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Adventitious and Normal Lung Sounds in the General Population: Comparison of Standardized and Spontaneous Breathing

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BACKGROUND: For clinical practice and research, it would be easier to auscultate lung sounds without simultaneously measuring air flow. This study evaluated whether the presence of adventitious lung sounds and the characteristics of normal lung sounds differ between spontaneous and standardized breathing in a general population. METHODS: A cross-sectional study was conducted with 116 subjects (53.4% female, mean age 59.2 ± 11.6 y). The subjects reported heart/lung diseases and the degree of dyspnea, and spirometry was carried out. Lung sounds were recorded at 6 chest locations, first during spontaneous breathing and then during breathing with a standardized air flow of 1.5 L/s. Crackles and wheezes were identified by 4 observers. Intensity and frequency of normal lung sounds in the 100–2,000 Hz band were determined. RESULTS: Inspiratory crackles were heard in 19 subjects (16.4%) during spontaneous breathing and in 18 subjects during standardized breathing (15.5%). Only 5 subjects were identified with both methods (kappa = 0.13). Expiratory wheezes were heard in 18 subjects (15.5%) during spontaneous breathing and in 23 subjects during standardized breathing (19.8%). Nine subjects were identified with both methods (kappa = 0.32). The mean intensity and median frequency of normal lung sounds were significantly higher during standardized breathing than during spontaneous breathing, both at inspiration (23.1 dB vs 20.1 dB and 391.6 Hz vs 367.3 Hz) and expiration (20 dB vs17.6 dB and 376.3 Hz vs 355 Hz). Dyspnea was more frequently reported when expiratory wheezes were present, but this association was only statistically significant during standardized breathing (*P* = .03). During spontaneous breathing, increased mean intensity and median frequency during expiration were associated with an increased reporting of heart/lung diseases (*P* = .02 and *P* = .01, respectively). CONCLUSIONS: The mode of breathing had an impact on both adventitious and normal lung sounds. Although adventitious sounds were found with similar frequency between the modes of breathing, less than half of these subjects were identified with both methods. Spontaneous breathing was not inferior to standardized breathing in reflecting lung disease. *Key words: auscultation; lung sounds; crackles; wheezes; respiratory air flow.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Lung auscultation is a simple and noninvasive way to assess the function of the respiratory system,[1] and it does not require special resources beyond a stethoscope. These advantages of lung auscultation are especially important in primary care settings and in resource-constrained settings, where technologies for diagnostic tests, such as radiography and spirometry, are not available.

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The authors have disclosed no conflicts of interest.

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Lung sounds fall into 2 main categories, normal and adventitious sounds.[2] Normal lung sounds are generated by the air flow in the respiratory tract and are characterized by broad-spectrum noise.[2] Adventitious lung sounds are additional sounds superimposed on normal lung sounds, which can be continuous with a musical character (ie, wheezes), or discontinuous and explosive (ie, crackles).[2] The presence of adventitious lung sounds often indicates a pulmonary disorder, although they can also be present in healthy people.[1] Both normal and adventitious lung sounds are directly related to the movement of air, changes within lung morphology, and the presence of secretions,[1,3] and they have been used as clues for diagnosing lung diseases.[1] Lung sounds may thus be useful screening markers for lung diseases in the general population.

One concern when using lung auscultation as a screening tool is the influence of air flow on respiratory acoustics. In clinical practice, lung sounds are most commonly assessed with no strict control over air flow,[1] because patients are simply asked to breathe deeply with an open mouth. Conversely, standardized air flow is preferred in research settings[4,5] and is recommended by the computerized respiratory sound analysis (CORSA) guidelines.[6] For both clinical practice and research, however, it would be easier to rely on lung sounds auscultated without air flow measurements. In a study of subjects with COPD, the characteristics of normal lung sounds were found to differ between spontaneous and standardized air flows, whereas the characteristics of adventitious sounds did not differ between air flows.[5] Similarly, in subjects with pneumonia, congestive heart failure, and interstitial pulmonary fibrosis, the intensity of lung sounds changed significantly between normal breathing and deep breathing, whereas the number of crackles remained stable.[7] It is possible that the presence of adventitious lung sounds or the characteristics of normal lung sounds in the general population differ when breathing deeply with an open mouth and breathing at a modestly increased standardized air flow, but this has not yet been investigated.

If it is not required to simultaneously measure air flow when lung sounds are recorded to capture significant information on normal and adventitious lung sounds, this would greatly simplify the application of respiratory acoustic data capture in clinical settings. To test this hypothesis, this study evaluated the degree to which the presence of adventitious lung sounds and the characteristics of normal lung sounds differ between spontaneous and standardized breathing in a general population. In addition, because lung sounds have been previously related with diseases such as pneumonia and COPD, among others,[1,8] we explored whether the method of breathing influenced how lung sounds are related to indicators of lung disease.

QUICK LOOK

Current knowledge

One concern when using lung auscultation as a screening tool is the influence of air flow on respiratory acoustics. In clinical practice, lung sounds are commonly assessed by asking patients to breathe spontaneously with an open mouth, while in research settings standardized air flows are used. It has not yet been investigated in a general population whether the presence of adventitious lung sounds or characteristics of normal lung sounds differ between spontaneous and standardized breathing.

What this paper contributes to our knowledge

In a general population, similar to what happens in subjects with lung disease, the method of breathing affected both the presence of adventitious lung sounds and the characteristics of normal lung sounds. However, the frequency of crackles and wheezes were similar with both methods of breathing. In terms of reflecting lung disease, spontaneous breathing did not seem to be inferior to standardized breathing.

Methods

Study Design and Participants

This was a sub-study from the seventh Tromsø Study (Tromsø 7). The Tromsø Study, initiated in 1974, is a longitudinal, multipurpose, population-based Norwegian study conducted every 6–7 y in the Tromsø municipality.[9] For the Tromsø 7 in 2015–2016, all inhabitants of Tromsø age ≥ 40 y were invited; 21,083 participants attended for a first visit (65% of the invited), having a mean age of 57.3 y and 52.5% being female. A random selection of 9,253 individuals from the 21,083 participants was invited for a second visit to perform extended examinations, of whom 8,346 attended (90.2%). Due to human resources and time constraints, only 6,048 of the 8,346 attendees had their lung sounds recorded during spontaneous breathing (mean age 63.2 y, 54.7% female). Over a period of 4 weeks in September and October 2016, 116 subjects were consecutively selected for this sub-study (Fig. 1). The 116 subjects had their lung sounds recorded first during spontaneous breathing and then during standardized breathing. An enrollment target of 100 subjects was selected based on convention, as enrollment numbers of 50–100 subjects are typical in clinical agreement and reliability studies.[5,10,11] The study as a whole was approved by the Regional Committee for Medical and Health Research Ethics. Participants' written informed consent was obtained before data collection.

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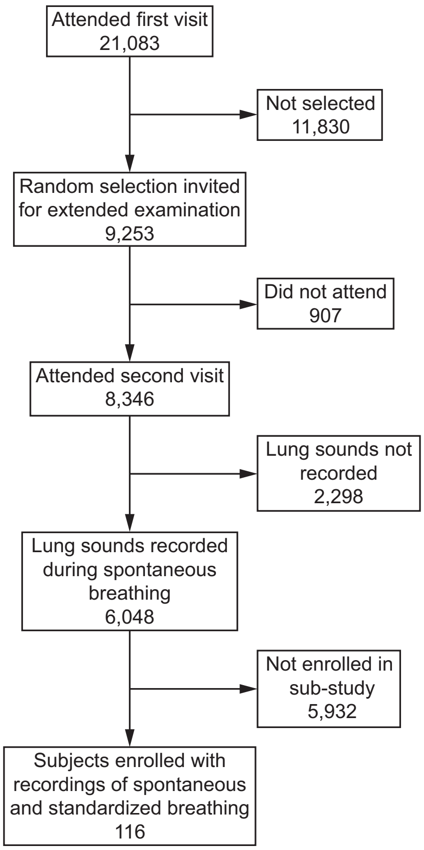

Fig. 1. Flow chart.

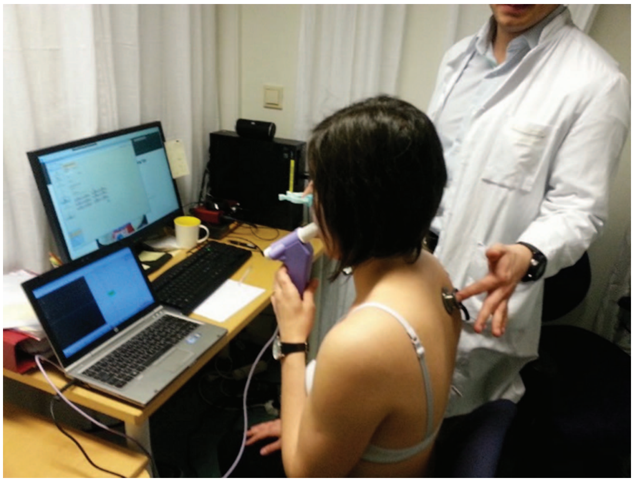

Fig. 2. Subject breathing with standardized air flow during recording of lung sounds.

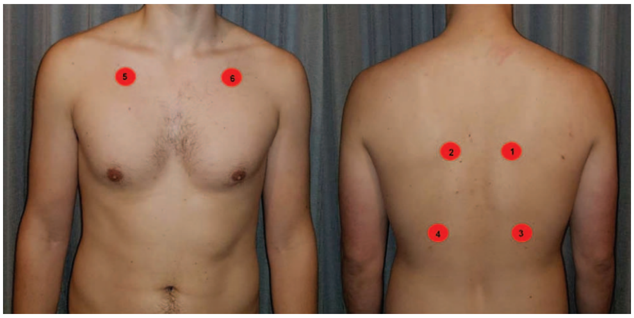

Fig. 3. Chest locations for lung sound recordings.

Data Collection

Sociodemographic data (age and gender), anthropometric measurements (height, weight, and body mass index), and clinical information (smoking status and self-reported heart or lung disease) were collected. Past or current heart or lung disease was reported, which included heart attack, stroke, heart failure, angina, atrial fibrillation, asthma, and COPD. Subjects reported their activity limitations resulting from dyspnea by selecting the statement from the modified Medical Research Council questionnaire (mMRC) that best described their limitations.[12] This questionnaire covers 5 grades of dyspnea on a scale from 0 to 4. Spirometry (SensorMedics Vmax 20c Encore, Viasys, Yorba Linda, California) was performed according to standardized guidelines,[13] and Global Lung Function Initiative reference values were used.[14]

Later the same day, lung sounds were digitally recorded with subjects in a seated position, first with spontaneous air flow and then with inspiratory and expiratory peak air flow of 1.5 L/s.[6] During spontaneous air flow, subjects were asked to breathe deeply with an open mouth. No recording of air flow was made to preserve the natural, spontaneous breathing pattern. During standardized air flow, subjects wore a nose clip and breathed through a mouthpiece connected to a spirometer (ndd Easy on-PC Spirometry System, Zurich, Switzerland). Biofeedback of the air flow was provided through a vertical color bar on the computer screen: during each inspiration/expiration, a yellow bar was displayed with a height proportional to the air flow generated, and when the target air flow was achieved the bar turned green (Fig. 2). Thus, subjects were instructed to reach the green color in each inspiration and expiration, and the recording was preceded by a training phase of at least 2 breathing cycles. The visual biofeedback and the recording of the air flow was provided by the research software WBreath v3.41.4.1 (ndd).

Lung sounds were recorded for 10 s at 6 chest locations, 3 on each side of the chest: on the back between the spine and the medial border of the scapula at the level of T4–T5; at the midpoint between the spine and the mid axillary line at the level of T9–T10; and on the front where the medioclavicular line crosses the second rib (Fig. 3). A wireless microphone (Sennheiser MKE 2-EW with Sennheiser wireless system EW 112-P G3-G, Sennheiser Electronics, Wedemark, Germany) placed in the tube of a Littmann Classic stethoscope (3M, Maplewood, Minnesota) was used in the recordings. Lung sounds were recorded during both spontaneous and standardized breathing, and the recordings were analyzed to identify adventitious lung sounds and to characterize normal lung sounds.

Analysis of Adventitious Lung Sounds

Manual identification of adventitious lung sounds is a challenging task, and agreement between observers is often only moderate.[15] To have a rigorous method of identification and to control the risk of over-identification of adventitious lung sounds, a 2-round process involving 4 observers was implemented.

In the first round, all 1,392 sound files (116 subjects × 6 locations × 2 breathing methods) sound files were classified independently by 2 trained observers, a physiotherapist/lung sound researcher (CJ), and a general practitioner/PhD student (JCAS). The observers classified each of the recordings as normal or abnormal by listening to and studying spectrograms (a visualized presentation of the sounds showing time on the *x* axis, frequency on the *y* axis, and intensity by color saturation) using Adobe Audition v5.0 (Adobe, San Jose, California). If abnormal, the observers further classified sounds as crackles, wheezes, or other abnormal sounds, and whether the abnormalities occurred during inspiration or expiration. The observers filled in a Microsoft Access form (Microsoft, Redmond Washington), written in English. When disagreements occurred between the 2 observers, the observers met face-to-face with a third observer, who was a general practitioner and experienced lung sound researcher (HM), to classify the sound based on the majority rule.

In a second round, a fourth observer who was a pediatrician and experienced lung sound researcher (HP) was involved in addition to the 3 observers. In this second round, all the sound files marked as having crackles or wheezes in the first round were again independently classified by 2 pairs of observers as present, absent, or uncertain and as inspiratory or expiratory.

After gathering all disagreements of this second round, a face-to-face meeting was held with the 4 observers to solve disagreements. To establish the presence of crackles or wheezes, an abnormal sound (crackle or wheeze) was considered to be present when 3 out of 4 observers considered it as such (ie, majority rule). All observers had acceptable results after a hearing capacity assessment. No instructions were given regarding the volume setting for audio playback.

Analysis of Normal Lung Sounds

All sound files were processed using algorithms written in Matlab (Mathworks, Natick, Massachusetts). Breathing phases were identified by CJ using the Respiratory Sound Annotation Software.[16] Normal lung sounds were analyzed based on the methodology proposed by Pasterkamp et al.[17] The mean intensity and the median frequency of normal lung sounds were determined in the 100–2,000 Hz band and were extracted per breathing phase and per chest location.

Statistical Analysis

Descriptive statistics were used to characterize the sample. Based on the air flow signal recorded with the WBreath software, mean inspiratory and expiratory peak air flow and volume per subject were determined by computing the mean of the 6 recordings during standardized air flow. To analyze the relative reliability of peak air flow and volume, the intraclass correlation coefficient (ICC) was determined.[18,19] Relative reliability was computed using the scores obtained from 6 recordings. The $ICC_{2,1}$ (2-way random single measures) was used and interpreted as excellent (ICC $>$ 0.9), good (ICC = 0.75–0.9), moderate (ICC = 0.5–0.75), or poor (ICC $<$ 0.5).[18,20]

A subject was identified as having inspiratory or expiratory crackles when crackle sounds were present in one or more chest locations, respectively. The same procedure was used to identify subjects with inspiratory or expiratory wheezes. McNemar tests were used to compare the proportion of subjects with crackles or wheezes between spontaneous and standardized air flows. To determine agreement on the presence of crackles or wheezes between breathing modes, the percentage of agreement and Cohen's kappa were used.[21] Cohen's kappa provides useful information about the reliability of categorical data and is a frequently applied statistical approach.[19] The Cohen's kappa values were interpreted as follows: $<$ 0 = no agreement, 0–0.20 = slight agreement, 0.21–0.40 = fair agreement, 0.41–0.60 = moderate agreement, 0.61–0.80 = substantial agreement, and 0.81–1.0 = almost perfect agreement.[21]

Paired *t* tests were used to analyze differences in the mean intensity and median frequency of normal lung sounds between spontaneous and standardized breathing. Chi-square tests were used to compare the presence of lung disease indicators in subjects with and without adventitious lung sounds based on both spontaneous and standardized breathing. Due to the small size of the study, indicators with the highest prevalences were selected: history of heart and/or lung disease, mMRC $\geq$ 1, and FEV_1 $<$ 80% predicted. Simple logistic regressions were also used to explore associations between these indicators and normal lung sounds during both spontaneous and standardized breathing.

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Table 1. Subjects' Characteristics

Female	62 (53.4%)
Age, y	59.2 ± 11.6 (40–84)
Body mass index, kg/m^2	27.3 ± 4.2 (20.4–41)
Smokers	
Current	14 (12.1%)
Former	49 (42.2%)
Never	53 (45.7%)
Indicators of lung disease	
History of heart and/or lung disease	19 (16.4%)
mMRC ≥ 1	37 (31.9%)
FEV_1 < 80% predicted	15 (12.9%)

Values are shown as mean ± SD (range) or as *n* (%). *N* = 116 subjects.
mMRC = modified British Medical Research Council questionnaire

Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM). Plots were created using GraphPad Prism 5.01 (GraphPad, La Jolla, California).

Results

Participants

A total of 116 subjects were enrolled, and all completed the study protocol. The 116 subjects (53.4% female) had a mean age of 59.2 ± 11.6 y. Fifty-three subjects (45.7%) never smoked, 22 (19%) reported heart and/or lung disease, 37 (31.9%) had an mMRC score ≥ 1, and 15 (12.9%) had a FEV_1 < 80% predicted (Table 1). The corresponding frequencies among the 6,048 subjects examined during spontaneous breathing in the larger study were similar to those found in the sub-study (40.5%, 27.4%, 31.9% and 12.7%, respectively).

Reliability of Standardized Breathing

During standardized breathing, subjects had a mean peak inspiratory air flow of 1.2 ± 0.3 L/s and a mean peak expiratory air flow of 1.5 ± 0.4 L/s. Good reliability was found for inspiratory and expiratory peak air flows ($ICC_{2,1}$ = 0.70, 95% CI 0.61–0.77 and $ICC_{2,1}$ = 0.85, 95% CI 0.80–0.89, respectively). Inspiratory volumes (1.1 ± 0.4 L) and expiratory volumes (1.4 ± 0.6 L) were found to have good to excellent reliability ($ICC_{2,1}$ = 0.85, 95% CI 0.81–0.89 and $ICC_{2,1}$ = 0.91, 95% CI 0.88–0.93).

Agreement on Adventitious Lung Sounds

Of the 116 subjects, 19 (16.4%) were identified as having inspiratory crackles during spontaneous breathing, and 18 (15.5%) had inspiratory crackles during standardized breathing (P = 1). Only 5 subjects with inspiratory crackles were identified with both methods. The percentage agreement for the presence of inspiratory crackles was 76.7%, with a kappa of 0.13 (slight agreement). A total of 18 (15.5%) subjects were identified as having expiratory wheezes during spontaneous breathing, and 23 (19.8%) subjects had expiratory wheezes during standardized breathing (P = .41). Nine of these subjects were identified with both methods. The percentage agreement for expiratory wheezes was 80.2%, with a kappa of 0.32 (fair agreement). Table 2 presents the agreement for the presence of crackles and wheezes between spontaneous and standardized breathing.

The proportion of subjects with inspiratory crackles and expiratory wheezes at each chest location is presented in Figure 4. Because only a small proportion of subjects were identified as having expiratory crackles or inspiratory wheezes (~5%) (Table 2), data per chest location are not presented.

No statistically significant association was found between crackles and mMRC score ≥ 1, independent of the air flow. An mMRC score ≥ 1 was reported more frequently when expiratory wheezes were present during standardized breathing (58.8%) than when wheezes were absent (31%) (P = .03). A similar tendency was found for spontaneous breathing (50% vs 33%), but the difference was not statistically significant. Crackles and wheezes were not associated with history of heart/lung disease, or FEV_1 < 80% predicted, and the results were similar during spontaneous and standardized breathing.

Normal Lung Sounds

The mean intensity and median frequency of normal lung sounds were significantly higher during standardized breathing than during spontaneous breathing, during inspiration (23.1 ± 2.2 dB vs 20.1 ± 1.7 dB and 391.6 ± 23.5 Hz vs 367.3 ± 21.6 Hz) and during expiration (20 ± 2.2 dB vs 17.6 ± 1.7 dB and 376.3 ± 27.4 Hz vs 355 ± 25.4 Hz) (P < .001). These differences remained significant when each chest location was considered separately (P < .001) (Fig. 5).

During spontaneous breathing, increasing mean intensity and median frequency during expiration were associated with an increased likelihood of reporting heart or lung diseases, with an odds ratio of 1.42 per dB (95% CI 1.07–1.89, P = .02) and of 1.02 per Hz (95% CI 1–1.04, P = .01), respectively. No such association was found during standardized breathing. Also during inspiration, increasing median frequency at spontaneous breathing appeared to be associated with an increased likelihood of having reduced lung function (FEV_1 < 80% predicted), but statistical significance was not achieved (odds ratio = 1.03 per Hz, 95% CI 1–1.06, P = .07). No statistically significant re-

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Table 2. Agreement Between Spontaneous and Standardized Breathing for the Presence of Crackles and Wheezes

Adventitious Lung Sound	Spontaneous Breathing	Standardized Breathing		Agreement (%)	Cohen's kappa (95% CI)	*P*
		Absent	Present			
Crackles						
Inspiratory	Absent	84 (72.4%)	13 (11.2%)	76.7	0.13 (−0.08 to 0.34)	.16
	Present	14 (12.1%)	5 (4.3%)			
Expiratory	Absent	110 (94.8%)	2 (1.7%)	94.8	−0.02 (−0.05 to 0)	.79
	Present	4 (3.4%)	0 (0%)			
Wheezes						
Inspiratory	Absent	110 (94.8%)	2 (1.7%)	95.7	0.26 (−0.18 to 0.71)	.004
	Present	3 (2.6%)	1 (0.9%)			
Expiratory	Absent	84 (72.4%)	14 (12.1%)	80.2	0.32 (0.11 to 0.54)	.001
	Present	9 (7.8%)	9 (7.8%)			

N = 116 subjects.

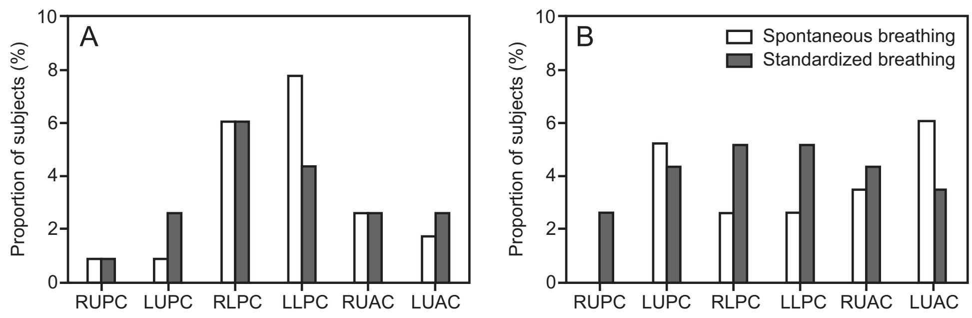

Fig. 4. Proportion of subjects with inspiratory crackles (A) or expiratory wheezes (B) in each chest location during spontaneous and standardized breathing (*N* = 116 subjects). LLPC = left lower posterior chest; RLPC = right lower posterior chest; LUAC = left upper anterior chest; RUAC = right upper anterior chest; LUPC = left upper posterior chest; RUPC = right upper posterior chest.

lationship was found between mMRC score ≥ 1 and the intensity or frequency of normal lung sounds.

Discussion

In general, we found low agreement in identifying crackles and wheezes between the two methods of breathing. Adventitious lung sounds had nearly the same frequency during spontaneous breathing as during standardized breathing, but they were often not heard in the same subjects. Normal lung sounds had higher intensity and frequency during standardized breathing than during spontaneous breathing. There were small differences in the associations found between lung sounds and lung disease indicators depending on the method of breathing.

Adventitious Lung Sounds

Inspiratory crackles were heard in 16.4% of the subjects during spontaneous breathing. This is a higher frequency than the 8.4% registered in primary care patients examined with an ordinary stethoscope, of whom almost one third had a known pulmonary disease.[22] It might be expected that more crackles are identified when 2 observers listen to 10-s recordings (each containing ≥ 2 breathing cycles) from 6 chest locations, than when a single physician listens to only 1 full breath at each chest location with an ordinary stethoscope.[23] In addition, when microphones are used, crackles with high-frequency components are easily heard, which would not be the case when using an ordinary stethoscope.[24]

Crackles are associated with critical transitions in the airway volume,[25,26] so it could also be expected that the frequency of crackles may be influenced by the breathing mode. The higher intensity of the normal lung sounds during standardized breathing indicate that the air flow (1.5 L/s) was probably greater than the air flow generated during spontaneous breathing.[3] The perception of crackles may be hampered by loud normal lung sounds,[27] but the decreased frequency of crackles (15.5%) due to this masking effect during standardized breathing might have been counterbalanced by a higher rate of crackles when the

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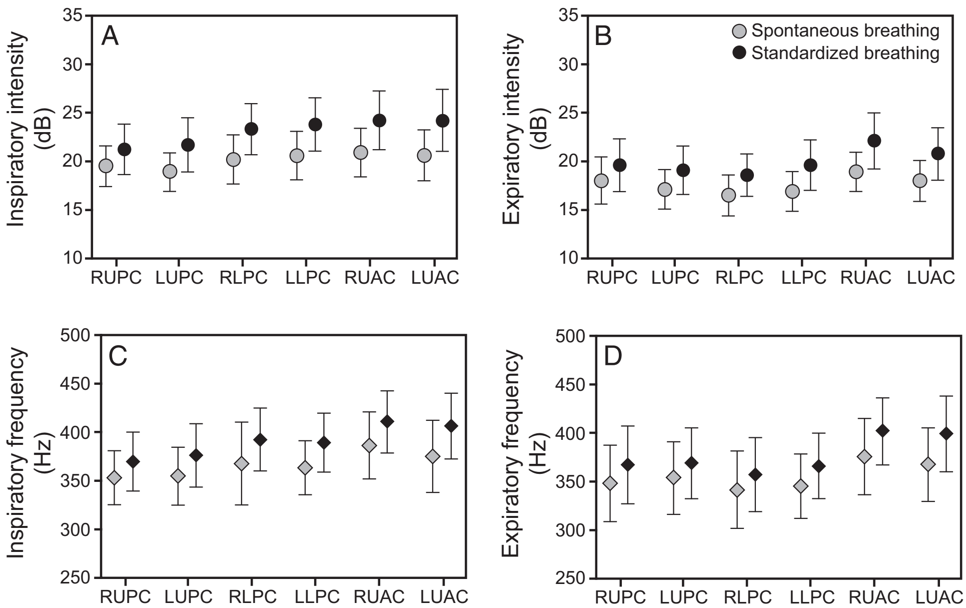

Fig. 5. Mean intensity (A and B) and median frequency (C and D) of normal lung sounds during spontaneous and standardized breathing at each chest location. Data are presented as mean ± SD. $P < .001$ for all comparisons. LLPC = left lower posterior chest; RLPC = right lower posterior chest; LUAC = left upper anterior chest; RUAC = right upper anterior chest; LUPC = left upper posterior chest; RUPC = right upper posterior chest.

inspiratory volume increased.[25,26] The proportion of subjects with crackles was also found to be similar when lung sounds were recorded during spontaneous breathing and with modestly increased air flow (0.7–1.0 L/s) in patients with COPD.[5]

Expiratory wheezes were present in 15.5% of subjects during spontaneous breathing, when expiration usually is passive. This frequency is similar to the frequency reported in the primary care study by Melbye,[22] in which wheezes were heard in 15.8% of subjects. Although not statistically significant, the frequency of expiratory wheezes was somewhat higher during standardized breathing than during spontaneous breathing (19.8% vs 15.5%). This was expected because forced expiration was often needed to obtain the target flow. The increased expiratory air flow could then be sufficient to achieve a critical transpulmonary pressure needed for generating wheezes, which was not achieved during spontaneous breathing.[28] It has been found that healthy subjects produce wheezes during forced expiratory maneuvers,[29] and even a higher frequency of wheezes could have been obtained with a further increase in target air flow.

The difference in air flow is not the only explanation for the low agreement in finding crackles and wheezes between the 2 modes of breathing. The considerable instability of generated adventitious lung sounds, even within short time frames, can also be an important factor. In some inter-observer studies in which observers have listened to the same subjects following each other, kappa agreement has been as low as 0.32–0.43 in reporting crackles and 0.43–0.51 in reporting wheezes.[30,31] A real change in the presence of the adventitious sounds probably contributed to the low agreement in these studies, because higher agreements have been found when the observers listen to the same lung sound recordings.[15,27] When listening to our recordings, we frequently observed that, in the same recording, crackles or wheezes can be present in some respiratory cycles and absent in others. In healthy people, which was the case of the majority of subjects included, these unstable adventitious lung sounds likely reflected a dynamic change in the airways in most instances rather than a permanent pathophysiology.[32,33] In some participants, crackles or wheezes were identified with both methods. These adventitious sounds are probably more stable in nature than the crackles and wheezes found with only one mode of breathing. Crackles have been found to be rather stable in patients with established lung conditions.[7] In addition, crackles and wheezes may be more or less distinct and easily perceived, whereas "difficult sounds" may be subject to more disagreement. The rigorous classification procedure implemented in this study for confirming the observers' findings probably reduced the impact of the variation between observers in perceiving and describing lung sounds. However, some adventitious sounds that could have been initially identified by a third observer were probably missed in each mode of breathing.

With regard to associations with lung disease indicators, wheezes were found to be related with dyspnea (mMRC ≥ 1) with standardized air flow, and the same tendency was observed with spontaneous air flow. Wheezes have been

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previously associated with the St George Respiratory Questionnaire symptoms score, where scoring of dyspnea is included.[34] No other relationships between lung disease indicators and adventitious lung sounds were found. The low proportion of subjects with crackles or wheezes may explain the absence of statistically significant results. Future studies should explore associations between lung disease indicators and adventitious lung sounds in a larger sample to draw more definitive conclusions on the role of air flow.

Normal Lung Sounds

The mean intensity and median frequency of normal lung sounds during inspiration and expiration were higher with standardized air flow than with spontaneous air flow in all chest locations. These results agree with findings from previous studies, including small samples of younger healthy subjects[4,35] and patients with COPD.[5] However, in the case of intensity, these differences seem to be minor (1.5–3.7 dB) in comparison with differences reported as clinical meaningful (5–10 dB).[4] The mean intensity and median frequency found with both breathing methods were within the range of values of normal lung sounds in healthy subjects.[4,35,36]

Relationships between normal lung sounds and lung disease indicators were found only during spontaneous air flow. This finding may be related to the fact that lung sounds generated during standardized flow show less inter-individual variation than sounds generated during spontaneous flow and are associated with a low intra-individual variability.[37,38] Expiratory mean intensity and median frequency were positively associated with a history of heart or lung diseases, and inspiratory median frequency seemed to be associated with reduced lung function ($FEV_1 < 80\%$ predicted. These results are in line with previous studies showing that higher expiratory intensities are related with bronchoconstriction and airway inflammation[39] and higher median frequencies are related with bronchoconstriction and pneumonia.[40,41] To screen lung diseases, it may be more informative to use spontaneous air flow when evaluating normal lung sounds. The next step might be to explore whether normal lung sounds recorded during spontaneous or standardized air flow are also equally sensitive for evaluating treatment.

Study Limitations

There are several limitations to the present study. First, the sample included 116 subjects, which, according to Sim et al,[42] is enough to detect a statistically significant kappa of 0.4 with 10–20% positive ratings (presence of crackles/wheezes) by 2 methods (minimum subjects required was 66). However, the study was underpowered for evaluating associations between lung sounds and disease indicators in a general population, particularly after observing the considerable instability of adventitious sounds. Presence of heart or lung disease was assessed through self-report, which only represents diseases known by the subjects. The participants were aged ≥ 40 y, which means that our findings cannot be generalized to the younger general population. Future studies with larger samples and with younger subjects (including children and young adults) should be conducted. Lung sounds were recorded at 6 selected chest locations that are routinely used in clinical practice, but only 4 sites matched standardized locations defined by CORSA guidelines.[6] This may limit comparison of these results with other studies. During standardized air flow, all subjects were instructed to breathe at a target air flow of 1.5 L/s. This approach, although recommended by CORSA and used in a number of other studies,[4,5,35] does not take into account the different characteristics of each subject, such as sex, body size, and thoracic dimensions. Indeed, breathing at fixed target flows may be demanding, particularly in lightweight subjects (~50 kg), for whom 1.5 L/s constitutes a high flow (30 mL/s/kg).[17] When analyzing the performance of subjects during target air flow, we observed that subjects complied more easily with the expiratory target air flow (1.5 ± 0.4 L/s) than with the inspiratory (1.2 ± 0.3 L/s). This was also demonstrated by the difference in ICC of air flow (inspiratory 0.70 vs expiratory 0.85). To obtain comparable air flows, future studies could use personalized air flows (eg, 10–15% of the predicted maximum peak air flow), a method that is also recommended by CORSA.[6]

Conclusions

In a general population, the method of breathing had an impact on both adventitious and normal lung sounds. Although adventitious lung sounds were found with similar frequency between spontaneous and standardized breathing, less than half of the subjects with such lung sounds were identified with both methods of breathing. In addition, the intensity and frequency of normal lung sounds during standardized breathing was higher than during spontaneous breathing. Despite these differences, neither method of breathing was found to be superior in terms of reflecting associations between lung sounds and lung disease indicators.

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REFERENCES

1. Bohadana A, Izbicki G, Kraman SS. Fundamentals of lung auscultation. N Engl J Med 2014;370(8):744-751.

2. Sovijärvi ARA, Dalmasso F, Vanderschoot J, Malmberg LP, Righini G, Stoneman SAT. Definition of terms for applications of respiratory sounds. Eur Respir Rev 2000;10(77):597-610.
3. Kiyokawa H, Pasterkamp H. Volume-dependent variations of regional lung sound, amplitude, and phase. J Appl Physiol 2002;93(3):1030-1038.
4. Fiz JA, Jane R, Lozano M, Gomez R, Ruiz J. Detecting unilateral phrenic paralysis by acoustic respiratory analysis. PLoS ONE 2014;9(4):e93595.
5. Jácome C, Marques A. Computerized respiratory sounds are a reliable marker in subjects with COPD. Respir Care 2015;60(9):1264-1275.
6. Rossi M, Sovijärvi ARA, Piirilä P, Vannuccini L, Dalmasso F, Vanderschoot J. Environmental and subject conditions and breathing manoeuvres for respiratory sound recordings. Eur Respir Rev 2000;10(77):611-615.
7. Vyshedskiy A, Ishikawa S, Murphy RL Jr. Crackle pitch and rate do not vary significantly during a single automated-auscultation session in patients with pneumonia, congestive heart failure, or interstitial pulmonary fibrosis. Respir Care 2011;56(6):806-817.
8. Murphy RL. Special articles: in defense of the stethoscope. Respir Care 2008;53(3):355-369.
9. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromsø study. Int J Epidemiol 2012;41(4):961-967.
10. Berry MP, Martí J-D, Ntoumenopoulos G. Inter-rater agreement of auscultation, palpable fremitus, and ventilator waveform sawtooth patterns between clinicians. Respir Care 2016;61(10):1374.
11. Figueroa-Casas JB, Broukhim A, Vargas A, Milam L, Montoya R. Inter-observer agreement of spontaneous breathing trial outcome. Respir Care 2014;59(9):1324.
12. Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2016. Available at: http://goldcopd.org. *Accessed June 20, 2018*.
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.
14. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324-1343.
15. Melbye H, Garcia-Marcos L, Brand P, Everard M, Priftis K, Pasterkamp H. Wheezes, crackles and rhonchi: simplifying description of lung sounds increases the agreement on their classification: a study of 12 physicians' classification of lung sounds from video recordings. BMJ Open Respir Res 2016;3(1):e000136.
16. Dinis J, Campos G, Rodrigues J, Marques A. Respiratory sound annotation software. *Proc Int Conf Health Informatics* 2012;183-188.
17. Pasterkamp H, Powell RE, Sanchez I. Lung sound spectra at standardized air flow in normal infants, children, and adults. Am J Respir Crit Care Med 1996;154(2 Pt 1):424-430.
18. Fleiss J. Reliability of measurement. In: *Design and analysis of clinical experiments*, Fleiss J, ed. New York: John Wiley & Sons; 1986:1-32.
19. Kottner J, Audige L, Brorson S, Donner A, Gajewski BJ, Hrobjartsson A, et al. Guidelines for reporting reliability and agreement studies (GRRAS) were proposed. J Clin Epidemiol 2011;64(1):96-106.
20. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15(2):155-163.
21. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33(1):159-174.
22. Melbye H. [The usefulness of clinical pulmonary examination in the diagnosis of bronchial obstruction]. Tidsskr Nor Lægeforen 1998;118(13):1999-2003.
23. Dennison R. PASS CCRN! Missouri: Mosby, 2013.
24. Abella M, Formolo J, Penney DG. Comparison of the acoustic properties of six popular stethoscopes. J Acoust Soc Am 1992;91(4):2224-2228.
25. Pasterkamp H, Kraman SS, Wodicka GR. Respiratory sounds. Advances beyond the stethoscope. Am J Respir Crit Care Med 1997;156(3 Pt 1):974-987.
26. Vyshedskiy A, Alhashem RM, Paciej R, Ebril M, Rudman I, Fredberg JJ, et al. Mechanism of inspiratory and expiratory crackles. Chest 2009;135(1):156-164.
27. Kiyokawa H, Greenberg M, Shirota K, Pasterkamp H. Auditory detection of simulated crackles in breath sounds. Chest 2001;119(6):1886-1892.
28. Ploysongsang Y, Baughman RP, Loudon RG, Rashkin MC. Factors influencing the production of wheezes during expiratory maneuvers in normal subjects. Respiration 1988;54(1):50-60.
29. Fiz JA, Jané R, Homs A, Izquierdo J, García MA, Morera J. Detection of wheezing during maximal forced exhalation in patients with obstructed airways. Chest 2002;122(1):186-191.
30. Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. Lancet 1988;1(8590):873-875.
31. Holleman DR Jr., Simel DL, Goldberg JS. Diagnosis of obstructive airways disease from the clinical examination. J Gen Intern Med 1993;8(2):63-68.
32. Thacker RE, Kraman SS. The prevalence of auscultatory crackles in subjects without lung disease. Chest 1982;81(6):672-674.
33. Workum P, Holford SK, Delbono EA, Murphy RLH. The prevalence and character of crackles (rales) in young women without significant lung disease. Am Rev Respir Dis 1982;126(5):921-923.
34. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145(6):1321-1327.
35. Fiz JA, Gnitecki J, Kraman SS, Wodicka GR, Pasterkamp H. Effect of body position on lung sounds in healthy young men. Chest 2008;133(3):729-736.
36. Pasterkamp H, Sanchez I. Effect of gas density on respiratory sounds. Am J Respir Crit Care Med 1996;153(3):1087-1092.
37. Sanchez I, Vizcaya C. Tracheal and lung sounds repeatability in normal adults. Respir Med 2003;97(12):1257-1260.
38. Mahagnah M, Gavriely N. Repeatability of measurements of normal lung sounds. Am J Respir Crit Care Med 1994;149(2):477-481.
39. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Lung sound analysis can be an index of the control of bronchial asthma. Allergol Int 2017;66(1):64-69.
40. Malmberg LP, Sovijarvi AR, Paajanen E, Piirila P, Haahtela T, Katila T. Changes in frequency spectra of breath sounds during histamine challenge test in adult asthmatics and healthy control subjects. Chest 1994;105(1):122-131.
41. Sánchez Morillo D, Astorga Moreno S, Fernández Granero MÁ, León Jiménez A. Computerized analysis of respiratory sounds during COPD exacerbations. Comput Biol Med 2013;43(7):914-921.
42. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther 2005;85(3):257-268.