

RESEARCH ARTICLE**Lung Sounds in Bronchial Asthma****Author**

Yukio Nagasaka*, Michiko Tsuchiya

Affiliations

Rakuwakai Kyoto Pulmonary Center
Rakuwakai Otowa Hospital
Otowachinji-cho 2, Yamashina-ku, Kyoto 607-8062, Japan

***Corresponding author**

Yukio Nagasaka
Phone +81 75 593 4111
Fax +85 75 581 6935
E-mail: pulmedyn228jp@yahoo.co.jp

Abstract

Since the historical article by Forgacs in 1978, many studies have clarified the changes of lung sounds due to airway narrowing as well as the mechanism of genesis of these sounds. Studies using bronchoprovocation have shown that an increase of the frequency and/or intensity of lung sounds was a common finding of airway narrowing and correlated well with lung function in bronchial asthma. Bronchoprovocation studies also showed that wheezing may not be as sensitive as changes in basic lung sounds in acute airway narrowing in adult asthmatics.

In lung sound analysis, narrow airways cause an increase in the frequency of breath sounds and lung sound intensity, implying when the patient has higher than normal breath sounds, i.e., bronchial sounds, he or she may have airway narrowing. Recent studies reported that this increase of breath sounds suggested worsening of airway inflammation in rather stable patients with bronchial asthma. As it is difficult to detect subtle changes in lung sounds by auscultation alone, automated sound analysis will be expected.

Introduction

The stethoscope was introduced by Laennec 200 years ago. Since then, increased understanding of lung sounds in bronchial asthma encourages a use of the stethoscope in its management.^{1, 2} Auscultation of the chest offers real time information of the airways and is an optimal tool for monitoring fluctuating conditions in bronchial asthma.^{3,4} In this review, the authors summarized our previous review in 2012⁵ and added clinically useful findings since then.

Auscultation of the chest offers real time information on the pathophysiology of airways in bronchial asthma. Modern understanding and nomenclature of lung sounds started with a historical article by Forgacs in 1978.¹ At that time, asthma was recognized as a disease of repetitive bronchoconstriction and the wheezing was the only auscultatory finding in asthma. In mid-1980s, asthma was recognized as a chronic bronchial inflammatory disease.⁶⁻⁸

Recent studies show that lung sounds are useful tools to assess the airway inflammation in asthma even in asymptomatic and not wheezing asthma patients.^{3,4,9-11}

Nomenclature of lung sounds

An international agreement on lung sounds was reached at an International Symposium on Lung Sounds held in 1986¹² (Table 1). Lung sounds were divided into breath sounds and adventitious sounds. Normal breath sounds i.e., vesicular breath sounds are mostly inspiratory sounds with a soft quality. Bronchial breath sounds are heard around trachea and central airways in normal subjects and have a prominent expiratory component. Adventitious lung sounds were subdivided into continuous (wheezes, rhonchi) and discontinuous (crackles). The lung sound terminology used by physicians and co-medical personnel still needs more uniformity and acceptability as will be discussed.¹³⁻¹⁵

Table 1: Classification and nomenclature of lung sounds

Adopted from Mikami (Chest 1987, Ref. 12) and modified for this review

Bold letter names are discussed in this review.

Lung sounds

1. Breath sounds

(1) **Vesicular breath sounds**

(2) **Bronchial breath sounds**

2. Adventitious sounds

(1) Rales (sound source is in the lung)

1) Continuous adventitious sounds:

wheezes (high-pitched),

rhonchi (low-pitched, singular; rhonchus)

rumbling rhonchi (rumbling or snoring sounds)

2) Discontinuous adventitious sounds:

Coarse crackles

Fine crackles

(2) Others (sound source is in the pleura or the pericardium)

1) Hamman' sign

2) Pleural friction rub

Vesicular breath sounds are mostly inspiratory sounds with a soft quality. Bronchial breath sounds are heard around trachea and central airways in normal subjects. Bronchial breath sounds have a prominent expiratory component and harsher quality.^{16, 17} (Figure 1) Recent

studies disclosed that when bronchial breath sounds were heard in asymptomatic asthmatics, these subjects have subclinical airway inflammation.^{3, 4, 9-11} Wheezes are continuous adventitious lung sounds and are divided into polyphonic and monophonic.^{1, 12} (Figure 2) Rhonchi are low-pitched

continuous adventitious sounds. Sometimes rumbling sounds.^{18, 19} (Figure 3) The rhonchi are used for low pitched wheezes and sometimes are used to describe later.

Figure 1. Sound spectrogram of normal breath sounds, a: vesicular breath sound, b: bronchial breath sound

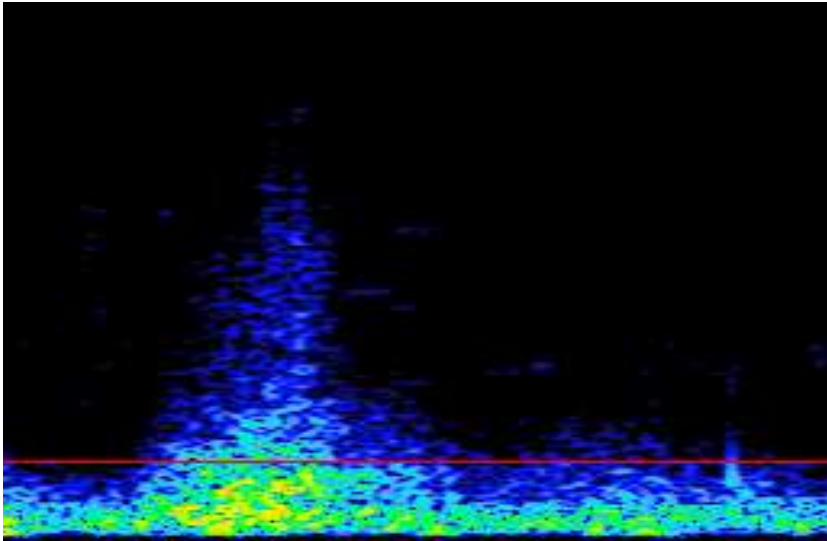


Figure 1a

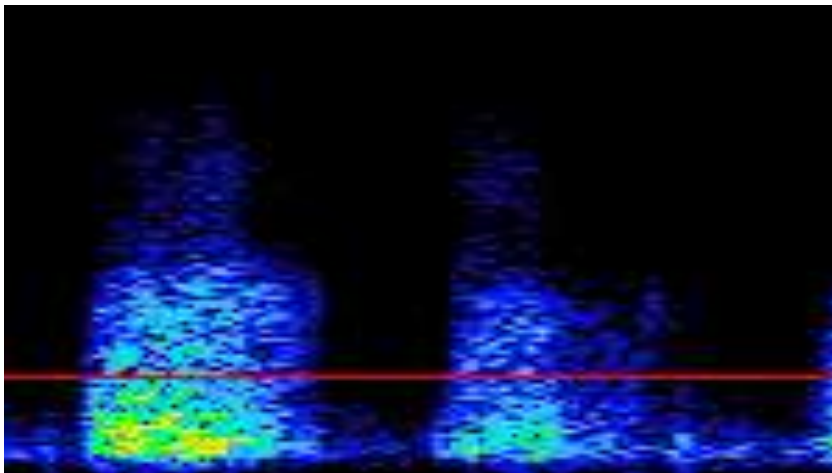


Figure 1b

Horizontal axis is time (Three seconds in this figure) and vertical axis is sound frequency (horizontal red line is 300 Hz) for the sound spectrogram. In the sound spectrogram, sound power is shown as brightness and color. Bigger peak in the left side shows the inspiratory sound and smaller peak in the right side shows the expiratory sound although expiratory sound is much bigger in bronchial sound than in vesicular sound.

Figure 2. Sound spectrogram of wheezes, a: monophonic wheezes, b: polyphonic wheezes.

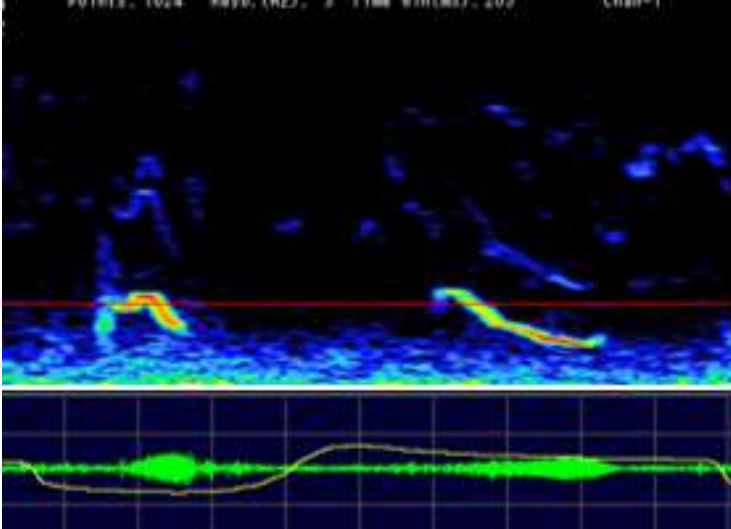


Fig. 2a

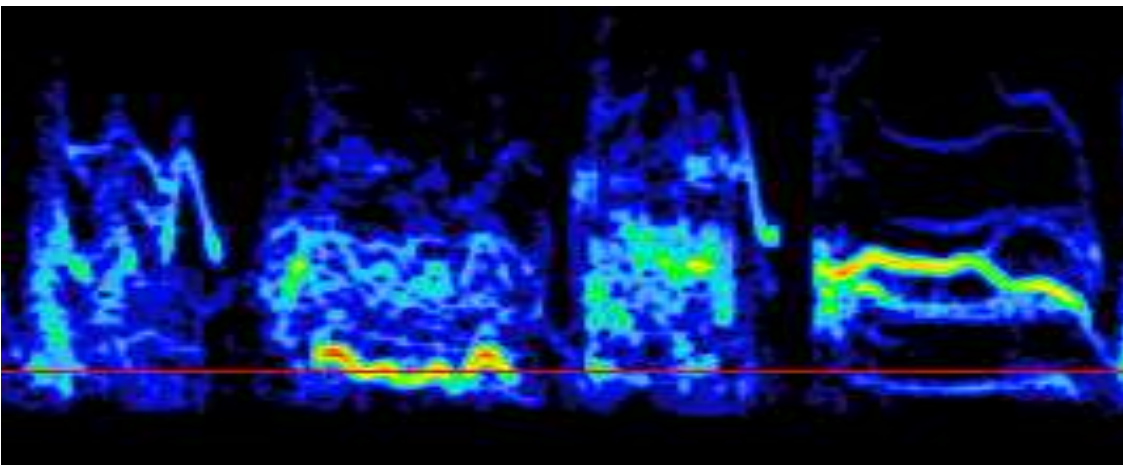


Fig. 2b

Horizontal axis is time (Three seconds in this figure 2a and seven seconds in figure 2b) and vertical axis is sound frequency (red horizontal line is 200 Hz). Figure 2a shows one respiratory cycle, inspiration (left) and expiration (right) and Figure2b shows two respiratory cycles. Horizontal bright wavy lines show wheezes.

Monophonic wheezes (Figure 2a) show one bright wavy line both in mid inspiratory and expiratory phase. Darker wavy lines at doubled frequency show harmonics of basic wheezes. Polyphonic wheezes (Figure 2b) show several wavy lines that have different shape in both inspiratory and expiratory phases.

Figure 3. Time-expanded wave-form of low pitch wheezes. (Figure 3a) and rumbling rhonchi (Figure 3b).

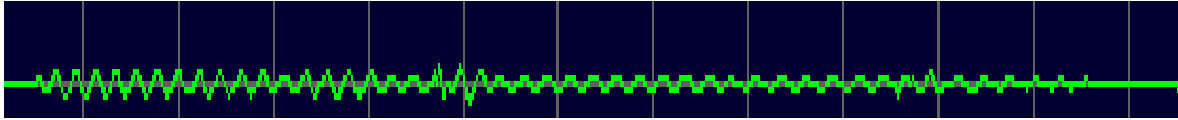


Figure 3a

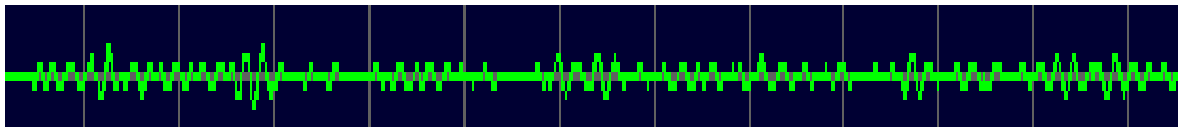


Figure 3b

Low pitch wheezes (Figure 3a) show regular continuous sine waves and sound power (amplitude of wave) and frequency (pitch of wave) varies little. Sine waves are waning gradually. Rumbling rhonchi (Figure 3b) show irregular sine waves both in amplitude and pitch that repeat wax and wane.

Bronchoprovocation tests and lung sounds

In bronchoprovocation tests, methacholine (MCh), acetylcholine (Ach), or histamine (His) are used. Ach and MCh act mainly on trachea, and His acts mainly on bronchi.²⁰ In children, wheezing and/or subjective symptoms such as cough and chest tightness was detected at a relatively low His concentration.^{21,22} In adults, significant increase of breath sounds as increase of the median frequency of breath sound (F50) was noted before wheezing appeared.²³⁻²⁵ At times, wheezing was not detected even when the FEV1 fell by 55% and 61% from the baseline.²⁵ Shreur and colleagues reported that, at similar levels of

airway obstruction, changes in both the frequency and intensity of sound with airflow were higher in asthmatics than in normal subjects.^{26,27}

Spence et al.²⁸ suggested that expiratory wheezes were produced when there was a flow limitation mainly in the central airway while inspiratory wheezes were produced when there was flow limitation in rather peripheral airways. Their finding supports our daily experience that small inspiratory wheezes can be heard only in a limited area on the chest wall.

Pasterkamp et al.²⁹ reported that in asthmatic children, airway narrowing induced by MCh was accompanied by a significant decrease of lung sound intensity

(LSI) at low frequencies during inspiration and an increase in LSI at high frequencies during expiration. These changes were fully reversed after inhalation of salbutamol.

Habukawa et al.³⁰ found that a change in the highest frequency of inspiratory breath sound (HFI) and expiratory breath sound (HFE) by MCh challenge corresponded with changes in the forced expiratory parameters. Shreur et al.³¹ found that, during allergen-induced asthmatic response, increase of LSI and induced wheezes were more prominent during a late asthmatic response (LAR) than in an early asthmatic response (EAR).

Niimi et al.³² reported that airway wall thickening occurred in patients with asthma and was not limited to those with severe disease. The degree of airway wall thickening related to the duration and the degree of airflow obstruction. Habukawa et al.³³ made a guinea pig asthma model and found that the LSI in the middle frequency range correlated well with peripheral airway wall thickness. These findings in morphological changes in asthma further support the findings in the bronchoprovocation studies that the breath sounds are sensitive indicator of airway narrowing in asthmatic patients.

Forced expiration and lung sounds

Studies using forced expiratory wheezes (FEW) contributed to analyze the

genesis of wheezing. Gavriely and colleagues³⁴⁻³⁶ found that flow limitation suggested by sudden decrease of transpulmonary pressure (Ptp) preceded the onset of FEW and the flutter of airway wall was a feasible mechanism for the generation of wheezing. They also suggested that, during a forced expiratory maneuver, the choke point moves peripherally and the frequency of wheezes changed in an inconsistent manner. This finding is in contrast with a stridor, stenotic sound of upper airways, that shows little fluctuation in frequency.

Shreur et al.³¹ found that FEW differed little between normal and asthmatic subjects but quiet lung sounds were lower in intensity and higher in pitch in asthmatics than in control subjects. Fiz et al.³⁷ found a linear inverse relationship between FEV1% (% FEV1/FVC) and the logarithm of number of FEW among all examined subjects including bronchial asthma, COPD and normal control subjects.³⁸ Korenbaum et al.³⁹ reported that the duration of FEW > 1.8 sec. was a sensitive index of bronchial obstruction.

Mechanism of wheeze generation

Studies using FEW indicated that the flow limitation was a necessary condition to produce wheezes.³⁴⁻⁴⁰ Korenbaum et al.⁴¹⁻⁴³ reported that the generation of FEW may be fitted with a

model of vortex shedding in the bronchial tree and suggested that vortex shedding in central airways are possible mechanisms for the generation of expiratory wheezes.

Gavriely et al.⁴⁴ introduced collapsible tubes as an experimental model of airway collapse and generation of wheezes. They found that the vortex-induced wall vibration and viscid flutter in a soft tube were the most probable mechanism for the production of wheezes. They also found that inspiratory wheezes were generated by the same flutter/flow limitation mechanisms as expiratory wheezes.⁴⁵

Akasaka et al.⁴⁶ inserted a small microphone in the bronchi of patients during their asthmatic attack and found that the wheezes were caused by the resonance of the bronchial wall when the vibrating frequency was coincident with its specific frequency. They also found a good correspondence between wheezes picked up inside of the bronchial tree and those recorded on the chest wall.

Wheezes need a certain speed of airflow to reach flow limitation that produce vortex-shedding and airway wall oscillation. Patients' effort to breathe in and out deeper and faster is useful in detecting wheezes. Wheezes are usually better heard over the trachea because of low-pass filtering effect of the lung, although some localized short wheezes and/or inspiratory wheezes may be

missed by tracheal auscultation alone.

Wheezing, rhonchi and rumbling rhonchi

Wheezes are continuous musical lung sounds¹ and have sinusoidal wave appearance on time-expanded wave-form analysis (TEWA)² (Figure 3). On sound-spectrogram, wheezes appear as thin wavy belts.^{18, 47} Wheezes with a single basal sound or only with its harmonics in sound-spectrogram are called monophonic wheezes. Wheezes with variable wavy belts other than harmonics in sound spectrogram are called polyphonic wheezes.⁴⁷ (Figure 2) Rietveld et al.⁴⁸ raised the efficacy of sound pattern recognition of wheezes during His challenge for detection of airway obstruction.

We found more inflammatory cells in induced sputum in patients with polyphonic and/or prolonged wheezes. Dissonant and thick polyphonic wheezes or prolonged wheezes suggest that the patients have severe airway inflammation that may need systemic corticosteroids for treatment.⁴⁹

Low-pitched continuous adventitious sounds with a dominated frequency of about 200 Hz or less have been called as rhonchi. There are two types of low-pitched continuous adventitious sounds. One is low-pitched wheeze that have whistling character and sinusoidal structures in TEWA. The other is rumbling

or snoring sound that have a more complex and repetitive wave form in TEWA.¹⁸ (Figure 3) Low -pitch wheezes generally suggest airway narrowing of milder degree than high-pitched wheezes. Rumbling sounds suggest presence of retained bronchial secretion and airway inflammation as suggested by increase of FeNO (fractional exhaled nitric oxide) and eosinophils in peripheral blood, while the pulmonary function showed no difference between those with and without rumbling rhonchi.¹⁹ We are proposing to call the rhonchi with rumbling character as rumbling rhonchi and differentiate them from simple low-pitch wheezes.⁵⁰

Vesicular and bronchial breath sounds

Vesicular breath sounds are normal breath sounds and are primarily inspiratory sounds. Bronchial breath sounds have a prominent expiratory component and are normally heard in the upper chest close to the trachea, or high back between the scapulae. (Figure 1) Breath sounds with clearly audible expiratory component are called as bronchial breath sounds.

Breath sounds are generated in the large airways as turbulence in the airstream.⁵¹ Airflow turbulence begins at a critical flow velocity, when the Reynolds number exceeds approximately 2,000. The Reynolds number is defined by the tube diameter and length, flow velocity, dynamic

viscosity, kinematic viscosity and density of the flowing substance. Among these factors, airflow velocity is the major determinant of Reynolds number in respiration. In quiet breathing, Reynolds number exceeds 2,000 only in the trachea.⁵² Rapid or deep breathing increases the Reynolds number two or threefold easily and Reynolds number in the mainstem bronchi, lobar bronchi and major branches increase up to more than 2,000. By suggesting the patients to breath rapid and deeper a bit more than usual, more air turbulence will be generated in their central airways and auscultation on the chest wall becomes more efficient.

Three reasons are considered why inspiratory sounds are louder than expiratory sounds in normal vesicular breath sounds. 1. Inspiratory flow velocity is larger than expiratory flow velocity. 2. Inspiratory airflow hit the bifurcation of dividing bronchi and produce more airflow turbulence. 3. Inspiratory airflow and sounds towards chest wall and the stethoscope while expiratory airflow goes away from the chest wall.

Implication of vesicular and bronchial breath sounds in asthma

As shown in the section of bronchoprovocation tests, an increase in the LSI is a good index of acute bronchospasm.²¹⁻²⁶ When there is airway narrowing, bronchial airflow velocity increases and the

breath sounds are called as bronchial breath sounds.

We measured the LSI in adult asthmatics and found expiratory (E) / inspiratory (I) ratio of sound intensity was 0.27 and 0.72 in vesicular and bronchial breath sounds, respectively. The highest audible frequency of inspiratory (HFI) and expiratory (HFE) breath sounds was 250 Hz (HFE) / 420 Hz (HFI) in vesicular breath sounds and 470 Hz (HFE) / 490 Hz (HFI) in bronchial breath sounds.⁵³

As have been stated, acute airway narrowing results in an increase in LSI.²¹⁻²⁶ These changes in breath sounds were also observed in sustained airway narrowing. Habukawa et al.⁴ measured HFI and HFE in asymptomatic stable asthmatic children. They observed an inverse correlation between HFI and forced expiratory parameters. They treated those cases with inhaled corticosteroids (ICS) and found an increase in expiratory flow correlated with a decrease in HFI after treatment.

We reported that markers of airway inflammation, such as FeNO and percentage of inflammatory cells in induced sputum were higher in asthmatic patients who had bronchial breath sounds than in patients who had vesicular breath sounds.⁵⁴

Shimoda et al.³ compared the expiratory-inspiratory ratios of sound power in the low-frequency (100-195 Hz) range (E-I LF) from patients with asymptomatic

asthma with those of healthy controls. The E-I LF correlated with the sputum eosinophil ratio and FeNO,⁵⁵ airway impedance,^{56,57} and also correlated with the improvement of FEV1/FVC ratio during treatment with inhaled corticosteroids (ICS).⁵⁸ This study showed that louder expiratory breath sounds implied more eosinophilic airway inflammation in asymptomatic patients with asthma. They also reported that E/I LF and E/I MF (middle frequency: 200-400 Hz) monitoring with 7-point lung sound recordings may be used to detect inflammation of the entire airway.¹⁰ Similar to respiratory function and FeNO, E/I MF was a useful indicator for monitoring the efficacy of ICS in asthmatic patients.⁵⁹ The combination of E/I MF and FeNO was useful to assess the condition of airway narrowing and the degree of airway inflammation.⁶⁰

These observations are in accordance with reports in the bronchial provocation tests. When expiratory breath sounds are clearly heard in asthmatic patients, these patients may have airway narrowing caused by airway inflammation. However, sometimes it is difficult to tell exactly whether the sounds detected are vesicular or bronchial in clinical settings. Automated analysis of lung sounds is expected to overcome these difficulties.

Computerized automated analysis of lung sounds

In 1983, Charbonneau et al.⁶¹ raised the possibility of computerized automated analysis of tracheal sounds to discriminate asthmatics from normal subjects. They found that the sound spectral features, i.e., frequency (Hz) vs. amplitude of asthmatic subjects, were different from those of normal subjects. In 1991, Tinkelman et al.⁶² used computer digitized airway phonography (CDAP) and tried to differentiate asthmatic from normal children by analyzing the intensity of lung sounds. They were able to differentiate wheezing from non-wheezing subjects and postulated that CDAP was a reproducible and quantifiable method to detect airway obstruction. In 1996, Malmberg et al.⁶³ evaluated lung sounds of a few typical lung diseases by a computerized method called self-organizing map (SOM). They found that SOM was useful to differentiate subjects with emphysema from normal controls but not very effective to differentiate subjects with asthma and fibrosing alveolitis from normal controls. Lenclud et al.⁶⁴ studied the usefulness of the tracheal sound analyzer ELEN-DSA, which allows automatic detection of wheezes from recorded sounds, but this was shown to have relatively poor characteristics for detecting wheezing. In 1999, Rietveld et al.⁶⁵ recorded the tracheal sound of normal and

asthmatic subjects and detected wheezes by the computerized recognition of differences in the breath sound spectrum. They found that wheezes detected by this method were observed when there was a decrease of more than 20% in the peak expiratory flow rate (PEF) (sensitivity, 88%; specificity, 92%). Those studies published before 2000 aimed at computerized monitoring of breath sounds and/or wheezes in asthmatic patients but were not automated yet.

Gavriely⁶⁶ published a technological approach to automated digital data acquisition and processing of breath sounds in 1995, and he developed a commercial device (PulmoTrack [®]) that enabled the automated and continuous monitoring of wheezes. Several reports suggested the usefulness of this device.⁶⁷⁻⁶⁹ Boner et al.⁶⁸ reported that T_w/T_{tot} (= duration of wheeze / duration of recording) correlated with changes in the peak expiratory flow rate (PEF). Bibi et al.⁶⁹ reported on the usefulness of cough and wheeze monitoring in pediatric asthma and found that asthmatic children who had increased cough rates after Albuterol inhalation experienced longer hospital stays.

Recently, Habukawa et al.^{70, 71} reported that the airflow and body size of children can be estimated by analyzing tracheal and chest wall breath sounds. They are planning to develop an automated lung sound analyzer that will detect changes in

basic breath sounds. Their study enables the automated correction of breath sounds by body size and airflow by analyzing breath sounds alone and will make automated analysis of breath sounds easier. These studies that analyzed basic breath sounds, are expected to improve the sensitivity and specificity of automated breath sound analysis in the management of asthma.

Summary

The results from broncho-provocation studies showed that an increase in the frequency and intensity of breath sounds is more sensitive than the

appearance of wheezing. Flow limitation and subsequent flutter of the airway wall are believed to be the mechanism of the genesis of wheezing. Changes in breath sounds in airway narrowing are explained by an increase in the flow, which increases the Reynolds number and airflow turbulence. Automated and computerized analysis of lung sounds is expected to make lung sounds more useful in the management of bronchial asthma.

References

1. Forgacs P. The functional basis of pulmonary sounds. *Chest* 1978; 73: 399-405.
2. Murphy RL. In defense of the stethoscope. *Respir Care* 2008; 53: 355-69.
3. Shimoda T, Nagasaka Y, Obase Y, Kishikawa R, Iwanaga T. Prediction of airway inflammation in patients with asymptomatic asthma by using lung sound analysis. *J Allergy Clin Immunol Pract.* 2014; 2: 727-32.
4. Habukawa C, Nagasaka Y, Murakami K, Takemura T. High-pitched breath sounds indicate airflow limitation in asymptomatic asthmatic children. *Respirol.* 2009; 14: 399-403.
5. Nagasaka Y. Lung Sounds in Bronchial Asthma. *Allergol Int.* 2012; 61: 353-63
6. Holtzman MJ, Fabbri LM, O'Byrne PM, Gold BD, Aizawa H, Walters EH, et al. Importance of airway inflammation for hyperresponsiveness induced by ozone. *Am Rev Respir Dis.* 1983; 127:686-90
7. Aizawa H, Chung KF, Leikauf GD, Ueki I, Bethel RA, O'Byrne PM, et al.. Significance of thromboxane generation in ozone-induced airway hyperresponsiveness in dogs. *J Appl Physiol* 1985; 59: 1918-23.
8. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31: 143-178.
9. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Lung sound analysis and airway inflammation in bronchial asthma. *J Allergy Clin Immunol Pract.* 2016; 4: 505-11.
10. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Ishimatsu A, Kishikawa R, et al. Lung sound analysis helps localize airway inflammation in patients with bronchial asthma. *J Asthma Allergy.* 2017; 10: 99-108.
11. Habukawa C, Murakami K, Horii N, Yamada M, Nagasaka Y. Evaluation of airflow limitation using a new modality of lung sound analysis in asthmatic children. *Allergology Int* 2015; 64:84-9.
12. Mikami R, Murao M, Cugell DW, Chretien J, Cole P, Meier-Sydow J, et al. International symposium on lung sounds, synopsis of proceedings. *Chest* 1987; 92: 342-5.
13. Pasterkamp H, Montgomery M, Wiebicke W. Nomenclature used by health care professionals to describe breath sounds in asthma. *Chest* 1987; 92: 346-52.
14. Wilkins RL, Dexter JR, Murphy RL Jr, DelBono EA. Lung sound nomenclature survey. *Chest* 1990; 98: 886-9.

15. Nagasaka Y, Yasuda S, Ieda Y, Sugiura T. Changes of lung sound nomenclature in Japan since 1985 World Congress of Lung Sound. 32nd International Lung Sound Association Meeting, Tokyo, 2007.
16. Dalmay F, Antonini MT, Marquet P: Acoustic properties of the normal chest. *Eur Respir J* 1995; 8: 1761-9.
17. Nagasaka Y, Shimoda T, Yasuda S, Murakami K, Habukawa C. Numerical description of vesicular and bronchial breath sounds. 36th International Lung Sound Association Meeting, Manchester, UK, 2011.
18. Nagasaka Y, Yasuda S, Murakami K, Habukawa C, Kiyokawa H: Are “rhonchi” just a low pitch wheezes denoting bronchial narrowing or rumbling sounds denoting bronchial secretion? 35th International Lung Sound Association Meeting, Toledo, OH, USA, 2010
19. Nagasaka Y, Tsuchiya M, Nakanishi Y, Sakaguchi C, Ajimizu H, Morikawa N, et al. Rumbling rhonchi. Rumbling rhonchi in bronchial asthma: Their relation to airway inflammation. 42nd International Lung Sound Association Meeting, Tromso, Finland, 2017
20. Molfino NA, Slutsky AS, Hoffstein V, McClean PA, Rebeck AS, Drazen JM, et al. Changes in cross-sectional airway areas induced by methacholine, histamine and LTC₄ in asthmatic subjects. *Am Rev Resp Dis* 1992; 146: 577-80.
21. Beck R, Dickson U, Montgomery MD, Mitchell I. Histamine challenge in young children using computerized lung sound analysis. *Chest* 1992; 102: 759-63.
22. Malmberg LP, Sorva R, Sovijarvi ARA. Frequency distribution of breath sounds as an indicator of bronchoconstriction during histamine challenge test in asthmatic children. *Pediatr Pulmonol* 1994; 18: 170-7.
23. Malmberg LP, Sovijarvi ARA, 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: 122-132.
24. Anderson K, Aitken S, Carter R, Macleod JES, Moran F. Variation of breath sound and airway caliber induced by histamine challenge. *Am Rev Respir Dis* 1990; 141: 1147-50
25. Spence DPS, Bentley S, Evans DH, Morgan MDL. Effect of methacholine induced bronchoconstriction on the spectral characteristics of breath sounds in asthma. *Thorax* 1992; 47: 680-3.
26. Shreur HJW, Vanderschoot J, Zwinderman AH, Dijkman JH, Sterk PJ. Abnormal lung sounds in patients with

- asthma during episodes with normal lung function. *Chest* 1994; 106: 91-9.
27. Shreur HJW, Vanderschoot J, Zwinderman AH, Dijkman JH, Sterk PJ. The effect of methacholine-induced acute airway narrowing on lung sounds in normal and asthmatic subjects. *Eur Respir J* 1995; 8: 257-65.
 28. Spence DP, Graham DR, Jamieson G, Cheetham BM, Calverley PM, Earis JE. The relationship between wheezing and lung mechanics during methacholine-induced bronchoconstriction in asthmatic subjects. *Am J Respir Crit Care Med* 1996; 154: 290-4.
 29. Pasterkamp H, Consunji-Araneta R, Oh Y, Holbrow J. Chest surface mapping of lung sounds during methacholine challenge. *Pediatr Pulmonol* 1997; 23: 21-30.
 30. Habukawa C, Murakami K, Mochizuki M, Takami S, Murayama R, Tadaki H, et al. Changes in the highest frequency of breath sounds without wheezing during methacholine inhalation challenge in children. *Respirology*, 2010; 15: 485-90.
 31. Shreur HJW, Diamant Z, Vanderschoot J, Zwinderman AH, Dijkman JH, Sterk PJ. Lung sounds during allergen-induced asthmatic response in patients with asthma. *Am J Respir Crit Care Med* 1996; 153: 1474-80.
 32. Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med* 2000; 162: 1518-23.
 33. Habukawa C, Murakami K, Sugitani K, Ohtani T, Saputra GP, Kashiwayama K, et al. Changes in lung sounds during asthma progression in a guinea pig model. *Allergology Int* 2016; 65: 425-31.
 34. Gavriely N, Kelly KB, Grotberg JB, Loring SH. Forced expiratory wheezes are a manifestation of airflow limitation. *J Appl Physiol* 1987; 62: 2398-403.
 35. Gavriely N, Kelly KB, Grotberg JB, Loring SH. Critical pressure required for generation of forced expiratory wheezes. *J Appl Physiol* 1989; 66: 1136-42.
 36. Beck R, Gavriely N. The reproducibility of forced expiratory wheezes. *Am Rev Respir Dis* 1990; 141: 1418-22.
 37. Fiz JA, Jane R, Salvatella D, Izquierdo J, Lores L, P Caminal P, et al. Analysis of tracheal sounds during forced exhalation in asthma patients and normal subjects. *Chest* 1999; 116: 633-8.
 38. Fiz JA, Jane R, Homs A, Izquierdo J, Garcia MA, Morera J. Detection of wheezing during forced exhalation in patients with obstructive airways. *Chest* 2002; 122: 186-91.

39. Pochektova IA, Korenbaum VI. Forced expiratory tracheal noise duration in bronchial obstruction among young men. Numerical description of vesicular and bronchial breath sounds [abstract]. The 34th Annual Conference of International Lung Sounds Association, Haifa, Israel, 2009.
40. Kraman SS. The forced expiratory wheeze. Its site of origin and possible association with lung compliance. *Respiration* 1983; 44: 189-96.
41. Korenbaum VI. Statistical simulation of vortex shedding on bronchial tree bifurcations as mechanism of tracheal forced expiratory wheezes origin healthy subjects [abstract]. The 34th Annual Conference of International Lung Sounds Association, Haifa, Israel, 2009.
42. Korenbaum VI, Safronova M, Dyachenko A, Pochektova IA. Statistical analysis of forced expiratory wheezes origin healthy subjects [abstract]. The 35th Annual Conference of International Lung Sounds Association, Toledo, OH, USA, 2010.
43. Dyachenko A, Korenbaum VI, Tagiltsev A. Measurements of forced expiratory noise over trachea and infrascapular region [abstract]. The 36th Annual Conference of International Lung Sounds Association, Manchester, UK, 2011.
44. Gavriely N, Palti Y, Alroy G, Grotberg JB. Measurement and theory of wheezing breath sound. *J Appl Physiol* 1984; 57: 481-92.
45. Gavriely N. Inspiratory wheezes and intra-thoracic inspiratory flow limitation [abstract]. The 34th Annual Conference of International Lung Sounds Association, Haifa, Israel, 2009
46. Akasaka K, Konno K, Ono Y, Mue S, Abe C. Acoustical studies on respiratory sounds in asthmatic patients. *Tohoku J Exp Med* 1975; 117: 323-33
47. Nagasaka Y, Yasuda S, Ieda Y, Komiya T, Hatanaka T, Sugitatu S, et al. An analysis of the pitch of the wheezing in bronchial asthma. *Clinical Pharmacology and Therapy*. 2004; 14: 547-52 (in Japanese with an English abstract).
48. Rietveld S, Dooijes EH, Rijssenbeek-Nouwens LHM, Smit F, Prins PJM, Kolk AMM, et al. Characteristics of wheeze during histamine-induced airway obstruction in children with asthma. *Thorax* 1995; 50: 143-8.
49. Nagasaka Y, Tsuchiya M, Minami T, Kominami R, Yamada R, Igarachi T, et al. Airway Inflammation and wheezes - monophonic or polyphonic. *J Jap Resp Soci*. 2013; 2: s353
50. Pasterkamp H. Psychoacoustics of auscultation. 42nd International Lung

- Sound Association Meeting, Tromso, Finland, 2017
51. Lehrer S. Understanding lung sounds. 3rd Ed New York: WB Saunders; 2002.
 52. Sera T, Tanishita K. Anatomical aspects of airway flow and gas transport in the pulmonary system. *Med Imag Tech* 2002; 20: 654-9. (in Japanese with an English abstract)
 53. Nagasaka Y, Shimoda T, Yasuda S, Murakami K, Habukawa C. Numerical description of vesicular and bronchial breath sounds. 35th International Lung Sound Association Meeting, Toledo, OH, USA, 2011.
 54. Nagasaka Y, Yasuda S, Ieda Y, Shimoda S, Habukawa C. Vesicular and broncho-vesicular sounds and airway inflammation in asthma. 30th International Lung Sound Association Meeting, Halkidiki, Greece, 2006.
 55. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Airway inflammation phenotype prediction in asthma patients using lung sound analysis with fractional exhaled nitric oxide. *Allergol Int.* 2017; 66: 581-5.
 56. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Peripheral bronchial obstruction evaluation in patients with asthma by lung sound analysis and impulse oscillometry. *Allergol Int.* 2017; 66: 132-8
 57. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Lung sound analysis and the respiratory cycle dependence of oscillometry in asthma patients. *Intern Med.* 2019; 58: 47-52.
 58. 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: 64-9
 59. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Lung sound analysis is useful for monitoring therapy in patients with bronchial asthma. *J Investig Allergol Clin Immunol.* 2017; 27: 246-51.
 60. Shimoda T, Obase Y, Nagasaka Y, Asai S. Phenotype classification using the combination of lung sound analysis and fractional exhaled nitric oxide for evaluating asthma treatment. *Allergol Int.* 2018; 67: 253-8.
 61. Charbonneau G, Racineux JL, Sudraud M, Tuchais E. An accurate recording system and its use in breath sounds spectral analysis. *J Appl Physiol.* 1983; 55: 1120-7.
 62. Tinkelman DG, Lutz C, Conner B. Analysis of breath sounds in normal and asthmatic children and adults using

- computer digitized airway phonography (CDAP). *Respir Med.* 1991; 85: 125-31.
63. Malmberg LP, Kallio K, Haltsonen S, Katila T, Sovijarvi ARA. Classification of lung sounds in patients with asthma, emphysema, fibrosing alveolitis and healthy lungs by using self-organizing maps. *Clin Physiol.* 1996; 16: 115-29.
64. Lenclud C, Cuttita G, Gansbeke DG, Visconti A, Muylem AV, Bellia A, et al. Evaluation of nocturnal bronchoconstriction by all night tracheal sound monitoring. *Thorax* 1996; 51: 694-8.
65. Rietveld S, Oud M, Rijssenbeek-Nouwens LHM, Vaghi D, Dooijes EH. Characteristics of diagnostic significance of spontaneous wheeze in children with asthma. Results of continuous in vivo sound recording. *J Asthma* 1999; 36: 351-8.
66. Gavriely N. Digital data acquisition and preprocessing of breath sounds. In: Gavriely N. *Breath sounds methodology*. Boca Raton, FL: CRC Press, 1995; p. 55-97.
67. Prodhon P, Dela Rosa RS, Shubina M, Haver KE, Matthews BD, Buck S, et al. Wheeze detection in pediatric intensive care unit: Comparison among physician, nurses, respiratory therapists, and a computerized respiratory sound monitor. *Respir Care* 2008; 53: 1304-9.
68. Boner AL, Piacentini GL, Peroni DG, Irving CS, Goldstein D, Gavriely N, Godfrey S. Children with nocturnal asthma wheeze intermittently during sleep. *J Asthma* 2010; 47: 290-4.
69. Bibi H, Gavriely N. Cough monitoring during bronchodilator administration in pediatric asthma. 34th International Lung Sound Association Meeting, Haifa, Israel, 2009.
70. Habukawa C, Murakami K, Horii N, Yamada M, Nagasaka Y. The influence of airflow and body size on breath sounds in healthy children. *Jpn J Clin Physiol* 2011; 41: 69-74.
71. Habukawa C, Murakami K, Endoh M, Horii N, Nagasaka Y. Treatment evaluation using lung sound analysis in asthmatic children. *Respirology.* 2017; 22: 1564-9