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Longitudinal changes in time domain spirogram indices and their variability

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Longitudinal changes in time domain spirogram indices and their variability. T. Nakadate, T. Sato, J. Kagawa. ©ERS Journal Ltd 1994.

ABSTRACT: The purpose of this study was to describe longitudinal changes in time domain spirogram indices and their variability.

We therefore measured forced expiratory spirograms of 326 middle-aged male employees in two asbestos-using factories four times over 5 yrs. From the original sample of 326, 225 healthy subjects, who provided reliable results for three or more surveys, were selected for analysis. The mean and standard deviation of transit time and their log-transformed values (MTT, STT, ln(MTT), and ln(STT), respectively), as well as two indices of the estimated time constant distribution (Mu and Sigma, respectively) were analysed using a longitudinal model.

The longitudinally estimated annual increase of MTT, STT, ln(MTT), and ln(STT) was about three times larger than the cross-sectional estimate, whilst they were comparable in Mu and Sigma. A highly significant contribution of between-subject variability was found in all indices. This was particularly remarkable in the mean components. The between-subject variability was about eight times larger than the error variance in Mu, and three times in MTT and ln(MTT).

We conclude that the longitudinal data of transit time indices should not be compared with cross-sectional reference values, and that the magnitude of error variance of these indices in longitudinal repeated measurements will be rather less than the cross-sectional counterpart reported previously.

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Transit time analysis is a method of analysing a forced expiratory spirogram in a time domain. It was first proposed by workers in Johns Hopkins University [1], who considered a spirogram to be a summation of many small volume increments, each having a transit time, and calculated the statistical moments around the origin. Transit time indices have been examined in studies on lung growth [2], the effects of smoking [3–6], and peripheral airway function [7, 8]. PERMUTT and MENKES [9] extended this analysis to obtain two parameters of the time constant distribution in lungs, namely Mu and Sigma, applying a mathematical model to forced expiratory spirograms.

Indices obtained by these methods are theoretically independent of lung volumes, and are sensitive primarily to events in the terminal part of forced expirations. Therefore, it might be possible to hypothesize that early changes in chronic airflow limitation caused by hazardous materials in general and occupational environments can be detected using these indices, because those changes are considered to occur in the peripheral region of lungs and to manifest as an elongation of time of forced expiration. Although cross-sectional variability and normal ranges of these indices were reported in a study of asymptomatic nonsmokers [10], little is known about long-term changes in these indices.

Another important question concerns the magnitude of error variance in these indices with long-term repeated measurements. It has been pointed out that a longitudinal study is more effective than a cross-sectional study in detecting a mild effect of inhaled materials on forced expiratory volume in one second (FEV_1) [11]. This is partly due to the fact that the error variance of longitudinal design is usually smaller than that of cross-sectional design, to which between-subject variability contributes significantly. Even in the case of time domain spirometric indices, this would be the case when their error variance in repeated measurements is significantly small compared with the cross-sectionally observed error variance of these measurements.

The purpose of this study was: firstly, to describe longitudinal changes in those indices with ageing; and, secondly, to estimate the magnitude of their between subject variability and error variance with repeated measurements, based on longitudinally followed-up spirometric data, especially with a view to comparing the results with cross-sectional estimates.

Subjects and methods

Study subjects

Study subjects were all male employees of two asbestos-using factories. They have been followed-up

since 1985, largely on an annual basis, by the authors [12]. At the first survey in March 1985, a total of 326 subjects was enrolled in this longitudinal study, and underwent examinations including chest radiography, spirometry, and inquiry as to respiratory symptoms, and gave their approval to join this study. Follow-up surveys have been conducted in the same season every year, excluding 1987, using the same procedure as in 1985. In this report, the data obtained in the first four surveys up to 1989 were analysed.

Questionnaire survey

The standardized questionnaire of the American Thoracic Society (ATS-DLD-78-A) [13] was utilized to obtain respiratory symptoms, past histories of illnesses, and smoking history, with slight modifications and translation into Japanese. Chronic cough was defined as an affirmative answer to question 7E in the ATS-DLD-78-A. Similarly, chronic phlegm, chronic wheeze, and breathlessness were based on the answers to questions 8E, 10A-2 and/or 10A-3, and 13B, respectively.

Spirometry

Spirograms were measured with a dry, rolling-seal spirometer (Chestac 65, Chest Co. Ltd, Japan). The plastic bell of the spirometer was connected to a rotary encoder, which released a pulse voltage with each 10 ml change in volume. Time data were sampled when the pulses were generated. Time elapsed and volume changes between pulses provided the magnitude of flow at that time. These data were all calculated with a personal computer and stored on a floppy disk. The spirometer could show volume-time and flow-volume curves simultaneously on a visual display for each forced expiratory manoeuvre. According to the company's specification, the frequency response of the plastic bell was acceptable (±2%) up to 10 Hz, measured with added small volume oscillation. The beginning of forced expiration was determined by the back extrapolation method, and expiration was considered to end when flow became negative. The accuracy of the encoder was checked every day, before and after the morning and afternoon sessions, using a 2 *l* syringe. The spirometer was equipped with a thermometer. Routine body temperature and pressure saturated with water vapour (BTPS) correction was carried out on the forced vital capacity (FVC) and FEV_1 data when subjects finished each manoeuvre. The room temperature was also recorded to evaluate the background condition.

The forced expiration manoeuvre was conducted in a standing position. A noseclip was not used because full inspiration prior to FVC was from room air, and the mouthpiece was inserted just before expiration. However, the subjects were asked to wear a noseclip when some leak of expired gas through their nose was conceivable. Subjects were asked to repeat the FVC manoeuvre up to seven times to obtain acceptable, reproducible results on three occasions. Whether or not each manoeuvre was acceptable was evaluated according to the criteria of the American Thoracic Society [13], based on the measured values, and on the shape of flow-volume and volume-time curves. In each survey, the subjects who completed an acceptable FVC manoeuvre at least twice were considered to have provided reliable results. The figures for each index used for the analysis were derived from the best manoeuvre with the largest sum of FVC and FEV_1. To minimize the measurement bias across the surveys, all examinations were carried out by one examiner, with the same apparatus throughout all surveys.

Time domain spirogram indices

Based on the volume, flow and time elapsed data stored on a floppy disk, the first two moments of transit time and duration of expiration were calculated for each exhalation with a personal computer, after back extrapolation correction for time zero. The mean and the standard deviation of transit times (MTT and STT, respectively) were defined according to RACINEUX *et al.* [14]. Then the transit times and duration of expiration were used to estimate Mu and Sigma according to the method of PERMUTT and MENKES [9], using the HITAC system of the Tokyo University Computer Center. We preliminarily examined the distributions of MTT, STT, Mu and Sigma. Several forms of transformation of these indices were also examined. The result revealed that the log-transformed data might be suitable for general linear regression analysis in the case of MTT and STT, as reported by MILLER *et al.* [10]. Therefore, statistical analyses were conducted on log-transformed MTT and STT (ln(MTT) and ln(STT), respectively), in addition to the above four indices.

Analysis

According to the results of previous reports [9, 10], we have hypothesized a linear relationship between these indices and age. We thus used the following longitudinal model to estimate the effect of age on the indices and their variability:

$$F_{ij} = a + c_1 * AGEstart_i + c_2 * \Delta AGE_{ij} + B + e_{ij}$$
$$(i = 1 \sim 225,\ j = 1, 2, 3, 4)$$

where F_{ij}: pulmonary function index of subject i on survey j; a: intercept; c_1, c_2: regression coefficient; $AGEstart_i$: age of subject i at the 1st survey; ΔAGE_{ij}: increase of age of subject i on survey j; B: random effect of subject ($B \sim N(0, \sigma_B^2)$); and e_{ij}: residual of subject i on survey j ($e_{ij} \sim N(0, \sigma_E^2)$).

In this model, one regression coefficient, c_1, indicates a cross-sectional difference in pulmonary function by age between subjects, and the other, c_2, indicates a longitudinal pulmonary function change with ageing within subjects. Between subject variation, σ_B^2, was

estimated by including the effect of subjects, B, as a random effect in the model. The sources of longitudinal error variance, σ_E^2, would be within-subject variation, between-survey variation, and other unidentified variations at testing which are considered to occur at random.

All statistical procedures were carried out with the SAS statistical packages at the Tokyo University Computer Center. The MIXED procedure was used for fitting the longitudinal model.

Results

Of 326 workers registered in 1985, we could not complete the follow-up for 17 subjects because they retired or transferred before 1989. Fifteen subjects who had been diagnosed as having pneumoconiotic changes in radiography, bronchiectasis, emphysema, or bronchial asthma, were excluded because they could have shown different ageing pattern in pulmonary function from others, due to their disorders. Furthermore, another 69 subjects were excluded because they could not perform acceptable spirometric manoeuvres at two or more surveys, or could not give reliable estimates of Mu or Sigma at two or more surveys. That was because the inclusion of those subjects with only one or two reliable meas-urements would possibly cause a serious bias to the estimation of age coefficients and variability. As a result, 853 measurements of 225 workers, who provided acceptable routine spirometric measurements and time domain analysis indices for three or more surveys, were analysed.

Table 1 shows the age distribution, current cigarette consumption, the ratio of FVC to the predicted value by

Table 1. – Distribution of age, smoking habits, and conventional spirometric results at the first survey (1985) and the last survey (1989)

		1985	1989*
Age yrs	30–39	103 (46)+	51 (23)
	40–49	99 (44)	125 (56)
	50–59	23 (10)	49 (21)
Smoking habits†			
Never smoked		41 (18)	41 (18)
Former smoker		38 (17)	42 (19)
Current smoker	1–14	33 (15)	24 (11)
	15–24	90 (40)	96 (43)
	>25	22 (10)	19 (8)
%FVC	60–69	2 (0.9)	2 (0.9)
	70–89	58 (26)	55 (24)
	90–109	141 (63)	130 (58)
	110–129	24 (11)	38 (17)
FEV_1%	60–69	1 (0.4)	3 (1.3)
	70–79	31 (14)	43 (19)
	80–89	165 (73)	160 (71)
	>90	28 (12)	19 (8)

*: data from the third survey, conducted in 1988, were used for 14 subjects who were not examined in 1989. +: n values and figures, in parenthesis, are the percentages in the group. †: n of cigarettes smoked per day %FVC: ratio of forced vital capacity to the predicted value [15] on a percentage scale; FEV_1%: ratio of forced expiratory volume in one second to FVC on a percentage scale.

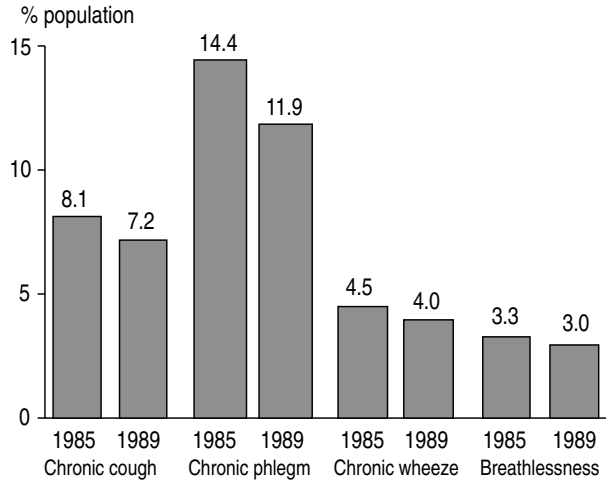

Fig. 1. – Prevalences of chronic respiratory symptoms at the first survey (1985) and at the last survey (1989). Data from the third survey, conducted in 1988, were used for 14 subjects who were not examined in 1989.

YOKOYAMA and MITSUFUJI [15] on a percentage scale (%FVC), and the ratio of FEV_1 to FVC on a percentage scale (FEV_1%), at the first and last surveys. Figure 1 shows changes in the prevalence of chronic respiratory symptoms between the two surveys. The relative frequency of current smoking at the first survey was about 65%, and was almost equal to the rate in the general Japanese population in the 1980s [16]. Those who had never smoked constituted about 20% of the subjects analysed. There was a small number of subjects who had changed their smoking habits during the follow-up period. Although the cohort included workers exposed to asbestos dust, the level of %FVC and of FEV_1% were fairly good. The most frequent symptom was chronic phlegm, followed by chronic cough. A small decrease was observed in these prevalences during follow-up.

The mean value of MTT, STT, Mu, and Sigma within each subject during follow-up was plotted against his mean age in figures 2, 3, 4 and 5, respectively.

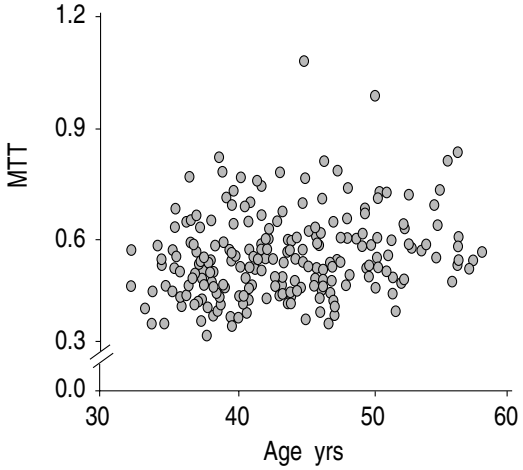

Fig. 2. – Scatter diagram of mean values of MTT within each subject during follow-up, plotted against his mean age, in the 225 subjects analysed. MTT: mean transit time.

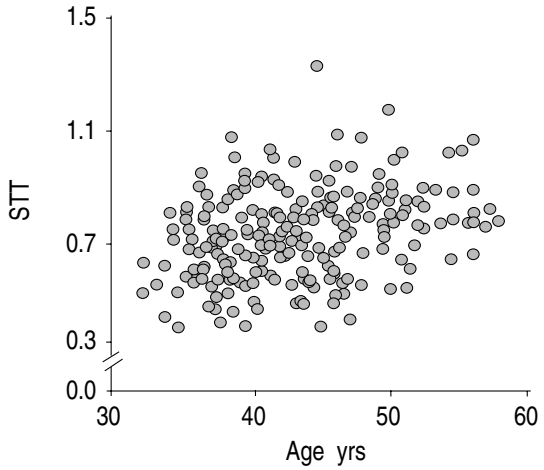

Fig. 3. – Scatter diagram of mean values of STT within each subject during follow-up, plotted against his mean age in the 225 subjects analysed. STT: standard deviation of transit time.

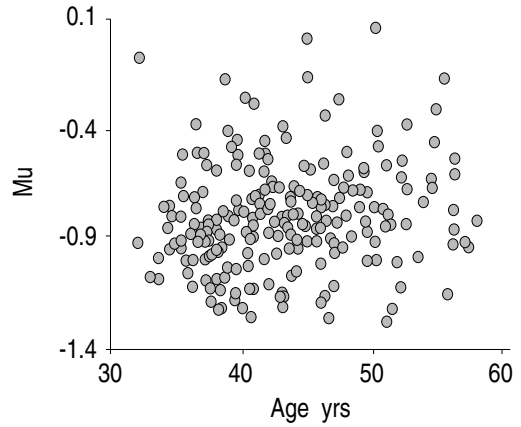

Fig. 4. – Scatter diagram of mean values of Mu within each subject during follow-up, plotted against his mean age in the 225 subjects analysed. Mu: index of estimated time constant distribution.

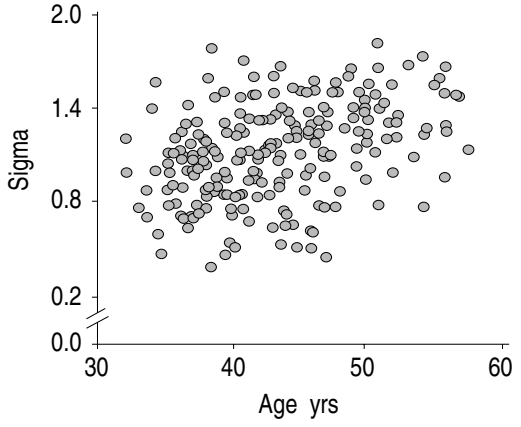

Fig. 5. – Scatter diagram of mean values of Sigma within each subject during follow-up, plotted against his mean age in the 225 subjects analysed. Sigma: index of the estimated time constant distribution.

A positive but weak association with age was found in all indices. However, we could not find any tendency suggesting that the association was nonlinear. Therefore, it seemed appropriate to consider the effect of age to work linearly on the time domain spirometric indices. Overall mean and standard deviation among 853 measurements, as well as the residual standard deviation of the longitudinal model, are shown in table 2. The introduction of the model reduced the magnitude of standard deviation to one or two-thirds, corresponding to at least a 50% reduction in variance. These results suggest that the goodness of fit of the longitudinal model is satisfactory in each index.

Longitudinally and cross-sectionally determined age coefficients for time domain indices are shown in table 3. A remarkable difference was noted in transit time indices between the two types of estimates. The longitudinal estimate was about three times larger than its cross-sectional counterpart. In the case of time constant distribution indices, however, the two types of estimate did not differ to a statistical degree.

Between-subject and error variances estimated in the longitudinal model are presented in figure 6. In the mean component of the indices, MTT, ln(MTT) and Mu, between-subject variance was markedly larger than longitudinal error variance; about eight times in Mu, and three times in MTT and ln(MTT). Even in their dispersion component, the former was larger than the latter, although the difference between the two types of variances was small.

Table 2. – Mean and standard deviation (SD) among a total of 853 measurements of each index and residual standard deviation (RSD) of the logitudinal model

	Mean±SD	RSD
MTT	0.56±0.13	0.06
STT	0.73±0.19	0.12
ln(MTT)	-0.61±0.21	0.11
ln(STT)	-0.35±0.27	0.17
Mu	-0.80±0.26	0.09
Sigma	1.12±0.37	0.24

MTT: mean transit time; STT: standard deviation of transit time; ln(MTT): log-transformed value of MTT; ln(STT): log-transformed value of STT; Mu and Sigma: indices of estimated time constant distribution.

Table 3. – Comparison of longitudinal and cross-sectional age coefficient

	Age coefficient	
	Longitudinal	Cross-sectional
MTT	0.0135 (0.0014)*	0.0044 (0.0012)
STT	0.0261 (0.0027)	0.0075 (0.0017)
ln(MTT)	0.0224 (0.0024)	0.0077 (0.0021)
ln(STT)	0.0329 (0.0037)	0.0105 (0.0024)
Mu	0.0092 (0.0020)	0.0061 (0.0028)
Sigma	0.0216 (0.0054)	0.0196 (0.0032)

*: standard errors of the estimates are in parenthesis. For abbreviations see legend to table 2.

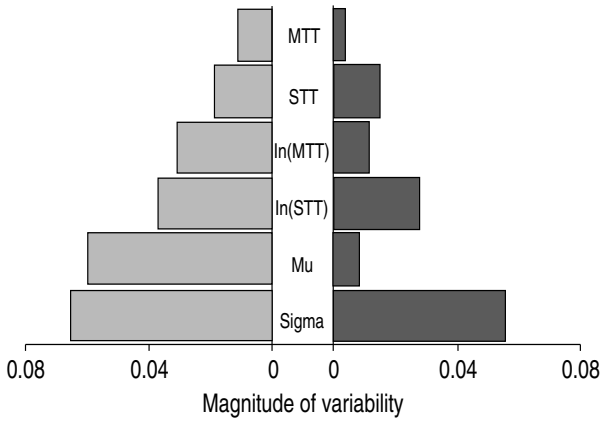

Fig. 6. – Comparison of the magnitudes of between-subject and error variations estimated in the longitudinal model. ▭: between-subject variance; ▬: error variance. MTT: mean transit time; STT: standard deviation of transit time; ln(MTT): log-transformed value of MTT; ln(STT): log-transformed value of STT; Mu and Sigma: indices of estimated time constant distribution.

Table 4. – Correlation coefficients between room temperature at the time of testing and the residual of time domain spirometric indices in the logitudinal model used in this study

	r*	t†
MTT	0.054	0.119
STT	0.035	0.302
ln(MTT)	0.055	0.110
ln(STT)	0.035	0.314
Mu	0.067	0.053
Sigma	-0.014	0.682

*: correlation coefficient; †: t-value under the hypothesis that r is equal to zero. For further abbreviations see legend to table 2.

Room temperatures at the testing were in the range 12–24°C. However, 92% of total of 853 measurements were made under the condition of ≥17°C. Examination of the effect of BTPS correction on time domain spirometric indices is presented in table 4. The figures in the table are correlation coefficients between room temperature at the time of testing and the residuals of the indices in the model. None was significantly different from zero.

Discussion

The analysis of maximal forced expiration in the time domain was theoretically expected to be more sensitive than conventional indices to the events in the terminal part of forced expirations, and this is an area where the early changes of chronic airflow limitations (CAL) would be manifested. Accordingly, there have been numerous studies [2–8] on the indices obtained by this method, especially as regards transit times. However, few studies have reported on reference values of these indices. The first study on reference values was reported by MILLER *et al*. [10]. They presented the regression equation of the first two moments, Mu and Sigma, for age and height in 226 asymptomatic nonsmokers. For Japanese subjects, MARUMO *et al*. [17] reported the mean and standard deviation of Mu and Sigma in 94 asymptomatic, healthy male volunteers.

Whilst the mean values of MTT, ln(MTT) and Mu in this study showed only a minimal difference from those of previous studies, the Sigma, STT and ln(STT) were remarkably different, even when differences in age and height distribution between this study and those of previous studies were considered. Based on the regression equation by MILLER *et al*. [10], for example, a man of almost the same age and height as the mean of the subjects of this study (40 yrs and 160 cm) would be expected to have a Sigma of 0.838. However, the mean Sigma of this study was 1.081; about 30% larger than that reported by MILLER *et al*. [10]. One possible explanation for this difference would be the difference in sample population. This study included smokers and workers occupationally-exposed to possibly harmful materials, although they were healthy at the time the surveys were conducted. In their original report on Mu and Sigma, PERMUTT and MENKES [9] showed that a significant difference in the age coefficient between smokers and nonsmokers was present in Sigma, but not in Mu. JANSEN *et al*. [5] also observed that the effect of smoking was more evident in the dispersion components of transit time than in mean transit time among asymptomatic smokers. Therefore, inclusion of smokers might have caused the increase in the mean values of Sigma, STT and ln(STT) observed in our study subjects. Similarly, it seems reasonable to consider the possibility that subclinical change caused by occupational exposure produced the increases in Sigma, STT and ln(STT), but not in Mu, MTT and ln(MTT).

The other factor to be considered is the difference in the method used to measure forced spirograms. In particular, the most significant problem would be in temperature correction. In their detailed study of this point, PINCOCK and MILLER [18] revealed that conventional BTPS correction might lead to important errors in recorded spirograms. They recommended the use of a heated pneumotachograph or a heated spirometer to avoid the distortion of forced spirograms. In a longitudinal field survey, however, it is quite difficult to maintain the accuracy of a pneumotachograph with a wide flow range comparable throughout all surveys. It might be possible that the minimal difference in its linearity would be integrated to become a conspicuous error in volume data. In addition, it was not practical to keep a spirometer heated during a field survey. Accordingly, we used a rolling-seal type spirometer and employed routine BTPS correction to maintain the comparability of volume data throughout the follow-up period. As a consequence, the data of transit times and time constant parameters in this study might have been affected by the cooling of gas during expiration. That would lead to underestimation of Mu and overestimation of Sigma, to some extent. However, over 90% of measurements were recorded under the condition of 17–24°C, that met the recommendation of the American Thoracic Society [13].

Furthermore, no significant association was found between room temperature at testing and the residuals of the indices in the model used in this analysis. Therefore, there was apparently no serious systematic bias due to BTPS correction, although there might be some random error due to it.

This study was designed primarily to assess longitudinal change and variability of transit times and time constant distribution parameters, since little has been reported on this aspect of these indices. In all indices considered in this study, a significant contribution of age was observed in both the longitudinal and cross-sectional estimates. These results indicate that the mean and the dispersion of time constant distribution in peripheral lung units increase with ageing. In the case of Mu and Sigma, longitudinal and cross-sectional estimates of the age coefficient had comparable values. According to MILLER *et al.* [10], cross-sectionally determined age coefficients of time domain indices in nonsmoking males were 0.0081 for Mu and 0.0192 for Sigma. PERMUTT and MENKES [9] reported a statistically significant difference in the age coefficient for Sigma between smokers and nonsmokers; 0.023 for smokers and 0.0142 for nonsmokers. This study showed an age coefficient for time constant distribution parameters comparable to that of previous studies.

In the case of transit times, on the contrary, the longitudinal and cross-sectional estimates of the age coefficient were somewhat different from each other. In other words, the longitudinal estimates were generally larger than their cross-sectional counterparts, and the difference was statistically significant. There may be two important factors potentially producing serious bias in longitudinal estimates of the age coefficient: a measurement bias and a learning effect. If there was a considerable bias in spirometric measurements between the surveys, a longitudinal comparison of the data would be inappropriate. To avoid such a bias, the spirometric measurements were carried out by one examiner, using an identical procedure and the same apparatus throughout all surveys. A learning effect, or improved performance of the spirometric manoeuvre, is generally inevitable in pulmonary function tests, when subjects are not familiar with the manoeuvre, because the procedure is primarily effort-dependent. However, the discrepancy was only seen in the transit time indices; MTT, STT, ln(MTT) and ln(STT). The time constant distribution indices, Mu and Sigma, calculated from the same forced expiration data did not show a statistically significant difference between the two types of age coefficients. Therefore, it is unlikely that the discrepancy can be attributed to the sources of bias considered here.

One important methodological factor is the problem of the truncation of spirograms. In the analysis of a spirogram in the time domain, most spirograms can be considered to be analogous to truncated exponentials. Older subjects often terminate the forced expirations before expelling all of the gas that could have been removed with a longer time of expiration, and younger subjects tend to show a sudden termination of flow, presumably due to a limitation of thoracic motion [9]. It has been pointed out that transit time indices are adversely affected by such inevitable truncation [10]. Time constant parameters, Mu and Sigma, were proposed to overcome this point, by applying a mathematical model to a spirogram. They describe the essentials of volume-standardized spirograms and are, theoretically, expected to be less susceptible to such a truncation. Therefore, the discrepancy between cross-sectional and longitudinal age coefficients found in the transit time indices, but not in the time constant distribution indices, might be related to the truncation of spirograms.

A similar discrepancy has been reported in conventional spirometric indices. In a 5 yr follow-up observation of 52 white males, GLINDMEYER *et al.* [19] reported that the cross-sectionally determined age regression coefficient for FVC and FEV_1 was more than twice the longitudinal annual change computed from the same data. They concluded that the discrepancy was due to the cohort effect. WARE *et al.* [20] also reported that the cross-sectionally estimated rate of loss of FEV_1 was larger in young subjects, but was smaller in aged subjects, than the longitudinal estimates in their large scale longitudinal study. We also found that the cross-sectionally estimated declines of FVC and FEV_1 were several times larger than those of their longitudinal counterparts in this study cohort [12].

The results of this and previous studies indicate that there could be a systematic difference in the level of pulmonary function indices among age-cohorts. In the case of conventional indices, such as FVC and FEV_1, this could be caused by past harmful influences in elderly subjects [19], such as illness, malnutrition, or a history of environmental and/or occupational exposure. In the transit time indices determined in this study, however, the difference by age cohorts was in a direction opposite to that of conventional indices. In other words, elderly subjects in this study showed better results in transit times than would have been expected longitudinally. The healthy-worker effect might explain this type of systematic difference in transit times by age cohorts. At this point in time, however, we cannot specify particular factors contributing to the effect of age cohorts observed in this study. Further study is needed to clarify this point. However, it is worth noting that transit time estimates are apparently more susceptible to the effect of age cohorts than time constant distribution estimates. Accordingly, observed longitudinal changes in the transit time indices of study cohorts should be compared with longitudinal control data, but not with cross-sectional prediction equations.

It is well-known that the relatively large variability of conventional spirometric measurements obtained in cross-sectional examinations is caused primarily by between-individual variability. For example, KNUDSON *et al.* [21] reported that the residual standard deviation in a regression model, in which age and height were taken into consideration, was about 14% for FVC and FEV_1, 27% for forced expiratory flow at 50% of FVC (FEF_{50}), and 36% for forced expiratory flow at 25% of FVC (FEF_{25}) in terms of the coefficient of

variation. However, within-individual variability in these indices, as estimated by repeated measurement in a short period of time [22–24], was quite small; in the range of 3–5% for FEV_1, and 8–14% for FEF_{50} and FEF_{25} in terms of the coefficient of variation. These results indicate that between-individual differences in the level of spirometric indices contributed in large part to the relatively large variability of these indices observed cross-sectionally.

In these circumstances, a longitudinal study gives more precise estimates of temporal changes than a cross-sectional study of the same size, because the former eliminates between-subject variability from the comparison of interest. The larger the between-subject variability, the more the difference in precision and statistical power between longitudinal and cross-sectional designs [25]. Therefore, before utilizing an index in longitudinal studies, it would be useful to examine the magnitude of between-subject variability of the index in comparison with error variances.

In the case of transit times and time constant distribution parameters, there has been no reported data regarding this point. The results of this study show that the between-subject variation contributed significantly to the total variability of the time domain spirometric indices, producing marked effects on the mean components of transit time and time constant distribution as compared with dispersion components. The between-subject variation was about eight times larger than the longitudinal error variance in Mu, and about three times larger than that in MTT and ln(MTT). Accordingly, the error variance in a longitudinal design will be expected to be several times smaller than that in a cross-sectional design. Therefore, as far as the magnitude of error variance is concerned, longitudinal studies appear to give more precise estimates of temporal changes in these indices than a cross-sectional design, especially in their mean components.

In the dispersion components, however, the difference between the between-subject and error variances was not so large as in the case of mean components. It may simply have been caused by a larger experimental noise on these indices. However, as another explanation, the difference in variability between these two types of indices, mean and dispersion components, might be explained by the particular aspect of lung condition they reflect. As cited earlier, PERMUTT and MENKES [9] showed that a significant difference in the age coefficient between smokers and nonsmokers was present in Sigma, but not in Mu. They also reported that inhalation of methacholine caused a striking change in Mu, but not in Sigma. Their results indicate that Mu reflects an evenly distributed change across all peripheral units, and that Sigma corresponds to the change occurring in a small portion of peripheral lung units. According to their findings, it would be reasonable to consider mean components, such as Mu, MTT and ln(MTT), as being less variable within a subject, as compared to dispersion components, such as Sigma, STT and ln(STT).

In conclusion, a longitudinal observation of time domain spirograms in middle-aged healthy male workers revealed that there was a discrepancy between the longitudinal and cross-sectional estimates of the age coefficient in transit time indices, but not in time constant distribution indices. Although further study is needed to elucidate the cause of this discrepancy, observed longitudinal changes should not be compared with cross-sectional reference values at least in the case of transit time indices. In addition, the between-subject variability contributed significantly to the total variability of time domain spirometric indices, as in the case of conventional spirometric indices. The contribution was more marked in the mean components of these indices, and the difference in the magnitudes of their contributions might be attributable to differences in aspects of the mean and dispersion components of the indices, possibly reflecting the condition of peripheral regions of the lungs.

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