Change in lung function in never-smokers with nontuberculous mycobacterial lung disease: A retrospective study

Takehiko Kobayashia, Kazunari Tsuyuguchib,⁎, Toru Araic, Taisuke Tsujia, Toshiya Maekuraa, Yu Kuraharaa, Chikatoshi Sugimotoc, Shojiro Minomoe, Keiko Nakaoa, Sayoko Tokuraa, Yumiko Sasakia,b, Seiji Hayashia, Yoshikazu Inouec, Katsuhiro Suzukia

a Department of Internal Medicine, National Hospital Organization, Kinki-Chuo Chest Medical Center, Sakai City, Osaka, Japan
b Department of Infectious Diseases, Clinical Research Center, National Hospital Organization, Kinki-Chuo Chest Medical Center, 1180 Nagasone-cho, Kita-Ku, Sakai City, Osaka 591-8555, Japan
c Clinical Research Center, National Hospital Organization, Kinki-Chuo Chest Medical Center, Sakai City, Osaka, Japan

ARTICLE INFO

Keywords:
Lung function
Never-smoker
Nontuberculous mycobacterial lung disease
Bronchiectasis

ABSTRACT

Purpose: Never-smokers account for a large proportion of subjects in general population studies on nontuberculous mycobacteria lung disease (NTM-LD). However, the influence of NTM infection on the lung function of never-smokers has not yet been evaluated. The aim of this study was to determine how NTM-LD impairs the lung function in never-smokers, and whether there are an association between successful NTM-LD treatment in radiologic outcomes and improvement in lung function of never-smokers with NTM-LD or not.

Methods: We performed a retrospective study of patients (1) who have never smoked during their lifetime; (2) with at least two respiratory specimens from sputum, one bronchial washing sample, or one lung tissue that were culture positive for the same NTM species; and (3) who underwent at least two pulmonary function tests. We enrolled healthy never-smokers as the control group.

Results: In 22 never-smokers with NTM-LD, the median forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) at baseline was lower than those in 9 healthy never-smokers [1800 vs 2080 ml (p = 0.23) and 2230 vs 2620 ml (p = 0.06)], respectively. The median change in FEV1 in never-smokers with NTM-LD was lower than that in healthy never-smokers [−70 vs 20 ml per year (p = 0.07), respectively]. On univariate analysis, baseline %-predicted FEV1 in never-smokers with NTM-LD was associated with changes in FVC (p = 0.026) and FEV1 (p = 0.013). Anti-NTM treatment was administered for at least 1 year in 19 patients (86.4%). The relationship between worsening chest CT findings and rapid progressive decline in both FVC (p = 0.66) and FEV1 (p = 0.23) were not significant.

Conclusion: Never-smokers with NTM-LD showed lung function decline. There was no association between successful NTM-LD treatment in radiologic outcomes and improvement in lung function of never-smokers.

Introduction

The prevalence and mortality rates of nontuberculous mycobacterial lung disease (NTM-LD) have been globally increasing [1–5]. Radiologic features of fibrocavitary disease, anemia, low body mass index (BMI), high C-reactive protein, and coexistence with chronic pulmonary aspergillosis have been known to be negative prognostic factors of NTM-LD [6,7]. Pulmonary function tests (PFTs) provide a convenient way to objectively assess lung function for the management of patients with chronic obstructive pulmonary disease (COPD) and interstitial pneumonia [8]. In these cases, the rapid decline in lung function is a negative prognostic factor [9,10]. Among never-smokers, prior pulmonary tuberculosis (PTB) infection and bronchial asthma are risk factors for lung function impairment [11]. Pulmonary infection with nontuberculous mycobacteria (NTM) leads to air trapping, distal to the small airways [12]. However, the effect of chronic inflammation caused by NTM on lung function decline in the long-term remains unclear. Never-smokers make up a large proportion of subjects in general population studies of NTM-LD. The influence of NTM infection on the long-term lung function of never-smokers has not yet been determined. We conducted a retrospective study to determine how NTM-LD may impair the lung function in never-smokers compared with that in healthy never-smokers, and whether
there are an association with a substantial decline and response to anti-NTM treatment.

Materials and methods

Study participants

This study was conducted at the Kinki-Chuo Chest Medical Center, a 385-bed center in Southern Osaka that specializes on pulmonary disease. We performed a retrospective study of consecutive patients with at least two respiratory specimens from sputum, one bronchial washing/brushing samples, or one lung tissue that was culture-positives for the same NTM species between August 1, 2012 and August 31, 2015. Patients were enrolled if (1) they fulfilled the diagnostic criteria of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines [13], (2) underwent at least two PFTs, and (3) had never smoked during their lifetime. We also excluded patients with other comorbidities (e.g., PTB, bronchial asthma, and interstitial pneumonia, which impaired lung function). We also enrolled healthy never-smokers as the control group, (1) patients visited our hospital for medical checkups between August 1, 2012 and August 31, 2015, (2) had no respiratory symptoms, (3) had never smoked during their lifetime, and (4) showed no abnormal lesion on chest CT and underwent at least two PFTs. This study was approved by the institutional review board of National Hospital Organization Kinki-Chuo Chest Medical Center (No. 566, date of approval: December 22/2016). Informed consent was waived because of the retrospective nature of the study.

Data collection

Information on a patient history was obtained during an outpatient visit. Height and weight were measured. Data on use of inhaled medications and the course of anti-NTM treatment were collected from the medical records. The patients received combination antibiotic therapy, as recommended by the ATS and IDSA [13].

Pulmonary function test

A CHESTAC-800 spirometer from CHEST was used. A forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) of <70% was considered to indicate airflow obstruction. The predicted FEV1 (%) was calculated on the basis of age, sex, and height, according to the ATS/European Respiratory Society guideline [14]. Each machine was calibrated daily before use. Each patient performed at least three forced expiratory maneuvers that fulfilled the criteria of repeatability [14] from diagnosis day to the last available PFT. Baseline PFT was defined as PFT performed most closely after the date of the diagnosing the NTM lung disease. In each patient, annual lung function change (ml/year) was calculated as [(the last FEV1 or FVC)-(FEV1 or FVC at baseline)]/follow-up duration (years). Rapid progression of FEV1 or FVC decline was defined as >40 ml loss per year [10,15].

Evaluation of radiologic findings

We classified chest radiography and computed tomography (CT) findings at the time of diagnosis as either fibrocavitary disease, nodular bronchiectatic disease, or mixed form [16]. Deterioration was defined as progressively increasing nodules, infiltration, or consolidation on follow-up chest CT findings. No deterioration was defined as stable disease without significant interval changes on both available chest CT images and PFTs. Lesions that demonstrated a waxing and waning pattern during follow-up were reevaluated by comparing the baseline and most recently available CT findings. Chest CT findings were independently evaluated by two pulmonary specialists (TK and TT). In case of disagreement of interpretations, consensus was reached by discussion.

Bacteriologic outcomes of treatment for NTM

We classified patients according to their treatment and outcomes, which were evaluated by comparing baseline and last follow-up PFT. Disease progression in terms of bacteriologic outcomes was determined by the interval between the date of diagnosis and the date on follow-up after one year. After 12 months of treatment, culture conversion or relapse was assessed periodically. Negative conversion was defined as two consecutive negative cultures within three months after chemotherapy for 12 months. Sputum samples were collected and assayed for mycobacterial cultures once every 2 months in clinical practice. If the patient could not expectorate even after sputum induction, sputum conversion was considered to be from positive to negative. Relapse was defined as sputum conversion to positive (at least one positive sputum culture) after a preceding conversion from positive to negative.

Statistical analysis

Statistical analyses were performed using the JMP statistical software (12th version, SAS Institute Inc., Cary, NC). Proportions and medians were used to describe the demographic, clinical, and radiographic characteristics. Linear regression analysis was used to identify factors associated with changes in FEV1 and FVC on follow-up. The analyses included all never-smokers and excluded patients with other comorbidities (e.g., PTB, bronchial asthma, and interstitial pneumonia) that might strongly influence lung function impairment.

Results

The characteristics of the 22 never-smokers with NTM-LD and 9 asymptomatic never-smokers without any other respiratory comorbidity are summarized in Table 1. The median age and the proportion of men were similar between 9 asymptomatic never-smokers and 22 never-smokers with NTM, nontuberculous mycobacteriosis; FVC, vital capacity; FEV1, forced expiratory volume in 1 s; DM, diabetes mellitus; LC, lung cancer; CKD, chronic kidney disease

| Table 1 | Never-smokers with nontuberculous mycobacterial lung disease vs those without. |
|---------|--------------------------------------------------------------------------------|
| Age, years | Never-smokers with NTM lung disease | Healthy group | p-value |
|          | (n = 22) | (n = 9) |         |
| Male, n (%) | 70 (48-85) | 64 (45-80) | 0.50 |
| Body mass index (kg/m2) | 19.2 (13.9–23.9) | 20.5 (15.7–41.7) | 0.30 |
| Comorbidity |                                         |                |         |
| Aspergillosis, n (%) | 2 (9.1) | 0 (0.0) | 1.00 |
| DM, n (%) | 0 (0.0) | 1 (1.1) | 0.29 |
| LC, n (%) | 2 (9.1) | 0 (0.0) | 1.00 |
| GERD, n (%) | 2 (9.1) | 0 (0.0) | 1.00 |
| CKD, n (%) | 2 (9.1) | 0 (0.0) | 1.00 |
| HTN, n (%) | 0 (0.0) | 1 (1.1) | 0.29 |
| Baseline spirometry |                                         |                |         |
| FVC, ml | 2230 (1270–3570) | 2620 (2080–4490) | 0.06 |
| FVC, % predicted | 92.5 (55.7–142.8) | 108.3 (76.4–125.8) | 0.15 |
| FEV1, ml | 1800 (860–3130) | 2080 (1460–3450) | 0.23 |
| FEV1, % predicted | 87.6 (45.3–139.5) | 94.8 (68.5–117.3) | 0.74 |
| FEV1/FVC | 78.5 (67.7–97.5) | 76.1 (62.4–94.1) | 0.24 |
| Interval days between baseline and last spirometry | 2.76 (0.58, 5.83) | 1.80 (0.31, 6.63) | 0.05 |
| Changes in lung function |                                         |                |         |
| FVC change, mL/year | −80 (−440.0 to 0.0) | −140 (−390.0 to 80) | 0.76 |
| FEV1 change, mL/year | −70 (−340 to 50) | 20 (−0.4 to 16) | 0.07 |
NTM-LD. The most common NTM species isolated alone was Mycobacterium avium complex (MAC) in 90.9% never-smokers with NTM-LD. All never-smokers with NTM-LD had nodular bronchiectasis pattern on radiography. No patients showed emphysema on their CT findings.

Anti-NTM treatment was administered for at least 1 year in 19 patients (86.4%) (Table 3).

In all 22 never-smokers with NTM-LD, the median values of FEV1 and FVC at baseline were lower than those in the control group (healthy never-smokers) [1800 vs 2080 ml (p = 0.23) and 2230 vs 2620 ml (p = 0.06), respectively]. The median change in FEV1 in never-smokers with NTM-LD was lower than that in healthy never-smokers [−70.0 vs 20 ml (p = 0.07)] (Table 1, Fig. 1). In univariate analysis, baseline %-predicted FEV1 was associated with changes in FVC (β coefficient = −0.361; p = 0.026) and FEV1 (β coefficient = −0.519; p = 0.013; Table 2). The relationships between worsening chest CT findings and rapid progressive decline in both FVC (p = 0.66) and FEV1 (p = 0.23) were not significant. Among 10 patients who received successful treatment based on bacteriologic outcome, rapid progressive decline was seen in FVC in 9 patients and in FEV1 in 4 patients (Table 4).

**Table 3**
Initial treatment of nontuberculous mycobacterial lung disease in never-smokers.

| Use of chemotherapy | 19 (86.4) |
|---------------------|-----------|
| RFP + EB + CAM      | 12 (54.5) |
| RFP + EB           | 1 (4.5)   |
| RFP + CAM          | 2 (9.1)   |
| RFP + EB + CAM + SM| 1 (4.5)   |
| EM + LVFX          | 1 (4.5)   |
| RFP + CAM + STFX   | 1 (4.5)   |

CAM, clarithromycin; EB, ethambutol; RFP, rifampicin; STFX, satifloxacin hydrate; LVFX, levofloxacin.

**Table 2**
Nontuberculous Mycobacterium species in never-smokers with nontuberculous mycobacterial lung disease (n = 22).

| Species                                         | 11 (50.0) |
|------------------------------------------------|-----------|
| M. intracellular                               | 9 (40.9)  |
| M. avium + M. abscessus complex               | 1 (4.5)   |
| M. avium + M. kansasii                        | 1 (4.5)   |
| Other bacterial infectious disease             |           |
| P. aeruginosa                                  | 2 (9.1)   |

**Discussion**

The present study underscored two notable clinically relevant issues. First, patients with NTM-LD showed a decline in lung function even without tobacco exposure. Second, the success of NTM-LD treatment in never-smokers was not associated with an improvement in lung function.

The present study revealed that the tendency of decline in lung function of never-smokers with NTM-LD was a little greater than that of healthy never-smokers (FVC, p = 0.76; FEV1, p = 0.07) In healthy Japanese individuals who had never smoked, the mean annual FEV1 and FVC decline were 19.6 ml and 22.2 ml, respectively [17–20]. A retrospective study by Lee et al reported a decline in lung function in patients with NTM-LD, 38% of whom were never-smokers [21]; however, the population of this previous study was collected from a mycobacterial laboratory registry database of a single medical center.

The other highlight of our study was the absence of an association between successful NTM-LD treatment in radiologic/bacteriologic outcomes and improvement in lung function of never-smokers. We considered that chronic inflammation due to NTM might have affected lung function decline even after successful treatment with anti-NTM chemotherapy.

![Fig. 1. Annual change in FVC and FEV1.](image-url)
The impact of NTM-LD treatment on lung function change is controversial. With regard to antibiotic treatment, Khan et al. reported an improvement in FEV₁ in patients with MAC-LD [22], and Park et al. found that treatment failure of NTM-LD was an important predictor of lung function decline [15]. In contrast, Mehta et al. observed no substantial changes in lung function [23].

The present study focused on lung function decline in NTM-LD without the effect of tobacco exposure in never-smokers alone. However, it remains unclear whether pulmonary function declined at the time of negative conversion due to the retrospective nature of the study. All patients with NTM-LD in this study had nodular bronchiectatic disease. In bronchiectasis, there is excessive airway inflammatory response secondary to bacterial stimulation; this airway hyper-reactivity correlates with bacterial burden and may persist even after the infection is controlled [24]. For patients with persistent decrease in lung function even after successful treatment of NTM-LD, effective management of bronchiectasis should be considered [25,26]. Henkle et al. reported that 55% of patients had a history of inhaled corticosteroid use in the US Bronchiectasis and NTM Research Registry, with relatively few patients taking suppressive antibiotic therapies (e.g., macrolide therapy) [27]. Further studies are needed to assess whether the therapeutic intervention for NTM-LD would contribute the rate of improvement in lung function in the long term.

Our study did not clarify whether the impact on lung function decline in NTM-LD was caused by inflammation due to the NTM itself, regardless of tobacco exposure. Nevertheless, we suggest that NTM-LD in never-smokers is a progressive disease with heterogeneity in lung function changes. Low baseline lung function was associated with poor prognosis of NTM-LD [6]. Kim et al. reported that in the natural course of MAC disease, even in the presence of nodular bronchiectasis, low FEV₁ at baseline was associated with an increased risk of worsening chest CT findings [28]. In the present study, %predicted FEV₁ at baseline was associated with FVC and FEV₁ decline. However, there are other confounding variables in the background of the patients with NTM-LD. The lung function in patients with NTM-LD could be affected by the exposure to ambient pollution [29] and passive smoking [30]. It could also be affected by the inflammation of other pathogens (e.g., Pseudomonas aeruginosa) and the heterogeneity of treatment regimens (including macrolide vs not including macrolide).

The present study had several limitations. First, its retrospective nature has resulted in a small sample size and selection bias. Second, it could also be affected by the inflammation of other pathogens and the heterogeneity of treatment regimens. Third, we performed PFTs without evaluating residual volume (RV) routinely. Mehta et al. reported that RV may be improved in asthmatic patients with NTM-LD [23], and a recent study suggested that RV reversibility would be a good indicator of small airway dysfunction in bronchiectasis [31]. A prospective observational study of patients with NTM-LD should examine the association between therapeutic response and change in lung function based on PFTs at regular intervals.

Conclusion
In never-smokers with NTM-LD, lung function can decline. There was no association between successful NTM-LD treatment in radiologic outcomes and improvement in lung function of never-smokers.

Ethics approval and consent to participate
This study was approved by the institutional review board of National Hospital Organization Kinki-Chuo Chest Medical Center (No. 566, date of approval: December 22, 2016). Informed consent was waived because of the retrospective nature of the study.

Disclosure
Not applicable.

The authors are partially supported by a grant from the National Hospital Organization Respiratory Network, Japan.

Conflicts of interest
The authors declare no conflicts of interest.

Acknowledgments
Not applicable.

References
[1] Morimoto K, Iwai K, Uchimura K, et al. A steady increase in nontuberculous mycobacteriosis mortality and estimated prevalence in Japan. Am Am Thorac Soc 2011;11:1–8.
[2] Donohue MJ, Wymer L. Increasing prevalence rate of nontuberculous mycobacteria infections in five states, 2008-2013. Am Am Thorac Soc 2016;13:2143–50.
[3] Morimoto K, Hasegawa N, Inumi K, et al. A laboratory-based analysis of nontuberculous mycobacterial lung disease in Japan from 2012 to 2013. Am Am Thorac Soc 2016;17:49–56.
[4] Marras TK, Thodore P, Ying AM, Jamieson F. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997-2003. Thorax 2007;62:661–4.
[5] Mirsaeidi M, Machado RF, Garcia JG, Schraufnagel DE. Nontuberculous mycobacterial disease mortality in the United States, 1999-2010: a population-based comparative study. PLoS One 2014;9:91879.
[6] Hayashi M, Takayasugi N, Kanauchi T, Miyahara Y, Yanagisawa T, Segita Y. Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2012;185:575–83.
[7] Zoumot Z, Boutou AK, Gill SS, et al. Mycobacterium avium complex infection in non-cystic fibrosis bronchiectasis. Respirology 2014;19:714–22.
[8] Pasveers RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med 2001;163:1256–76.
[9] Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/ERS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015;192:3–19.
[10] Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011;365:1184–92.
[11] Myong JP, Yoon HK, Rhee CK, Kim HR, Koo JW. Risk factors for lung function impairment among the general non-smoking Korean population. Int J Tuberc Lung Dis 2015;19:1019–26.
[12] Kubo K, Yamazaki Y, Masubuchi T, et al. Pulmonary infection with Mycobacterium
avium-intracellulare leads to air trapping distal to the small airways. Am J Respir Crit Care Med 1998;158:979–84.

[13] Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of Nontuberculous Mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367–416.

[14] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38.

[15] Park HY, Jeong BH, Chon HR, Jeon K, Daley GL, Koh WJ. Lung function decline according to clinical course in nontuberculous mycobacterial lung disease. Chest 2016;150:1222–32.

[16] Moore EH. Atypical mycobacterial infection in the lung: CT appearance. Radiology 1999;187:777–82.

[17] Nishitsuji M, Fujimura M, Shibata K. Longitudinal decline of forced expiratory volume in one second in non-smoking Japanese women. Nihon Kokyuki Gakkai Zasshi 2006;44:301–4.

[18] Morgan WK, Reger RB. Rise and fall of the FEV1. Chest 2000;118:1639–44.

[19] Griffith KA, Sherrill DL, Siegel EM, et al. Predictors of loss of lung function in the elderly: the cardiovascular health study. Am J Respir Crit Care Med 2001;163:61–8.

[20] Nishitsuji M, Fujimura M, Oribe Y, et al. Influence of smoking on longitudinal decline in one-second forced expiratory volume in clinically healthy Japanese men: a longitudinal study. Nihon Kokyuki Gakkai Zasshi 2003;41:691–5.

[21] Lee MR, Yang CY, Chang KP, et al. Factors associated with lung function decline in patients with non-tuberculous mycobacterial pulmonary disease. PLoS One 2015;8:58214.

[22] Khan Z, Miller A, Bachan M, Donath J. Mycobacterium Avium complex (MAC) lung disease in two inner city community hospitals: recognition, prevalence, co-infection with Mycobacterium Tuberculosis (MTB) and pulmonary function (PF) improvements after treatment. Open Respir Med J 2010;4:76–81.

[23] Mehta M, Chapman KB, Heffer M, Marrs TK. Impact of pulmonary nontuberculous mycobacterial treatment on pulmonary function tests in patients with and without established obstructive lung disease. Respir Med 2015;20:987–93.

[24] Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. Eur Respir J 2008;31:396–406.

[25] McDonnell MJ, Aliberi S, Goeminne PC, et al. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. Thorax 2016;71:1110–8.

[26] Guan WJ, Chen RC, Zhong NS. The bronchiectasis severity index and FACED score for bronchiectasis. Eur Respir J 2016;47:382–4.

[27] Henkle E, Aksamit TR, O’Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels MLA, et al. Adult patients with bronchiectasis: a first look at the US bronchiectasis research registry. Chest 2017;151:982–92.

[28] Kim SJ, Park J, Lee H, et al. Risk factors for deterioration of nodular bronchiectatic Mycobacterium avium complex lung disease. Int J Tuberc Lung Dis 2014;18:730–6.

[29] Adam M, Schikowski T, Carsin AE, Cai Y, Jacquemin B, Sanchez M. Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. Eur Respir J 2015;45:38–50.

[30] Hagstad S, Bjerg A, Ekerljung L, Backman H, Lindberg A, Ronmark E. Passive smoking exposure is associated with increased risk of COPD in never smokers. Chest 2014;145:1298–304.

[31] Dejan R., Pierachille S., Givanni S., Francesca D., Erodado S., Francesco B., Peter G. G., Jamse D.C., Stefana A., Pathphysiology of bronchiectasis: beyond FEV1 and airflow obstruction, Abstract book, 2nd world bronchiectasis conference 211–212.