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Long-term clearance from small airways decreases with age

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ABSTRACT: The prevalence of respiratory symptoms increases with age. Age has been found to be negatively associated with large airway clearance. The small airways region is considered important for development of airway disease.

Clearance after the first 24 h was studied in 46 healthy subjects with a wide age distribution, (mean 42, range 19–81 yrs). All subjects inhaled monodisperse 6 μm Teflon particles labelled with ^{111}In, with an extremely slow inhalation flow (0.05 L·s^{-1}). The particles were mainly deposited in the small conducting airways. Lung retention was measured at 0 and 24 h, and at 7, 14 and 21 days after inhalation.

Significant relationships were found for the individual 24 h "large" airway clearance in per cent of initial lung deposition with age, forced expiratory volume in one second and forced vital capacity. Age was negatively associated with "small" airway clearance after 24 h as estimated at 2, 7, 14 and 21 days. Using stepwise linear regression only age remained significantly associated to clearance.

In conclusion, small airway clearance over 21 days was found to decrease with age. This might be one factor associated with the high prevalence of respiratory symptoms associated among the elderly.

KEYWORDS: Ageing, bronchitis, clearance, particles, small airways, Teflon

The prevalence of chronic bronchitis increases with age. Nonspecific respiratory symptoms are common among the elderly, which affects quality of life. A large number of people suffer from chronic bronchitis. In Sweden, 3% of the male population [1] and 3% in an adult population in Stockholm, both males and females, were reported to suffer from chronic bronchitis [2]. It has been shown that patients with chronic bronchitis, with and without obstructed airways, usually have impaired mucociliary transport in their airways [3–6]. Furthermore, patients with immotile ciliary syndrome, also called primary ciliary dyskinesia, a disease caused by absent or extremely slow mucociliary clearance in the airways, have similar signs and symptoms in the airways as patients with chronic bronchitis [7, 8]. These results indicate that impaired mucociliary clearance is a pathogenic factor for development of chronic bronchitis. Mucociliary clearance as measured during a short time period (hours) has previously been shown to be negatively correlated with age [9–11]. However, MORTENSEN *et al*. [12] found no influence of age on mucociliary clearance among 53 lifelong nonsmokers. Studies of nasal ciliary beat frequency and age have given conflicting results [13, 14]. The overall conclusion is that mucociliary clearance probably decreases with age, but other factors such as smoking, are more important. Long-term airway clearance of particles after shallow bolus inhalation has been followed for 9 months using magneto-pneumographic methods [15]. The current findings indicate a large fraction cleaning with a half-time of 109 days *i.e.* quite different from what has previously been studied regarding mucociliary clearance. The alveolar clearance phase has been found to be even slower. Half-times estimated from measurements of elimination of radiolabelled particles between 250 and 900 days have been reported to be >2 yrs [16]. In previous studies, mucociliary clearance was investigated mainly in larger and medium sized airways and only to a minor extent in smaller airways. Long- or medium-term clearance after a day or two probably better reflects small airways [17]. Histopathological investigations indicate that chronic obstructive lung disease starts in the small airways [18]. The hypothesis that small airways are involved in the development of disease is a good reason to study clearance of retained fractions in the small airways. The increased prevalence of respiratory symptoms among the elderly might be associated with an age-dependent decrease in clearance function.

For editorial comments see page 563.

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A technique has been developed [19] to deposit particles mainly in the smallest ciliated airways, *i.e.* the bronchioles, using rather large particles (6 μm) and an extremely slow inhalation flow (0.05 $L \cdot s^{-1}$). Calculations of deposition using different theoretical models indicate that a major fraction of the particles should deposit in small ciliated airways [20–23]. Another advantage of using this technique is that the regional particle deposition is independent in respect to airway constriction [24].

The purpose of the present study was to compare airways clearance for 3 weeks in different age groups of healthy controls using the extremely slow inhalation technique. Clearance during the first 24 h represents particles cleared from large and medium sized airways. Clearance after 24 h will, in the current study, represent small airways. The primary question of this study was ''does small airway clearance decrease with age?''

MATERIALS AND METHODS

Subjects and design

Long-term clearance (typically up to 21 days) from small airways was studied in 46 nonsmoking, healthy subjects with a wide age distribution, mean (range) 42 (19–81) yrs. Of the subjects, 13 were aged $\leqslant$24 yrs, eight were aged 25–29 yrs, seven 30–49 yrs, nine 50–64 yrs and nine >65 yrs. Pulmonary function (mean$\pm$SD (range)) was normal, with forced expiratory volume in one second (FEV_1) 105$\pm$16% predicted (78–149), and FEV_1/forced vital capacity (FVC) 80$\pm$6.7% pred (64–99). Personal and lung function data are given in table 1. All subjects inhaled monodisperse 6 μm Teflon particles labelled with ^{111}In with an extremely slow inhalation flow (0.05 $L \cdot s^{-1}$). Mean particles size ranged from 6.0–6.5 μm and inhalation flow varied between 0.043–0.050 $L \cdot s^{-1}$ for the different exposures. Radioactivity in the lungs was measured at 0, 24 and 48 h, as well as 1, 2 and 3 weeks after inhalation of the particles. The ethics committee of Human Research at the Karolinska Institutet and the Isotope Committee at the Karolinska Hospital (both Stockholm, Sweden) approved the study.

Lung function tests

FVC and FEV_1 were measured using a Lung Function Laboratory 2100 (SensorMedics, Yorba Linda, CA, USA). The subjects wore a noseclip and performed the tests in a sitting position. Airway resistance (R_{aw}) was measured using a panting technique within a whole-body plethysmograph (Transmural Body Box 2800; SensorMedics). All lung function parameters were determined according to the criteria proposed by QUANJER [27].

Production of the test particles

All the Teflon particles were produced using the same batch of colloidal Teflon and labelled with ^{111}In (half-life 68 h) by a spinning disc technique [28, 29]. The particles were monodisperse and the mean geometric particle diameter was measured in a light microscope (Visopan projection microscope; Reichert, Austria). The mean aerodynamic diameter was calculated from the density of the Teflon particles, 2.13 $g \cdot cm^{-3}$, as measured by PHILIPSON [29]. This method to estimate the aerodynamic diameter has been confirmed by direct measurements of the settling velocity in air [30]. Mean particles size ranged from 6.0–6.5 μm, with geometric standard deviation 1.06–1.13 for the different exposures. The particles were made wet and well dispersed by the addition of 0.2% tergitol solution. Before atomisation they were washed in water at 37°C. Before use, the particles were allowed to sediment and the supernatant liquid was removed and replaced with distilled water. The leakage of radioactivity in water (37°C) was estimated during the periods of lung clearance measurements by repeated measurements of activities in filter and filtrate. The leakage *in vitro* during the 3 week measuring periods was <2%.

Inhalation of the particles

Distilled water (0.3 mL), with ~2 mg Teflon particles per mL, was sprayed into a 25-L glass chamber with an atomiser (Beckman Instruments Inc, Fullerton, CA, USA). The subjects wore a noseclip and inhaled the particles in a sitting position. The participants first made a moderately deep exhalation outside the chamber, followed by long inhalations from the chamber. The inhalation flow was measured with a pneumotachograph, placed between the aerosol chamber and the mouthpiece, and was displayed on-line. By looking at the recorder needle, the participants could inhale at a fairly constant rate throughout the inspiration. All participants were trained to inhale in this manner before they inhaled the test particles. Between each inhalation from the chamber, the participant could rest and breathe quietly outside the chamber. Exhaled activity, for similar exposure conditions, has previously been shown to be 0–2% [19]. Measured inhalation flow varied between 0.041–0.050 $L \cdot s^{-1}$ for the different exposures. Details are presented in table 2.

Measurement of radioactivity

Immediately after inhalation, and 24 h later, radioactivity was measured using two 127×51-mm NaI detectors fitted with collimators [21–26]. The γ-spectra from each detector were acquired separately. The radioactivity deposited in the lungs was 0.1 MBq [31].

The activity in the lungs was measured at 24 and 48 h and 1, 2 and 3 weeks after inhalation using the whole-body scanner at the Swedish Radiation Protection Institute (Stockholm, Sweden) [32]. Retention at 24 h was normalised to 100%. Measurements at 2 and 3 weeks were adjusted using interpolation to day 14 and 21, in the few cases when the measured point differed by $\geqslant$1 day. The scanner has three large NaI detectors. The front of each detector facing the subject was provided with focusing slit collimators of lead. The γ-spectra from each detector were acquired separately giving a total of 210 spectra from one measurement. The spectra were later analysed so the activity in the lung could be distinguished from the activity in the stomach. The technique has previously been described in detail by FALK *et al*. [21].

At 2 and 3 weeks after the inhalation, when the activity in the gastro-intestinal tract was insignificant compared with the lung, a more sensitive lung counter, involving a stretcher with the subject in supine position, was used [33]. Five NaI detectors (diameter 127×101 mm) were placed close to the chest of the subject; two against the back, two under each armpit and one above the sternum. The relative positions between the five detectors were fixed at the same position during all measurements. The relative sensitivity between the scanner and the lung counter was established, for each participant, by repeated measurements in the two systems within an hour.

TABLE 1 Personal and lung function data in healthy subjects

Sex	Age yrs	Height cm	Weight kg	FVC L	FVC % pred	FEV_{1} L	FEV_{1} % pred	R_{aw} kPa·s·L^{-1}	Reference
M	19	178	67	4.11	78	3.45	78	0.200	[21]
M	20	185	82	5.68	100	4.48	95	0.140	[21]
M	21	187	90	6.20	107	4.48	93	0.159	[22]
F	21	165	63	4.30	114	3.64	111	0.161	[25]
F	22	168	62	3.90	100	3.23	95	0.172	[25]
M	22	184	100	7.35	131	5.87	125	0.135	[26]
M	22	181	73	5.63	104	4.62	101	0.112	[26]
M	23	173	110	4.43	89	3.88	92	0.191	[22]
F	23	169	60	3.92	99	3.90	113	0.082	[26]
M	23	174	73	6.82	136	5.04	118	0.167	[26]
M	24	181	74	5.92	109	4.75	104	0.140	[21]
F	24	165	64	4.20	112	3.30	100	0.245	[25]
F	24	175	66	4.63	110	4.11	111	0.161	[25]
F	25	168	76	4.33	111	3.81	112	0.140	[26]
F	26	150	62	2.71	88	2.30	86	0.198	[22]
F	26	162	52	3.36	93	2.65	84	0.139	[25]
F	27	170	57	3.97	101	3.12	91	0.180	[21]
M	27	185	86	7.23	129	5.73	122	1.161	[26]
M	28	192	95	6.25	105	4.75	96	0.120	[21]
M	28	168	72	4.24	92	3.87	99	0.071	[25]
F	28	166	58	4.69	126	3.97	122	0.119	[26]
M	30	182	76	5.30	99	4.10	92	0.140	[21]
F	33	160	56	3.58	107	2.65	92	0.187	[22]
M	33	181	80	5.77	111	4.20	97	0.100	[25]
M	34	178	64	5.16	103	4.14	99	0.160	[26]
M	35	174	79	4.44	93	3.80	96	0.080	[21]
M	42	179	73	5.89	121	3.75	94	0.103	[26]
M	45	172	85	4.48	102	3.25	90	0.198	[22]
F	51	167	72	4.21	132	3.04	112	0.099	[25]
M	57	164	70	3.86	107	3.41	117	0.044	[25]
F	57	158	75	3.34	127	2.72	123	0.260	NP
F	58	169	80	3.12	101	2.07	79	0.181	NP
M	60	178	85	4.28	99	3.13	91	0.096	NP
M	61	174	89	4.22	103	3.21	100	0.129	NP
M	62	173	70	4.99	125	3.85	122	0.130	[21]
F	64	164	64	3.94	146	3.33	146	0.227	NP
F	64	167	81	3.30	116	2.95	123	0.110	NP
F	65	170	74	3.43	116	2.89	116	0.166	NP
M	67	166	77	3.43	99	2.88	106	0.156	NP
F	67	161	56	3.02	121	2.64	127	0.225	NP
M	67	178	70	4.74	114	3.65	113	0.184	NP
M	71	169	90	4.88	138	4.05	149	0.091	NP
M	71	170	74	3.22	90	2.56	93	0.394	NP
F	74	161	65	2.69	116	2.06	108	0.146	NP
F	76	159	68	2.47	114	1.82	102	0.353	NP
F	81	160	42	2.08	100	1.56	92	0.148	NP

M: male; F: female; FVC: forced vital capacity; FEV_{1}: forced expiratory volume in one second; R_{aw}: airway resistance; NP: data not yet published.

Statistical analysis

Associations between variables were tested with linear regression analysis:

$$\text{dependent} = \text{constant} + \text{B} \times \text{independent} \quad (1)$$

The correlations were considered as significant if 95% confidence intervals for B (slope) did not include 0; B=0 corresponds to a horizontal line. Stepwise linear regression was used to select significant explaining variables for multiple regression analysis.

RESULTS

The current results are compiled from previous published and new unpublished data from the current authors. No significant

TABLE 2 Exposure data

Age yrs	Duration min	Breaths n	Breath duration s	Flow L·s^{-1}	Particle size μm	GSD	Reference
33	24	18	33	0.048	6.1	1.13	[22]
26	26	16	33	0.042	6.1	1.13	[22]
21	23	16	41	0.044	6.1	1.13	[22]
45	29	24	42	0.047	6.1	1.13	[22]
23	28	20	38	0.047	6.1	1.13	[22]
20	8	6	36	0.046	6.2	1.07	[21]
62	8	4	68	0.05	6.2	1.07	[21]
30	6	4	48	0.046	6.2	1.07	[21]
28	6	6	31	0.05	6.2	1.07	[21]
27	10	8	29	0.047	6.2	1.07	[21]
19	8	8	31	0.042	6.2	1.07	[21]
24	8	6	49	0.049	6.2	1.07	[21]
35	7	7	34	0.047	6.2	1.07	[21]
26	4	4	33	0.043	6.5	1.06	[25]
28	4	4	31	0.045	6.5	1.06	[25]
57	4	4	33	0.046	6.5	1.06	[25]
24	4	4	32	0.046	6.5	1.06	[25]
51	4	4	35	0.045	6.5	1.06	[25]
24	4	4	35	0.045	6.5	1.06	[25]
21	4	4	31	0.046	6.5	1.06	[25]
22	4	4	32	0.045	6.5	1.06	[25]
33	4	4	35	0.047	6.5	1.06	[25]
23	4	5	21	0.047	6.4	1.07	[26]
22	4	4	38	0.046	6.4	1.07	[26]
28	4	4	35	0.046	6.4	1.07	[26]
23	4	4	30	0.044	6.4	1.07	[26]
22	5	4	34	0.047	6.4	1.07	[26]
25	3	4	25	0.043	6.4	1.07	[26]
42	3	4	26	0.047	6.4	1.07	[26]
34	5	4	#	#	6.4	1.07	[26]
27	4	4	37	0.049	6.4	1.07	[26]
65	5	4	31	0.047	6.1	1.07	NP
81	4	6	17	0.041	6.1	1.07	NP
71	4	5	22	0.046	6.1	1.07	NP
71	3	6	16	0.044	6.1	1.07	NP
67	4	5	25	0.048	6.1	1.07	NP
76	4	6	12	0.045	6.1	1.07	NP
67	6	5	34	0.047	6.1	1.07	NP
67	8	8	29	0.047	6	1.08	NP
64	8	8	33	0.047	6	1.08	NP
57	5	4	43	0.049	6	1.08	NP
61	10	8	37	0.048	6	1.08	NP
74	9	10	24	0.047	6	1.08	NP
58	10	10	21	0.042	6	1.08	NP
64	8	10	20	0.049	6.2	1.06	NP
60	4	4	33	0.048	6.2	1.06	NP

GSD: geometric standard deviation; NP: data not yet published. #: data missing due to computer error.

correlation was found between initial lung deposition of total deposition (%) and age ($r=0.05$; $p>0.73$), nor with lung function (FEV_1, FVC % pred). All associations were poorer than $r<0.24$ and $p>0.14$. Significant relationships were found for the individual 24 h clearance values as percentage of initial lung deposition ($Clearance_{24}$) with age, FEV_1 and FVC, r=-0.46, 0.43 and 0.39, respectively. Pulmonary function (% pred) was not associated with $Clearance_{24}$, $r<0.02$. Age was strongly associated with FEV_1 and FVC, r=-0.62 and -0.55 respectively, and was also associated with FEV_1 % pred, r=0.31. Using stepwise linear regression, including age and FEV_1 or FVC, only age remained significantly associated to clearance (fig. 1).

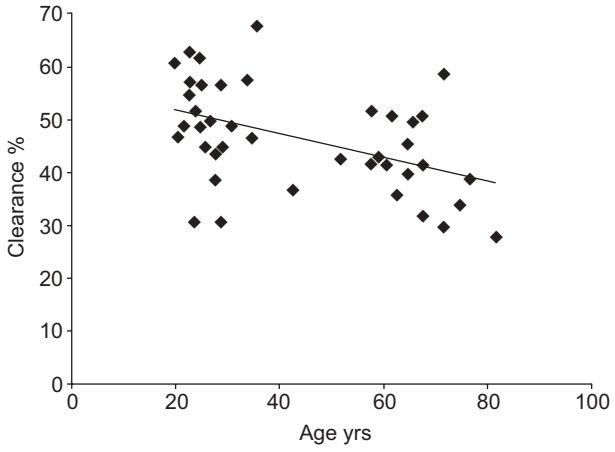

FIGURE 1. Clearance in 24 h (%) of initial deposition as a function of age. Twenty-four h clearance values as a percentage of initial lung deposition=56–0.22×age; r=-0.46; p=0.003.

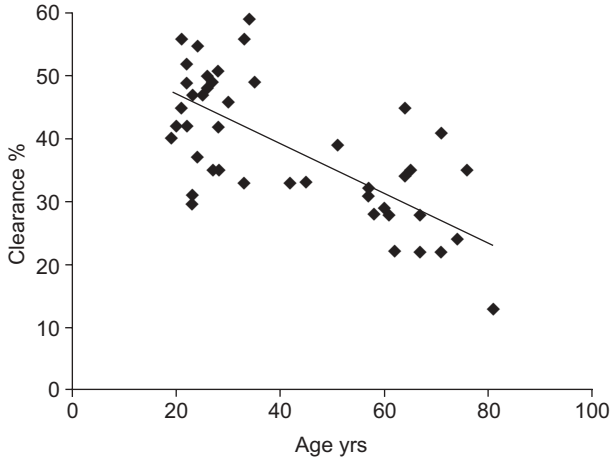

FIGURE 2. Clearance (%) after 24 h as a function of age. Clearance is estimated as the difference in retention at 24 h and 21 days; 24 h retention=100%. Clearance day 1–21=55–0.40×age; r=0.70.

Retention after the first day was normalised to 100%. Figure 2 illustrates particle clearance between day 1 and 21 after inhalation as a function of age. Clearance day 1–21=55–0.40×age, r=-0.70. Age was associated with clearance values for the different time points, r=-0.50, -0.55, -0.66 and -0.70. FEV_1 and FVC also showed associations with correlation coefficients r in the range 0.28–0.42, and generally were somewhat stronger for FEV_1. Age remained significant, explaining variability for retention at 21 days when FEV_1 was also included in multiple regression analysis. T-value for age was 5.2 ($p<0.001$), while FEV_1 did not add significantly to the model, T-value=0.21 and $p>0.83$. Similar results were obtained for all other combinations of age and pulmonary function including FEV_1, FVC, R_{aw} and FEV_1/FVC. This shows that pulmonary function does not add any extra explanation for clearance when age is considered.

DISCUSSION

Clearance from small airways seems to have different kinetics compared with mucociliary transport. It is difficult to study clearance from this region. The current findings have compiled data regarding lung retention of particles over 3 weeks in relation to age. The present data have, in part, been published previously with a different focus other than age [21, 22, 25, 26]. Data in the present study are from subjects chosen to be healthy with a wide age distribution range, *i.e.* 19–81. A significantly slower large and small airway clearance was found with increasing age (figs. 1 and 2). The effect found for ageing on 24 h clearance is in agreement with previous literature [9–14]. This study focused on clearance from the smallest ciliated airways making use of a special inhalation technique. Small airways are probably the most important or sensitive region in chronic respiratory diseases, such as chronic bronchitis and asthma [18]. The effect of age on small airway clearance is significant at all time points after 24 h, but the effect is clearer for later time points. Deposition using large particles and extremely slow inhalation, as was carried out in the present study, has been shown to be insensitive to airway dimensions [26]. Data was also analysed that took pulmonary function into account. In bivariate analysis pulmonary function, such as FEV_1 and FVC, was positively associated with clearance between days 1–21. Pulmonary function was also negatively associated with age. The association between age and pulmonary function is expected with the experience from standard equations used for predicted lung function, including age [27]. The associations between pulmonary function variables and clearance did not remain significant when age was included in multiple regression, indicating that age is a stronger predictor for large and small airway clearance. Decreased mucociliary clearance in large airways has repeatedly been shown to be associated to chronic bronchitis with and without airways obstruction [3–6]. Furthermore, patients with primary ciliary dyskinesia, a disease caused by absent or extremely slow mucociliary clearance in the airways, have similar signs and symptoms in the airways as patients with chronic bronchitis [7, 8].

The mechanism responsible for smaller airways clearance is not known, but particles are retained much longer in small airways, days to weeks compared with hours, for large airways. Predicted deposition in the alveolar region cannot explain the much higher experimentally measured retention after 24 h (~50%). Furthermore, clearance kinetics is different from alveolar clearance using similar particles. For 6 μm particles, inhaled with the extremely slow inhalation technique, clearance between 1 day and 3 weeks post-inhalation has been shown to be significantly faster than when similar particles were inhaled at 0.5 $L \cdot s^{-1}$ [21, 22]. For the latter, normal flow, there was a significant fraction deposit in the alveolar region and only to a minor extent in the small ciliated airways. For 6 μm particles inhaled at 0.5 $L \cdot s^{-1}$, there was no evidence of any substantial retained fraction after 24 h in the ciliated airways [34].

The present finding of slower long-term clearance in the elderly is interesting since chronic bronchitis is highly age dependent [35]. The test subjects in the present study were chosen as healthy, nonsmoking subjects. The authors' interpretation is that small airway clearance decreases with age,

irrespective of whether symptoms are present or not. It is reasonable that small airway clearance is associated with increased risk for development of bronchitis symptoms [7, 8]. In an earlier study, a relationship was found between FEV_1 values and clearance for subjects with chronic bronchitis [23]. Subjects with cystic fibrosis and FEV_1 <70% were found to have worse long-term clearance compared with those with FEV_1 >70% [36]. This indicates that there might also be an association between small airways clearance and development of airway obstruction. The current data do not allow any conclusions regarding whether decreased mucociliary function precedes any lung function effect or *vice versa*. Decreased pulmonary function and decreased small airway clearance might be a part of normal ageing.

In conclusion, significant negative associations were found for the individual 24 h ''large'' airway clearance (%) of initial lung deposition with age. Similar results have been reported previously. Furthermore, it was found that small airways clearance, between day 1 and day 21, decreases with age among healthy subjects. This might be one factor contributing to the high prevalence of respiratory symptoms associated with increasing age.

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