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CLINICAL STUDY OF INHALED AEROSOLS TOTAL DEPOSITION IN HEALTHY ADULTS AND CHILDREN

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ABSTRACT

Inhalation is the first step towards respiratory tract intake of chemical and radioactive toxics. Particle deposition in human airways has been described by several authors as showing large individual variations. This study intends to contribute to assess this variability limits especially with reference to age.

The method used is basically a measurement of retention, by difference between inhaled and exhaled air concentrations, of inert monodispersed aerosols, during controlled breathing. Particles of 1, 2, 3 um MMAD (polystyrene latex) are measured in size and concentration by laser velocimetry. A Fleish pneumotachograph is used for controlling respiratory parameters.

Healthy subjects, male and female, undergo the test at various tidal volumes, frequencies and flow rates, simulated resting and exercising ventilation; their respiratory function is also explored in a very complete way. 20 adults between 23 and 54 years have been tested in order to assess the laboratory reference values.

25 children, 8 under the age of 8 years, and 17 between 8 and 15 years, have been tested in a similar way.

Compared to adults, children, especially under 8 years, have different total deposition mean values, higher for spontaneous and quiet controlled breathing, lower for exercising controlled breathing.

Total deposition is dependent on particle size, higher for 2 than for 1 um MMAD, but also, on lung volume, V.C., T.L.C., F.R.C., to which it is inversely proportionnal.

The prevision of probabilities for inhaled particles deposition is important for the risk assessment of chemical and radioactive airborne toxicants. If the particle size dependence of deposition is clear among human subjects, its relationship with anatomical features as well as with age requires further investigations, to assess biological variability and to evaluate the individual risk levels.

Total deposition has shown a large intersubject variability, reported by G. GIACOMELLI-MALTONI [1] W. STAHLHOFEN [2] and J. HEYDER [3], not only during spontaneous breathing, but also when tidal volume and respiratory frequency are controlled.

This variability has been defined as a specificity of lung dimensions and anatomical arrangements [3], in agreement with the statistical airway model of C.P.YU [4].

It has also been related to the breathing pattern by W.L. DENNIS [5], total deposition increasing with minute ventilation, for particles greater than 1.5 µm MMAD*, and by N. FOORD [6], who defined an impaction parameter, D^2F (D = particle diameter, F = minute ventilation).

However, W. STAHLHOFEN and J. HEYDER [2,3] rather indicated a combination of dependence of individual morphology and breathing pattern varying with the deposition mechanism of each particle size.

In order to contribute to determine the respective importance of these factors, we measured total deposition in healthy adults and in healthy children in similar conditions, spontaneous and controlled breathing; each subject had been explored already with respect to respiratory function, and his lung volumes and air flows parameters were considered as providing in vivo a good picture of individual morphology.

The comparison to make between adults and children data requires an attempt to describe the relationship between lung indices and anatomical variables from childhood to adulthood.

In adults, the predicted lung values are expressed as functions of body size, with respect to sex differences, and of age : dynamical volumes and airflows decreasing, and reserve volumes increasing after 25 years.

Although many authors [7] are reporting that body size and lung growth are achieved around 18 years in boys and 16 years in girls, some have observed that the lung is growing until 20 to 25 years [8].

Furthermore, it is not clear how lung air flows and volumes are growing throughout adolescence, for the relationship between height and lung indices is undergoing several changes during this time [9] . A sex effect is also observed, leading to treat most of lung indices separately for boys and girls. For example, some regressions for adults and children are compared and given in appendix.

The adult breathing pattern, according to J.E. COTES [15] has the following mean values at rest :

- Tidal volume, VT

  M : VTl = 0.4 - 1.5

  F : VTl = 0.3 - 0.85

- Respiratory frequency, F

  $F\ min^{-1} = 12\text{-}20$

- Minute ventilation VE

  M : $VEl \times mn^{-1} = 6.15$

  F : $VEl \times mn^{-1} = 4.12$

* MMAD = mass median aerodynamic diameter

- In children, the breathing pattern was investigated by C. GAULTIER et al [17], between 4 and 16 years; they gave the following statements :

- Tidal volume increases with age in absolute value but not when normalized for body weight; so does the mean inspiratory flow normalized by body weight.

- Respiratory frequency decreases with age, while inspiratory time Ti increases; both reach adult values at 13 years.

The ratio of Ti/TT (TT = total respiratory cycle duration) does not change significantly with age. At exercise, ventilation is increased both by tidal volume and frequency.

In adults VT is increasing proportionally to vital capacity up to $\frac{VC}{2}$ and F up to $30 \times mn^{-1}$.

In children the VT increase is limited, as V.C. is small, and the increase by frequency is not so efficient because of the concommitent increase of dead space ventilation.

In order to take into account all these notions, the controlled breathing pattern has been choosen as follows :

Breathing pattern	Ventilation at rest			Hyperventilation		
	F	Ti	VT/Ti	F	Ti	VT/Ti
Adults VT = 1000	15	2	500	30	1	1000
Children 8 to 15 y VT = 500	15	2	250	30	1	500
Children under 8 y VT = 300	20	1.5	200	35	0.86	350

VT = tidal volume in ml
F = respiratory frequency in min^{-1}
Ti = inspiratory time in sec
$\frac{VT}{Ti}$ = mean inspiratory flow in $ml \times sec^{-1}$

Materials and methods

A group of 20 non smoker adults, 10 men and 10 women, aged 21 to 54 years was tested along with 25 children, aged 5.5 to 15 years. According to their ventilation features, the children were separated in three age groups :

- 8 children aged 5.5 to 8 years included,
- 9 children aged 8.5 to 12 years included,
- 8 children aged 12.5 to 15 years included.

All the subjects were healthy, clinically and with respect to respiratory function, which was explored by spirometry : vital capacity (V.C.), total lung capacity (T.L.C.), residual volume (R.V.), forced residual capacity (F.R.C.) and air flows : forced expired volume in 1 sec (FEV 1).

A Fleisch pneumotachograph was used to measure the respiratory parameters, tidal volume (VT) and respiratory flow rates, during the retention test, which was performed by each subject during spontaneous breathing and during controlled breathing, simulating ventilation at rest and hyperventilation.

The anatomical dead space (Vd) was calculated and the alveolar ventilated volume (A.V.) was obtained from VT-Vd.

The total deposition of inhaled monodispersed aerosols of inert polystyrene latex, 1, 2 and 3 um MMAD was measured by difference between inhaled and exhaled air concentrations.

An oral respiratory monitoring device including visual volume and auditive frequency signals was developed. The airborne particles were measured in the inhaled and expired gases by a laser velocimeter (APS 33 from TSI) giving directly the aerodynamic diameters and concentrations of particles. Each subject deposition was measured twice or three times for each particle size and breathing pattern, and the mean value was given.

The obtained data were treated by unidimensional statistical method, mean values, standard deviation of the parameters and variation coefficient ($\frac{\sigma}{\bar{X}}$) , and the group effect was studied by the non parametric test of KRUSKAL and WALLIS [18]. A principal component analysis [19] was made separately for adults and children, including individual lung indices, ventilation values, and deposition data.

Results

1. The mean respiratory function values are displayed in table 1 for the adults and in table 2 for the children. The adult values are separated in two subgroups male and female, but the children are not, because the experimental data were not found differend for boys and girls, and because of the small number ob subjects after beeing divided in three age groups.

TABLE 1

20 HEALTHY ADULTS NON SMOKERS					MEAN RESPIRATORY FUNCTION VALUES					
		Age (y)	Height (cm)	Weight (kg)	V.C. (l)	R.V. (l)	FEV 1 ($l \times sec^{-1}$)	T.L.C. (l)	FRC (l)	V_d (l)
MEN n = 10	$\bar{X}$:	29.5	174.5	68.4	5.45	1.82	4.47	7.31	3.56	0.180
	σ :	3.3	8.2	5.3	0.48	0.28	0.46	0.59	0.47	0.012
WOMEN n = 10	$\bar{X}$:	34.9	160.5	54.6	3.61	1.43	3.05	5.04	2.65	0.155
	σ :	10.6	4.4	1.74	0.46	0.33	0.30	0.56	0.43	0.01

2. The mean total deposition values are displayed in table 3 for the adults and in table 4 for the children; as was expected, from the litterature data, these values are increasing with the particle size in all subjects groups and for all the different breathing patterns.

TABLE 2

25 HEALTHY CHILDREN		Age (y)	Height (cm)	Weight (kg)	V.C. (l)	R.V. (l)	FEV 1 (l x sec^{-1})	T.L.C. (l)	FRC (l)	V_d (l)
					MEAN RESPIRATORY FUNCTION VALUES					
A ≤ 8 y, n = 8	$\bar{X}$:	7.4	121.6	21.3	1.26	0.675	1.14	1.94	0.99	0.065
	σ :	0.8	6.5	4.06	0.29	0.21	0.24	0.30	0.20	0.003
8 < A ≤ 12, n = 9	$\bar{X}$:	11.3	141.9	34.7	2.19	0.76	1.95	2.95	1.42	0.095
	σ :	1.0	11.3	8.9	0.46	0.25	0.49	0.57	0.33	0.018
12 < A ≤ 15, n = 8	$\bar{X}$:	13.6	153.2	46.1	2.64	0.89	2.31	3.54	1.69	0.111
	σ :	0.8	6.2	8.4	0.51	0.37	0.52	0.64	0.46	0.010

In the adult group the deposition data are very similar for both sexes, except for the controlled inhalation of 3 μm particles; in the children group, some data of resting controlled breathing are significantly different in the younger children.

The individual data are dispersed in all groups, especially for the spontaneous breathing pattern, where the variation coefficient is greater than for controlled breathing; in children the three breathing pattern give very dispersed values especially controlled hyperventilation in the youngest group.

The comparison between children and adults showssome different results for spontaneous breathing in the youngest, and for controlled hyperventilation between all children.

3. The multidimensional analysis shows a general lung size effect upon particle deposition data, in adults but even more in children where it meets with age effect; some deposition data are negatively correlated with lung volumes : V.C., T.L.C., F.R.C., Vd, and air flows, FEV 1.

TABLE 3

PERCENT TOTAL DEPOSITION MEAN VALUES IN ADULTS

		Spontaneous breathing			Controlled breathing					
					at rest			hyperventilation		
Tidal volume V_T (ml)		M: $\bar{X}$: 737, σ : 180		F: 677, 220	1000			1000		
inspiratory time ti (sec)		M: $\bar{X}$: 2.12, σ : 0.56		F: 2.07, 0.56	2			1		
mean inspiratory flow $\frac{V_T}{ti}$ (ml x sec^{-1})		M: $\bar{X}$: 370, σ : 110		F: 331, 80	500			1000		
MMAD μm		1	2	3	1	2	3	1	2	3
20 healthy adults, 10 M	$\bar{X}$:	13.0	23.5	27.7	16.3	30.7	36.5*	14.7	27.4	39.7
	σ :	6.4	8.0	10.0	2.8	5.0	5.0	5.6	6.2	7.3
	$\frac{\sigma}{\bar{X}}$:	0.49	0.34	0.36	0.17	0.16	0.14	0.38	0.22	0.18
10 F	$\bar{X}$:	12.5	22.9	29.8	16.8	32.7	42.6*	16.2	31.5	46.5
	σ :	5.1	8.5	8.1	5.1	4.9	5.3	3.3	5.6	4.7
	$\frac{\sigma}{\bar{X}}$:	0.41	0.37	0.27	0.30	0.15	0.12	0.20	0.18	0.10

* Significantly different with $p \leq 0.05$ by the Kruskal and Wallis non parametric test

TABLE 4

PERCENT TOTAL DEPOSITION MEAN VALUES IN CHILDREN

		Spontaneous breathing			Controlled breathing					
MMAD µm		1	2	3	1	2	3	1	2	3
Tidal volume V_T (ml)		$\bar{x}$: 343	σ: 91		at rest		300	hyperventilation		
Inspiratory time ti (sec)		1.34	0.33		1.5			0.86		
mean inspiratory flow $\frac{V_T}{ti}$ (ml x sec^{-1})		271	100		200			350		
Age ≤ 8 y	(n):	(8)	(8)	(3)	(5)	(5)	(1)	(7)	(7)	(3)
	$\bar{x}$:	19.1	35.0•	37.0	22.6	36.4*	/	14.0•	24.4•	35.1•
	σ :	9.9	10.9	8.1	9.6	11.7		10.5	11.9	10.8
	$\frac{\sigma}{\bar{x}}$:	0.52	0.31	0.22	0.42	0.32		0.75	0.49	0.31
Age 8-12 y	V_T (ml):	435	61				500			
	ti (sec):	1.24	0.37		2			1		
	$\frac{V_T}{ti}$ (mlxsec^{-1})	375	103		250			500		
	(n) :	(9)	(9)	(5)	(7)	(7)	(4)	(9)	(9)	(5)
	$\bar{x}$:	13.3	26.9	29.4	17.6	35.4*	45.1*	8.4•	23.8•	27.1•
	σ :	8.4	9.7	6.3	6.0	4.9	3.1	6.3	11.4	9.4
	$\frac{\sigma}{\bar{x}}$:	0.63	0.46	0.21	0.34	0.14	0.07	0.75	0.48	0.35
Age 12-15 y	V_T (ml):	579	261				500			
	ti (sec)	1.63	0.58		2			1		
	$\frac{V_T}{ti}$ (mlxsec^{-1})	359	111		250			500		
	(n)	(8)	(8)	(5)	(7)	(7)	(5)	(7)	(7)	(5)
	$\bar{x}$:	12.2	24.0	31.8	13.3	24.3*	34.3*	9.7•	22.9•	32.9•
	σ :	2.2	3.1	5.7	4.2	5.4	3.3	3.1	3.6	3.5
	$\frac{\sigma}{\bar{x}}$:	0.18	0.13	0.18	0.31	0.22	0.10	0.31	0.16	0.11

* significantly different from other children groups) ($p < 0.05$ by the Kruskal and Wallis non parametric test)

• " " " adults

A ventilation effect is apparent in adults where VT and AV are positively correlated (r : 0.5 to 0.7) with the different particle size deposition values in spontaneous breathing. In children these parameters are not correlated.

DISCUSSION - CONCLUSION

Those preliminary results of the total deposition of 1, 2 and 3 µm particles in human airways show important individual variations somehow related to body size and lung volumes, smaller volumes having larger deposition. This fact explains a faint sex-effect in adult deposition and a more apparent age effect in children.

The spontaneous breathing pattern, increases individual variability among adults, and some relationship is found between deposition and the quantity of inhaled air. In children the variability is large for all the breathing patterns, for the age related growth probably hides the ventilation effect observed in the adult group.

Finally, compared to adults, children have lower deposition values for hyperventilation and seem to have higher deposition values for quiet breathing, especially for 1 and 2 µm particles which have predominant sedimentation properties.

Individual variability, is probably somehow related to lung volumes and ventilation, and therefore, age dependent, but, as observed by J. Heyder and al [3], some other morphological arrangements and physiological features of the individual have to be involved.

APPENDIX

1. Vital capacity V.C.

- adults values [10]

  $M : V.C.l = 5.76\ H^{*}m - 0.026\ Ay^{*} - 4.34$

  $F : V.C.l = 4.43\ Hm - 0.026\ Ay - 2.89$

- children values

  . Age 5 - 11 years [11]

  $M : V.C.ml = -3312 + 40.01\ Hcm$

  $F : V.C.ml = -2689 + 34.35\ Hcm$

  . Age 10 - 19 years [12]

  $M : V.C.ml = 1.95 + 1.69\ Ln\ Hcm - 0.017\ Ln\ Ay + 0.38\ Ln\ W^{*}kg$

  $F : V.C.ml = 0.99 + 1.68\ Ln\ Hcm + 0.18\ Ln\ Ay.$

2. Forced residual capacity F.R.C.

- adults values [10]

  $M : F.R.C.l = 2.34\ Hcm + 0.009\ Ay - 1.09$

  $F : F.R.C.l = 2.24\ Hcm + 0.001\ Ay - 1$

- children values

  . Age 5 - 11 [13]

  $M + F : F.R.C.\ ml = -1840 + 24\ Hcm$

  . Age 11 - 15 [14]

  $M : F.R.C.\ ml = 126\ e\ (0.0181\ Hcm)$

  $F : F.R.C.\ ml = 68.2\ e\ (0.0217\ Hcm)$

  . Age 16 - 22 [14]

  $M : F.R.C.\ ml = 225\ e\ (0.0150\ Hcm)$

  $F : F.R.C.\ ml = 408\ e\ (0.00989\ Hcm)$

3. Dead space : Vd

- adult values [15]

  $M + F : Vd\,ml = Ay + (Wkg \times 2.2 \times 10^{-3})$

- children values [16]

  $M + F : Vd_{ml} = 758.5 \times 10^{-6} \times Hcm^{2.363}$

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* H = standing height
A = age
W = weight

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