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Asthmatic subjects stratification using autonomic nervous system information

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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

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

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:

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

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:

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

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 $d_{\text{HR}}(t)$ derived from the QRS detection marks. Defining the resulting components as $d_{\text{HRM}}(t) = 1/T(t)$, and then $m(t)$ can be estimated as:

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

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 $\mathrm{m} = [m(0), m(1), \ldots, m(N-1)]^T$ (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:

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

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]:

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

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 ($\mathrm{m_r}$ and $\mathrm{m_{r^\perp}}$ respectively) can be obtained as:

$$\begin{aligned} \mathrm{m_r} &= \mathrm{Pm}, \\ \mathrm{m_{r^\perp}} &= \mathrm{m} - \mathrm{m_r}. \end{aligned} \quad (6)$$

The estimated spectra of both components, $\widehat{S}_\mathrm{r}(F)$ and $\widehat{S}_{\mathrm{r}^\perp}(F)$, 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, $\mathrm{P}_{\mathrm{r}^\perp}^{\mathrm{LF}}$, and the respiratory-related power, $\mathrm{P_r}$, were obtained as:

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

where $\overline{\mathrm{HR}}$ represents the mean HR expressed in Hz. Finally, the ratio $\mathrm{SB_u} = \mathrm{P}_{\mathrm{r}^\perp}^{\mathrm{LF}}/\mathrm{P_r}$ 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]:

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

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_i, randomly permute the observations of θ_i, 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 $d_{\mathrm{ij}} = \epsilon_{\mathrm{ij}} - \epsilon_\mathrm{i}$.
4. For each predictor variable, compute the mean and standard deviation ($\bar{d}_\mathrm{j}$ and σ_j) of the differences d_{ij}.
5. Finally, obtain the out-of-bag permuted predictor importance for each θ_i as $\bar{d}_\mathrm{j}/\sigma_\mathrm{j}$.

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-

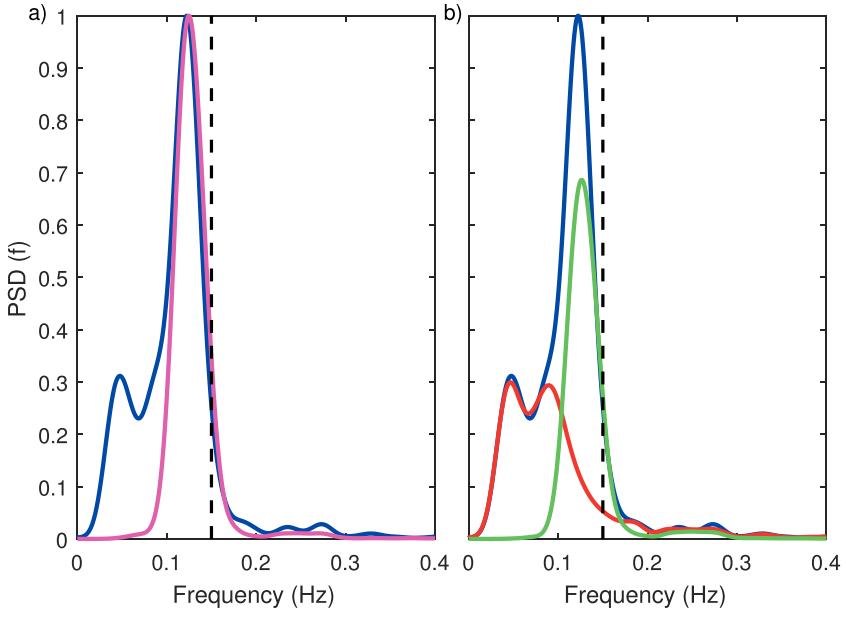

Fig. 1. (a) Normalized power spectral density of the modulating signal (blue) and the respiratory effort (pink) in a 5-min segment. Note that the respiratory activity lays below 0.15 Hz (black dashed line). (b) Orthogonal subspace projection was applied to separate the respiratory-related (green) and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

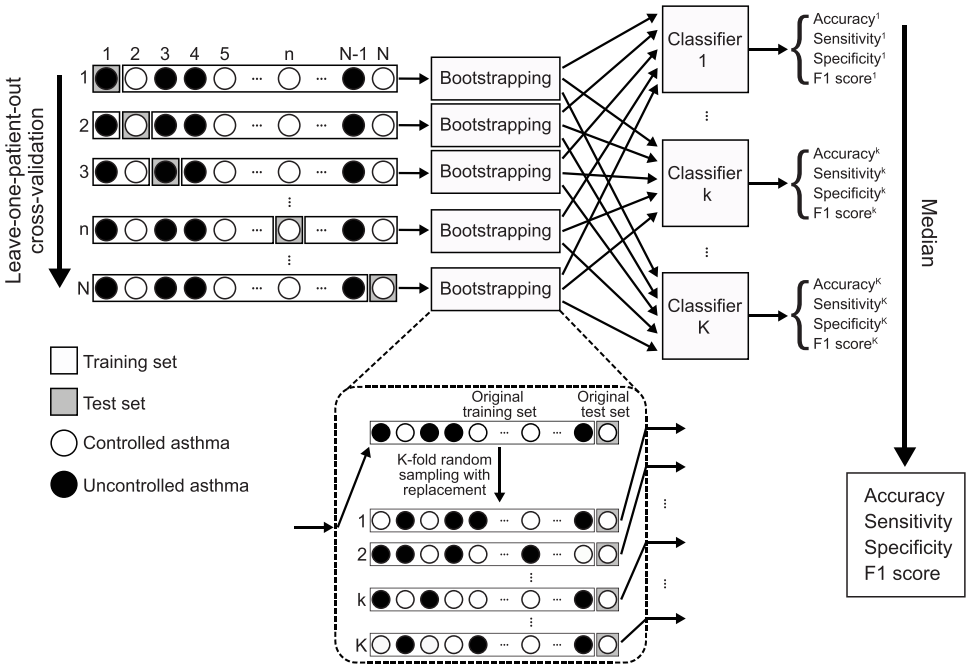

Fig. 2. A schematic of the combination of the leave-one-patient-out cross-validation with bootstrapping is displayed. White and black circles represent the subjects with controlled and uncontrolled asthma, respectively. After defining a training (white rectangle) and a test (gray square) set, bootstrapping 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 *k*NN 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, $P_{r^{\perp}}^{LF}$ 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]
$P_{r^{\perp}}^{LF}$ (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]

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 *k*NN 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 *k*NN classifier). On the other hand, the HRV features represented an added value in the *k*NN 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, $P_{r^{\perp}}^{LF}$ 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, $P_{r^\perp}^{LF}$}
	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}

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 ($P_{r^\perp}^{LF}$) 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, $P_{r^{\perp}}^{LF}$ 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 $P_{r^{\perp}}^{LF}$ 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.

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Declaration of Competing Interest

The authors report no declarations of interest.

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