Linear and Nonlinear Analysis of Base Lung Sound in Extrinsic Allergic Alveolitis Patients in Comparison to Healthy Subjects

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Keywords
Interstitial lung disease, base lung sound, linear and nonlinear analysis

Summary
Objective: Pulmonary disorders are frequently characterized by the presence of adventitious sounds added to the breathing or base lung sound (BLS). The aim of this work was to assess the features of BLS in extrinsic allergic alveolitis (EAA) patients in comparison to healthy subjects, applying linear and nonlinear analysis techniques.

Methods: We investigated the multichannel lung sounds on the posterior chest of 16 females, 8 healthy and 8 EAA patients, when breathing at 1.5 L/s. BLS linear features were obtained from the power spectral density (PSD) while nonlinear features were extracted by the concepts of irregularity and complexity, i.e., spectral, sample and multiscale entropy.

Results: The results demonstrated that spectral percentiles of BLS were lower in EAA patients than in healthy subjects but statistical significance (p < 0.05) was obtained only for expiration at the left apical and both basal regions. Also, the maximum amplitude of the PSD in patients reached statistical significance (p < 0.05) for the expiratory phase at basal regions. In the case of nonlinear techniques, significant lower values (p < 0.05) were obtained for EAA patients during both respiratory phases at left apical and both basal regions.

Conclusion: In conclusion, we found that BLS in chronic EAA patients is characterized by lower spectral percentiles, lower irregularity and lower complexity than in healthy subjects suggesting the feasibility of its clinical usefulness by screening its temporal alteration.

1. Introduction

Lung sounds (LS) are defined as those sounds “heard or detected over the chest wall or within the chest, including breath and adventitious sounds.” Furthermore, breathing or base lung sound (BLS) has been related to airflow in the respiratory tract and arising from breathing maneuvers, excluding adventitious sounds [1]. The adventitious sounds are those additional sounds superimposed on BLS and their presence usually indicates a pulmonary disorder [2]. Accordingly, clinical utility of LS to detect pulmonary pathologies has been based on the analysis of isolated adventitious sounds [3–5] or whole LS information [6–9]. However, the clinical value of BLS by itself has been less clearly established and to assume it as normal is a common practice, even during overt lung pathologies.

A pioneer work on BLS analysis was reported by Urquhart et al in 1981 [10]. The authors proposed that structural changes in the airways and lung parenchyma, given by pulmonary disorders as asbestosis, cryptogenic fibrosing alveolitis and edema, reshape the power spectral density (PSD) of the LS; as the frequency content of adventitious sounds (crackles) was assumed beyond 400 Hz and PSD changes were detected below 400 Hz, the authors suggested that alteration of BLS explained the findings. Recently, using multichannel LS recordings combined with LS features extracted by an autoregressive model, Charleston-Villalobos et al. [9] evaluated the feasibility of a classification scheme to discriminate between normal subjects and patients suffering interstitial pneumonia. The authors found an acceptable performance (~92%) to detect patients even though crackles were absent on extensive areas on the posterior chest. Therefore, they suggested that BLS may be contain valuable clinical information to discriminate normal and abnormal sounds; however, BLS information was not studied independently as the aim of the work was to perform a discriminating task using the whole LS.

The extraction of LS features for discrimination purposes is usually carried out...
by linear techniques via the spectral analysis of the LS time series. However, recently the analysis of respiratory sounds by nonlinear techniques has been proposed [11–13]; furthermore, Faistauer et al. in 2005 [14] by a mathematical model to reproduce the general spectral characteristics of normal lung sounds found an affine behavior of LS as a direct consequence of the fractal properties of the bronchial tree and Ahlstrom et al. in 2006 [15] by surrogate tests for nonlinearity showed that LS in healthy subjects behave as nonlinear process. Up to now, the nonlinear LS analysis has limited scope since only fractal analysis has been applied to detect and classify crackles using LS [11, 12, 16, 17]. As a result, the possible value of nonlinear analysis of BLS is an open research field; in interstitial lung diseases it is known that crackles could be absent at the beginning of the inflammation process. Consequently, this study was focused on the analysis of isolated BLS and we hypothesize that BLS features are modified by structural lung alterations and it may be used to discriminate between healthy subjects and EAA patients. To corroborate our hypothesis we applied the classical linear techniques based on features extracted from the BLS power spectral density as well as entropy-based algorithms to get the nonlinear behavior of BLS. In the nonlinear framework, it was expected that BLS of EAA patients was characterized by lower irregularity and reduced complexity, when compared with the BLS of healthy subjects. We encourage the nonlinear analysis of BLS since up to the knowledge of the authors the concepts of irregularity and complexity have not been applied to BLS. So, the aim of the study is twofold: to evidence that BLS suffers alterations that could be used in the diagnosis of pulmonary diseases, and provide one step forward concerning the analysis of acoustic information by nonlinear techniques.

2. Materials and Methods

2.1 Subjects

In this study 16 female subjects were enrolled, 8 healthy non-smokers (control group) and 8 with clinical diagnosis of diffuse interstitial pneumonia (patients group). The health status of the control group was determined through clinical history, spirometry, ECG and X-ray. The interstitial pneumonia was diagnosed by clinical history, X-ray, pulmonary function tests, challenge tests, bronchoalveolar lavage and the structural condition of the lung was interpreted by two pneumologist – radiologist experts, by HRCT images. It is worthy to note that the experts were kept unaware of the acoustical studies. In all the patients, auscultation was performed by pneumologists confirming lung alteration by the presence of crackles. All subjects, residents of Mexico City (2,240 meters over sea level), gave a signed informed consent according to the principles of the Declaration of Helsinki and this study was approved by ethical review board of the National Institute of Respiratory Diseases.

Table 1 depicts the general characteristics of the healthy subjects and interstitial patients including anthropometric and pulmonary function test results. There were not significant differences between healthy subjects and patients for age and height (p > 0.05) but patients had lower weight (p < 0.05). Furthermore, statistical differences (p < 0.05) were also found in the pulmonary function test where patients showed hypoxemia, decreased DLCO, and restrictive spirometric pattern. The bronchoalveolar lavage and immunologic studies, performed few days after the acoustical study, confirmed the final diagnosis of chronic extrinsic allergic alveolitis (EAA).

2.2 Multichannel Acoustic Signals Recording

The volunteers were seated in a sound proof room wearing a nose clip and breathing at 1.5 L/s as close as possible while LS and airflow signals were recorded during 15 seconds. The multichannel LS acquisition was achieved by a 5 × 5 sensor array on the posterior chest, but in the present study we analyzed recordings from only four thoracic locations labeled as PLC1, PRC1, PLC4 and PRC4 (Figure 1) according to the sensor nomenclature proposed by Charleston-Villalobos et al. [18]. The selected sensors were positioned on both hemithorax, two on the left and two on the right, along the back projection from the mid-clavicular line on the apical (C1) and the basal regions (C4). The acoustic sensors were made up by inserting subminiature electret microphones (BT-1834; Knowles, IL, USA) in plastic bells, and they were tested in an anechoic box to assure a flat frequency response (± 3 dB) between

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 8)</th>
<th>EAA (n = 8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.4 ± 6.7</td>
<td>65.4 ± 6.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.3 ± 14.4</td>
<td>61.9 ± 10.9</td>
<td>0.03*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.0 ± 8.0</td>
<td>156 ± 10.0</td>
<td>0.3</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>94.7 ± 7.2</td>
<td>48.3 ± 18.1</td>
<td>0.0001*</td>
</tr>
<tr>
<td>FEV (%)</td>
<td>88.9 ± 8.5</td>
<td>52.7 ± 16.4</td>
<td>0.0001*</td>
</tr>
<tr>
<td>FEV/FVC (%)</td>
<td>85.3 ± 3.8</td>
<td>89.3 ± 5.7</td>
<td>0.6</td>
</tr>
<tr>
<td>RV (%)</td>
<td>89.6 ± 7.2</td>
<td>80.7 ± 12.5</td>
<td>0.4</td>
</tr>
<tr>
<td>FEF 25–75 (%)</td>
<td>84.2 ± 5.2</td>
<td>63.0 ± 15.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>95.4 ± 4.1</td>
<td>63.3 ± 13.3</td>
<td>0.0001*</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>72.2 ± 3.5</td>
<td>44.1 ± 9.4</td>
<td>0.0001*</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>94.5 ± 0.3</td>
<td>77.2 ± 7.6</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

The values are reported as mean ± standard deviation. EAA = extrinsic allergic alveolitis; FVC = forced vital capacity; FEV = forced expiratory volume; RV = residual volume; FEF = forced expiratory flow; DLCO = carbon monoxide pulmonary diffusion; PaO₂ = arterial partial pressure of oxygen; SaO₂ = arterial saturation of oxygen. * Statistically significant differences at p ≤ 0.05
0.5 and 3.0 kHz. Regarding the airflow, it was measured with a linear pneumotachometer (PNT-3813; Hans Rudolph Inc; KS, USA), attached to a differential pressure transducer with a range of ±2 cmH₂O (MP45-14-871; Validyne Engineering Corp; CA, USA) and a demodulator (CD19A; Validyne Engineering Corp; CA, USA). The pneumotachometer was calibrated with a rotameter, testing the response at different flows to guarantee a linear behavior. During the measurement, the airflow signal was displayed on a monitor in front of the subjects to provide them feedback to control the breathing maneuver until airflow target of 1.5 L/s was reached. The airflow and LS signals were digitized by a 12-bit A/D converter (ADC-6071; National Instruments; TX, USA) and sampled at 10 kHz to assure that digitization of data accomplished the recommendations of the ERS Task Force Report [19].

The acoustical study in patients was done before they underwent invasive procedures and initiated the corresponding therapeutic management; also, the pipeline for supplemental oxygen was removed.

2.3 BLS Segments Identification

For isolating BLS information, first LS signals were band-pass filtered between 75 and 1,000 Hz to minimize noise generated by mechanical activity of the heart and muscles or by skin friction. Afterward, filtered LS signals from both groups were displayed and visually analyzed to identify BLS segments avoiding adventitious sounds as crackles, wheezes, and squawks as well as artifacts. The crackles were identified according to the initial deflection width, duration of the first two cycles, and the largest deflection width as proposed by other authors [2, 20]. Wheezes were recognized whenever a continuous sinusoidal pattern higher than 100 milliseconds long was observed, whereas squawks were identified as those sinusoidal sounds with duration between 20 and 50 milliseconds and starting with a crackle sound [21].

Based on visual analysis BLS segments of 500 samples (50 milliseconds) were selected from both inspiratory and expiratory phases, assuring airflow of 1.5 ± 0.2 L/s. Due to the sampling frequency and acquisition time used in the study on average 6 respiratory cycles were acquired from each subject and only one segment of BLS was selected from each inspiratory and expiratory phases; consequently, the database includes around 384 inspiratory/expiratory BLS segments for healthy subjects and other 384 BLS segments for patients. Also, our previous studies pointed out low intrasubject variability in lungs sounds intensities in the course of respiratory cycles as the airflow is kept constant; to get a more reliable features of BLS of each subject we used the six available respiratory cycles. Furthermore, according to previous studies the airflow value impacts the magnitude of the LS signals and the authors have been used three airflows 1, 1.5 and 2 L/s. Based on our experience, 1 L/s produces low amplitude LS while 2 L/s is difficult to achieve for patients; consequently, 1.5 L/s has been used to acquire reliable acoustic measurements with the advantage that the majority of the patients has no problem to perform the breathing maneuver.

2.4 Linear and Nonlinear BLS Processing

2.4.1 Linear BLS Analysis

The BLS segments were modeled using their second order statistical information by univariate autoregressive model. The shift invariant linear all-pole filter, excited by white noise, is represented by the difference equation:

$$x[n] = - a_1 x[n-1] - a_2 x[n-2] - ... - a_q x[n-q] + v[n]$$  \hspace{1cm} (1)

where \(x[n]\), the actual sample of the BLS time series, is modeled by a linear combination of its \(q\) previous samples plus a white noise signal \(v[n]\) that is not correlated with \(x[n]\). The order of the model, denoted by \(q\) and fixed at six \([9]\), was determined by the Akaike information criterion while the set of the model coefficients, \(a_k, k = 1,...,q\), was calculated by the Burg’s method. Based on the linear modeling, the PSD of BLS segments, denoted as \(S_x(\omega)\), was estimated by:

$$\hat{S}_x(\omega) = \frac{\sigma_v^2}{1 + \sum_{k=0}^{q} d_k e^{-j \omega k}}$$ \hspace{1cm} (2)

where \(\sigma_v^2\) stands for the variance of the white noise signal and \(\omega\) corresponds to the digital frequency. Afterward, the percentile frequencies corresponding to the 25% \((P25)\), 50% \((P50)\), and 75% \((P75)\) of the total area under the PSD curve were obtained. Furthermore, the maximum amplitude \((MA)\) of the PSD and its corresponding frequency \((FMA)\) were also extracted.

2.4.2 Nonlinear BLS Analysis

There is a consensus that biological systems could show nonlinear dynamics, i.e.,
Table 3 Linear parameters of BLS from healthy subjects (control, n = 8) and patients with extrinsic allergic alveolitis (EAA, n = 8) during inspiratory flow around 1.5 L/s

<table>
<thead>
<tr>
<th>Sensor location</th>
<th>MA a.u.</th>
<th>FMA Hz</th>
<th>F25 Hz</th>
<th>F50 Hz</th>
<th>F75 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.85 ± 0.89</td>
<td>151.7 ± 15.5</td>
<td>168.0 ± 16.6</td>
<td>189.7 ± 15.6</td>
<td>202.5 ± 22.3</td>
</tr>
<tr>
<td>EAA</td>
<td>1.50 ± 1.32</td>
<td>191.7 ± 20.5</td>
<td>178.0 ± 21.8</td>
<td>169.1 ± 16.6</td>
<td>178.9 ± 15.6</td>
</tr>
<tr>
<td>Control</td>
<td>1.72 ± 1.50</td>
<td>197.1 ± 25.6</td>
<td>186.5 ± 25.4</td>
<td>171.6 ± 14.5</td>
<td>194.6 ± 25.6</td>
</tr>
<tr>
<td>EAA</td>
<td>2.33 ± 3.14</td>
<td>186.5 ± 14.5</td>
<td>184.3 ± 25.4</td>
<td>171.6 ± 14.5</td>
<td>194.6 ± 25.6</td>
</tr>
<tr>
<td>Control</td>
<td>1.25 ± 1.43</td>
<td>189.5 ± 12.9</td>
<td>188.4 ± 24.8</td>
<td>173.6 ± 13.9</td>
<td>176.1 ± 23.4</td>
</tr>
<tr>
<td>EAA</td>
<td>2.95 ± 3.75</td>
<td>189.5 ± 12.9</td>
<td>188.4 ± 24.8</td>
<td>173.6 ± 13.9</td>
<td>176.1 ± 23.4</td>
</tr>
<tr>
<td>Control</td>
<td>0.59 ± 0.53</td>
<td>189.7 ± 23.5</td>
<td>183.0 ± 21.2</td>
<td>175.2 ± 16.3</td>
<td>200.7 ± 16.3</td>
</tr>
<tr>
<td>EAA</td>
<td>2.23 ± 2.71</td>
<td>189.7 ± 23.5</td>
<td>183.0 ± 21.2</td>
<td>175.2 ± 16.3</td>
<td>200.7 ± 16.3</td>
</tr>
</tbody>
</table>

The values are reported as mean ± standard deviation. MA = PSD’s maximum amplitude in arbitrary units; FMA = frequency of maximum amplitude; Fxx = frequency at the xx percentile of PSD. Sensors location reported in Figure 1.
*Statistically significant differences (p < 0.05) when compared with control values.

Table 3 Linear parameters of BLS from healthy subjects (control, n = 8) and patients with extrinsic allergic alveolitis (EAA, n = 8) during expiratory flow around 1.5 L/s

<table>
<thead>
<tr>
<th>Sensor position</th>
<th>MA a.u.</th>
<th>FMA Hz</th>
<th>F25 Hz</th>
<th>F50 Hz</th>
<th>F75 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.25 ± 0.43</td>
<td>316.3 ± 177.7</td>
<td>189.2 ± 39.2</td>
<td>190.5 ± 23.37</td>
<td>157.4 ± 20.5* (p = 0.010)</td>
</tr>
<tr>
<td>EAA</td>
<td>0.62 ± 0.84</td>
<td>316.3 ± 177.7</td>
<td>189.2 ± 39.2</td>
<td>190.5 ± 23.37</td>
<td>157.4 ± 20.5* (p = 0.010)</td>
</tr>
<tr>
<td>Control</td>
<td>1.04 ± 2.07</td>
<td>212.0 ± 32.9</td>
<td>182.4 ± 21.1</td>
<td>182.7 ± 18.6</td>
<td>167.3 ± 21.2</td>
</tr>
<tr>
<td>EAA</td>
<td>1.72 ± 2.05</td>
<td>212.0 ± 32.9</td>
<td>182.4 ± 21.1</td>
<td>182.7 ± 18.6</td>
<td>167.3 ± 21.2</td>
</tr>
<tr>
<td>Control</td>
<td>0.16 ± 0.24</td>
<td>535.3 ± 242.0</td>
<td>177.8 ± 50.8* (p = 0.001)</td>
<td>202.7 ± 36.9</td>
<td>146.3 ± 27.8* (p = 0.004)</td>
</tr>
<tr>
<td>EAA</td>
<td>2.30 ± 4.91 (p = 0.048)</td>
<td>535.3 ± 242.0</td>
<td>177.8 ± 50.8* (p = 0.001)</td>
<td>202.7 ± 36.9</td>
<td>146.3 ± 27.8* (p = 0.004)</td>
</tr>
<tr>
<td>Control</td>
<td>0.28 ± 0.34</td>
<td>386.3 ± 243.6</td>
<td>185.2 ± 18.0* (p = 0.024)</td>
<td>201.0 ± 31.2</td>
<td>166.6 ± 17.7* (p = 0.015)</td>
</tr>
<tr>
<td>EAA</td>
<td>0.98 ± 1.45</td>
<td>386.3 ± 243.6</td>
<td>185.2 ± 18.0* (p = 0.024)</td>
<td>201.0 ± 31.2</td>
<td>166.6 ± 17.7* (p = 0.015)</td>
</tr>
</tbody>
</table>

The values are reported as mean ± standard deviation. MA = PSD’s maximum amplitude in arbitrary units; FMA = frequency of maximum amplitude; Fxx = frequency at the xx percentile of PSD. Sensors location reported in Figure 1.
*Statistically significant differences (p < 0.05) when compared with control values.

Biological systems are formed by subsystems that do not follow the superposition principle; furthermore, these subsystems interact in a complex way, spatial and temporarily [22, 23]. Consequently, time series associated to biological systems should be processed by nonlinear techniques to get the underlying system dynamics. One of the relevant concepts in the field of nonlinear analysis is the irregularity of a signal measured by entropy-based algorithms; entropy increases with the degree of disorder in the signal. Recently, Costa et al. proposed to measure the “structural richness” of a signal and associate it with its complexity since irregularity may produce misleading results; for instance, white noise has maximum entropy but the signal is not structural complex [22]. In this study we use sample entropy and spectral entropy to measure irregularity to overcome the difficulties of the approximate entropy, which is a biased estimator that strongly depends on the record length and lacks of consistency for different values of r and m [24], and multiscale entropy approach to measure complexity [22]. In the case of the respiratory system, the bronchial tree’s geometry can be assumed as fractal as stated by Ahlstrom et al. in 2006 [15], and then it is
plausible that the interaction of the airflow with airways, genesis of the LS, generates nonlinear process that could explain better the underlying chaotic dynamic behavior.

2.4.2.1 Sample Entropy (SampE)

Richman and Moorman in 2000 [24] proposed an irregularity measurement called sample entropy as:

\[ \text{SampE}(m, r, N) = - \ln \frac{U^{m+1}(r)}{U^m(r)} \]  

(3)

where \( m \) corresponds to the size of pattern vectors in the time series, \( r \) indicates a tolerance when one is looking for pattern vectors, \( N \) is the length of the original time series and \( U^m(r) \) provides the probability of occurrence of pattern vectors. For instance, for a given time series \( u[1], \ldots, u[N] \), for \( m = 2 \) and a positive real value of \( r \), it is necessary to look for data points that match patterns constructed with two and three components. In a first step, the number of data points that match (occurrences) the pattern vectors constructed as \( \tilde{u}_2(1) = \{u[1], u[2]\} \) and \( \tilde{u}_3(1) = \{u[1], u[2], u[3]\} \) is obtained; a match is defining if the maximum absolute difference between data points and pattern vectors is less than or equal to \( r \). In subsequent steps, the occurrences are added to the previous ones by repeating the former procedure and redefining the pattern vectors as \( \tilde{u}_2(i) = \{u[i], u[i + 1]\} \) and \( \tilde{u}_3(i) = \{u[i], u[i + 1], u[i + 2]\} \) with \( 2 \leq i \leq N - m \). Consequently, the irregularity of the time series is calculated using the probability of occurrence of pattern vectors with \( m \) and \( m+1 \) components, i.e., \( U^m(r) \) and \( U^{m+1}(r) \). In this study, the values \( m = 2 \) and \( r = \{0.1, 0.15, 0.2\} \) were used to get the sample entropy of the BLS segments. In order to be able to compare results among different time series, the BLS segments were normalized to have unitary variance. Since in this study \( r = 0.15 \) provided more evident differences between healthy and ill subjects, SampE results are reported only under such condition.

2.4.2.2 Spectral Entropy (SpecE)

In contrast to the sample entropy, information measure obtained in the time domain, the spectral entropy provides the irregularity of the time series in the frequency domain. For BLS, their relative power spectral density can be considered as a probability

<table>
<thead>
<tr>
<th>Sensor location</th>
<th>SampE ((m = 2, r = 0.15))</th>
<th>SpecE ((k = 1.75))</th>
<th>MSE ((m = 2, r = 0.15))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>EAA</td>
<td>Control</td>
</tr>
<tr>
<td>PLC1</td>
<td>0.59 ± 0.03</td>
<td>0.54 ± 0.03* ((p = 0.0023))</td>
<td>2.76 ± 0.25</td>
</tr>
<tr>
<td>PRC1</td>
<td>0.56 ± 0.04</td>
<td>0.54 ± 0.03</td>
<td>2.60 ± 0.24</td>
</tr>
<tr>
<td>PLC4</td>
<td>0.60 ± 0.03</td>
<td>0.52 ± 0.05* ((p = 0.0044))</td>
<td>2.90 ± 0.49</td>
</tr>
<tr>
<td>PRC4</td>
<td>0.61 ± 0.04</td>
<td>0.56 ± 0.04* ((p = 0.037))</td>
<td>3.20 ± 0.28</td>
</tr>
</tbody>
</table>

The values are reported as mean ± standard deviation. SampE = Sample entropy; SpecE = spectral entropy; MSE = multiscale entropy. Sensors location reported in Figure 1. *Statistically significant differences \((p < 0.05)\) when compared with control values.

<table>
<thead>
<tr>
<th>Sensor location</th>
<th>SampE ((m = 2, r = 0.15))</th>
<th>SpecE ((k = 1.75))</th>
<th>MSE ((m = 2, r = 0.15))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>EAA</td>
<td>Control</td>
</tr>
<tr>
<td>PLC1</td>
<td>0.68 ± 0.05</td>
<td>0.57 ± 0.05* ((p = 0.0016))</td>
<td>3.42 ± 0.43</td>
</tr>
<tr>
<td>PRC1</td>
<td>0.62 ± 0.05</td>
<td>0.57 ± 0.05</td>
<td>3.05 ± 0.48</td>
</tr>
<tr>
<td>PLC4</td>
<td>0.72 ± 0.04</td>
<td>0.58 ± 0.07* ((p = 0.00026))</td>
<td>3.66 ± 0.34</td>
</tr>
<tr>
<td>PRC4</td>
<td>0.69 ± 0.06</td>
<td>0.62 ± 0.03* ((p = 0.011))</td>
<td>3.54 ± 0.31</td>
</tr>
</tbody>
</table>

The values are reported as mean ± standard deviation. SampE = Sample entropy; SpecE = Spectral entropy; MSE = Multiscale Entropy. Sensors location reported in Figure 1. *Statistically significant differences \((p < 0.05)\) when compared with control values.
Statistically significant differences ($p < 0.05$) when compared with control values. The values are reported as mean ± standard deviation. SampE = Sample entropy; SpecE = spectral entropy; MSE = multiscale entropy. Sensors location reported in Figure 1.

Table 4 Nonlinear parameters for BLS from healthy subjects (Control, $n = 8$) and patients with extrinsic allergic alveolitis (EAA, $n = 8$) during inspiratory flows around 1.5 L/s

Table 5 Nonlinear parameters for BLS from healthy subjects (control, $n = 8$) and patients with extrinsic allergic alveolitis (EAA, $n = 8$) during expiration

distribution function and the spectral entropy can be calculated as:

$$SpecE(k) = \frac{1}{1-k} \ln \left[ \sum_{j} (P_{j})^{k} \right] \quad (4)$$

where $P_j = \frac{P_j}{\sum_j P_j}$ is the relative PSD, $k \in R$ and $P_j$ is the power spectral value at a certain frequency [25]. The parameter $k$ is used to make SpecE more or less sensitive to the shape of the power spectral density of the data, with higher $k$ parameter SpecE depends more on the probabilities of the more probable values and less on the more improbable ones. A low SpecE value implies a concentrated spectrum around a single frequency while a high SpecE implies a broad spectral content, i.e., the time series is more irregular. In this work, the BLS’s power spectral density (BLS-PSD) was calculated using a sixth order autoregressive model, whereas the SpecE was obtained using different values of $k$ in the set {1.25, 1.5, 1.75, and 2.0} according to other studies reported in the literature [25]. Since SpecE with $k = 1.75$ better emphasizes the statistical differences between healthy subjects and patients the SpecE results are only given for $k = 1.75$.

2.4.2.3 Multiscale Entropy (MSE)
The concept of complexity of a time series stated by the multiscale entropy is based on the computation of the sample entropy in different time scales. For the BLS analysis, the $N$-length selected segments denoted by $\{x_i, ..., x_{N}\}$ were divided in non-overlapping temporal windows including $r$ samples (scale) and afterwards a time average is obtained from each window. Consequently, a new time series $y^{(r)}$ with less temporal resolution than the original signal was computed according to:

$$y_{j}^{(r)} = \frac{1}{r} \sum_{i=(j-1)r+1}^{jr} x_{i}, \quad 1 \leq j \leq N/r, \quad (5)$$

where the length of $y^{(r)}$ is equal to $N/r$. The multiscale entropy was calculated getting the sample entropy of the original BLS time series and from each of the sequences $y^{(r)}$. The former procedure generates a curve, i.e., sample entropy value versus the scale.
Figure 2  Multiscale entropy curves for healthy group (rhombus) and EAA group (square) for the inspiratory phase with error bars indicating standard deviation around the mean. (a) and (b) correspond to the lung upper region while (c) and (d) to the lung lower region. The symbol * denotes statistically significant differences (p < 0.05) when compared with control values.

The BLS complexity measure was evaluated according to the following rules:

a) If the BLS complexity curve of one time series is above another, for the majority of the scales, then the first time series is considered more complex.

b) If the complexity curve decreases monotonically as the scale increases then the original time series contains relevant information only in the finest temporal scale.

The MSE for the selected BLS segments was computed by the method described by Costa et al. [22], with vector size fixed at \( m = 2.0 \), tolerance window \( r \) in the set \( \{0.1, 0.15, 0.2\} \), and \( \tau \) from 1 to 4. In the present study, the results by MSE are reported just for \( r = 0.15 \) as it provided the best way to discriminate between BLS from healthy and ill subjects.

2.5 Statistical Analysis

For linear and nonlinear acoustic features normal distribution was assessed by Kolmogorov-Smirnov test, and logarithmic correction was performed when data did not achieve normality. After assuring normality, statistical differences were assessed between the control group and patients by the Aspin-Welch unequal-variance test for independent samples. Also, multiple comparisons by three-way repeated measures ANOVA (factors: health status, sensors position from left to right, and from upper to lower regions) were performed. In all cases, a value of \( p \) less than 0.05 was considered as indicative of statistical significant difference.

3. Results

3.1. Linear Feature Analysis

▶ Table 2 and ▶ Table 3 show the spectral features values for the inspiratory and expiratory segments of BLS, respectively. The
MA values of the BLS-PSD for control and EAA groups were bigger in the inspiratory than in expiratory phase; however, both respiratory phases showed large MA dispersion. Furthermore, MA for EAA group tended to show higher values than for healthy subjects, but statistical significant difference (p < 0.05) was found only for PRC4 in the inspiratory phase and for PRC4 and PLC4 in the expiratory phase. Also, in both groups, MA at the apical regions (PLC1 versus PRC1) tended to be higher in the right hemithorax, but at the basal regions (PLC4 versus PRC4) the MA value was predominantly higher at the left hemithorax; in any case, there were no statistical differences (p > 0.05) between right and left hemithorax.

Regarding FMA, for the inspiratory phase none statistical differences were found (Table 2) while in the case of the expiratory phase (see table 3), the mean values in the healthy group were higher (>212 Hz) with larger dispersion (~200 Hz) than in EAA group, at PLC1, PLC4 and PRC4 positions; however, significant differences were found for PLC4 (p < 0.05) and PRC4 (p < 0.05).

Percentile frequencies values F25, F50 and F75 were similar (p > 0.05) for control and EAA groups in the inspiratory phase (Table 2). Conversely, in the expiratory phase the EAA group had lower frequencies than the control group and F25, F50, and F75 gave statistical differences (p < 0.05) for PLC1, PLC4 and PRC4 (Table 3). Particularly, F75 had an evident increment in its dispersion, but anyway this spectral feature provided statistical difference (Table 3).

### 3.3 Nonlinear Features Analysis

The SampE, SpecE and MSE features values in healthy subjects and EAA group for the inspiratory and expiratory phases are listed in Table 4 and Table 5, respectively. For the case of SampE, m was fixed to 2 and

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Figure 3  Multiscale entropy curves for healthy group (rhombus) and EAA group (square) for the expiratory phase with error bars indicating standard deviation around the mean. (a) and (b) correspond to the lung upper region while (c) and (d) to the lung lower region. The symbol * denotes statistically significant differences (p < 0.05) when compared with control values.

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three values of $r$ were explored 0.1, 0.15, and 0.2. In general, the results are consistent in the sense that the same conclusion can be reached but with $r = 0.15$ the lower $p$-values were obtained. SampE produced statistical significant differences ($p < 0.05$) for sensors PLC1, PLC4 and PRC4 in both respiratory phases, with lower SampE values characterizing the EAA group. On the other hand, by SpeE significant statistical difference between control and EAA groups was only achieved at the PRC4 position in the inspiratory phase; conversely, in the expiratory phase all the sensors were significantly different ($p < 0.5$) except for PRC1. Finally, the MSE values in the inspiratory phase, with same parameters as SampE, indicate significant statistical differences ($p < 0.5$) for PLC1 and PLC4, at four scales, and for PRC4 at three scales; only the sensor PRC1 did not show differences in any scale. As can be seen in Figure 2, all the healthy subjects’ MSE curves are above EAA group’s curves but PRC1, meaning that the respiratory system for healthy subjects is more complex than the system for the EAA group. It is worthy to note that the bigger separation between MSE curves was obtained at sensor PLC4.

For the expiratory phase, the MSE curves are summarized in Figure 3, confirming significant statistical differences for all the sensors except PRC1.

### 4. Discussion and Conclusions

In contrast to the common approach of acoustic evaluation of interstitial lung diseases through adventitious sounds, the present study was based on the hypothesis that BLS has relevant information that could be revealed by signal processing techniques. To address this perspective, linear and nonlinear processing techniques were applied to BLS segments from healthy subjects and interstitial patients breathing around 1.5 L/s. Given that EAA is the interstitial lung disease most commonly seen at the National Institute of Respiratory Diseases with a female to male ratio of 9 : 1 [26], this study included only female patients with this pathology.

The main finding of our study discloses a significant discrimination of BLS between healthy subjects and patients with EAA by the two types of explored analysis techniques, linear and nonlinear. The linear technique highlighted lower percentile frequencies for EAA group mainly during the expiratory phase, whereas the nonlinear techniques provided significant lower values for spectral entropy, sample entropy and multiscale entropy in EAA group for both respiratory phases.

Traditionally, LS abnormality by auscultation has been established through the detection of adventitious sounds [6, 7]. In the case of interstitial lung diseases, it is known that crackles could be absent or be of coarse type at the beginning of the inflammation process. When fibrosis emerges the crackles usually increase in number, become of fine type, and predominate in the inspiratory phase. In the present study it was assumed that BLS could convey information about lung abnormality independently of the presence of crackles, since the lung structure is altered in interstitial lung diseases due to the inflammatory and fibrotic processes. Our results sustain this point of view and suggest that quantitative BLS analysis could be useful for detecting pulmonary disorders even when crackles are not perceptible. This observation becomes important if we take into account that during the process of the disease many areas of the lungs seem normal at clinical auscultation.

By spectral analysis, other authors have explored LS in patients with interstitial lung diseases [8, 10, 27]. Ono et al. in 2009 [8] reported results in inspiratory LS (including adventitious sounds) using a single microphone on the lower posterior thoracic region and based on percentile frequencies. Without controlling airflow, the authors found that F50 and F75 were higher in interstitial patients with a great variability for the ill group, but the spectrum of patients without fine crackles was similar to that of the healthy group. The authors considered that the differences between normal and ill subjects were due to the presence of crackles and alteration in sound transmission. In addition, they indicated that for detecting interstitial pneumonia condition, the usefulness of these frequencies was inferior to auscultation. Similar arguments, based on the effect of crackles embedded into BLS, were proposed by Gavriely and Cugell in 1995 [27] who also observed higher percentile frequencies from only one subject suffering lung fibrosis. It is worthy to note that our results on spectral values of isolated BLS in EAA group were completely opposite as percentile frequencies were lower, but we remark that crackles were not included and specifically we explored patients with EAA.

Urquhart et al. [10] assumed to work with BLS and found that spectral density features could differentiate between healthy subjects and the interstitial group. The authors used a single microphone on the lower region during inspiration without controlling airflow, and they considered that crackles do not have spectral components in the band from 0 to 400 Hz, but it is now known that crackles contain such frequencies [2, 28]. Furthermore, they reported that the main power spectral peak of BLS was below 100 Hz without any consideration that heart sounds emerge in these frequencies.

Some differences are noted between our assumption and methodology with respect to previous studies. In this work the main assumption is that BLS is altered by the pulmonary disease regardless of the presence of adventitious sounds. Methodologically, our data came from patients with chronic EAA breathing at controlled airflow, we used a multichannel approach, and also we assessed the ability of nonlinear techniques over linear techniques to extract valuable BLS features.

In general, interstitial lung diseases show a pattern of pulmonary consolidation with an augmented pulmonary density. Experimental studies exploring the effect of lung volume and consolidation have found that sound transmission is frequency dependent [29]. So, the transmission of high frequencies improves in consolidated lung, but the high frequencies are attenuated when lung volume is increased [30, 31]. Therefore, we should expect that patients with a predominant inflammatory process would have a trend toward higher values of percentile frequencies, even in absence of adventitious sounds or crackles. However, chronic EAA usually develops bronchiolitis with evidence of air trapping and alveolar destruction similar to emphysema [32, 33]...
that could explain the shift toward lower percentile frequencies in our patients. In fact, most of our patients showed a mixed pattern of pulmonary function, restrictive-obstructive, with mild or moderate fibrosis, and with some areas of air trapping.

It seems that spectral analysis is unconvincing for discriminating abnormal BLS in interstitial patients, as the percentile frequencies did not reach statistical significance during the inspiratory phase (Table 2 and Table 3). Although MA tended to be higher in the EAA group, the magnitude of MA dispersion precludes its utility. Also, FMA was similar between the studied groups.

Conversely, nonlinear techniques were more consistent to discriminate BLS between healthy and EAA patients. Indeed, during both phases of the breathing cycle statistical differences were found at the same sensors position. We interpret that the altered structure of the airways and the lung parenchyma in chronic EAA patients [34], was manifested as reduced irregularity and complexity of the BLS. Accordingly, the behavior of the MSE curves clearly allowed discriminating between the studied groups, indicating a decreased complexity of the BLS in patients. Moreover, the MSE curves in the expiratory phase pointed out that BLS contains valuable information to detect pulmonary alterations, even though the amplitude of the BLS was small. It is worthy to mention that MSE curves for healthy subjects and patients were more spaced out in the expiratory phase than in the inspiratory phase, which seems consistent with the discriminatory capacity of the linear technique. It is plausible that the above issue may be related to the type of BLS sources as the expiratory sources are more central [35]. Hence, the expiratory BLS could be carrying more information through its propagation to the thoracic surface as compared to the inspiratory BLS.

To our knowledge, there are not previous studies in the literature analyzing isolated BLS in patients against healthy subjects by nonlinear techniques. Also, this is the first study with the aim to show evidence of the utility of BLS to discriminate patients suffering EAA, but further studies are needed to validate the clinical usefulness of BLS in EAA disease as well as other pulmonary diseases.

Our study had limitations as it included few patients where all of them were females; perhaps, this unsought bias helped us to be more consistent as the clinical, physiological, and radiological data were very similar among patients. A second limitation is related to the procedure to isolate BLS segments; two pneumologists carefully reviewed sound segments from inspiratory and expiratory phases for healthy subjects and patients by visual and auditory procedure to be sure that the selected segments were free of artifacts or crackles, the procedure was time consuming. As a result, the data base used in the present study only includes information from four pulmonary sites. Another possible drawback is that linear and nonlinear techniques did not point out significant statistical differences at sensor PRC1. However, both processing techniques are in agreement on that acoustical information is present at PRC1 as percentile frequencies were comparable for both groups and MSE curves did not show the classical behavior for a noise signal. Furthermore, the pneumologists heard the acoustic information from patients and healthy subjects and they described them as sounding like each other. At the moment, the authors could not add more arguments to this issue until more studies are dedicated to investigate the spatial complexity on the whole thorax. The results reported in this paper were just for chronic patients; consequently, it seems interesting to explore the BLS behavior in a wider range of pulmonary conditions that includes acute, subacute and chronic EAA patients, where either the inflammatory or the fibrotic process might be predominant.

Based on this research, we conclude that it is plausible to discriminate BLS from patients with EAA when comparing with BLS from normal subjects by features obtained by linear techniques and more robustly by its irregularity and complexity indexes. Therefore, our results confirm the idea of Urquhart et al. that BLS by itself provides useful information, which seems a promising technique at the bedside for screening the temporal alteration of pulmonary patients. It is worthy to note that pneumologists were unable to discriminate BLS from healthy subjects and patients by the classical auscultation procedure. Also, BLS analysis may be relevant at early stages of pulmonary diseases when the detection of pulmonary disorders becomes difficult as many areas of the lungs could appear normal at clinical auscultation. Finally, the authors are planning to extend this research by creating a nonlinear map with the hope to obtain a better spatial description of the pulmonary disease.

References