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SHORT COMMUNICATION

Novel method for sputum induction using the Lung Flute in patients with suspected pulmonary tuberculosis

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ABSTRACT

Background and objective: **The Lung Flute is a small self-powered audio device that generates sound waves, which vibrate in tracheobronchial secretions. This was a preliminary trial to evaluate the usefulness of the Lung Flute for sputum sampling in patients suspected of pulmonary tuberculosis (TB).**

Methods: **Thirty-four patients who were not expectorating sputum, but for whom sputum examination was required for the differential diagnosis of TB or other diseases, were enrolled in the study. Patients were instructed to blow out fast and hard through the Lung Flute and to repeat this for a total 20 sets of two blows each.**

Results: **Using the Lung Flute, sputum samples were collected within 10 or 20 min from 30 of 34 patients (88%). The device permitted a rapid diagnosis of TB in seven of 15 confirmed TB cases. In three patients acid-fast bacillus smears were positive. In four patients acid-fast bacillus smears were negative, but PCR tests for TB were positive. Hyperventilation-related symptoms occurred in three patients.**

Conclusions: **The application of the Lung Flute may represent a promising technique for the rapid diagnosis of pulmonary TB.**

Key words: audio device, diagnosis, polymerase chain reaction, sputum induction, tuberculosis.

SUMMARY AT A GLANCE

The usefulness of a small audio device for sputum sampling was evaluated in patients with suspected pulmonary tuberculosis. This preliminary report indicates that the device may be clinically useful for the rapid diagnosis of pulmonary tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a major health problem in the Western Pacific region, which accounts for about one-third of the global TB burden. In addition, TB is the leading cause of death worldwide, among individuals infected with HIV.

Sputum examination is a key diagnostic procedure for patients suspected of having pulmonary TB, including those for whom bronchoscopy is planned.[1,2] In addition, early identification of persons with TB remains the most effective way of preventing TB transmission. However, some patients are unable to produce sputum for examination. In such cases, sputum induction by aerosol inhalation and/or gastric aspiration has been preferred.[3,4]

The Lung Flute (Medical Acoustics, Buffalo, NY, USA) is a small self-powered audio device that generates sound with a frequency of 18–22 Hz with an output of 110–115 dB using a pressure of 2.5 cm H_2O. This sound wave, when generated at the mouth by mild exhalation, travels back down the tracheobronchial tree and vibrates in tracheobronchial secretions. The device consists of a mouth piece and a reed inside a 36.8-cm rectangular hardened plastic tube (Fig. 1). The Lung Flute supplements the natural mucus clearing system by artificially vibrating the airways and cilia at frequencies between 16 and 25 Hz.[5]

The Lung Flute was approved by the US Food and Drug Administration for sputum induction for diagnostic purposes in 2006, and it was registered for sale in the European Union as a Class 1 medical device in 2007. Recently, analysis of samples obtained using the Lung Flute revealed no statistically significant differences in biological markers or cell counts as compared with sputum samples induced using hypertonic saline in patients with chronic bronchitis (Sanjay Sethi, unpubl. data, 2006). There have been no published clinical studies examining its use in the diagnosis of TB. In a preliminary trial, we have evaluated the usefulness of the Lung Flute for sputum sampling in patients with suspected pulmonary TB.

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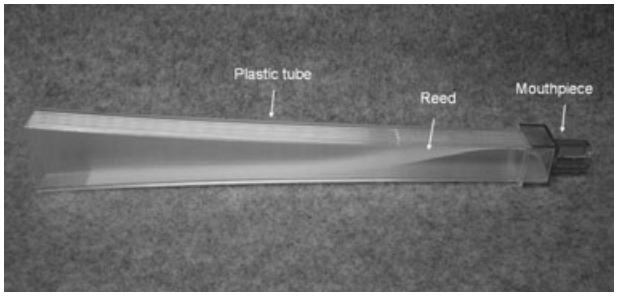

Figure 1 The Lung Flute consists of a mouth piece and a reed inside a 36.8-cm plastic tube.

METHODS

Thirty-four patients, who were not expectorating sputum spontaneously, but for whom sputum examination was required in order to make the differential diagnosis between TB and other diseases such as non-tuberculous mycobacterial (NTM) lung disease, were enrolled between December 2006 and August 2007. Patients were aged 18 years and over, and their CXR showed lesions such as scattered infiltrates and cavities, suggesting pulmonary TB. After initial screening based on symptoms and CXR at primary care clinics, patients suspected of having pulmonary TB were referred to the TB clinic at Tokyo Metropolitan Fuchu Hospital. Patients with hypoxaemia ($SaO_2 < 90\%$ by pulse oximetry) and those with bronchial asthma were excluded.

Experimental use of the Lung Flute was approved by the ethics committee at Tokyo Metropolitan Fuchu Hospital, as the device has yet to be cleared for use in patients by the Japanese authority. Individual Lung Flutes were supplied for each patient by Medical Acoustics, Tokyo, Japan. Written informed consent was obtained from all patients.

Of the 34 patients, 10 were male and 24 female, their mean age was 51 ± 19 (SD) years, and the numbers of never, former and active smokers were 23, 7 and 4, respectively. Radiologically, the disease was unilateral in 19 patients, and cavities were present in four patients.

On or close to the day of their first visit to the clinic, patients were instructed to blow out fast and hard through the Lung Flute and to repeat the manoeuvre for a total of 20 sets of two blows each. Printed instructions were handed to the patients, and they were directly supervised in the use of the device by physicians and nurses as follows:[6]

1 Sit with back straight. Tilt head slightly downward so throat and windpipe are wide open.
2 Inhale a little deeper than normal. Place lips completely around mouthpiece.
3 Blow out through the Lung Flute like blowing out a candle. It makes a fluttering sound.
4 Remove the mouthpiece from mouth and take a quick breath.
5 Replace the mouthpiece and blow out again. Wait 5 s while taking a couple of breaths.
6 Repeat for a total of 20 sets of two blows each.
7 Do not use diaphragm or abdominal muscles to try to force out more air.
8 Prepare a glass of water to drink after examination.
9 Cough up sputum into a sterile container.

For all patients, use of the Lung Flute and sputum induction were performed in a negative ventilation room, as a precautionary infection control measure. Patients remained in the room for up to 30 min, until they produced sputum. The microbiology laboratory complied with the guidelines for TB examination of the Japanese Society of Tuberculosis.[7]

Sputum specimens collected from patients were homogenized with a mucolytic agent (N-acetyl-L-cysteine) and decontaminant (1–2% sodium hydroxide solution) to render bacteria nonviable. Smears were prepared directly from the clinical specimens and were reconfirmed using concentrated preparations. Acid-fast bacillus (AFB) in stained smears was examined microscopically by the fluorochrome procedure. PCR nucleic acid amplification was performed on specimens using the AMPLICOR MTB assay (Roche, Basel, Switzerland), regardless of the AFB smear results. All specimens were cultured for mycobacteria using the mycobacterial growth indicator tube (MGIT) system (Becton Dickinson, Franklin Lakes, NJ, USA). The presence of *Mycobacterium tuberculosis* was confirmed by immunochromatography using anti-MPB64 monoclonal antibodies (Capilia TB assay; Becton Dickinson, Tokyo, Japan). Other species of mycobacteria were identified by the nucleic acid amplification test for *Mycobacterium avium* complex or the DNA-DNA hybridization technique (Kyokuto Pharmaceutical Industrial Co. Ltd., Tokyo, Japan).

The exact volume of sputum induced was recorded for 17 of 34 patients. Thirty patients completed a voluntary self-complete questionnaire after using the Lung Flute. The following questions were asked: (i) Is it easy to use the Lung Flute? (ii) Is it easy to understand the instructions on how to use the Lung Flute? (iii) Did you have a cough after using the Lung Flute? (iv) Did you produce sputum after using the Lung Flute? (v) Did you have increased phlegm after using the Lung Flute? and (vi) Any comments?

RESULTS

Using the Lung Flute, sputum samples were collected from 30 of 34 patients (88%), who did not produce sputum spontaneously. The procedure was successful in nine of 10 male patients (90%) and 21 of 24 female patients (88%). With regard to smoking status, it was successful in 11 current smokers and ex-smokers (100%) compared with 19 of 23 non-smokers (83%).

Patients expectorated sputum within 10 or 20 min after using the device. The volume of sputum induced after using the Lung Flute ranged from 1 to 5 mL, although data were recorded for only 17 patients. Nine patients expectorated 1 mL or less of sputum (Table 1).

The final diagnosis was confirmed as pulmonary TB in 15 patients (bacteriological diagnosis regardless of specimens in 12, clinical diagnosis in 3), NTM lung

Table 1 Number of patients by volume of sputum obtained with the Lung Flute

Volume of sputum (mL)	Number of patients (%)
<1	4 (24)
1	5 (29)
2	3 (18)
4	4 (24)
>5	1 (6)

Sputum volume was only recorded for 17 patients.

Table 2 Diagnostic yield when the Lung Flute was used in patients with tuberculosis ($n = 15$)

Yield	Number of patients (%)
Rapid TB diagnostic yield	7 (47)
AFB smear-positive/PCR-positive†	3 (20)
AFB smear-negative/PCR-positive†	4 (27)
AFB smear-negative/PCR-negative	5 (33)
Culture-positive	1 (7)
Culture-negative‡	4 (27)
Did not expectorate‡	3 (20)

† Culture-positive and Capilia TB assay-positive.

‡ See text for explanation of further examinations for the diagnosis of TB.

AFB, acid-fast bacillus; TB, tuberculosis.

disease in 9 (*M. avium* 3, *Mycobacterium gordonae* 1, *Mycobacterium xenopi* 1, *Mycobacterium fortiutum* 1, possible NTM 3) and other diseases in 10. A case that did not satisfy the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) microbiological criteria for NTM lung disease but met the clinical criteria was defined as a 'possible NTM case'.[8]

For three patients the AFB smear was positive and TB-PCR was also positive, while for four patients the AFB smear was negative but TB-PCR was positive (Table 2). 'Rapid TB diagnosis' was defined as AFB smear-positive and/or TB-PCR-positive in sputum on the day or a few days after the first visit, without awaiting the culture results. By this definition the Lung Flute yielded rapid TB diagnoses in seven of 15 TB patients (47%). In these patients, TB treatment was started immediately, without further examinations such as gastric juice sampling or fibreoptic bronchoscopy (FB). Within 6 weeks, the diagnosis was confirmed bacteriologically by positive culture results and a positive Capilia TB assay.

Of the five patients for whom a rapid diagnosis was not made (AFB smear-negative and TB-PCR-negative), one was AFB culture-positive and Capilia TB-positive in induced sputum, one was AFB culture-positive on follow-up sputum examination, and two were diagnosed from FB specimens. The remaining patient was diagnosed clinically after improvement with TB treatment, although the FB specimens were negative.

There were three patients who did not produce sputum but who were diagnosed with TB. One was AFB smear-positive on the day after sputum induction, one was QuantiFERON-TB 2G-positive but FB-negative, and one showed a clinical response to treatment.

Eight of the nine patients with NTM lung disease expectorated sputum with the Lung Flute. Only one patient was AFB smear-positive and *M. avium* PCR-positive, three were AFB culture-positive, and four were culture-negative in sputum induced with the Lung Flute.

The Lung Flute was user-friendly for 22 (73%) patients as assessed by the voluntary questionnaire completed by 30 of 34 patients. Eighteen (60%) patients answered that it was easy to understand the instructions. Cough after use of the Lung Flute was reported by 10 patients (33%), expectoration immediately after use by 8 (27%), and increased sputum by 4 (13%).

Adverse events associated with use of the Lung Flute included mild sore throat after blowing into the device in four patients (12%) and hyperventilation-related symptoms in three patients (9%), including dizziness in two (6%), headache in one (3%) and discomfort when breathing in one (3%). These symptoms did not necessitate medical treatment and improved rapidly.

DISCUSSION

Use of the Lung Flute enabled rapid diagnosis of TB in 47% of confirmed TB patients, who had produced no sputum prior to using the device. The device was user-friendly as assessed by a questionnaire completed by the patients.

No major adverse effects were observed when using the Lung Flute. Some patients complained of dizziness and discomfort, and were advised to take three or more slow breaths between the two sets of blows. Complaints of a sore throat may have been due to mucus collecting in the throat, and this could be reduced by drinking water after sputum induction.

Acid-fast bacillus smears were positive in some patients who produced 1 mL or less of sputum after using the Lung Flute. Warren *et al.* indicated that use of more than 5 mL of spontaneous sputum increased the sensitivity of AFB smears for *M. tuberculosis*.[9] However, the relationship between volume of induced sputum and sensitivity for diagnosis of TB has not been well studied. Brown *et al.* suggested that there was no association between sputum volume and positive culture results.[10]

To our knowledge, this is the first report of the clinical use of the Lung Flute in diagnosis of TB. The device may represent a new technology for sputum induction for the diagnosis of pulmonary TB. The Lung Flute for sputum induction was invented recently by Hawkins in the USA. Tracheal ciliary beating motion creates vibrations at 25 Hz that help to clear mucus.[11] The Lung Flute artificially produces sound that resonates with the natural frequency and consequently makes mucus secretions thinner and

more easily expelled by coughing.[5] Although the Lung Flute depends on patient effort, it is non-invasive and easy to use. The device does not require special equipment or an electric power supply, and the patient need not have an empty stomach before using it. Patients can easily carry the device and use it at home repetitively.

Generally, an induced sputum sample can be obtained by having the patient inhale a hypertonic saline mist for a patient who cannot cough up sputum on his or her own. In addition, repeated sputum induction could considerably improve diagnostic sensitivity for the diagnosis of pulmonary TB.[12] Microscopic examination of three consecutive sputum specimens is recommended in patients suspected of having pulmonary TB.[13] But, most patients feel discomfort of throat during the inhalation of irritant hypertonic saline. In clinical practice, single induced sputum specimen has been obtained for patients who are unable to produce sputum. If effective and convenient sputum sampling can be performed at the first visit to a medical provider, a physician may make a rapid diagnosis of pulmonary TB and the early triage of patients who have infectious TB. In such sense, using the Lung Flute may a potential method for sputum induction.

There are some limitations to the present study. This was a preliminary investigation performed only in the setting of a TB clinic, and the number of patients was small. In addition, the effects of various factors, such as age, smoking status, symptoms and radiological TB stage on the utility of the Lung Flute, were not assessed. The fundamental effectiveness of the device needs to be verified by comparing the Lung Flute with a dummy device that does not contain a reed. Finally, a randomized controlled study is needed to compare the Lung Flute with the current recommended method of sputum induction by hypertonic saline inhalation for the diagnosis of TB.

In summary, use of the Lung Flute may be a promising technique for the rapid diagnosis of pulmonary TB. The diagnostic yield using the Lung Flute needs to be confirmed in controlled studies.

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