Estimation of Alveolar Deposition Ratio of Inhaled Radioaerosol

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ISAWA, T., TESHIMA, T., HIRANO, T., EBINA, A. and KONNO K. *Estimation of Alveolar Deposition Ratio of Inhaled Radioaerosol.* Tohoku J. exp. Med., 1985, **145** (3), 259-267 — The lung retention ratio (LRR) and the alveolar deposition ratio (ALDR) are mandatory to calculate the other three indices for quantitatively evaluating mucociliary clearance function of the ciliated airways; the airway deposition ratio (ADR), the airway retention ratio (ARR) and the airway clearance efficiency (ACE). According to our original method, the LRR required 2-hr continuous measurement of radioactivity in the thorax and the ALDR a repeat measurement at 24-hr after radioaerosol inhalation. The 2-hr continuous measurement is, however, too long for a clinical examination and the 24-hr repeat measurement cumbersome. The purpose of the study was to find a way to get the ALDR by calculation without repeating the 24-hr measurement and by counting radioactivity for the shortest possible period and yet without sacrificing the visual evaluation by compiling radioaerosol inhalation lung cine-scintigraphy. By using the derived formulae listed in Table 1, the ALDR was calculable. Forced expiratory volume (FEV) in one sec divided by FEV in per cent ($FEV_{1.0}$ %), the initial 60 min measurement of radioactivity without repeating 24-hr measurement, and smoking history were the minimum requirements to calculate the ALDR. The calculated ALDR appeared reliable enough to estimate the other indices. — radioaerosol inhalation lung cine-scintigraphy; alveolar deposition ratio; airway clearance efficiency; airway retention ratio; lung retention ratio.

Mucociliary clearance in the lungs is now visualized in vivo as an actual movement of mucus on the airways by radioaerosol inhalation lung cine-scintigraphy (Isawa et al. 1981). By this method we have learned that the cephalad and axial transport of mucus as seen in the normal subjects is deranged in various ways in disease status (Isawa et al. 1981, 1984a, b).

Our original method was to continuously measure radioactivity over the thorax for 120 min following inhalation of radioaerosol and to repeat the measurement for 10 min at 24-hr. The data obtained during the initial 2-hr was utilized

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for compiling "radioaerosol inhalation lung cine-scintigraphy" and calculating "lung retention ratios" (LRR) during each 10 min period in the initial 120 min and the data obtained at 24-hr for calculating "alveolar deposition ratio" (ALDR). The LRR's represent the overall radioactivity remaining in the lungs in per cent during each 10 min as compared with the radioactivity during the initial 10 min, whereas the ALDR represents the radioactivity remaining in the lungs in per cent at 24-hr which was therefore equivalent to the LRR at 24-hr; the LRR at 24-hr was conveniently defined as the fraction of inhaled radioactivity depositing in the nonciliated alveolar space of the lungs (Isawa 1984a). This ALDR is mandatory to calculate the proposed three other indices of "airway deposition ratio" (ADR), "airway retention ratio" (ARR) and "airway clearance efficiency" (ACE). The LRR is the index to indicate the overall lung clearance, while the latter three indices the status of mucociliary clearance on the ciliated airways.

These indices would be informative when we compare inter- or intra-individual differences in the mucociliary clearance mechanisms such as before and after a use of a drug or between different disease entities.

The initial measurement for 120 min we have been doing is practically too long for a clinical examination and the repeat measurement at 24-hr is also cumbersome.

The purpose of the present study was to find whether or not we could shorten the initial examination time and whether we could get ALDR by calculation without repeating the measurement at 24-hr.

MATERIALS AND METHODS

Eighty-two consecutive subjects were studied. They completed the initial 2-hr study, the repeat study at 24-hr and lung function tests from November 1, 1982 through December 15, 1983. Sixty-six were patients with various chest diseases; 47 were male and 19 female. Bronchogenic carcinoma, 15, obstructive airways disease, 14 (1* (female)), interstitial fibrosis, 11 (5*), bronchial asthma in remission, 6 (1*), hemoptysis of unknown origin, 6 (4*), bronchiectasis, 4 (3*), sarcoidosis, 3 (2*), pulmonary tuberculosis, stable, 2 (2*), lung abscess, 2, fibrothorax, 2, and Swyer-James syndrome, 1 (1*). Their age ranged from 50 to 82 with the average of 70. The remainder sixteen were normal male subjects. Their age ranged from 28 to 76 with the average of 44.

As reported previously (Isawa et al. 1981, 1984a, b), ultrasonically generated 99 m Tc-albumin aerosol was inhaled in the sitting position and successive 10 sec images of the lungs were continuously made from anteriorly with a gamma camera connected to a computer for 2-hr from immediately after the completion of aerosol inhalation, while the subjects laid supine comfortably on the bed.

Alveolar deposition ratio (ALDR) were obtained by dividing the corrected residual 10 min radioactivity in the right and left lungs at 24-hr by the corresponding radioactivity during the first 10 min of the initial measurement.

Lung function tests were done within 3 days of inhalation studies and included forced expiratory volume (FEV), its per cent of the predicted (% FEV) (Baldwin et al. 1984), forced expiratory volume in one second divided by FEV ($FEV_{1.0}\%$), maximum mid-expiratory flow rate (MMF), expiratory flow at 50% and 25% of FEV ($\dot{V}_{50}$, $\dot{V}_{25}$, respectively), and their percentages of the predicted, peak-flow ($\dot{V}_P$) and its per cent of the

predicted (Cherniack and Rader 1972), vital capacity (VC) and its per cent of the predicted (VC%), functional residual capacity (FRC), total lung capacity (TLC) and its per cent of the predicted (TLC%), residual volume (RV) and its per cent of the predicted (RV%), RV/TLC, carbon monoxide diffusing capacity (D_{LCO}) by single breath method and D_{LCO} divided by alveolar ventilation (D_{LCO}/V_A).

A simple linear regression model of $y = a + bx$, was preliminarily applied to find which parameter of pulmonary function data had the best correlation with the ALDR. Both $\text{FEV}_{1.0}\%$ and MMF had the greatest coefficients of the determination (r^2). Because both $\text{FEV}_{1.0}\%$ and MMF indicate the degree of airway obstruction, the $\text{FEV}_{1.0}\%$ was selected as an independent variable to be used in the following.

Thus from lung function data $\text{FEV}_{1.0}\%$ has been selected as an independent variable. From the initial 2-hr continuous measurement we have now the LRR for every 10 min. Either LRR_{60} or LRR_{120} has been selected as another independent variable and the multiple linear regression functions were derived following the model of $z = a + bx + cy$ between ALDR (z) and independent variables separately for the groups of patients ($n = 66$), the patients and normal subjects combined ($n = 82$), and the normal subjects ($n = 16$).

In the normal subjects ($n = 16$) the amount of smoking in packyear (PY) and either LRR_{60} or LRR_{120} were also selected as independent variables for the multiple linear regression model. A simple linear regression function of $z = a + by$ was also derived for the group of normal subjects between ALDR (z) and PY. After deriving either multiple or simple linear regression functions residual analysis was made to determine if there was any particular tendency of deviation in the point estimate of σ or standard deviation (SD); here $\sigma^2 = \text{error mean square (MSE)}$. Student t -test was done to evaluate each coefficient of multiple or simple regression correlation. The sum of the squares, i.e., total sum of square (SSTO), error sum of square (SSE) and regression sum of square (SSR) were calculated for the analysis of variance and F^* value was obtained by dividing the regression mean square (MSR) by the MSE; here, $\text{MSR} = \text{SSR}/P$, and $\text{MSE} = \text{SSE}/(N - P + 1)$. P was the number of variables or the degree of freedom. N was the number of subjects. Paired t -test was done to evaluate the difference in the fitted values obtained by different multiple or simple linear regression functions (Neter et al. 1982).

To evaluate the validity of the estimated ALDR, the observed or the actual airway clearance efficiency (ACE) was compared with the fitted or the calculated ACE based on the estimated ALDR.

RESULTS

The relationships between $\text{FEV}_{1.0}\%$ and the ALDR and the LRR_{60} and the ALDR are shown in Fig. 1 and 2, respectively. The coefficients of determination (r^2) were 0.43 and 0.22, respectively.

As shown in Table 1, the coefficients b and c of each formula derived separately for the patients group and the group including all the subjects showed a close resemblance to each other, respectively, when the same pairs of variables $\text{FEV}_{1.0}\%$ and LRR_{60} , or $\text{FEV}_{1.0}\%$ and LRR_{120} were selected. Although the coefficients of multiple correlation (r) were slightly greater when LRR_{120} was used than when LRR_{60} was used as an independent variable, F^* was far greater than F values at p less than 0.01 in any of the multiple linear regression functions. In the group of only normal subjects whose $\text{FEV}_{1.0}\%$ were greater than 73%, the cigarette consumption in PY played an important role in determining the ALDR as reported previously (Isawa et al. 1984a). When PY and LRR_{120} were selected,

Fig. 1 FEV_{1.0} % versus alveolar deposition ratio (ALDR). The coefficient of determination (r^2) was 0.43.

Fig. 2 Lung retention ratio at 60 min (LRR₆₀) versus alveolar deposition ratio (ALDR). The coefficient of determination (r^2) was 0.22.

Fig. 3 Observed alveolar deposition ratio (ALDR) versus fitted ALDR by the multiple linear regression $ALDR = -48.08 + 0.47 \times FEV_{1.0} \% + 0.59 \times LRR_{60}$ ($r = 0.780$, $p < 0.0001$).

TABLE 1. *Statistical relationships in the three populations ; patients, patients and normal subjects combined, and normal subjects*

Subjects	N	Independent variables	Coefficients for $z = a + bx + cy$			Correlation coefficients (r)	F*
			a	b	c		
Patients	66	FEV _{1.0} %, LRR ₆₀	-47.03	0.44	0.59	0.813 ‡*	63.55 ‡
	61	FEV _{1.0} %, LRR ₁₂₀	-38.12	0.42	0.54	0.852 ‡*	79.36 ‡
Overall	82	FEV _{1.0} %, LRR ₆₀	-48.08	0.47	0.59	0.780 ‡*	63.13 ‡
Patients + Normal	76	FEV _{1.0} %, LRR ₁₂₀	-38.37	0.46	0.52	0.798 ‡*	65.66 ‡
Normal	16	PY, LRR ₆₀	59.71	-0.50	-0.12	0.838 ‡*	17.66 ‡
	15	PY, LRR ₁₂₀	49.46	-0.47	0.00	0.835 ‡*	16.12 ‡
	16	PY	49.33	-0.47		0.845 ‡*	39.82 ‡

‡ $p < 0.01$, ‡* $p < 0.001$ FEV_{1.0} % : Forced expiratory volume in one second/Forced expiratory volume in percent.LRR₆₀ or LRR₁₂₀ : Lung retention ratio either at 60 min or 120 min.

PY : Pack-year.

Fig. 4. Residual plots. Horizontal axis indicates fitted alveolar deposition ratio (ALDR) and the vertical axis, the residuals or the difference between the observed and the fitted values.

the multiple linear regression nearly coincided with the simple linear regression which used only PY as the independent variable. The reason why the number of subjects (N) was different between 60 and 120 min was that 5 patients and one normal subject could not keep still on the bed for longer than 90 min due to physiological necessities.

From the practical point of view, the multiple linear regression of ALDR =

$48.08 + 0.47 \times \text{FEV}_{1.0}\% + 0.59 \times \text{LRR}_{60}$ appeared usable as a predictor of ALDR in all subjects including patients and normal subjects as shown in Fig. 3. There was no statistical difference by the paired *t*-test between the fitted ALDR's derived by the above formula which used $\text{FEV}_{1.0}\%$ and LRR_{60} and those by the formula using $\text{FEV}_{1.0}\%$ and LRR_{120} . The plotting of residuals for the formula above mentioned indicated that all points scattered fairly evenly within 2 SD (Fig. 4).

The observed or actual ACE's versus the fitted or calculated ACE's based on the multiple linear regression $\text{ALDR} = -48.08 + 0.47 \times \text{FEV}_{1.0}\% + 0.59 \times \text{LRR}_{60}$

Fig. 5. Observed airway clearance efficiency (ACE) versus fitted ACE based on $\text{ALDR} = -48.08 + 0.47 \times \text{FEV}_{1.0}\% + 0.59 \times \text{LRR}_{60}$ in the 82 subjects studied. The correlation was statistically significant with the correlation coefficient (*r*) of 0.950 (*p* < 0.0001).

Fig. 6. Observed airway clearance efficiency (ACE) versus fitted ACE based on $\text{ALDR} = 59.71 - 0.50 \times \text{PY} - 0.12 \times \text{LRR}_{60}$ in the 16 normal subjects. The correlation was statistically significant with the correlation coefficient (*r*) of 0.972 (*p* < 0.0001).

Fig. 7. Observed airway clearance efficiency (ACE) versus fitted ACE based on $\text{ALDR} = 49.33 - 0.47 \times \text{PY}$ in the 16 normal subjects. The correlation was statistically significant with the correlation coefficient (r) of 0.978 ($p < 0.0001$).

are shown in Fig. 5. The relationship between them was statistically significant with the correlation coefficient (r) of 0.950 ($p < 0.0001$). Figs. 6 and 7 show the relationship among the 16 normal subjects whose fitted ACE's were calculated based on $\text{ALDR} = 59.71 - 0.50 \times \text{PY} - 0.12 \times \text{LRR}_{60}$ and $\text{ALDR} = 49.33 - 0.47 \times \text{PY}$, respectively. In either case the correlation was statistically significant with r over 0.970 ($p < 0.0001$).

DISCUSSION

By using the multiple linear regression $\text{ALDR} = -48.08 + 0.47 \times \text{FEV}_{1.0} \% + 0.59 \times \text{LRR}_{60}$, we could shorten the initial measurement time from 120 to 60 min and did not have to repeat the measurement at 24-hr, and still we could get a fairly good estimate of ALDR. Thus we think that an easier and more practical method to study mucociliary clearance mechanisms has been established by the present revision of our original proposal (Isawa et al. 1981, 1984a, b).

The question is whether the estimated or the fitted values really reflect the true or the observed ALDR's. As far as analysis of variance, the plotting of the residuals and the respective resemblance of coefficients b and c were concerned, the use of LRR_{60} instead of LRR_{120} as an independent variable seemed justified so that we could complete the measurements in 60 min. The 360 frames obtained during the 60 min period were sufficient in most cases to compile a cine-sциntigraphy of diagnostic usefulness even considering that the mucociliary transport velocity is rather slow in the order of 0.3–1.5 cm/min (Wanner 1977). When regional quantitative information is required, however, the repeat measurement at 24-hr is mandatory.

The present study has indicated that the smaller the $FEV_{1.0}\%$, the lower becomes the ALDR as seen in Fig. 1. But the reverse was not always true. This probably means that when the airway obstructive disturbance becomes severer, the alveolar penetration of inhaled aerosol is accordingly disturbed. In patients whose $FEV_{1.0}\%$ values were large, however, for example, as in some patients with interstitial fibrosis, the ALDR tended to be diminished probably because of the pathological changes in the small airways (Fulmer and Roberts 1980). We have also confirmed that the earlier statement that smoking greatly effects the degree of alveolar penetration in the normal subjects (Isawa et al. 1984a). The ALDR was influenced by the amount of smoking in packyear (PY) in the normal subjects who were judged "healthy" from every aspect of clinical history, chest x-rays, lung function tests and so on. Subclinical pathological changes in normal smokers could have contributed to the decrease in the ALDR (Isawa et al. 1984a). Smoking could have also affected the ALDR in patients group, combined with other factors such as recurrent infections, predisposition, air pollution and so on, because most of our patients except for a few women patients used to be smokers. The use of $FEV_{1.0}\%$ and LRR_{60} in the above mentioned multiple linear regression also circumvents the use of the multiple or simple linear regression functions derived for the normal subjects because there were no statistical differences between the ALDR's estimated either by this formula or the latter formula using PY and either LRR_{60} or LRR_{120} or simply PY as independent variables. As could be judged from Figs. 5, 6, and 7, the application of calculated ALDR to estimating the ACE was satisfactory enough to be used in the actual situation.

After all the multiple linear regression of $ALDR = -48.08 + 0.47 \times FEV_{1.0}\% + 0.59 \times LRR_{60}$ seems to be a reasonable formula to predict the ALDR in all subjects. When a subject is healthy and his or her spirometry shows $FEV_{1.0}\%$ larger than 75%, the formula $ALDR = 49.71 - 0.50 \times PY - 0.12 \times LRR_{60}$ or simply $ALDR = 49.33 - 0.47 \times PY$ would be applicable. Once the LRR and the ALDR are available, we can calculate other indices such as the airway deposition ratio (ADR), the airway retention ratio (ARR) and the airway clearance efficiency (ACE) as we have done here to evaluate the mucociliary clearance of the ciliated airways.

Spirometry and the initial measurement of radioactivity for 60 min are found to be adequate enough both for compiling "radioaerosol inhalation lung cine-sциntigraphy" for the visual evaluation and for calculation of the indices for the quantitative evaluation of mucociliary clearance mechanism in the lungs.

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