Impact of Cigarette Smoking on Maximal Expiratory Flows in a General Population: the Takahata Study

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Abstract

Background Maximal expiratory flows (MEFs) depend on the elastic recoil pressure in the alveoli, airway resistance and bronchial collapsibility. MEFs at lower levels of vital capacity [MEFs at x% FVC (MEFx)] would indicate the patency of peripheral airways. In Japan, a ratio of MEF₅₀ to MEF₂₅ (MEF₅₀/MEF₂₅) greater than 4.0 is used as an index of injury to the small airways in subjects without airflow limitation. However, to date there have been no epidemiological investigations relating to this index. The aim of this study was to evaluate the impact of cigarette smoking on MEFs in a general population, and to assess the validity of using this index to evaluate injury to the small airways.

Methods Subjects aged 40 years or older (n=2,917), who had participated in a community-based annual health-check in Takahata, Japan, were enrolled in the study. MEF₇₅, MEF₅₀ and MEF₂₅ were measured in these subjects.

Results In smokers, as compared with never-smokers, the percentage predicted MEFs (%MEFs) decreased according to the aging of the population, except in the case of %MEF₂₅ in females. In males, but not in females, %MEFs decreased significantly with an increase in cigarette consumption. In both genders, MEF₅₀/MEF₂₅ was slightly, but significantly, elevated with aging of the population. In addition, 36.5% of subjects who participated in this health-check had MEF₅₀/MEF₂₅ values greater than 4.0. No difference in MEF₅₀/MEF₂₅ was observed between smokers and never-smokers.

Conclusion Cigarette smoking enhanced the age-related decline in MEFs. Since many healthy subjects aged 40 years or older have MEF₅₀/MEF₂₅ values greater than 4.0, the use of this criterion may over-estimate the presence of small airway disease.

Key words: maximal expiratory flow, cigarette smoking, community-based health check, spirometry, small airway injury

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Introduction

Cigarette smoking causes a variety of respiratory disorders, including chronic obstructive pulmonary disease (COPD) (1, 2). The prevalence of airflow limitation in Japanese people aged 40 years or older is 10.9% (16.4% for males, 5.0% for females) (3). The smoking rate among Japanese males is gradually decreasing, but it is still higher than that in Western countries (4, 5). Recently, there has been some concern that the prevalence of COPD in Japanese females will increase, because the smoking rate is rising in fe-

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Spirometry is widely used to diagnose respiratory diseases, and to evaluate the severity of lung disease. The forced vital capacity (FVC) maneuver can be used to evaluate the condition of the airways. Among the spirometry parameters, FVC and forced expiratory volume in 1 second (FEV₁) are clinical markers of respiratory disease. A %FVC value (relative to the reference value) of <80% indicates restriction of the lung, whereas an FEV₁/FVC of <70% indicates airflow limitation (6). If the maneuver is performed correctly, forced expiratory flows at <75% of FVC are independent of effort (6, 7). Mead et al demonstrated that maximal expiratory flows (MEFs) at <75% of FVC are determined by the elastic recoil pressure in the alveoli and the resistance in airways upstream of the equal pressure point (8). Pride et al also showed that the factors determining MEFs were elastic recoil, airway resistance, and bronchial collapsibility (9). Based on the wave speed theory, the choke point for high lung volume occurs in the segmental bronchi. During forced expiration, the choke point shifts to more peripheral airways in accordance with the reduction in lung volume (10, 11). Because expiratory flow limitation at low lung volumes occurs at these shifting choke points, MEFs at the lower range of vital capacity [MEF at 50% FVC (MEF₅₀), and at 25% FVC (MEF₂₅)] would detect elevation of resistance in the peripheral airways (10, 11). Despite the clinical importance of MEFs, there has been no study evaluating this parameter among Japanese subjects participating in an annual health check. Moreover, there have been few studies describing the effect of cigarette smoking on MEFs in healthy individuals (12).

The ratio of MEF₅₀ to MEF₂₅ (MEF₅₀/MEF₂₅) is sometimes used in Japan as an index of injury to the small airways, although this index has not been standardized internationally (13-15). In small airway disease, MEF₂₅ is thought to decrease more than MEF₅₀, resulting in the elevation of MEF₅₀/MEF₂₅, even in subjects with no abnormality in FVC or FEV₁ (14). In the Japanese textbook on pulmonary function tests, the MEF₅₀/MEF₂₅ is described as being a useful parameter (16). Previously, Takishima and colleagues demonstrated that MEF₅₀/MEF₂₅ was less than 3.0 in healthy subjects in their twenties and thirties. This ratio increased with age, and appeared to be >3.0 in half of the healthy subjects in their fifties (14). Japanese pulmonary physicians appear to use an MEF₅₀/MEF₂₅ value greater than 4.0 as an index of small airway injury in subjects of any age (16). However, the validity of using this as a clinical criterion is unclear, as there is currently no epidemiological data to support it.

In this study, we derived predictive equations for MEFs in never-smoking subjects with normal spirometry (%FVC and FEV₁/FVC) results, who were participating in a health check in Takahata town, Yamagata, Japan. In order to epidemiologically assess the effect of cigarette smoke on the airways, cross-sectional comparisons were performed of age-related changes in %MEFs (ratios relative to reference values) between never-smokers and former/current smokers. In addition, the validity of using MEF₅₀/MEF₂₅ as a clinical indicator of injury to the small airways of smokers was evaluated.

Materials and Methods

This study was based on a secondary analysis of data that has been previously analyzed and reported (17).

Study population

This study formed part of the Molecular Epidemiological Study utilizing the Regional Characteristics of 21st Century Centers of Excellence (COE) Program and the Global COE Program in Japan. Details of the study methodology have been described elsewhere (18, 19). This study was approved by the institutional ethics committee and all participants gave written informed consent.

This study utilized a community-based annual health check, in which all inhabitants of Takahata town (total population 26,026) in northern Japan, who were aged 40 years or older, were invited to participate. This region has a resident population of 15,222 adults aged 40 years or older (7,109 males and 8,113 females). From June 2004 through to November 2005, 1,380 males and 1,735 females (a total of 3,165 subjects) participated in the program and agreed to enroll in the study. Two hundred and forty-eight subjects were excluded from the analysis due to unacceptable spirometry data that did not meet the Japanese Respiratory Society (JRS) criteria (20). Data for a total of 2,917 subjects (1,325 males, 1,592 females) was entered into the final statistical analyses.

Subjects used a self-report questionnaire to document their medical histories, current use of medications, and clinical symptoms. Current, former, and never-smokers were categorized according to their questionnaire responses. Subjects who categorized themselves as “never-smokers”, despite indicating a number of cigarettes smoked per day or a number of years of smoking, were categorized as “former smokers”. The details and analyses of FVC, FEV₁ and FEV₁/FVC in these subjects have been described previously (17). Most subjects did not report a history of pulmonary disease (17). Ten and eight percent of the subjects in this study population had airflow limitation and lung restriction, respectively (17, 21). The Brinkman index [cigarettes inhaled/day x duration of smoking (years)] was used as an estimate of cigarettes inhaled over the lifetime of the subject.

Measurements

The spirometric parameters, MEF at 75% of FVC (MEF₇₅), MEF₅₀, and MEF₂₅, were measured using standard techniques, with subjects performing FVC maneuvers on a CHESTAC-25 part II EX instrument (Chest Corp., Tokyo, Japan), according to the guidelines of the JRS (20). A bronchodilator was not administered prior to measurements. The
Figure 1. Age related changes in maximal expiratory flow at 75%, 50% and 25% of forced vital capacity. The relationships between age and maximal expiratory flows at 75% of forced vital capacity (MEF₇₅) (A, males; B, females), 50% of forced vital capacity (MEF₅₀) (C, males; D, females), and 25% of forced vital capacity (MEF₂₅) (E, males; F, females) are shown. Open circles, never-smokers; closed circles, former/current smokers. Dotted line, regression line for never-smokers; solid line, regression line for former/current smokers. The differences in the slopes of the regression lines between never-smokers and former/current-smokers were compared by analysis of covariance (ANCOVA), as indicated in the inset. MEFs were reduced in accordance with a shift to aging population. Smoking significantly increased the slope of the regression line representing this relationship, except for MEF₅₀ and MEF₂₅ in females.

Statistical analysis

Predictive equations for MEF₇₅, MEF₅₀, and MEF₂₅ were derived by multiple linear, backward step-wise regression, using SigmaPlot version 11.0 software (Systat Software, Inc., San Jose, CA, USA). The differences in the slopes obtained by regression analysis, between never-smokers and former/current-smokers, were compared by analysis of covariance (ANCOVA). ANCOVA was performed using JMP version 8 software (SAS Institute Inc., Cary, NC, USA). A significant difference was defined as p<0.05.

Results

Fig. 1 shows the relationship between age and absolute values of MEF₇₅, MEF₅₀, and MEF₂₅ in both former/current smokers and never-smokers. Smoking significantly increased
the slope of the regression line representing this relationship, except in the case of MEF50 and MEF25 in females. Fig. 2 shows the relationship between age and MEFs in never-smokers, whose spirometric values were normal. Even in these subjects, MEFs were reduced in accordance with the aging of the population. Because absolute MEF values were not adjusted for age or body size, we attempted to compare the age-related changes in MEFs using standardized values. As shown in Table 1, age, body height (HT), and body weight (BW) were associated with MEFs. For the never-smoking subjects, whose spirometry results (%FVC and FEV1/FVC) were normal, equations for MEF75, MEF50, and MEF25 that predicted their reference values were derived by the multiple linear (backward step-wise) regression method: MEF75 (male)=−0.163−(0.0417×age) + (0.0593×HT), R²=0.148, standard error of estimate (SEE)=1.649, p<0.001; MEF75 (female)=0.225−(0.031×age) + (0.0391×HT) + (0.0082×BW), R²=0.167, SEE=1.135, p<0.001; MEF50 (male)=1.675−(0.0274×age) + (0.024×HT), R²=0.095, SEE=1.147, p<0.001; MEF50 (female)=1.85−(0.0339×age) + (0.0215×HT), R²=0.193, SEE=0.864, p<0.001; MEF25 (male)=0.513−(0.0136×age) + (0.0158×HT)−(0.00973×BW), R²=0.11, SEE=0.502, p<0.001; MEF25 (female)=1.989−(0.0182×age), R²=0.196, SEE=0.363, p<0.001.

Since Japanese equations for MEF50 and MEF25 are made available by the JRS, the predicted values obtained from the equations derived in the present study were compared with those obtained from the JRS equations (22). There were significant relationships between the predicted values of MEF75 and MEF50 from this study and those from the JRS equations: MEF75 (male), r=0.999; MEF75 (female), r=0.996; MEF50 (male), r=0.998; MEF50 (female), r=0.998. The corresponding mean differences (JRS value-value from this study) were:
Table 1. Correlations between Maximum Expiratory Flow and Age, Height or Weight, as Evaluated by Univariate Linear Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>age</td>
<td>-0.0601</td>
<td>0.00808</td>
<td>&lt;0.001</td>
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<tr>
<td>MEF75 (M)</td>
<td>HT</td>
<td>0.0897</td>
<td>&lt;0.001</td>
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<td></td>
<td>BW</td>
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<tr>
<td>age</td>
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<td>0.00321</td>
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<tr>
<td>MEF75 (F)</td>
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<td>0.0728</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>BW</td>
<td>0.027</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>age</td>
<td>-0.0349</td>
<td>0.00554</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF50 (M)</td>
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<td>&lt;0.001</td>
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<tr>
<td></td>
<td>BW</td>
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<td>0.002</td>
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<tr>
<td>age</td>
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</tr>
<tr>
<td>MEF50 (F)</td>
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<td>BW</td>
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<tr>
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<td></td>
<td>BW</td>
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<tr>
<td>age</td>
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<td>0.00101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF25 (F)</td>
<td>HT</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>BW</td>
<td>0.00298</td>
<td>0.023</td>
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</table>

MEFx, maximum expiratory flow at x% forced vital capacity; M, male; F, female; HT, body height; BW, body weight

MEF75 (male), -0.13 ± 0.28 L/sec; MEF50 (female), -0.04 ± 0.00 L/sec; MEF25 (male), 0.24 ± 0.26 L/sec; and MEF25 (female), 0.19 ± 0.08 L/sec.

Using these equations, the relationship between age and %MEFs in never-smokers and former/current smokers was evaluated (Fig. 3). In smokers, as compared with never-smokers, %MEFs accordingly decreased with a shift to aging population, except for %MEF25 in females.

The decline in %MEFs relative to the amount of cigarette smoke inhaled was assessed. Fig. 4 shows the relationship between cigarette consumption [Brinkman index] and %MEFs in smokers. In male smokers, %MEF75, %MEF50, and %MEF25 declined slightly, but significantly, with an increase in the Brinkman index. However, in female smokers, %MEFs remained unchanged with an increase in the Brinkman index.

In both males and females, MEF50/MEF25 was slightly, but significantly, elevated with increasing age of the population. No difference in MEF50/MEF25 was observed between smokers and never-smokers (Fig. 5). As shown in Table 2, the proportion of subjects with MEF50/MEF25 greater than 4.0 was 36.5% (38.4% in never-smokers and 32.5% in former/current-smokers). In addition, an inverse correlation between Brinkman index and MEF50/MEF25 was observed in this population (r=-0.054, p=0.0034).

**Discussion**

We derived predictive equations for MEF75, MEF50, and MEF25 in a Japanese population aged 40 years or older with normal spirometric values, that participated in an annual health check. The predicted values obtained from the equations derived in this study were significantly associated with the values obtained from the JRS equations. A cross-sectional comparison of the age-related changes in %MEFs between smokers and never-smokers was made. In male smokers, %MEFs accordingly decreased with a shift to the aging population, as compared with %MEFs of male never-smokers. Furthermore, in male smokers, %MEFs were slightly, but significantly, reduced with an increase in the Brinkman index. Therefore, this study demonstrated epidemiologically the harmful effect of long-term cigarette smoke inhalation on MEFs, which were indicative of patency at various levels of the airways, as well as parenchymal damage, in male smokers. In females, smoking significantly increased the slope of the regression line representing the relationship between age and %MEFs, except in the case of %MEF25. In female smokers, the %MEFs remained unchanged with an increase in the Brinkman index. Since only 70 female smokers were included in the present study, this limited number of female participants may not have provided the statistical power to show a significant relationship be-
MEFs depend on airway resistance and the elastic recoil pressure of the alveoli (8, 23). Airway patency is a factor that determines airway resistance (9). In addition, alveolar elastic recoil pressure is a source of the expiratory drive, and by contracting the airways, it is a source of airway patency (8). In the emphysematous lung, reduced elastic recoil pressure causes collapse of airways, resulting in airway narrowing and expiratory flow limitation (24). Because forced expiratory flows at less than 70% of FVC are independent of effort, resistance and collapsibility of the more peripheral airways are theoretically reflected in MEFs at a lower percentage of the FVC remaining to be exhaled (6, 7). Therefore, as compared with %MEF75 and %MEF50, %MEF25 reflects the patency of the more peripheral airways. In this study, %MEF75, %MEF50 and %MEF25 were reduced in male smokers, as compared with male non-smokers. In addition, these MEFs decreased with increases in the Brinkman index. These results suggest that cigarette smoking injures a wide range of airways and/or the lung parenchyma.

MEF50/MEF25 is used as a marker for injury to the small airways. Even in the absence of abnormal FVC and FEV1, MEF50/MEF25 values greater than 4.0 are considered to indicate the presence of small airway disease (13-15). However,
the validity of this as a clinical criterion is unclear, as there is currently no epidemiological data to support this. In contrast to previous findings demonstrating that MEF50/MEF25 was less than 3.0 in healthy subjects aged in their twenties and thirties, Fig. 5 and Table 2 show that MEF50/MEF25 in many healthy subjects aged 40 years or older was greater than 4.0. Therefore, the criterion of MEF50/MEF25, as a marker of small airway disease, can only be used in younger populations, whereas for older populations, the single criterion of MEF50/MEF25 does not appear to be sufficient for diagnosing the presence of small airway disease. Further measurements such as the closing volume test and respiratory resistance test using the impulse oscillation system, are also required to evaluate the function of the small airways (25, 26). Moreover, in the present study, since there was no difference in the MEF50/MEF25 between smokers and never-smokers, MEF50/MEF25 was not confirmed to be a useful marker for cigarette smoke-induced airway damage. As shown in Fig. 3, both %MEF50 and %MEF25 were reduced as a result of cigarette smoking. This simultaneous reduction of %MEF50 and %MEF25 in smokers probably resulted in the absence of a difference in MEF50/MEF25 between smokers and non-smokers (Fig. 5).

As MEFs are measured at specified percentages of FVC, variability in FVC contributes to variability in the measured forced expiratory flow. FVC values vary markedly depending on the effort of the subject and consequently MEF75, MEF50, and MEF25 are sensitive to such variability. This contributes to the large residual standard deviations for the MEF prediction equations. In the present study, the SEEs for the MEF prediction equations were large. Even when these factors are taken into consideration, the data presented here is valuable, because the differences in MEFs were analyzed for large numbers of smokers and never-smokers, and the harmful effect of cigarette smoke on the airways and lung parenchyma were demonstrated epidemiologically.

The limitations of this study were the low participation rate for all inhabitants of the town, and the distribution of
employment, annual incomes or lifestyles of the subjects was not available, further analyses could not be performed.

In conclusion, predictive equations for MEF$_{25}$, MEF$_{50}$, and MEF$_{25}$ were derived for a Japanese population aged between 40 and 90 years, who participated in an annual health check, and whose pulmonary function parameters were normal. Using these reference values, the age-related change in standardized MEFs was shown to be significantly greater in the smoking population than in the never-smoking population. This is further epidemiological evidence of the harmful effects of cigarette smoking on the airways and lung parenchyma. Moreover, the validity of using values of MEF$_{25}$/MEF$_{50}$ greater than 4.0 as an index of small airway disorder was not confirmed in this population aged 40 years or older. Therefore, clinicians should be aware that the presence of small airway disease should not be diagnosed by only this criterion, but rather the results of other examinations, such as the closing volume test, must be taken into consideration.

The authors state that they have no Conflict of Interest (COI).

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