary nature of the current study, no fine hyper-parameter tunning was addressed. The number of employed decision trees for feature relevance determination, as well as the Pearson correlation and the feature relevance thresholds were adjusted empirically. For the LR classifier, the conventional logit cost function was employed. Euclidean distance was used as the distance metric for the kNN algorithm, whereas the number of neighbors was set to 7 (this value was set empirically, as it provided the best classification performance). No regularization was applied in any of the cases, since overfitting reduction was addressed through the cross-validation/bootstrapping strategy described in the previous section, and also by limiting the number of features to the square root of the number of subjects in the smallest group [36]. Finally, regarding the selected values for K_{train} and K_{test}, the former was selected to be much larger than the later (K_{test} was selected as 1% of K_{train}), in order to ensure a large variety of training examples.

3. Results

Decreased SDNN, SDSD, RMSSD, pNN50, TP, $P_{r^2}^{LF}$ and P_r were assessed in the uncontrolled with respect to controlled asthmatics. These results are displayed in Table 3.

Table 3
Median [25th, 75th percentiles] of the parameters that were significantly different among groups (* indicates $p < 0.05$).

	Controlled	Uncontrolled
SDNN (ms)	36.36 [26.13, 50.56]	23.46* [20.92, 27.41]
SDSD (ms)	18.85 [14.33, 31.51]	13.94* [10.29, 15.64]
RMSSD (ms)	18.83 [14.32, 31.47]	13.92* [10.28, 15.61]
pNN50 (%)	0.84 [0.42, 10.30]	0.00* [0.00, 0.55]
TP (a.u. $\times 10^{-3}$)	13.65 [5.27, 23.59]	4.85* [2.61, 5.73]
$P_{r^2}^{LF}$ (a.u. $\times 10^{-3}$)	5.01 [2.58, 9.94]	2.02* [1.55, 3.22]
P_r (a.u. $\times 10^{-3}$)	2.66 [1.11, 6.79]	0.85* [0.27, 1.70]

The performance of the different classification approaches is shown in Table 4. Best performance, as measured by F1 score, was achieved when using the LR classifier, in the case of considering the clinical features (F1 = 0.75), and with the kNN classifier when using HRV features (F1 = 0.61). In both cases, the accuracy achieved with the HRV features was similar to that of the clinical ones (70% vs. 80% with the LR classifier, and 68.33% vs. 70% with the kNN classifier). On the other hand, the HRV features represented an added value in the kNN and SVM (cubic kernel) classifiers, as reflected by the increased performance with respect to using only clinical features.

Regarding the feature selection, FEV_1, $FEV_{1\%}$ and IgE were the most frequently selected clinical features (IgE was closely followed by FeNO), whilst SDNN, $P_{r^2}^{LF}$ and P_r were the most relevant HRV features (see Table 5).

Table 4
Median [25th, 75th percentiles] of the accuracy, sensitivity, specificity and F1 score obtained for each type of classifier when the subjects were classified based on their degree of asthma control. The sensitivity, specificity and F1 score were computed considering the uncontrolled asthma group as the positive class. The results correspond to the case of employing clinical features, HRV features, or a combination of both.

		Acc. (%)	Sens. (%)	Spec. (%)	F1
LR	Clin	**80.00 [76.67, 83.33]**	**72.73 [72.73, 81.82]**	**84.21 [78.95, 89.47]**	**0.75 [0.70, 0.78]**
	HRV	70.00 [63.33, 73.33]	54.55 [54.55, 63.64]	73.68 [68.42, 78.95]	0.57 [0.52, 0.64]
	All	**80.00 [76.67, 83.33]**	**72.73 [72.73, 81.82]**	**84.21 [78.95, 89.47]**	**0.75 [0.70, 0.78]**
*k*NN	Clin	70.00 [66.67, 73.33]	54.55 [54.55, 63.64]	78.95 [73.68, 84.21]	0.60 [0.52, 0.67]
	HRV	68.33 [63.33, 73.33]	63.64 [54.55, 72.73]	68.42 [68.42, 73.68]	0.61 [0.55, 0.67]
	All	**73.33 [70.00, 76.67]**	**72.73 [63.64, 81.82]**	**73.68 [68.42, 78.95]**	**0.67 [0.61, 0.72]**
SVM (linear kernel)	Clin	**80.00 [76.67, 83.33]**	**63.64 [63.64, 72.73]**	**89.47 [84.21, 94.74]**	**0.70 [0.67, 0.74]**
	HRV	65.00 [60.00, 70.00]	54.55 [45.45, 63.64]	73.68 [68.42, 78.95]	0.52 [0.43, 0.61]
	All	**80.00 [76.67, 83.33]**	**63.64 [63.64, 72.73]**	**89.47 [84.21, 94.74]**	**0.70 [0.67, 0.74]**
SVM (quadratic kernel)	Clin	**80.00 [76.67, 83.33]**	**63.64 [54.55, 63.64]**	**89.47 [89.47,94.74]**	**0.70 [0.63, 0.74]**
	HRV	63.33 [60.00, 70.00]	54.55 [45.45, 63.64]	68.42 [63.16, 73.68]	0.55 [0.48, 0.61]
	All	**80.00 [76.67, 83.33]**	**63.64 [54.55, 63.64]**	**89.47 [89.47,94.74]**	**0.70 [0.63, 0.74]**
SVM (cubic kernel)	Clin	66.67 [63.33, 73.33]	54.55 [45.45, 63.64]	78.95 [73.68, 78.95]	0.55 [0.45, 0.64]
	HRV	63.33 [60.00, 70.00]	54.55 [45.45, 63.64]	68.42 [68.42, 73.68]	0.51 [0.48, 0.60]
	All	**76.67 [73.33, 80.00]**	**63.64 [54.55, 72.73]**	**89.47 [84.21, 89.47]**	**0.67 [0.60, 0.73]**
SVM (RBF kernel)	Clin	**80.00 [73.33, 83.33]**	**54.55 [54.55, 63.64]**	**89.47 [84.21, 94.74]**	**0.67 [0.60, 0.71]**
	HRV	66.67 [63.33, 73.33]	54.55 [45.45, 63.64]	78.95 [73.68, 78.95]	0.55 [0.45, 0.64]
	All	**80.00 [73.33, 83.33]**	**54.55 [54.55, 63.64]**	**89.47 [84.21, 94.74]**	**0.67 [0.60, 0.71]**

Bold values indicates the best performing approach in each case.

Table 5
Features selected for each type of classifier, when considering the clinical or HRV features separately, and when combining both. The criterion for feature selection was to maximize the F1 score of the uncontrolled group.

		Selected features
LR	Clinical	{FEV_1, FeNO, IgE}
	HRV	{SDNN, $P_{\tau^c}^{LF}$}
	All	{FEV_1, FeNO, IgE}
*k*NN	Clinical	{FEV_1, $FEV_{1,\%}$}
	HRV	{SDNN, $P_{\tau^c}^{LF}$}
	All	{SDSD, P_r, FEV_1}
SVM (linear kernel)	Clinical	{FEV_1, $FEV_{1,\%}$, IgE}
	HRV	{SDNN, $P_{\tau^c}^{LF}$, P_r}
	All	{FEV_1, $FEV_{1,\%}$, IgE}
SVM (quadratic kernel)	Clinical	{FEV_1, $FEV_{1,\%}$, IgE}
	HRV	{SDNN, $P_{\tau^c}^{LF}$}
	All	{FEV_1, $FEV_{1,\%}$, IgE}
SVM (cubic kernel)	Clinical	{$FEV_{1,\%}$}
	HRV	{SDNN, $P_{\tau^c}^{LF}$}
	All	{SDNN, $FEV_{1,\%}$, FeNO}
SVM (RBF kernel)	Clinical	{FEV_1, $FEV_{1,\%}$, IgE}
	HRV	{SDNN, $P_{\tau^c}^{LF}$}
	All	{FEV_1, $FEV_{1,\%}$, IgE}

4. Discussion

ANS is acknowledged as a modulator of lower airway inflammation [15] and control [13,14]. Therefore, the altered autonomic activity [16–21] and respiratory dynamics [37–39] observed in asthmatics and subjects with lower airway obstruction suggest that ANS dysfunction might play an important role in the pathogenesis of asthma. In this work, we evaluated the capability of ANS assessment for stratifying asthmatic subjects attending to their degree of asthma control, in comparison with the use of clinical features. ANS was assessed from time- and frequency-domain HRV analyses. A preliminary inspection of the respiratory rate revealed that it was lower than or very close to 0.15 Hz in some subjects, which remains the lower limit of the HF band traditionally employed in frequency-domain HRV analysis [29]. For this reason, the HRV signals were decomposed in their respiratory-related and -unrelated components, so that frequency-domain analysis is still suitable. The OSP algorithm was used for this decomposition, given its performance in previous works [33]. Although it is a linear method which does not consider some nonlinearities that may be relevant [33], it shows to be sufficient for this particular application.

Regarding the results displayed in Table 3, a reduction in the sympathetic ($P_{\tau^c}^{LF}$) and vagal (SDSD, RMSSD, pNN50 and P_r) components of HRV, as well as in the total HRV (SDNN, TP), were obtained in the uncontrolled asthma with respect to the controlled asthma group, in concordance with previous studies by *Lutfi* [22,23]. However, whereas *Lutfi* reported increased vagal dominance in controlled asthmatics, we did not find a similar tendency. This might be explained by methodological and demographic differences with respect to the work by *Lutfi*. First, no respiratory information is reported in [22,23], so that increased vagal dominance in controlled with respect to uncontrolled asthmatics might be due to differences in respiratory rate among groups. Additionally, uncontrolled asthmatics in [22,23] present a much severer condition than in our case, as indicated by their lower $FEV_{1,\%}$ and ACT scores.

The physiological interpretation of reduced HRV in uncontrolled asthma is not straightforward. Hampered autonomic control could affect catecholamine circulation, which is thought to play a protective role in asthma [15,40], as suggested by broncho-constriction following β-blockade which is not seen in non-asthmatics [15]. On the other hand, previous studies have related increased vagal dominance in response to autonomic challenge or during sleep with asthma severity [16–21]. Therefore, it is possible that asthmatic subjects with a worse prognosis present a decreased autonomic control during rest, but their vagal pathways respond exaggeratedly to certain stimuli, yielding to the hyper-responsiveness characteristic of asthma [41].

As reflected in Table 1, the uncontrolled asthma group was composed by a lower relative number of males than the controlled group. Whereas males usually present increased sympathetic and decreased vagal tone than females [42], we assessed lower P_r in the uncontrolled asthma group, suggesting that the differences in ANS activity between controlled and uncontrolled asthmatics may be due to other causes than sex. Since the age range was very similar among groups, the reductions in the cardiorespiratory interactions due to aging were not considered here.

Given the existing differences in HRV among groups, we tested the capability of several types of classifiers to correctly classify the patients based on their asthma control. The feature selection process described above was repeated twice: once using only the clinical features and another using only ANS-derived features. As reflected in Table 4, similar performance was achieved when employing clinical and HRV features in several classifiers, although the F1 score was generally higher in the former approach. In the case of using only HRV features, best performance was achieved with the LR and *k*NN classifiers. In both cases, the accuracy was around 70%, which is the same than that of the ACT in patients who are new to the follow-up of an asthma specialist [5], and similar to that reported for ACT when it was first introduced [43]. As reflected in Table 5, the most selected HRV features independently of the classifier type were SDNN, $P_{r^2}^{LF}$ and P_r, thus suggesting that not only the total HRV, but also the independent linear contribution of the sympathetic and the vagal branches of the ANS are important for patient stratification. Regarding the clinical features, FEV_1, $FEV_{1\%}$ were the most selected, followed by IgE levels. This can be explained by the fact that, in spite of a consistent decrease in FEV_1/FVC and an increase in FeNO and IgE with poor symptoms control (see Table 1), the only clinical parameters that were able to distinguish between the degree of symptomatology control were the FEV_1 and $FEV_{1\%}$ (and the ACT and the MiniAQLQ questionnaires, which remain the gold standards in this classification criterion). Although absence of statistical differences in the other clinical features might be explained by sample size, airway function appears as the most relevant characteristic of the considered population.

Additionally, we considered the combination of clinical and HRV features in a single classification scheme, in order to explore the possible added value of the latter. The combination of clinical and HRV features outperformed the case when only clinical features were used for some of the tested classifiers. As reflected in Table 4, best performance was achieved with the SVM with cubic kernel, so it is possible that the complex interactions among the clinical and the HRV features cannot be properly exploited with lower order approaches.

The use of ANS-derived information has some desirable properties. First, it is very noninvasive in nature, and can be acquired in a continuous manner and using a less cumbersome equipment, without requiring a visit to the hospital or trained personnel. Hence, it could represent a potential contribution for the improvement of asthma self-monitoring using wearable devices and/or mobile applications. Moreover, a continuous assessment of autonomic activity could shed some light on the physiological mechanisms underlying a worsening of asthma control. Actually, and as described above, a large number of studies have addressed the potential of ANS assessment for the characterization of asthma severity [16–21] or control [22,23]. Nevertheless, none of these studies have addressed the potential added value of the proposed methodologies in comparison or combined with the most commonly used clinical features, which is addressed in this work. Interestingly, some of the aforementioned studies employ autonomic challenge to emphasize ANS reactivity. In this work basal conditions were considered, although the use of autonomic tests deserves to be considered.

Another group of studies have focused on the analysis of respiratory activity or respiratory sounds [11,12] or respiratory activity [10]. The methodologies proposed on those studies present a very good performance in stratifying asthmatic subjects, although they also present some limitations. Whereas the use of respiratory sounds could present some limitations in the characterization of the level of asthma control (due to characteristic variable airway obstruction in ashtma [1,2]) the reliable assessment of respiratory activity usually requires cumbersome equipment or trained personnel. In contrast, the assessment of HRV can be performed by means of a chest-band, or even a smartwatch.

There are some limitations that should be considered when interpreting the results of this work. First, and given the preliminary nature of this study, the dataset is composed by a small number of subjects, and it is imbalanced regarding patient classification. These limitations prevent from dividing the subjects in the traditional training, cross-validation, and test sets, since this would only amplify the problem. In order to reduce the impact of the low amount of data, we adopted the classification approach presented in [36], consisting of a combination of leave-one-patient-out cross-validation and boostrapping. With this methodology, the performance for each subject was tested in several different types of classifiers that had been trained with different subsets of the original dataset, so that the median performance of all the classifiers can be regarded as a much more robust measurement than if only leave-one-patient-out cross-validation was applied. The reduced number of subjects in the minority class also limited the maximum number of features to be considered in the classifiers, in order to minimize over-fitting. Additionally, the ANS-derived features were extracted from only 10 min of ECG and respiratory effort recordings, so that they represent the instantaneous ANS status of each subject, and not an average ANS condition. However, the subjects were requested to remain seated and without talking for some minutes prior to biosignals acquisition, so that the most possible basal state was considered. On the contrary, the use of 10-min recordings also constitutes a strength of this study, since it represents a low time-consuming test which, given its noninvasive nature, could eventually be realized without needing to attend to the clinic, being useful for self-monitoring. Nonetheless, evaluation in larger datasets is required, and the assessment of the autonomic response of the subjects to different autonomic tests would probably contribute to improve the classification performance. The use of HRV for ANS assessment has received some criticism concerning the physiological contribution to the commonly employed frequency bands [44]. In this work, the use of OSP decomposition ensures that the frequency components contributing to $P_{r^2}^{LF}$ are unrelated to respiratory activity, likely having its origin in sympathetic modulation. Nevertheless, the use of HRV analysis is widely extended in the literature, and has been often considered for the evaluation of autonomic activity in asthmatics [16–21,23,22]. In what concerns the assessment of peripheral eosinophilia and inflammation, it was based on predefined thresholds for which there is still no consensus.

5. Conclusion

In conclusion, noninvasive ANS assessment has been presented as a potential tool for asthma control stratification. The univariate analysis of the ANS-derived features revealed a reduced HRV in uncontrolled with respect to controlled asthmatics. Using this autonomic information in the stratification of the patients resulted in a similar performance than using only clinical features in various of the tested approaches, and also in an equal performance than the widely employed asthma control tests. Additionally, the combination of HRV and clinical features outperformed the use of clinical features alone in some cases. Therefore, ANS assessment through noninvasive cardiorespiratory signals analysis could represent an added value for the monitoring of asthma patients outside the clinic and using a less specific equipment, being useful for self-management.

Author contributions

All authors equally contributed to the conception of the work, revising it critically for important intellectual content, final approval of the version to be published, and to the discussion and interpretation of the results. Additionally, RB, PL, EG and VP supervised this work, also giving methodological support. LS, JG and VP were responsible of the dataset acquisition, and contributed with physiological interpretation support. CV contributed with methodological support. Finally, JM was responsible for drafting this work.

Acknowledgments

This work was supported by grant BES-2015-073694 and projects RTI2018-097723-B-I00, PID2019-104881RB-I00, and PID2019-105674RB-I00 from Ministerio de Economía y Competitividad. Also by Gobierno de Aragón through Reference Group BSICoS (T39-20R) and project LMP44-18, cofunded by FEDER 2014-2020 "*Building Europe from Aragon*", by CIBER in Bioengineering, Biomaterials & Nanomedicine (CIBER-BBN) through Instituto de Salud Carlos III and by Proyectos Integrados de Investigación de Asma (PII-Asma) through Sociedad Española de Neumología y Cirugía Torácica (SEPAR). The computation was performed by the ICTS NANBIOSIS, specifically by the High Performance Computing Unit of CIBER-BBN at University of Zaragoza.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] Global initiative for asthma, Global Strategy for Asthma Management and Prevention, 2018. Available from: http://www.ginasthma.org.
[2] V. Plaza, M. Blanco, G. García, J. Korta, J. Molina, S. Quirce, et al., Highlights of the Spanish asthma guidelines (GEMA), version 5.0, Arch. Bronconeumol. (2020).
[3] H.K. Reddel, et al., An official American thoracic society/European respiratory society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice, Am. J. Respir. Crit. Care Med. 180 (1) (2009) 59–99.
[4] M. Schatz, et al., The relationship of asthma impairment determined by psychometric tools to future asthma exacerbations, Chest 141 (1) (2012) 66–72.
[5] M. Schatz, et al., Asthma control test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists, J. Allergy Clin. Immunol. 117 (3) (2006) 549–556.
[6] N.C. Smeeton, et al., Agreement between responses to a standardized asthma questionnaire and a questionnaire following a demonstration of asthma symptoms in adults, Am. J. Epidemiol. 163 (4) (2006) 384–391.
[7] A.C. Wu, J.F. Carpenter, B.E. Himes, Mobile health applications for asthma, J. Allergy Clin. Immunol. Pract. 3 (3) (2015) 446.
[8] A.J. Simpson, et al., Perspectives of patients and healthcare professionals on mhealth for asthma self-management, Eur. Respir. J. 49 (5) (2017).
[9] S. Majumder, T. Mondal, M.J. Deen, Wearable sensors for remote health monitoring, Sensors 17 (1) (2017) 130.
[10] V.-P. Seppä, A.S. Pelkonen, A. Kotaniemi-Syrjänen, J. Viik, M.J. Mäkelä, L. P. Malmberg, Tidal flow variability measured by impedance pneumography relates to childhood asthma risk, Eur. Respir. J. 47 (6) (2016) 1687–1696.
[11] F.G. Nabi, K. Sundaraj, C.K. Lam, Identification of asthma severity levels through wheeze sound characterization and classification using integrated power features, Biomed. Signal Process. Control 52 (2019) 302–311.
[12] A. Karimizadeh, M. Vali, M. Modaresi, Multichannel lung sound analysis to detect severity of lung disease in cystic fibrosis, Biomed. Signal Process. Control 64 (2021) 102266.
[13] M. Lewis, A. Short, K. Lewis, Autonomic nervous system control of the cardiovascular and respiratory systems in asthma, Respir. Med. 100 (10) (2006) 1688–1705.
[14] J. Morrison, S. Pearson, H. Dean, Parasympathetic nervous system in nocturnal asthma, Br. Med. J. (Clin. Res. Ed.) 296 (6634) (1988) 1427–1429.
[15] P.J. Barnes, Neuroeffector mechanisms: the interface between inflammation and neuronal responses, J. Allergy Clin. Immunol. 98 (5) (1996) S73–S83.
[16] O. Emin, et al., Autonomic nervous system dysfunction and their relationship with disease severity in children with atopic asthma, Respir. Physiol. Neurobiol. 183 (3) (2012) 206–210.
[17] J. Milagro, et al., Nocturnal heart rate variability spectrum characterization in preschool children with asthmatic symptoms, IEEE J. Biomed. Health Inform. 22 (5) (2017) 1332–1340.
[18] J. Milagro, et al., Noninvasive cardiorespiratory signals analysis for asthma evolution monitoring in preschool children, IEEE Trans. Biomed. Eng. (2019).
[19] J. Kallenbach, et al., Reflex heart rate control in asthma: evidence of parasympathetic overactivity, Chest 87 (5) (1985) 644–648.
[20] B. Zahorska-Markiewicz, et al., Circadian heart rate variability in asthma, Med. Sci. Monit. 3 (1) (1997) CR52–CR56.
[21] P.K. Shah, et al., Clinical dysautonomia in patients with bronchial asthma: study with seven autonomic function tests, Chest 98 (6) (1990) 1408–1413.
[22] M.F. Lutfi, Patterns of heart rate variability and cardiac autonomic modulations in controlled and uncontrolled asthmatic patients, BMC Pulm. Med. 15 (1) (2015) 119.
[23] M.F. Lutfi, Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability, Lung India 29 (3) (2012) 254.
[24] J. Vega, et al., Validation of the spanish version of the asthma control test (ACT), J. Asthma 44 (10) (2007) 867–872.
[25] I. Pin, et al., Use of induced sputum cell counts to investigate airway inflammation in asthma, Thorax 47 (1) (1992) 25–29.
[26] E. Juniper, et al., Development and validation of the mini asthma quality of life questionnaire, Eur. Respir. J. 14 (1) (1999) 32–38.
[27] J.P. Martínez, et al., A wavelet-based ECG delineator: evaluation on standard databases, IEEE Trans. Biomed. Eng. 51 (4) (2004) 570–581.
[28] J. Mateo, P. Laguna, Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal, IEEE Trans. Biomed. Eng. 50 (3) (2003) 334–343.
[29] Task Force of the European Society of Cardiology, Heart rate variability: standards of measurement, physiological interpretation, and clinical use, Circulation 93 (5) (1996) 1043–1065.
[30] R. Bailón, et al., The integral pulse frequency modulation model with time-varying threshold: application to heart rate variability analysis during exercise stress testing, IEEE Trans. Biomed. Eng. 58 (3) (2011) 642–652.
[31] L. Bernardi, et al., Effects of controlled breathing, mental activity and mental stress with or without verbalization on heart rate variability, J. Am. College Cardiol. 35 (6) (2000) 1462–1469.
[32] D. Widjaja, et al., Separation of respiratory influences from the tachogram: a methodological evaluation, PLOS ONE 9 (7) (2014) e101713.
[33] C. Varon, et al., Unconstrained estimation of HRV indices after removing respiratory influences from heart rate, IEEE J. Biomed. Health Inform. (2018).
[34] L. Breiman, Random forests, Mach. Learn. 45 (1) (2001) 5–32.
[35] B. Efron, R.J. Tibshirani, An Introduction to the Bootstrap, CRC Press, 1994.
[36] J. Bolea, et al., Pulse rate and transit time analysis to predict hypotension events after spinal anesthesia during programmed cesarean labor, Ann. Biomed. Eng. 45 (9) (2017) 2253–2263.
[37] G. Citterio, et al., Decay of inspiratory muscle activity in chronic airway obstruction, J. Appl. Physiol. 51 (6) (1981) 1388–1397.
[38] C. Shee, Y. Ploy-Song-Sang, J. Milic-Emili, Decay of inspiratory muscle pressure during expiration in conscious humans, J. Appl. Physiol. 58 (6) (1985) 1859–1865.
[39] T. Ritz, E. Simon, A.F. Trueba, Stress-induced respiratory pattern changes in asthma, Psychosom. Med. 73 (6) (2011) 514–521.
[40] T. Jartti, Asthma, asthma medication and autonomic nervous system dysfunction, Clin. Physiol. 21 (2) (2001) 260–269.
[41] A.D. Fryer, D.B. Jacoby, Muscarinic receptors and control of airway smooth muscle, Am. J. Respir. Crit. Care Med. 158 (supplement_2) (1998) S154–S160.
[42] I. Antelmi, et al., Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease, Am. J. Cardiol. 93 (3) (2004) 381–385.
[43] R.A. Nathan, et al., Development of the asthma control test: a survey for assessing asthma control, J. Allergy Clin. Immunol. 113 (1) (2004) 59–65.
[44] D.L. Eckberg, Sympathovagal balance: a critical appraisal, Circulation 96 (9) (1997) 3224–3232.

4.2 Artículo 2

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

Lorena Soto-Retes, Javier Milagro, Astrid Crespo-Lessmann, Elena Curto, Eder F. Medina, Raquel Bailón, Eduardo Gil, Pablo Laguna, Vicente Plaza.

Ann Allergy Asthma Immunol. 2024 Oct;133(4):430-436.

Doi: 10.1016/j.anai.2024.07.022. Epub 2024 Jul 27.

PMID: 39074657.

IF: 5.8

Ann Allergy Asthma Immunol 133 (2024) 430–436

Contents lists available at ScienceDirect

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 Biomèdica 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, Olaguibel 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.

5. Resumen global de los resultados

Resumen global de los resultados

El conjunto de investigaciones realizadas demuestra la viabilidad de evaluar el control del asma a través del SNA de manera no invasiva, especialmente en casos de asma grave.

En el estudio 1 publicado, en relación con los resultados presentados en la Tabla 1, se observó una desregulación en la actividad vagal objetivada a través de la VRC en los parámetros más comúnmente utilizados como son el: SDSD, RMSSD, pNN50 y Pr. Asimismo, se identificó un desequilibrio en la VRC total, evidenciado por la desregulación de los parámetros SDNN y TP en el grupo de asma no controlada en comparación con el grupo de asma controlada.

Tabla 1. Parámetros de la VRC más utilizados para discriminar el control del asma

Median [25th, 75th percentiles] of the parameters that were significantly different among groups (* indicates $p < 0.05$).

	Controlled	Uncontrolled
SDNN (ms)	36.36 [26.13, 50.56]	23.46* [20.92, 27.41]
SDSD (ms)	18.85 [14.33, 31.51]	13.94* [10.29, 15.64]
RMSSD (ms)	18.83 [14.32, 31.47]	13.92* [10.28, 15.61]
pNN50 (%)	0.84 [0.42, 10.30]	0.00* [0.00, 0.55]
TP (a.u. $\times 10^{-3}$)	13.65 [5.27, 23.59]	4.85* [2.61, 5.73]
$P_{r^{\perp}}^{LF}$ (a.u. $\times 10^{-3}$)	5.01 [2.58, 9.94]	2.02* [1.55, 3.22]
P_r (a.u. $\times 10^{-3}$)	2.66 [1.11, 6.79]	0.85* [0.27, 1.70]

Se analizaron el resto de parámetros de la VRC recogidos a través del ECG en función a las variables clínicas, funcionales y biológicas recogidas, demostrando que los parámetros: SDNN, PLF r⊥ y Pr fueron las variables más relevantes asociadas a

indicadores de inflamación y obstrucción en el asma: FEV1, la IgE y la FeNO (ver Tabla 2).

Tabla 2. Selección de variables más relevantes en la VRC asociadas a la función pulmonar, la IgE y la FeNO.

		Selected features
LR	Clinical	{FEV_1, FeNO, IgE}
	HRV	{SDNN, $P_{r^{\perp}}^{LF}$}
	All	{FEV_1, FeNO, IgE}
*k*NN	Clinical	{FEV_1, $FEV_{1,\%}$}
	HRV	{SDNN, $P_{r^{\perp}}^{LF}$}
	All	{SDSD, P_r, FEV_1}
SVM (linear kernel)	Clinical	{FEV_1, $FEV_{1,\%}$, IgE}
	HRV	{SDNN, $P_{r^{\perp}}^{LF}$, P_r}
	All	{FEV_1, $FEV_{1,\%}$, IgE}
SVM (quadratic kernel)	Clinical	{FEV_1, $FEV_{1,\%}$, IgE}
	HRV	{SDNN, $P_{r^{\perp}}^{LF}$}
	All	{FEV_1, $FEV_{1,\%}$, IgE}
SVM (cubic kernel)	Clinical	{$FEV_{1,\%}$}
	HRV	{SDNN, $P_{r^{\perp}}^{LF}$}
	All	{SDNN, $FEV_{1,\%}$, FeNO}
SVM (RBF kernel)	Clinical	{FEV_1, $FEV_{1,\%}$, IgE}
	HRV	{SDNN, $P_{r^{\perp}}^{LF}$}
	All	{FEV_1, $FEV_{1,\%}$, IgE}

En el estudio 2 publicado, se agruparon 30 pacientes con asma grave según el control del mismo discriminado por el cuestionario de autocumplimentación ACT, y el riesgo de ansiedad y depresión discriminado por el cuestionario de autocumplimentación HADS; 10 de los pacientes con asma no controlada en comparación con los pacientes con asma controlada mostraron diferencias significativas ($P < 0.05$) en los parámetros analizados más frecuentemente relacionados hallados en el Estudio 1, demostrando desregulaciones en la VRC medidos a través del ECG: 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]) y Pr (0.0003 [0.00025] vs 0.0007 [0.00060]) respectivamente (véase Tabla 3).

Tabla 3. Resultados de la VRC en pacientes con asma controlada y no controlada.

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).

Un total de 13 pacientes con riesgo de ansiedad y depresión en comparación con los pacientes sin riesgo, demostraron diferencias significativas ($P < 0.05$) en los parámetros de la VRC medidos a través del ECG para: SDNN (26.5 [7.9] vs 45.6 [31.3]), pNN50 (0.75 [1.4] a 7.12 [12.6]), TP (0.0005 [0.00048] a 0.0012 [0.0008]) y Pr (0.0003 [0.00027] a 0.0008 [0.00062]) (véase Tabla 4).

Tabla 4. Resultados de la VRC en pacientes con asma y el riesgo de ansiedad y depresión

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).

6. Resumen global de la discusión

6.1 Discusión general

Esta Tesis Doctoral, presenta como principal hallazgo que los pacientes con asma grave no controlada, en comparación a los pacientes con asma grave controlada, tenían un SNA más deprimido.

En el estudio 1, primero se describió la metodología empleada para evaluar el SNA a partir del análisis no invasivo de la VRC, tanto en el dominio del tiempo como en el de la frecuencia. Durante la inspección preliminar de la frecuencia respiratoria, se observó que en algunos sujetos asmáticos se encontraba por debajo o muy cerca de 0,15 Hz, que es el límite inferior de la banda HF tradicionalmente utilizada para el análisis de la VRC (46). Por ello, las señales de VRC se descompusieron en sus componentes respiratorios y no respiratorios, lo que permitió un análisis adecuado en el dominio de la frecuencia. Para realizar esta descomposición se utilizó el algoritmo OSP, dado su buen desempeño en estudios previos (76).

En cuanto a los resultados, se evidenció una reducción en los componentes simpáticos (PLF r⊥) y vagales (SDSD, RMSSD, pNN50 y Pr) de la VRC, así como en la VRC total (SDNN, TP), en sujetos con asma no controlada en comparación con aquellos con asma controlada, en concordancia con estudios previos (63,64). Sin embargo, a diferencia de los resultados publicados, quienes reportaron un aumento del predominio vagal en asmáticos controlados, en nuestro estudio no se encontró una tendencia similar. Esta discrepancia podría explicarse por diferencias metodológicas, ya que en dichos estudios no se detalló la información sobre la frecuencia respiratoria y caracterización del asma (63, 64). Por lo tanto, el aparente aumento del predominio vagal en asmáticos no controlados respecto a los controlados podría deberse a diferencias en la frecuencia

respiratoria entre los grupos, asociado a que la caracterización del asma en nuestro estudio fue mucho más exhaustiva.

La interpretación fisiológica de la disminución de la VRC en el asma no controlada es compleja. Un control autonómico alterado podría influir en la circulación de catecolaminas, consideradas protectoras en el asma, como lo demuestra la broncoconstricción observada tras el bloqueo β en asmáticos, pero no en individuos sin asma (65,66). Adicionalmente, estudios previos han asociado un mayor predominio vagal en respuesta a estímulos autonómicos o durante el sueño con la gravedad del asma (31-32, 66-68). Esto sugiere que los pacientes asmáticos podrían tener un control autonómico basal disminuido, mientras que sus vías vagales responden de forma exagerada a ciertos estímulos, contribuyendo a la hiperreactividad característica de la enfermedad (28).

Los datos obtenidos mostraron que el grupo de asma no controlada contenía proporcionalmente menos varones que el grupo controlada. Aunque la literatura sugiere que los hombres suelen tener un tono simpático más alto y un tono vagal más bajo que las mujeres (69), en nuestro estudio se detectó una Pr inferior en el grupo de asma no controlada en ambos sexos. Esto apunta a que las diferencias en la actividad del SNA entre pacientes con asma controlada y no controlada podrían originarse en factores distintos del género. Igualmente, la edad comparable entre los grupos permitió considerar irrelevantes las reducciones en las interacciones cardiorrespiratorias ligadas al envejecimiento. Se analizaron, asimismo, diversas variables como la función pulmonar, la FeNO y la IgE total, constatándose un rendimiento discriminatorio semejante a través de la VRC.

En el estudio 2, mediante datos objetivos obtenidos de la medición no invasiva de la VRC, se logró diferenciar a pacientes con asma grave no controlada de aquellos con asma

controlada, independientemente de su gravedad. Asimismo, se demostró que los trastornos del ánimo más comunes asociados al asma, como la depresión y la ansiedad, se relacionan con una disminución de los parámetros de la VRC en pacientes con peor función pulmonar. Nuestros resultados sugieren que la vía del SNP podría tener un rol en la patogénesis del asma, dada la alteración de la actividad del SNA, especialmente en pacientes con asma grave no controlada y comorbilidades como la depresión y la ansiedad. Una fortaleza de este estudio radica en el uso de un marcador neurobiológico como la VRC para estratificar a los pacientes con asma según su nivel de control (como se detalla en el estudio 1). El hallazgo más relevante fue la detección de una reducción en los componentes vagales (RMSSD, pNN50, Pr y TP) en el grupo de asma no controlada en comparación con el grupo de asma controlada. Este resultado respalda los hallazgos por otros autores, quienes documentaron que el mal control del asma se asoció con modulaciones deprimidas de la VRC, y que los pacientes con mejor función pulmonar presentaban una VRC superior a la de aquellos con asma grave (63,64).

La disminución de los componentes vagales de la VRC observada en pacientes con asma no controlada sugiere una compleja relación entre la inflamación y el control nervioso de las vías respiratorias. Respecto al deterioro del control autonómico, se conoce la rapidez con la que ocurren los cambios en el tono broncomotor en el asma. Hace décadas se propuso que los individuos con asma podrían tener una regulación anómala de las vías respiratorias por el sistema nervioso autónomo, con un desequilibrio entre las vías excitatorias e inhibitorias que resulta en hiperreactividad bronquial (74,75). No obstante, otros estudios en asma grave señalan un aumento del predominio vagal en respuesta a pruebas autonómicas (respiración profunda, maniobra de Valsalva y ortostatismo) y durante el sueño (31,32,35). Por lo tanto, es posible que el SNA en pacientes con asma grave se encuentre deprimido durante la inactividad o la relajación, y que la

broncoconstricción se produzca cuando las vías vagales se activan o responden de forma exagerada a los estímulos (45).

De manera similar, los pacientes con riesgo de desarrollar trastornos del estado de ánimo, frecuentemente observados en personas con asma como la depresión y la ansiedad, exhibieron una actividad del SNA reducida en todos los parámetros evaluados, sin diferencias significativas en PLFn. En comparación con los pacientes con asma controlada, aquellos con control deficiente y una espirometría obstructiva (FEV1 <70% del valor predicho) mostraron una VRC disminuida, sin importar los niveles de inflamación medidos por FeNO, esputo inducido, eosinofilia periférica o IgE total. Cabe resaltar que, aunque los trastornos del estado de ánimo como la depresión y la ansiedad son inherentes a los pacientes con asma grave (36,37,40,19,70,71), un aspecto relevante de nuestro estudio es la naturaleza objetiva de los resultados del SNA, que pueden enriquecer la información obtenida a través de cuestionarios autoevaluados (16,22,72,73).

Observamos diferencias significativas entre los grupos en relación con los trastornos del estado de ánimo evaluados mediante el cuestionario HADS: los pacientes con asma grave y riesgo de depresión y/o ansiedad presentaban una peor función pulmonar, un control del asma menos óptimo, una calidad de vida deteriorada y una actividad del SNP disminuida en comparación con los pacientes sin riesgo de estos trastornos según el HADS. No obstante, a pesar de que se sabe que los pacientes con asma no controlada sufren trastornos del estado de ánimo (48), en nuestro estudio, la depresión y la ansiedad se vincularon con la alteración del SNP, lo que suscita la interrogante de si estos trastornos son una consecuencia o una comorbilidad separada del asma grave no controlada originada por una desregulación del SNA.

6.2 Aportaciones e implicaciones clínicas.

Este estudio destaca el papel potencial del SNA en el control del asma y su relación con la depresión y la ansiedad. Hasta donde sabemos, ningún estudio se ha centrado específicamente en el rol del SNA concretamente en el SNP, a pesar de la existencia de investigaciones que abordan la respuesta del SNA a intervenciones farmacológicas y provocaciones bronquiales.

El análisis de la VRC debe realizarse de forma rigurosa y considerando la fisiología, ya que las amplias variaciones intra e interindividuales pueden complicar la interpretación de los resultados. Sin embargo, cuando se lleva a cabo en un marco adecuado, este análisis se convierte en una herramienta no invasiva de gran utilidad para potenciar el diagnóstico y el tratamiento personalizado de diversas afecciones.

En este sentido, y si futuros estudios confirman nuestros hallazgos, se podría subrayar el papel fisiopatológico del SNA —especialmente del SNP— en el control del asma asociado a la depresión y la ansiedad. Esto justificaría el desarrollo de nuevas líneas de investigación dirigidas a identificar terapias innovadoras, tanto farmacológicas como no farmacológicas, enfocadas en el SNA. Además, podría impulsarse la creación de una herramienta clínica complementaria, objetiva y no invasiva para consultas especializadas en asma grave. Dicho dispositivo, basado en tecnología inalámbrica o aplicaciones móviles, facilitaría la monitorización remota o continua, ofreciendo un enfoque integral para la evaluación del control del asma y los trastornos del estado de ánimo.

6.3 Limitaciones

Las principales limitaciones de esta Tesis Doctoral se derivan de su diseño, ya que es un estudio unicéntrico con un número limitado de participantes, lo que restringe la capacidad de generalizar los resultados y extraer conclusiones definitivas. Por el tiempo limitado disponible y el uso de un electrocardiograma cedido por el grupo de interpretación de bioseñales y simulación computacional de la Universidad de Zaragoza, no fue posible ampliar el tamaño muestral. Asimismo, los costes y la complejidad de las muestras de esputo inducido, junto con algunas determinaciones, como el cortisol en pelo y en saliva, solo pudieron realizarse en un número reducido de pacientes y, en última instancia, no se utilizaron debido a la limitación en el volumen de muestra para obtener resultados confiables en relación con los trastornos emocionales asociados al estrés. Por ello, se recomienda replicar los análisis en un grupo externo para corroborar los resultados obtenidos.

Además, dado que en ambos estudios se realizaron determinaciones poco habituales o no validadas, sería aconsejable incluir controles sanos o aumentar el número de participantes. En los estudios realizados en pacientes asmáticos tratados con β2-agonistas de corta y larga acción y anticolinérgicos de larga acción, persiste la incertidumbre sobre el posible efecto antiinflamatorio y colinérgico de estos fármacos y su influencia en los marcadores medidos en la VRC.

No obstante, una fortaleza del estudio es la exhaustiva caracterización de la población asmática, que cuenta con evidencia objetiva de asma, basada en criterios como la reversibilidad broncodilatadora, la función pulmonar, biomarcadores de inflamación y el estado alérgico.

7. Conclusiones

Conclusiones

1. La evaluación no invasiva de la actividad del sistema nervioso autónomo mediante la VRC permite distinguir entre pacientes con asma controlada y no controlada.
2. Las personas con asma grave no controlada, presentan una actividad desregularizada o deprimida del sistema nervioso autónomo.
3. Pacientes con asma no controlada, así como aquellos con depresión y/o ansiedad, presentan una actividad desregularizada del sistema nervioso autónomo.
4. La evaluación no invasiva de la actividad autonómica podría representar una técnica no invasiva complementaria a las habitualmente empleadas para establecer el nivel de control del asma.

8. Líneas de futuro

Líneas de futuro

La presente Tesis Doctoral explora el papel potencial del sistema nervioso autónomo (SNA) en el control del asma y su relación con la depresión y la ansiedad. Hasta donde se tiene conocimiento, la investigación previa ha centrado su atención en la respuesta del SNA a la intervención farmacológica y a la provocación bronquial. En este contexto, si futuros estudios confirman estos hallazgos, se reforzaría la evidencia sobre el papel fisiopatológico del SNA, en particular del sistema nervioso parasimpático (SNP), en el control del asma y su vínculo con los trastornos del estado de ánimo. Esto justificaría el desarrollo de nuevas investigaciones dirigidas a la identificación de dianas terapéuticas, tanto farmacológicas como no farmacológicas, enfocadas en la regulación del SNA. Asimismo, abriría la posibilidad de desarrollar una herramienta clínica complementaria, objetiva y no invasiva para su aplicación en consultas especializadas en asma grave. Dicha herramienta podría facilitar la monitorización remota o continua mediante dispositivos inalámbricos o aplicaciones móviles, proporcionando un enfoque más integral y preciso para la evaluación del control del asma y los trastornos emocionales asociados.

9. Bibliografía

1. GINA. Global Strategy for Asthma Management and Prevention. 2024. Available at: http://www.ginasthma.org. Accessed August 16.

2. OMS. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.

3. GEMA. Guía Española para el manejo del Asma. 2024. Available at: http://www.gemasma.com/ Accessed August 16.

4. Martinez-Moragon E, Serra-Batlle J, De Diego A, Palop M, Casan P, Rubio-Terre C, et al. Coste económico del paciente asmático en España (estudio Asmacost). Arch Bronconeumol. 2009; 45: 481-6.

5. Bousquet J, Jeffery P, Busse W, Johnson M, Vignola A. Asthma. From Bronchoconstriction to Airways Inflammation and Remodeling. Am J Resp Crit Care Med. 2000; 161: 1720-45.

6. O'Byrne PM, Inman MD. Airway hyperresponsiveness. Chest. 2003; 123: 411S-6.

7. Cockcroft DW, Davis B. Mechanisms of airway hyperresponsiveness. J Allergy Clin Immunol. 2006; 118: 551-9.

8. Black JL, Roth M, Lee J, Carlin S, Johnson PR. Mechanisms of airway remodeling: airway smooth muscle. Am J Resp Crit Care Med. 2001; 164: S63-6.

9. Boulet LP, Chapman KR, Cote J, Kalra S, Bhagat R, Swystun V, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med. 1997; 155: 1835-40.

10. Cartier A, L'Archeveque J, Malo JL. Exposure to a sensitizing occupational agent can cause a long-lasting increase in bronchial responsiveness to histamine in the absence of significant changes in airway caliber. J Allergy Clin Immunol. 1986; 78: 1185-9.

11. Porsbjerg C, Melén E, Lehtimäki L, Shaw D. Asthma. Lancet. 2023 Mar 11;401(10379):858-873.

12. Stoloff SW, Boushey HA. Severity, control, and responsiveness in asthma. J Allergy Clin Immunol. 2006; 117: 544-8.

13. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008; 32: 545-54.

14. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. J Allergy Clin Immunol. 1996; 98: 1016-8.

15. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al.; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med. 2004; 170: 836-44.

16. Vega JM, Badia X, Badiola C, Lopez-Vina A, Olaguibel JM, Picado C, et al.; Covalair Investigator Group. Validation of the Spanish version of the Asthma Control Test (ACT). J Asthma. 2007; 44: 867-72.

17. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: Systematic review and meta-analysis. J Allergy Clin Immunol. 2013; 131: 695-703.

18. Ahmedani BK, Peterson EL, Wells KE, Williams LK. Examining the relationship between depression and asthma exacerbations in a prospective follow-up study. Psychosom Med. 2013 Apr;75(3):305-10.

19. Kewalramani A, Bollinger ME, Postolache TT. Asthma and mood disorders. Int J Child Health Hum Dev.2008;1(2):115–123.

20. Clark VL, Gibson PG, Genn G, Hiles SA, Pavord ID, McDonald VM. Multidimensional assessment of severe asthma: A systematic review and meta-analysis. Respirology. 2017 Oct;22(7):1262-1275. doi: 10.1111/resp.13134. Epub 2017 Aug 3. PMID: 28776330.

21. Radhakrishna N, Tay TR, Hore-Lacy F, Hoy R, Dabscheck E, Hew M. Profile of difficult to treat asthma patients referred for systematic assessment. Respir. Med. 2016; 117: 166–73.

22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6):361–370.

23. McCorry, L. K. Physiology of the autonomic nervous system. Am J Pharm Educ. 2007; 71(4):78.

24. Silverthorn, D. U. Human physiology: An integrated approach. 2016; 6th ed. Pearson.

25. Lewis, M, A. Short, and K. Lewis. Autonomic nervous system control of the cardiovascular and respiratory systems in asthma. Respir Med 2006; 100(10):1688–1705.

26. Fenech, A., et al. Mutation screening of the muscarinic M2 and M3 receptor genes in normal and asthmatic subjects. Br J Pharmacol 2001; 133(1):43–48.

27. Fryer, A. D. and D. B. Jacoby. Muscarinic receptors and control of airway smooth

muscle. Am J Respir Crit Care Med 1998; 158(Suppl 2):S154–S160.

28. Minette, P., et al. A muscarinic agonist inhibits reflex bronchoconstriction in normal but not in asthmatic subjects. J Appl Physiol 1989; 67(6):2461–2465.

29. McGrath, K.W., et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. Am J Respir Crit Care Med 2012; 185(6):612–619.

30. Garrard, C. S., et al. Spectral analysis of heart rate variability in bronchial asthma. Clin Auton Res 1992; 2(2):105–111.

31. Kallenbach, J., et al. Reflex heart rate control in asthma: evidence of parasympathetic overactivity. Chest 1985; 87(5):644–648.

32. Shah, P. K., et al. Clinical dysautonomia in patients with bronchial asthma: study with seven autonomic function tests. Chest 1990; 98(6):1408–1413.

33. Tokuyama, K., et al. Beat-to-beat variation of the heart rate in children with allergic asthma. J Asthma 1985; 22(6):285–288.

34. Emin, O., et al. Autonomic nervous system dysfunction and their relationship with disease severity in children with atopic asthma. Respir Physiol Neurobiol 2012; 183(3):206–210.

35. Zahorska-Markiewicz, B., et al. Circadian heart rate variability in asthma. Med Sci 1997; Monit 3(1):CR52–CR56.

36. 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.

37. 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):123–38.

38. 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.

39. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European UBIOPRED adult severe asthma cohort. Eur Respir J. 2015; 46 (5):1308–1321.

40. Amelink M, Hashimoto S, Spinhoven P, Pasma HR, SterkPJ, Bel EH, et al. Anxiety, depression and personality traits in severe, prednisone-dependent asthma. Respir Med. 2014; 108 (3):438–444.

41. Valenza G. Depression as a cardiovascular disorder: central autonomic network, brain-heart axis, and vagal perspectives of low mood. Front. Netw. Physiol. 2023; 3:1125495.

42. 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.

43. Citterio, G., et al. Decay of inspiratory muscle activity in chronic airway obstruction. J Appl Physiol 1981; 51(6):1388–1397.

44. Shee, C., Y. Ploy-Song-Sang, and J. Milic-Emili. Decay of inspiratory muscle pressure during expiration in conscious humans. J Appl Physiol 1985; 58(6):1859–1865.

45. Ritz, T., E. Simon, and A. F. Trueba. Stress-induced respiratory pattern changes in asthma. Psychosom Med 2011; 73(6):514–521.

46. 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.

47. 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.

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 metaanalyses. 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. Rajendra Acharya, U., Paul Joseph, K., Kannathal, N. et al. Heart rate variability: a review. Med Bio Eng Comput 2006; 44, 1031–1051.

54. Leif Sörnmo, Pablo Laguna, Bioelectrical Signal Processing in Cardiac and Neurological Applications. Elsevier Academic Press 30 Corporate Drive. 2005. (8 chapters, 2 appendices, 668 pp) ISBN 13: 978-0-12-437552-9.

55. Valentinuzzi ME. Bioelectrical signal processing in cardiac and neurological applications and electromyography: physiology, engineering, and noninvasive applications. Biomed Eng Online. 2007 Jul 3;6:27. doi: 10.1186/1475-925X-6-27.

56. Siepmann M, Weidner K, Petrowski K, Siepmann T. Heart Rate Variability: A Measure of Cardiovascular Health and Possible Therapeutic Target in Dysautonomic Mental and Neurological Disorders. Appl Psychophysiol Biofeedback. 2022 Dec;47(4):273-287.

57. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. Psychoneuroendocrinology. 2008 Nov;33(10):1305-12.

58. Shaffer, F. and J. Ginsberg. An overview of heart rate variability metrics and norms.

Front Public Health 2017; 5:258.

59. Malliani, A., et al. Cardiovascular neural regulation explored in the frequency

domain. Circulation 1991; 84(2):482–492.

60. Pagani, M., et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ

Res 1986; 59(2):178–193.

61. Reyes del Paso, G. A., et al. The utility of low frequency heart rate variability as

an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of

previous studies. Psychophysiology 2013; 50(5):477–487.

62. Kantz, H. and T. Schreiber. Nonlinear time series analysis, volume 7. 2004; Cambridge university press.

63. Lutfi, M.F. Patterns of heart rate variability and cardiac autonomic modulations in controlled and uncontrolled asthmatic patients. BMC Pulm Med 2015; 15, 119.

64. Lutfi MF. Autonomic modulations in patients with bronchial asthma based on short-term heart rate variability. Lung India. 2012 Jul;29(3):254-8.

65. Morrison J F J, Pearson S B, Dean H G. Parasympathetic nervous system in nocturnal asthma *Br Med J (Clin Res Ed)* 1988; 296 :1427

66. Jartti T. Asthma, asthma medication and autonomic nervous system dysfunction. Clin Physiol. 2001 Mar;21(2):260-9. doi: 10.1046/j.1365-2281.2001.00323.x. PMID: 11318835.

67. Emin O, Esra G, Aysegül D, Ufuk E, Ayhan S, Rusen DM. Autonomic nervous system dysfunction and their relationship with disease severity in children with atopic asthma. Respir Physiol Neurobiol. 2012 Sep 30;183(3):206-10. doi: 10.1016/j.resp.2012.07.002. Epub 2012 Jul 9. PMID: 22789502.

68. Milagro J, Gil E, Lazaro J, Seppa VP, Malmberg LP, Pelkonen AS, Kotaniemi-Syrjanen A, Makela MJ, Viik J, Bailon R. Nocturnal Heart Rate Variability Spectrum Characterization in Preschool Children With Asthmatic Symptoms. IEEE J Biomed Health Inform. 2018 Sep;22(5):1332-1340. doi: 10.1109/JBHI.2017.2775059. Epub 2017 Nov 17. PMID: 29990113.

69. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol. 2004 Feb 1;93(3):381-5.

70. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. Thorax. 1998 Dec;53(12):1066-74.

71. Lehrer PM, Isenberg S, Hochron SM. Asthma and emotion: a review. J Asthma. 1993;30(1):5-21.

72. 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 Jul;14(1):32-8. doi: 10.1034/j.1399-3003.1999.14a08.x. PMID: 10489826.

73. Sanjuàs C, Alonso J, Sanchís J, Casan P, Broquetas JM, Ferrie PJ, Juniper EF, Antó JM. Cuestinario de calidad de vida en pacientes con asma: la versión española del Asthma Quality of Life Questionnaire [The quality-of-life questionnaire with asthma patients: the Spanish version of the Asthma Quality of Life Questionnaire]. Arch Bronconeumol. 1995 May;31(5):219-26. Spanish.

74. Barnes PJ. Neuroeffector mechanisms: the interface between inflammation and neuronal responses. J Allergy Clin Immunol. 1996 Nov;98(5 Pt 2):S73-81; discussion S81-3. PMID: 8939180.

75. Barnes PJ. Neural mechanisms in asthma. Br Med Bull. 1992 Jan;48(1):149-68. doi: 10.1093/oxfordjournals.bmb.a072531. PMID: 1352167.

76. Varon C, Lazaro J, Bolea J, Hernando A, Aguilo J, Gil E, Van Huffel S, Bailon R. Unconstrained Estimation of HRV Indices After Removing Respiratory Influences From Heart Rate. IEEE J Biomed Health Inform. 2019 Nov;23(6):2386-2397.

10. Anexo

10.1 Comunicaciones en congresos nacionales e internacionales.

10.1.1 Comunicación 1.

Lorena Soto Retes, Jordi Giner Donaire, Eder Mateus Medina, Javier Milagro Serrano, Eduardo Gil Herrando, Raquel Bailón Luesma, Carolina Varon, Vicente Plaza Moral. Papel del sistema nervioso autónomo en el asma grave. Arch Bronconeumol. 2018;54 Supl Congr 1:1-34 ISSN: 0300-2896

Estadísticos de muestras relacionadas

		Media	N	Desviación típ.	Error típ. de la media
Par 1	FEV1PREAZT	79,21	19	19,083	4,378
	FEV1POSTAZT	88,68	19	19,678	4,514

Correlaciones de muestras relacionadas

		N	Correlación	Sig.
Par 1	FEV1PREAZT y FEV1POSTAZT	19	,823	,000

Estadísticos de muestras relacionadas

		Media	N	Desviación típ.	Error típ. de la media
Par 1	ACTPRE	14,25	20	3,359	,894
	ACTPOST	20,15	20	3,407	,762

Prueba de muestras relacionadas

		gl	Sig. (bilateral)
Par 1	ACTPRE - ACTPOST	19	,000

Estadísticos de muestras relacionadas

		Media	N	Desviación típ.	Error típ. de la media
Par 1	EXACERBACIONESGRAVESANTESAZT	,57	21	,658	,144
	EXACERBACIONESGRAVESPOSTAZT	,05	21	,218	,048

Prueba de muestras relacionadas

		gl	Sig. (bilateral)
Par 1	EXACERBACIONESGRAVESANTESAZT - EXACERBACIONESGRAVESPOSTAZT	20	,000

Estadísticos de muestras relacionadas

		Media	N	Desviación típ.	Error típ. de la media
Par 1	EXACERBACIONESMODERADASANTESAZT	3,10	21	,768	,168
	EXACERBACIONESMODERADASPOSTAZT	1,00	21	,840	,207

Prueba de muestras relacionadas

		gl	Sig. (bilateral)
Par 1	EXACERBACIONESMODERADASANTESAZT - EXACERBACIONESMODERADASPOSTAZT	20	,000

Figura 1.

de exacerbaciones moderadas y graves en los pacientes (AGNC), especialmente en los de fenotipo neutrofílico. Se observa además un aumento en el FEV1 y en el número de puntos del ACT (media de 20 puntos post-AZT). Reseñar que no hubo diferencias en cuanto a efectos secundarios (perfil hepático, EKG, audición, síntomas GI o hipersecreción bronquial purulenta) ni en eosinofilia periférica.

PAPEL DEL SISTEMA NERVIOSO AUTÓNOMO EN EL ASMA GRAVE

L. Soto Retes[1], J. Giner Donaire[1], E. Mateus Medina[1], J. Milagro Serrano[2], E. Gil Herrando[2], R. Bailón Luesma[2], C. Varon[3] y V. Plaza Moral[1]

[1]Hospital de la Santa Creu i Sant Pau y Grupo Investigador de las Enfermedades Respiratorias Crónicas (GREC), del Instituto de Investigaciones Biosanitarias del Hospital Sant Pau (IIB-Sant Pau), Barcelona, España. [2]Grupo BSICoS, Instituto de Investigación en Ingeniería de Aragón (I3A) y Centro de Investigación Biomédica en Red (CIBER), Zaragoza, España. [3]Departamento de Ingeniería Eléctrica (ESAT), Centro de Sistemas Dinámicos, Procesado de Señal y Análisis de Datos STADIUS, KU Leuven, Lovania, Bélgica.

Introducción: El asma es una enfermedad inflamatoria crónica, sin embargo, la broncoconstricción no siempre se explica por la inflamación bronquial, en particular, en un subgrupo de pacientes con asma grave. El sistema nervioso autónomo (SNA) juega un papel importante en el asma, fundamentalmente a través del parasimpático (por la vía colinérgica), favoreciendo la broncoconstricción. La hipótesis del presente estudio fue que la activación del SNA parasimpático (SNP) estaría involucrada en la patogenia del asma grave y podría medirse a través de métodos no invasivos, como la variabilidad del ritmo cardiaco (VRC). Objetivos: determinar la participación del SNA en la patogenia del asma grave.

Material y métodos: Estudio prueba de concepto transversal de grupos paralelos. Se reclutó a 25 asmáticos de diferente gravedad clínica (8 con asma leve, 9 con asma grave controlada y 8 con asma grave no controlada) según criterios de la guía GEMA 4,2, junto con un grupo control de 6 personas sanas. La monitorización de la respuesta del SNA se realizó mediante un electrocardiograma (ECG), obteniendo la VRC. Para la evaluación de la VRC, se utilizó la técnica de procesado de señal Orthogonal Subspace Projection, que permite evaluar el acoplo cardiorespiratorio (relación entre la actividad cardíaca [AC] y la respiratoria [AR]), estableciendo el porcentaje de la señal de VRC que es explicada por la actividad respiratoria.

Resultados: No se observaron diferencias significativas entre la AC y la AR al comparar los diferentes grupos como se demuestra en la figura. Sin embargo, se constató una tendencia hacia un incremento de la potencia del componente respiratorio (y por lo tanto una reducción del componente cardíaco) en los asmáticos. A nivel fisiológico, el aumento del acoplo cardiorespiratorio en asmáticos podría estar reflejando una mayor sincronización de la actividad respiratoria y cardíaca.

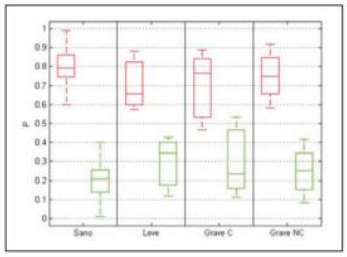

Figura 1. Porcentaje de la potencia (P) de la VRC debido a la actividad cardiaca (rojo) y respiratoria (verde) observada en los diferentes grupos.

Conclusiones: Si bien los resultados preliminares del estudio no parecen demostrar una participación del SNA en el asma y en el asma grave, se precisa un incremento de la muestra analizada para establecer conclusiones definitivas.

PERFIL DE SENSIBILIZACIÓN DE PACIENTES EN TRATAMIENTO CON OMALIZUMAB EN EL HOSPITAL DE JEREZ DE LA FRONTERA

J.M. Gálvez Lozano, C. Cabrera Galán, N.P. de la Cruz Castro, J.C. Rodríguez Fernández, Á. Cabeza Serrano, F. Pérez Grimaldi, J.D. García Jiménez y J.G. Soto Campos

Hospital Jerez de la Frontera, Jerez de la Frontera, Cádiz, España.

Introducción: Omalizumab es un anticuerpo monoclonal humanizado que se une a la inmunoglobulina E bloqueando su unión al receptor

10.1.2 Comunicación 2.

Soto Retes L, Giner Donaire J, Milagro Serrano J, Gil Herrando E, Bailón Luesma R, Plaza Moral V. Papel del sistema nervioso autónomo en el asma grave. J Investig Allergol Clin Immunol 2018; Vol. 28, Supplement 2: 127-303

Papel del sistema nervioso autónomo en el asma grave

Soto Retes L[1], Giner Donaire J[1], Milagro Serrano J[2], Gil Herrando E[2], Bailón Luesma R[2], Plaza Moral V[1]

[1] Servicio de Neumología y Alergia, Hospital de la Santa Creu i Sant Pau y del Instituto de Investigaciones Biosanitarias (IIB-Sant Pau), Barcelona
[2] Grupo BSICoS, Instituto de Investigación en Ingeniería de Aragón (I3A), IIS Aragón, Universidad de Zaragoza y Centro de Investigación Biomédica en Red (CIBER), Zaragoza

Objetivos/Introducción

El asma es una enfermedad inflamatoria crónica, sin embargo la broncoconstricción no siempre se explica por la inflamación, en particular en el asma grave. El sistema nervioso autónomo (SNA) juega un papel importante en el asma, fundamentalmente a través del parasimpático favoreciendo la broncoconstricción. Hipótesis: la activación del SNA parasimpático (SNP) estaría involucrada en la patogenia del asma grave y podría medirse a través de métodos no invasivos, como la variabilidad del ritmo cardiaco (VRC).

Objetivos: determinar la participación del SNA en la patogenia del asma grave.

Material y métodos

Estudio prueba de concepto transversal de grupos paralelos. Se reclutó a 10 pacientes con asma leve, 10 con asma grave controlada y 10 con asma grave no controlada, según criterios de la guía GEMA 4.2 y un grupo control de 10 sanos. La monitorización de la respuesta del SNA se realizó mediante un electrocardiograma (ECG), obteniendo la VRC. Para la evaluación de la VRC, se utilizó la técnica de procesado de señal *Orthogonal Subspace Projection*, que permite evaluar el acoplo cardiorespiratorio (relación entre la actividad cardíaca [AC] y la respiratoria [AR]), estableciendo el porcentaje de la señal de VRC que es explicada por la actividad respiratoria.

Resultados

No se observaron diferencias significativas entre la AC y la AR al comparar los diferentes grupos como se demuestra en la Figura. Sin embargo, se constató una tendencia hacia un incremento de la potencia del componente respiratorio (y por lo tanto una reducción del componente cardíaco) en los asmáticos. A nivel fisiológico, el aumento del acoplo cardiorespiratorio en asmáticos podría estar reflejando una mayor sincronización de la actividad respiratoria y cardíaca.

Conclusión

Si bien los resultados preliminares del estudio no parecen demostrar una participación del SNA en el asma y en el asma grave, se precisa un incremento de la muestra analizada para establecer conclusiones definitivas.

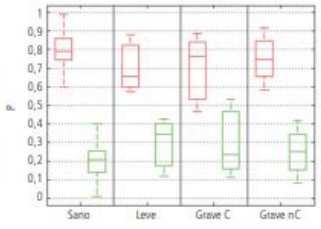

Figura. Porcentaje de la potencia (P) de la VRC debido a la actividad cardíaca (rojo) y respirat (verde) observada en los diferentes grupos.

10.1.3 Comunicación 3.

L. Soto-Retes; J. Milagro; A. Crespo-Lessmann; E. Curto; É. F. Mateus Medina; R. Bailón; E. Gil; P. Laguna; V. Plaza. The parasympathetic nervous system plays a key role in control and stress in patients with asthma (2024), Thematic poster session (TPS). Allergy, 79: 358-904. https://doi.org/10.1111/all.16300

Conclusion: These data suggest that Dynein adaptor Hook2 be elevated in plasma of patients with asthma, which raise the possibility that Dynein adaptor Hook2 be involved in asthma pathogenesis.
Conflicts of Interest: The authors did not specify any links of interest.

000086 | **A case of chronic cough induced by esophageal hypersensitivity**

Y. I. Koh[1,2]; J. E. Yu[2]; D. W. Sim[3,2]; S. Y. Park[3,2]
[1]*Chonnam National University Medical School, Chonnam National University Hospital, Gwangju, Korea, Republic of;* [2]*Chonnam National University Hospital, Gwangju, Korea, Republic of;* [3]*Chonnam National University Medical School, Gwangju, Korea, Republic of*
*Presenting author: Y. I. Koh

CASE REPORT

Background: It has been well known that chronic cough is caused by gastroesophageal reflux disease (GERD), although the mechanism is not clear. Recently, a new functional esophageal disorder named as esophageal hypersensitivity (EH) has been described, that is defined as the presence of reflux symptoms even in the absence of objective GERD evidences. It may be considered as hypersensitive reaction to normal reflux episodes. EH symptoms may be similar to GERD, indicating that EH may induce chronic cough, although not formally reported so far. Here, we describe a case of chronic cough induced by EH in an asthmatic patient.
Methods: 24-hour esophageal impedance and pH monitoring was performed to confirm the relationship between reflux episodes and cough.
Results: A woman visited with chest discomfort and chronic cough. Those symptoms had developed 3 years before, which was accompanied by globus and tickling sensation on throat. She had rhinitis symptoms. At first, methacholine bronchial provocation test was performed, resulting in PC_{20} of 11.3 mg/mL. Skin prick test was negative for all inhalant allergens. Asthma medications were started with a combination of inhaled corticosteroid and long-acting beta2 agonist together with leukotriene receptor antagonist. GERD medications were empirically taken. Two weeks later, visual analogue scale (VAS) for cough was decreased to 6. However, VAS was 8 after additional 4 weeks and 7 after additional 2 weeks, although further step-ups of asthma medications. Several antitussive drugs were tried. Medications for nonallergic rhinitis were added. However, VAS maintained between 4 and 6. Finally, 24-hour esophageal impedance and pH monitoring was done to diagnose GERD-induced chronic cough. However, acid exposure time was 0.2% (normal <4) and reflux episodes were 56 (normal <80). Nonetheless, for the relationship between reflux and cough, symptom index was 53.3% and symptom association probability was 97.6%. At this point, it might be recognized that most of cough may be induced by EH. After then, asthma medications were stepped down and reflux medications were increased. Two weeks later, VAS was decreased to 4, without
Conclusions: The case suggests that chronic cough may be induced by EH, based on 24-hour esophageal impedance and pH test. EH may be considered as a cause of chronic cough in a patient with reflux symptoms, even in the absence of objective GERD evidences. The mechanism should be investigated in the future.
Conflicts of Interest: The authors did not specify any links of interest.

000196 | **The parasympathetic nervous system plays a key role in control and stress in patients with asthma**

L. Soto-Retes[1]; J. Milagro[2]; A. Crespo-Lessmann[1]; E. Curto[1]; É. F. Matæus Medina[1]; R. Bailón[2]; E. Gil[2]; P. Laguna[2]; V. Plaza[1]
[1]*Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [2]*Biomedical Signal Interpretation and Computational Simulation (BSICoS) Group, Zaragoza, Spain*
*Presenting author: L. Soto-Retes

Background: Background: Patients with severe asthma often have uncontrolled disease and experience substantial emotional stress. The autonomic nervous system (ANS) plays an important role in asthma, mainly through the parasympathetic system (cholinergic pathway), which favours bronchoconstriction.
Objective: To determine the impact of the parasympathetic ANS (PANS) in asthma control and stress.
Method: Proof-of-concept cross-sectional study that analysed demographic and clinical variables reflecting asthma severity, asthma control, lung function, inflammation (cells from induced sputum), and stress-anxiety and quality of life according to validated questionnaires. Also conducted was a time-domain PANS analysis based on heart rate variability (HRV) statistics: the normal-to-normal (NN) interval (reflecting the time between consecutive beats), SDNN (standard deviation of the difference between consecutive NN intervals), SDSD and RMSSD (standard deviation and root mean square of successive NN differences, respectively), pNN50 (percentage of NN intervals greater than 50 ms), TP (total power, reflecting overall autonomic activity), and P_r (respiratory-related power).
Results: Included were 30 patients with asthma, grouped according to asthma control. The 10 patients with uncontrolled asthma compared to the patients with controlled asthma showed significant differences ($p < 0.05$) in SDNN (26.5 [8.2] vs 42.7 [29.7]), SDSD (14 [6.5] vs 24.1 [20]), 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 P_r (0.0003 [0.00025] vs 0.0007 [0.00060]). The 13 patients with stress compared to the patients without stress showed reduced values ($p < 0.05$) for SDNN (26.5 [7.9] vs 45.6 [31.3]), SDSD (13.4 [6.5] to 26.4 [20]), pNN50 (0.75 [1.4] to 7.12 [12.6]), TP (0.0005 [0.00048] to 0.0012 [0.0008]), and P_r (0.0003 [0.00027] to 0.0008 [0.00062]).
Conclusion: Our results suggest that PANS activity, depressed in patients with uncontrolled asthma and stress, could play a role in disease and stress control in patients with asthma.
Conflicts of Interest: The authors did not specify any links of interest.

10.2 Financiación.

- Proyectos Integrados de Investigación de Asma (PII Asma) de la Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Beca SEPAR PII Asma 2016.

  IP: Lorena Soto Retes

- Proyecto Zaragoza subvención BES-2015-073694 y los proyectos RTI2018-097723-B-I00, PID2019-104881RB-I00 y PID2019-105674RB-I00 del Ministerio de Economía y Competitividad. También por el Gobierno de Aragón a través del Grupo de Referencia BSICoS (T39-20R) y el proyecto LMP44-18, cofinanciado por FEDER 2014-2020 "Building Europe from Aragón", por el CIBER en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN) a través del Instituto de Salud Carlos III.

  IP: Javier Milagro