Abnormal Lung Sounds in Patients With Asthma During Episodes With Normal Lung Function*

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Even in patients with clinically stable asthma with normal lung function, the airways are characterized by inflammatory changes, including mucosal swelling. In order to investigate whether lung sounds can distinguish these subjects from normal subjects, we compared lung sound characteristics between eight normal and nine symptom-free subjects with mild asthma. All subjects underwent simultaneous recordings of airflow, lung volume changes, and lung sounds during standardized quiet breathing, and during forced maneuvers. Flow-dependent power spectra were computed using fast Fourier transform. For each spectrum we determined lung sound intensity (LSI), frequencies (Q25%, Q50%, Q75%) wheezing (W), and W%. The results were analyzed by ANOVA. During expiration, LSI was lower in patients with asthma than in healthy controls, in particular at relatively low airflow values. During quiet expiration, Q25% to Q75% were higher in asthmatics than in healthy controls, while the change of Q25% to Q75% with flow was greater in asthmatic than in normal subjects. The W and W% were not different between the subject groups. The results indicate that at given airflows, lung sounds are lower in intensity and higher in pitch in asthmatics as compared with controls. This suggests that the generation and/or transmission of lung sounds in symptom-free patients with stable asthma differ from that in normal subjects, even when lung function is within the normal range. Therefore, airflow standardized phonopneumography might reflect morphologic changes in airways of patients with asthma.

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Respiratory wheezes are a common auscultatory finding in patients with most types of obstructive airway diseases, and are particularly heard during episodes of asthma. Therefore, lung sounds are generally considered to provide clinically relevant information in asthma, even though this has not been substantiated by quantitative analysis of objective measurements. Asthma is a chronic inflammatory disease of the airways, characterized by exacerbations of coughing, wheezing, chest tightness, and difficult breathing. These symptoms are associated with variable airways obstruction and bronchial hyperresponsiveness, which can be established by measurement of lung function and by bronchial provocation tests. The airways in asthma are characterized by inflammatory changes, resulting in mucosal swelling of the airway wall, thickening of the basement membrane, smooth muscle hypertrophy or hyperplasia, and excessive mucus production. It has been established that even in patients with clinically stable asthma, without any current symptoms and with lung function within the normal range, these inflammatory changes are still present.

Lung sounds can be divided into normal and adventitious sounds. Normal lung sounds appear to be primarily generated by the complex turbulence within the large and medium-sized airways. Wheezes are associated with concurrent airflow limitation. This probably induces quick oscillations of intraluminal gas and collapsible airway walls when airflow has reached a critical velocity (Bernoulli effect). The characteristics of normal breath sounds as well as wheezes are influenced by airflow velocity and local properties of the airways. Therefore, it is likely that the morphologic changes in mild asthma influence the mechanical and geometric properties of the airways, thereby affecting the generation and/or transmission of lung sounds.

Swelling of the airway wall increases local airflow velocity, thereby enhancing the development of turbulence. This will result in louder lung sounds containing more high-frequency components. On the other hand, increased wall thickness in asthma will diminish the transmission of normal lung sounds.
from within the airway lumen to the chest wall due to an increased impedance mismatch between lumen and airway wall.\textsuperscript{10} This effect might be frequency-dependent as the dominant transmission pathways are likely to change significantly with frequency.\textsuperscript{11}

The occurrence of wheezing is dependent on mechanical and geometric properties at the site of the flow-limiting segment.\textsuperscript{9} These properties not only change as a result of morphologic alterations in the airway wall, but also because of jumps of the flow-limiting segment to other generations of the bronchial tree. These jumps are influenced by lung volume, elastic recoil pressure, transmural pressure, and again by mechanical and geometric properties of airways.\textsuperscript{12} The flutter theory predicts that airway wall swelling causes an increased occurrence of wheezing during expiratory flow limitation with decreasing airway diameter and increasing wall thickness.

In this study, we compared several characteristics of lung sounds (ie, lung sound intensity, frequency content, and wheezing parameters) between normal and mildly asthmatic subjects with normal lung function by quantitative analysis of airflow standardized phonopneumography. We expected to find a distinction between the subject groups in the intensity and pitch of normal lung sounds, as well as in the extent of wheezing. To study the sounds in conditions with and without flow limitation, the recordings were made during standardized quiet breathing as well as during maximal, forced maneuvers.

**METHODS**

**Subjects**

Nine atopic male adults with mild asthma (mean age, 24.6 years; range, 19 to 28 years) and eight healthy male controls (mean age, 21.9 years; range, 19 to 24 years) volunteered to participate in this study (Table 1). The patients with asthma had a history of episodic chest tightness and wheezing, but their condition was stable for at least 4 weeks prior to the study. Symptoms of asthma were controlled by on-demand usage of inhaled \( \beta_2 \)-adrenergic bronchodilators alone; such treatment was withheld for at least 12 h before the study visits. Corticosteroids, theophylline, antihistamines, cromolyn sodium, or nedocromil sodium were not used for at least 6 months prior to the study. The patients had positive skin-prick tests (wheal >3 mm) to one or more airborne allergens. The forced expiratory volume in 1 s (FEV\(_1\)) without bronchodilator was within the normal range in all asthmatic subjects (mean, 93.8 percent of predicted; range, 77 to 119 percent).\textsuperscript{13} They were hyperresponsive to inhaled methacholine, as indicated by a lowered provocative concentration required to cause a 20 percent decrease in FEV\(_1\) (PC20 ≤4.0 mg/ml).\textsuperscript{14}

The normal subjects had no history of lung disease, and no abnormalities were found by physical examination. None of them had used any relevant medication within 3 months before the study. The FEV\(_1\) was within the normal range (mean FEV\(_1\), 109.1 percent of predicted; range, 88 to 126 percent), and they had a normal airway responsiveness to methacholine (PC20 ≥25.0 mg/ml).

All subjects were life-long nonsmokers, and there was no history of respiratory tract infection within 4 weeks before the study. The study was approved by the Hospital Ethics Committee, and informed consent was obtained from all subjects.

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*\( \text{N/A} \) = normal or asthma; % pred = percentage of predicted value; metha = methacholine; \( \beta \text{prn} \) = inhaled \( \beta \)-agonist on demand; p value is between normal and asthmatic subjects.

Abnormal Lung Sounds in Patients With Asthma (Schreur et al)
Design
The study was divided into a screening day and two study days with a 2- to 3-day interval. The screening day was used to check the selection criteria and to familiarize the subjects with the recordings. On both study days, the subjects underwent identical procedures of measurements of FEV1 followed by phonendoscopy for determination of the repeatability. Between both days FEV1 had to be within 5 percent in each subject.

Measurements
At the beginning of each study day, total lung capacity (TLC), vital capacity (VC), and functional residual capacity (FRC) were determined using a constant volume body-box (Morgan Plethysmograph, Rainham/Gillingham, United Kingdom) by the painting-method with a frequency of 1 Hz. The mean values obtained from at least three tracings were used in the analysis. Subsequently, FEV1 was also determined using the body-box, using the highest value among two recordings.

Phonendoscopy consisted of registrations of lung sounds in a sound-proof room, simultaneously with measurements of airflow and lung volume changes at the mouth by spirometry (Spiroflow; Morgan, Rainham/Gillingham, United Kingdom). The subjects were seated in an upright position with their nose clipped. The lung sound recordings were made during two types of breathing maneuvers: (1) airflow and lung volume standardized continuous quiet breathing for 30 s with inspiratory and expiratory airflow rates up to 1.5 L/s, and with lung volumes between TLC=0.4XVC+1 L and TLC=0.4XVC−1 L. This enabled subjects of different body height to breathe at comparable relative lung volumes. And (2) during maximum forced inspiratory and expiratory flow-volume maneuvers (MIFV and MEFV, respectively) for 15 s. Soda lime was used to eliminate CO2 accumulation. To prevent reduction of the gas volume in the closed system due to the O2 uptake, 300 ml/min O2 was supplied to the spirometer during the breathing maneuvers.

Airflow and lung volume changes were displayed on an oscilloscope screen (Hewlett-Packard HP1741A) in front of the subject in a flow-volume loop format. The standardized quiet breathing maneuver started with a maximum inspiration toward TLC, used as a reference volume. Then, the subjects performed the standardized maneuvers by tracking a prescribed, flow-volume curve drawn on the oscilloscope screen. The actual phonendoscopic registration started 45 s after the TLC maneuver to enable the airways to recover from any deep breath effect on airflow tone. The recordings were accepted if the target flow and volume were not exceeded by more than 0.5 L/s and 0.25 L, respectively. The registrations during maximum forced maneuvers were made directly following the quiet maneuvers. Absence of flow limitation during the standardized quiet breathing maneuvers was evaluated by comparing the recorded flow-volume curves from these maneuvers with the flow-volume curves obtained from the maximum forced expiratory and inspiratory flow-volume maneuvers for coincidence or overlapping.

Lung sounds were recorded by placing microphones at three locations on the right chest wall over the second (Mic1) and fifth (Mic2) intercostal spaces at the midclavicular line, and over the ninth intercostal space at the midaxillary line (Mic3). These were piezoelectric air-coupled microphones (Sony ECM-150T, Japan), mounted in metal housings that were fixed to the chest wall by means of double-sided adhesive tape rings. The combination of microphone and housing had a measured frequency response from 150 Hz to 3 kHz (±5 dB). The signals obtained from the microphones were amplified and filtered (fourth-order Bessel filters: high-pass cut-off at 100 Hz and low-pass cut-off at 1.5 kHz). Lung volume, flow rate, and lung sounds were digitized at 5 kHz per channel (analog-to-digital converter: Metabyte Corp. DASH-16F, United States) and stored on the hard disk of a computer (MS-DOS, Mitac AT-386DX, Japan).

Signal Analysis
For each microphone, airflow-dependent power spectra were computed by fast Fourier transform on 100-ms intervals using a Hanning window. These intervals were centered at lung sound samples for which the corresponding airflow was a multiple integer of 0.1 L/s for quiet breathing maneuvers, and 0.3 L/s for the forced maneuvers. These power spectra were averaged between all respiration of one registration for each distinct airflow value, and separately for the limbs with increasing and with decreasing airflow.

For each spectrum, the following parameters were determined: (1) lung sound intensity (LSI) expressed as log-power of the area under the spectral curve; (2) frequency content in quartile power points (Q25%, Q50%, Q75%), and (3) the extent of wheezing (W). Peaks in the power spectrum were considered wheezes when above 150 Hz and at least three times higher than the baseline level. Finally, we determined the ratio of the number of spectra containing a wheeze to the total number of spectra (W% ). This was done separately for forced and quiet inspiration and expiration, and for the limbs of the flow-volume curve with increasing and with decreasing airflow.

Statistical Analysis
The repeatability of lung sound parameters LSI, Q25% to Q75%, W, and W% between study days 1 and 2 was analyzed using the intraclass correlation coefficient.

The effects of group (asthma or control), flow, and flow-limb on the lung sound parameters were examined using mixed-model ANOVA. To perform this analysis, the amount of data had to be reduced for computer memory reasons. Therefore, we used the averaged values of LSI, Q25%, Q50%, Q75%, W, and W% from day 1 and day 2 for further analysis. The analysis was performed separately for the three microphones, for both breathing manoeuvres, and for inspiration and expiration. Group (asthma or control), airflow, and flow-limb were used as independent variables, while LSI, Q25% to Q75%, and W were selected as dependent variables. The FEV1 percent predicted was applied as a co-variate in order to take into account any differences in FEV1 between subjects. The W% was analyzed similarly, but without taking the effect of airflow into account, as W% is being calculated over the full range in flow in a flow-limb.

For quiet breathing manoeuvres, the analysis was performed between 0.8 and 1.5 L/s, for the forced inspirations between 0.6 and 3.6 L/s, and for forced expirations between 0.6 and 6.0 L/s. P values less than 0.05 were considered to be significant. Intra-class correlation coefficients R1 greater than 0.60 were considered to be adequate.

RESULTS

Subject Characteristics
The difference in FEV1 between the study days was ±5 percent of the predicted value in any subject, and the mean FEV1 in all subjects was not significantly different between the study days (p=0.30). The mean FEV1 in asthmatic subjects was lower than in healthy controls (p=0.04) (Table 1). The other subject characteristics did not show significant differences between the groups or study days, apart from the PC20 which was used as a selection criterion. Body habitus, as expressed by the Quetélet-index
FIGURE 1. Lung sound intensity (LSI) vs airflow recorded by Mic2 during standardized quiet (top) and maximum forced breathing (below). Inspiration is displayed to the left, expiration to the right. During expiration LSI was lower in asthmatics (open circles) than in normal subjects (closed circles), and this effect was most evident at lower airflow values. LSI was not different between the groups during inspiration. Solid line=from maximal expiration to maximal inspiration; dotted line=from maximal inspiration to maximal expiration.

FIGURE 2. Median frequency (Q50%) vs airflow recorded by Mic2 during standardized quiet (top) and by Mic1 during maximum forced breathing (below). Inspiration is displayed to the left, expiration to the right. There was no difference between normal subjects (closed circles) and asthmatics (open circles) in Q50% during maximum forced expiration (below). However, Q50% was higher in asthmatic than in normal subjects during quiet expirations recorded by Mic2. Solid line=from maximal expiration to maximal inspiration; dotted line=from maximal inspiration to maximal expiration.
(weight/height$^2$), was also not significantly different between the subject groups (p=0.366).

**Lung Sound Intensity (LSI)**

The LSI was strongly dependent on airflow for all microphones and for both respiratory maneuvers (p<0.001) (Fig 1). This flow dependence was different between the increasing and decreasing flow-lims (p<0.001) (Fig 1). During both quiet and forced expiration, LSI was lower in patients with asthma than in healthy controls, and this effect was most evident at relatively low airflow values (p≤0.005) (Fig 1). For the inspiratory segments of both maneuvers, LSI was not different between the groups.

**Frequency Content (Q25%, Q50%, Q75%)**

The quartile power point frequencies Q25% to Q75% were strongly dependent on airflow in both maneuvers (p≤0.002) (Fig 2). Furthermore, at given airflows, Q25% to Q75% were different between the increasing and decreasing flow-lims (p≤0.002). The Q25% to Q75% were higher in patients with asthma than in healthy controls for quiet expirations recorded by Mic2 (p≤0.026). For Mic1 to Mic3, the change of Q25% to Q75% with flow was also greater in asthmatic than in normal subjects (p≤0.028). During maximum forced expirations, however, Q25% to Q75% did not discriminate between the subject groups.

**Wheezing (W and W%)**

Wheezing occurred rarely during forced inspiration (mean W [SD]: ≤3.1 percent [17.3] of spectra) and during quiet inspiration (≤0.53 percent [7.3]) and expiration (≤1.9 percent [13.5]). During forced expiration, wheezing was more prominent, in particular in the decreasing flow-limb (W≥31.1 percent [46.4]) (p<0.001) and at relatively high airflows (p≤0.003) (Fig 3). However, the extent of wheezing was not different between asthmatic patients and healthy controls during both breathing maneuvers (p≥0.152).

The W% was not different between the two groups either (p≥0.080). During forced expirations, W% was higher in the decreasing than in the increasing flow-limb (p≤0.001) (Fig 4). Similar results were found for quiet expirations for Mic1 (p=0.035) and Mic2 (p=0.019).

**Baseline FEV1**

By including the covariate FEV1 in the analysis, there was a significant effect of FEV1 in the comparison between asthmatic and normal subjects of LSI (p=0.004) for Mic1, and of Q50% (p=0.022) and Q75% (p=0.042) for Mic2 during quiet expiration. The covariate FEV1 changed the dependence of LSI on subject group from being not statistically significant (p=0.278) to significant (p=0.008). In none of the other analyses did the covariate reach significance.

**Repeatability**

Analysis of the repeatability showed that the intra-

\[ \text{FIGURE 3. Extent of wheezing (W) vs airflow recorded by Mic1 during maximum forced breathing. Inspiration is displayed to the left, expiration to the right. Wheezing was rare during inspiration. During expiration, wheezing was more prominent, in particular in the decreasing flow-limb with airflow values >2 L/s. W was not different between the groups. Closed circles=normal subjects; open circles=asthmatic subjects; solid line=from maximal expiration to maximal inspiration; dotted line=from maximal inspiration to maximal expiration.} \]
class correlation coefficient $R_1$ for LSI and Q25% to Q75% varied between 0.52 and 0.92 (Table 2). In general, $R_1$ was similar between the subject groups. However, the lowest values of $R_1$ were found in the asthmatic group. The reproducibility of W% in normal subjects was also satisfactory ($R_1 \geq 0.69$). In patients with asthma, however, the variation of W% between the days for Mic2 and Mic3 was much larger ($R_1 \leq 0.44$). As wheezing occurred rarely during quiet expiration, and quiet and forced inspiration, calculation of $R_1$ of W% and W for these parts of the recordings was not meaningful.

**Discussion**

The results of this study indicate that at given airflows, lung sounds are lower in intensity, and higher in pitch in asthmatic subjects as compared with healthy controls. This suggests that the generation and/or transmission of lung sounds are modified by morphologic changes in the airways of patients with asthma, even when lung function is within the normal range.

To our knowledge, this is the first study on lung sounds in mildly asthmatic subjects during an episode of normal spirometry. In many aspects, the results in these patients resemble those in normal subjects. Lung sound intensity, frequency content, and wheezing were strongly dependent on airflow in both groups. This is in agreement with earlier studies on intensity, spectral content. However, the airflow dependence of the spectral content is contrary to the findings by Kraman, probably due to the limitation of the flow range to inspiratory airflows greater than 1 L/s in the latter study. The in-

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**Table 2—Intraclass Correlation Coefficients of the Results of Study days 1 and 2 for Asthmatic and Normal Subjects**

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<tr>
<td>Q75%</td>
<td>0.71</td>
<td>0.71</td>
<td>0.57</td>
<td>0.66</td>
</tr>
<tr>
<td>W</td>
<td>0.60</td>
<td>0.57</td>
<td>0.52</td>
<td>—</td>
</tr>
<tr>
<td>W%</td>
<td>0.80</td>
<td>0.76</td>
<td>0.69</td>
<td>—</td>
</tr>
</tbody>
</table>
crease in frequency with airflow might have partially arisen from lung sounds starting to predominate low-frequency background noises, like heart and muscle sounds. In addition, the increase in frequency might have resulted from the increase in high-frequency turbulence at higher airflow velocities, when background noises were negligible.

The differences between the limbs of the flow-volume maneuvers with increasing and decreasing airflow in the present study indicate that the generation and/or transmission of lung sounds vary during the course of a respiration. This is possibly due to differences in lung volume, elastic recoil pressure, or transmural pressure at similar airflow values between increasing and decreasing flow-limb. It implies that lung sound analysis may be obscured, when airflow or lung volume are not taken into account.

Previous investigators have addressed the relationships between wheezing and flow limitation during forced expiration, and between wheezing and airflow narrowing during normal breathing in children and in adults. The recordings in those studies were made during episodes of airways obstruction due to several causes. Our data confirm and extend these findings, indicating a strong dependence of lung sound characteristics on airflow, and a strong between- and within-subject variability of wheezing, even when lung function is normal.

The reproducibility of LSI, frequency content (Q25% to Q75%), and the ratio of the number of "wheezy" spectra to the total number of spectra (W%) was satisfactory in both maneuvers. Although the intraclass correlation coefficient was usually similar between the subject groups, the lowest values were found in the asthmatic group. This indicates that the variability of the lung sound parameters between the study days was greater in asthmatic than in normal subjects. This is most likely due to the variable airflow narrowing inherent to asthma, even though lung function was stable between the 2 days, as indicated by the FEV\(_1\). This suggests that FEV\(_1\) does not reflect small changes in airway morphology in asthma. Lung sound analysis may provide a more sensitive indication of minor alterations in airway geometry. The better reproducibility of wheezes for Mic\(_1\) when compared with Mic\(_2\) and Mic\(_3\), might reflect the adjacency of Mic\(_1\) to the trachea. In these subjects with a normal lung function, wheezing during maximum forced expiration predominantly occurs in the larger airways and is not related to airflow narrowing due to asthma.

The present results may have been influenced by methodologic factors, for example, the selection of subjects, methods of measurements, or analysis. First, although FEV\(_1\) was within the normal range in all subjects, the mean value in asthmatic patients was lower than in healthy controls. To lessen any influence of the differences in FEV\(_1\) between the subjects, FEV\(_1\) percent predicted was used as a covariate in the analysis of variance. The covariance term was hardly ever significant, and when it was, it changed the outcome of the statistical analysis only in a single case. This indicates that the difference in FEV\(_1\) between the groups cannot explain the differences in lung sound parameters between the groups.

Second, airflow within the intervals from which the fast-Fourier transform spectra were obtained can deviate considerably from the nominal airflow for a given interval at the steepest parts of the flow-time curve. Variations in the flow-volume curves between the subject groups might have influenced the flow-range within these intervals. However, inspection of the superimposed flow-volume curves of all subjects showed a strong similarity of these curves between the subjects, except at the transitions between expiration and inspiration in both maneuvers, and at maximum airflow in forced maneuvers. Therefore, flows below 0.3 L/s in quiet and 0.6 L/s in forced maneuvers were excluded from statistical analysis, as well as flows exceeding 3.6 and 6.0 L/s in forced inspiration and expiration, respectively. However, we cannot exclude that differences in flow-range within 100-ms intervals between equal airflows of increasing and decreasing limb partially accounted for the differences found between these limbs.

Third, the relatively high sound amplitude near zero-flow arises partly from noises that are not related to respiration, e.g., heart and muscle sounds. However, the width of the interval from which the spectra were obtained is probably of more importance, as information from lung sounds generated at higher airflow, that are louder and dominate the spectral content, are included in the spectra near zero-flow. This is another reason for exclusion of the lowest airflow values from statistical analysis.

Finally, the wheeze detection mechanism may have influenced the results of the present study. Wheezes can be recognized in power spectra as sharp peaks with a duration greater than 200 to 250 ms. We did not record the duration of these peaks, but auditory verification of the recorded sounds enabled us to exclude the occurrence of adventitious breath sounds other than wheezes that could be responsible for such peaks. Peaks in the power spectra due to the statistical uncertainty of the fast-Fourier transform were smoothed by averaging the spectra of equal flows between all respirations within one registration. Averaging of spectra of successive respirations, including wheezes that vary in frequency between these respirations, can potentially lead to widening and lowering of the peaks in the averaged spectrum. However, inspection of pseudo-three-dimensional
plots displaying the spectra vs airflow before averaging showed that frequency and timing of the wheezes within one registration were very reproducible. Therefore, we considered the applied method for wheeze detection adequate.

How can we explain the difference in lung sound characteristics between the groups? These differences must result from alterations in the generation of lung sounds or the transmission of these sounds to the chest wall. The increase of LSI with expiratory airflow was greater in the patients with asthma than in the normal subjects, in particular when no wheezes were involved. These normal breath sounds result primarily from turbulence within the large airways. The power of these sounds is proportional to the square of the airflow velocity in the airways. This suggests that at given airflows at the mouth (L/s), the local airflow velocity (m/s) is higher in asthmatic than in normal airways. This is not unexpected, as the airway walls in asthmatic subjects are swollen, leading to relatively narrowed airway lumina. The increased airflow velocity is also likely to account for the increase in high-frequency components in patients with asthma, as an increased airflow velocity results in an increased turbulence containing additional high-frequency vortices. Nevertheless, we observed that lung sounds in asthmatic patients are weaker than in normal subjects. One could speculate that the transmission of sounds from the airway lumen to the chest wall is reduced in asthmatics. This is also not unexpected, as the transfer of sounds from the airway lumen to the airway wall is likely to be decreased by the increased mismatches of the acoustic impedance between lumina and walls due to the increased wall mass in asthmatics.

During wheezing, predominantly occurring in the decreasing flow-limb at high expiratory airflow, the sound intensity was not different between the groups. The power of wheezes resulting from flutter in collapsible airways is proportional to the airflow velocity in the flow-limiting segment, which is similar in both subject groups when flow limitation occurs in the same generation of the bronchial tree. This observation suggests that the transmission from the airway walls through the parenchymal tissue to the chest wall is not changed in asthma, in contrast to the transmission from airway lumen to airway wall.

Wheeze, caused by the mechanism of flutter in collapsible airways were rare in both subject groups during quiet expiration, when airflow velocity and transpulmonary pressure are too low to enable the Bernoulli effect to take place. During maximum forced expiration, intraluminal airflow will reach critical velocity, leading to flow limitation in all subjects. Accordingly, the extent of wheezing in both groups was similar. Wheezing during inspiration cannot easily be explained by the theory of flutter in collapsible airways, but possibly results from a comparable mechanism of vibration due to pressure variations resulting from airflow near mucus plugs or folds of airway walls.

What are the clinical implications of this study? The most prominent differences in sound intensity and frequency content between asthmatic patients with a normal lung function and healthy controls were found during quiet standardized breathing. The differences were large enough to be distinguished by ear as variations in loudness and pitch when heard in a direct comparison. This finding, in combination with the airflow dependence of the lung sound parameters, indicates the importance of using quiet, well-controlled flow-volume maneuvers during clinical auscultation.

In conclusion, the present study demonstrates that lung sound intensity and pitch are abnormal in symptom-free asthmatics with normal lung function. Furthermore, the reproducibility of the lung sound parameters between days appears to be lower in asthmatic subjects than in controls, probably due to variability of the generation and/or transmission of lung sounds secondary to changes in the airway morphology. Our results stress the usage of airflow- and lung volume-standardized phonopneumography in lung sound research, and highlight the importance of well-controlled breathing maneuvers during clinical auscultation.

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REFERENCES

17 Kraman SS. The forced expiratory wheeze: its site of origin and possible association with lung compliance. Respiration 1983; 44:189-96
18 Baughman RP, Loudon RG. Stridor: differentiation from asthma or upper airway noise. Am Rev Respir Dis 1989; 139:1407-09
22 Lessard CS, Wong WC. Correlation of constant flow rate with frequency spectrum of respiratory sounds when measured at the trachea. IEEE Trans Biomed Eng 1986; BME-33:461-63
26 Spence DPS, Bently S, Evans DH, Morgan MDL. Effect of methacholine induced bronchoconstriction on the spectral characteristics of breath sounds in asthma. Thorax 1982; 47:80-83
28 Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis 1993; 147:405-10