Factors influencing the regional deposition of inhaled particles in man

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Summary

1. Although ventilation in normal human lungs has been shown to decrease from apex to base, comparable observations are lacking in regard to particle deposition.

2. We compared regional ventilation and particle deposition in normal subjects by using radioactive xenon and a radioactive aerosol while sitting, lying, and while breathing at an increased rate. Both smokers and non-smokers were studied.

3. Particle deposition and ventilation were closely related, and the greater the ventilation the greater the deposition of particles, a situation which prevailed irrespective of position and breathing rate. While supine, the apex to base gradient for both ventilation and particle deposition decreased but did not entirely disappear. At higher respiratory rates, central deposition of particles, especially in smokers, increased.

4. We concluded that there are regional differences in the deposition of particles and that such differences are closely related to regional ventilation.

Key words: intrapleural pressure gradient, particle deposition, posture, regional ventilation.

Abbreviations: HRR, high respiratory rate; NRR, normal respiratory rate; $V_m$, minute volume; $V_t$, tidal volume.

Introduction

Numerous studies have shown that ventilation in the human lungs is uneven and decreases from apex to base [1–5]. This was first demonstrated by differential lobar bronchspirometry [5], and subsequently confirmed by methods using radioactive inert gases [1–4]. Comparable studies showing that regional deposition of particles is similarly uneven have not been carried out, although this matter has been the subject of discussion [6, 7]. Particle deposition might be expected to be closely related to ventilation, in that the greater the ventilation of a specific region of the lung, the more likely are the particles to be carried in the airstream to that region. Certain clinical observations, however, suggest that this assumption may not be justified. Thus silicosis and coal workers’ pneumoconiosis initially involve, and predominantly affect, the upper zones of the lungs [8], regions where ventilation is substantially less than elsewhere in the lungs [3]. In contrast, asbestosis predominantly affects the bases, as might be expected from the relatively greater basal ventilation [9]. Deposition is influenced not only by ventilation but by particle size and shape, airways geometry and breathing patterns [10, 11].

To study the factors influencing regional particle deposition in the lungs requires that measurements of regional ventilation and regional deposition are made within a short time of each other. This can be effected by measuring regional ventilation with a radioactive inert gas, and regional particle deposition by means of a tagged aerosol.

Methods

Subjects

Twenty-nine normal volunteers, who gave their informed consent, participated in the study. The protocol and Consent Form were approved by the Human Ethics Committee of the University...
of Western Ontario and by granting agencies. Seventeen of the volunteers were non-smokers (mean age 30, range 29-50 years), and 12 were smokers (mean age 30, range 19-51 years, mean pack years 12.4±15.3). None had a history of chest disease and all were without symptoms other than what three smokers referred to as a ‘smokers’ cough’. All had normal ventilatory capacity as defined by the forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) being above 80% of Morris’ predicted values [12]. The mean percentage FVC and FEV₁ for the non-smokers were 103.4% (range 94-118 SD ± 6.2) and 104.2% (range 95-120 SD ± 6.2) respectively. Comparable figures for smokers were 102.6% (range 92-111 SD ± 5.8) and 98.0% (range 84-104 SD ± 6.9). One smoker, despite a normal FEV₁ and FVC, had a marginal reduction in her expiratory flows at 50 and 75% of vital capacity (FEF_{25} and FEF_{75}).

In all studies, paired studies of regional ventilation and of regional deposition were made by posterior scintigraphic imaging after the inhalation of air containing 133Xe or 99mTc-labelled radioaerosol. All subjects breathed saline aerosol for 2 min before the aerosol study in order to accustom them to the equipment. Nose clips were always worn. The tidal volume (Vₜ) and minute volume (Vₘ) were measured for each minute over a 6 min period at a normal respiratory rate (NRR) and at a high respiratory rate (HRR) in eight subjects while breathing a non-tagged aerosol.

**Non-smokers.** Of the 17 non-smokers, 12 underwent studies of regional ventilation and aerosol deposition while sitting and breathing at a NRR. The resting rates varied between 12 and 18 breaths (mean 14.5)/min. Subsequently, five of these subjects were restudied supine, breathing at a NRR. Five of the remaining subjects were studied sitting while breathing at a HRR and in phase with a metronome set at 28 breaths/min. Two subjects who were initially studied in the standard fashion, 24 h later had the studies repeated after breathing 100% oxygen for 20 min, since it was felt that oxygen breathing might affect peripheral ventilation [13]. An additional five non-smoking subjects were studied supine, breathing at a NRR. These subjects had not been previously studied in the sitting position. Subsequently the studies were repeated while supine and breathing at a HRR.

**Smokers.** Twelve smokers were studied. All 12 underwent xenon and aerosol studies sitting and breathing at a NRR. Subsequently, seven had the studies repeated while supine and breathing at a NRR. The other five had the studies repeated sitting and breathing at a HRR.

**Studies of regional ventilation and aerosol deposition**

Ventilation studies using 133Xe and aerosol deposition studies were made by continuous recording from a gamma camera (Pho Gamma V: Siemens’ Electric, Downsview, Ontario,

![Fig. 1. Method of dividing lung fields into central, mid and outer zones, and into upper, mid and lower zones (posteroanterior view). The lower limit of the lung was defined by a horizontal line drawn at the upper limit of the diaphragmatic dome. The vertical height was then divided equally so as to form three zones. The hilum was located at the midpoint of the vertical height. Inner, intermediate and outer zones were defined by dividing the distance at the limit of the lower zone as shown.](image-url)
Factors influencing the regional deposition of inhaled particles in man

Directly after the xenon study, the aerosol study was carried out in each subject in the same position and at the same respiratory rate. Twenty-four to 48 h later the studies were repeated; if the initial study was carried out in the sitting position while breathing at a NRR, the second study was carried out 24–48 h later with the subject either lying supine or while breathing at a HRR.

133 Xe studies of regional ventilation

In the xenon studies subjects breathed from a 7 litres capacity spirometer (Warren Collins Incorporated, Braintree, MA, U.S.A.) to which 15–20 mCi of 133Xe had been added. Rebreathing continued for 5 min during which the concentration of the activity in the lung increased to approach equilibrium. At the end of rebreathing, the subject was allowed to breathe air for an additional 5 min, during which the exhaled gas was exhausted through an activated charcoal trap. A continuous recording was made for 15 min during both the wash-in and wash-out at one frame every 5 s.

A complex curve consisting of multiple exponents was obtained by plotting the output of a gamma camera positioned over the lungs during the wash-in. The most rapid component represents alveolar ventilation and slower components are due to xenon dissolving and progressing towards equilibrium in the blood, muscle, fat and other tissues [15, 16].

A single exponential function was fitted by a non-linear least-squares method to the earliest part of the wash-in curve, which predominantly represents alveolar ventilation for each lung region under study as suggested by Van der Mark et al. [17]. The earliest part of the curve was arbitrarily defined as twice the time taken for measured activity to reach half the 5 min 'equilibrium' value.

With this method for any given lung zone (i) the alveolar ventilation per unit lung volume (\( \lambda_i \)) is given by the expression

\[
\lambda_i = \frac{-\ln \left[ 1 - \frac{C_i(t)}{C_i(\text{equil.})} \right]}{t}
\]

where \( C_i(t) \) is the observed count rate at a given time (t) during the initial wash-in phase and \( C_i(\text{equil.}) \) is the observed count rate at equilibrium arbitrarily taken to be 5 min after the onset of wash-in. The substitution of data derived from the wash-out phase in the calculation of the \( \lambda_i \) yielded comparable results. Ventilatory differences from
zone to zone may be calculated by the following formula:

\[ IV_i = \frac{\lambda_i}{\lambda} \times 100 \]

where \( IV_i \) is the index of regional ventilation, \( \lambda_i \) is the alveolar ventilation per unit lung volume index for the zone and \( \lambda \) is the alveolar ventilation per unit lung volume for the total lung.

**Aerosol deposition**

An aerosol was prepared from colloidal particles of sulphur labelled with \(^{99m}\)Tc. Saline (4 ml, containing 60–80 mCi of labelled sulphur colloid) was placed in a high-flow nebulizer (Acorn Vix, Jamestown, CA, U.S.A.), through which air was bubbled at a flow rate of 8–10 litres/min.

The flow of air containing the radioaerosol then passed to a 30 litres distensible plastic bag which acted as a settling tank for larger particles [18]. This led to a mouthpiece from which the subjects breathed for approximately 5 min, thus allowing sufficient aerosol deposition to a maximum of 500 pCi (18.5 MBq) to permit subsequent imaging.

Aerosol particle size was measured with an Anderson sampler in the stream emerging from the nebulizer and again at the mouthpiece. The mass median diameter of the particles at the mouthpiece was 0.78 µm (geometric SD 1.39).

Regional deposition of aerosol particles was expressed as an index (ID) which was analogous to \( IV_i \) and which was determined as follows:

\[ ID_i = \frac{\text{Deposition per unit volume in zone } i}{\text{Deposition per unit lung volume in total lung}} \times 100 \]

The index may be calculated as:

\[ ID_i = \frac{A_i}{C_i (\text{equil.})} \times \frac{\sum A_i}{\sum C_i (\text{equil.})} \times 100 \]

where \( A_i \) is the count rate due to aerosol activity in zone i measured immediately after inhalation.

Although regional ventilation and deposition were calculated for all zones of both lungs, there were no significant zonal differences between each lung and the respective illustrations are based on the data obtained from the right lung only. In all but one subject, imaging was repeated after an interval of either 6 h or 24 h in order to ascertain the rate of clearance from the different regions.

The combined radiation dose for each subject was approximately 500 mrad (5 mGy) to the lungs and 5500 mrad (55 mGy) to the trachea [19, 20].

Statistical significance for the various sets of observations was determined with Student’s t-test and only when \( P \) was 0.05 or less were the paired observations accepted as differing significantly.

**Results**

At both the NRR and HRR, \( V_T \) and \( V_M \) increased during the first 2–3 min, but later decreased as the subject became accustomed to the mouthpiece. At the HRR, three subjects showed an increase in \( V_T \) and this remained up for the 6 min, while in the remainder, after an initial increase, \( V_T \) would gradually decrease (mean \( V_T \) 0.720 litre during the first minute and 0.566 litre during the sixth minute). The mean \( V_M \) for the aerosol studies while breathing at a HRR was 20.1 litres for the first minute and 16.1 litres for the sixth minute. During the third to sixth minutes (corresponding to the studies) mean \( V_M \) was 9.6 litres at NRR (mean flow rate 0.32 litre/s) and 16.8 litres at HRR (mean flow rate 0.56 litre/s).

It was apparent from the continuous imaging that there was little or no selective deposition of the aerosol in the central airways.

**Ventilation and aerosol deposition**

**Comparison of upper, mid and lower zones.** (a) Sitting, NRR. The regional differences in ventilation between the top and bottom of the lung that have been described by others were observed in both smokers and non-smokers. However, in smokers, the differences were significantly greater (Figs. 3 and 4). For both ventilation and aerosol deposition, the apex to base differences were statistically significant and regional deposition of aerosol closely resembled the regional distribution of inhaled xenon.

(b) Sitting, HRR. Regional ventilation and aerosol deposition at NRR and HRR in both non-smokers and smokers are shown in Figs. 3 and 4. An increase in the respiratory rate led to significantly greater ventilation and aerosol deposition in the upper zones and relatively less in the lower zones. In both smokers and non-smokers the effect was significantly greater with the aerosol than it was with the xenon.

(c) Supine, NRR and HRR. In non-smokers in the supine position, the disparity in ventilation between the top and the bottom of the lung
Factors influencing the regional deposition of inhaled particles in man

120
90
80
70

m xenon
XsnanHRR
Aerosol NRR
Aerosol HRR

Upper Mid Lower

FIG. 3. Indices for zonal ventilation and deposition in non-smokers, breathing at NRR and HRR. Bars represent 1 SD.

110
100
90
80
70

Upper Mid Lower

FIG. 4. Indices for zonal ventilation and deposition in smokers, breathing at NRR and HRR. Bars represent 1 SD.

diminished so that the difference was no longer statistically significant (Fig. 5). Ventilation became more nearly uniform in the upper, mid and lower zones. Similar changes were noted in regard to the deposition of aerosol. In smokers, although the gradient between the apex and the base likewise decreased, the difference remained statistically significant.

In the supine subject, breathing at a HRR significantly increased both ventilation and deposition in the upper zones (Fig. 6).

In the two subjects who were given oxygen before carrying out the studies, no significant effects on either ventilation or deposition were noted.

Comparison of central, mid and outer zones. Ventilation to the central, mid and outer zones showed no significant difference, no matter whether the subject was breathing at a NRR or HRR (Fig. 7). This was true for both the concentric zones (Fig. 1) and the inner, intermediate and peripheral zones in the same horizontal plane (Fig. 2), and affected both smokers and non-smokers. Regional deposition
M. J. Chamberlain, W. K. C. Morgan and S. Vinitski

Fig. 5. Indices for zonal ventilation and deposition in non-smokers sitting and supine while breathing at NRR. Bars represent 1 SD.

Fig. 6. Indices for zonal ventilation and deposition in non-smokers while supine and breathing at NRR and HRR. Bars represent 1 SD.

of the aerosol in the central, mid and outer zones at a NRR resembled the pattern seen with xenon, except that there was significantly more central deposition in the smokers, confirming the results of Dolovich et al. [21]. Comparison of the three areas, namely inner, intermediate and peripheral in the upper zone (Fig. 2) as compared with the corresponding area in the lower zone, showed less aerosol being deposited in the upper than in the equivalent area in the lower zone. In contrast, at a HRR the deposition of the radioaerosol was significantly greater than it was while the subject was breathing at a NRR (Fig. 8). This was especially evident with penetrance being significantly reduced in smokers.

In both non-smokers and smokers in the supine position breathing at a NRR, the distribution of the aerosol to the central, mid and outer zones was similar to that observed in the sitting position. At a HRR there was relatively more central deposition for both the sitting and supine positions.
Factors influencing the regional deposition of inhaled particles in man

Discussion

We deliberately chose particles with a mass median diameter below 1 μm to ensure that the majority would be deposited in the alveoli, thereby facilitating comparison between ventilation and deposition. The appearance of the images during scanning showed an almost complete absence of central deposition, and in addition at 24 h around 85% of particles remained in the lung parenchyma [22]. Thus we think that, for the most part, our measurements of particle deposition reflected alveolar and small airways deposition, and hence we were justified in comparing regional ventilation with regional deposition.

Measurement of the regional distribution of a radionuclide in the lungs by a gamma camera in a single fixed position introduces artifact. There is differential attenuation of the 99mTc and 133Xe by the tissues of the lung and chest wall because of their different gamma energies. The thickness of lungs and chest wall varies at different regions of the chest. Differential attenuation also affects the
perception of equal activities of the same radio-
nuclide situated at different places in the lung.  
This latter effect may come into play when the 
equilibrium of $^{133}$Xe is taken to represent lung 
uolume. However, the correction for volume will 
affect equally the indices for both ventilation and 
deposition. The differences between apex and 
base for both ventilation and deposition are so 
great ($P > 0.001$) that we do not believe the 
effects of the attenuation would substantially 
affect our results. Moreover, similar techniques 
have been used by others [6, 7]. The consistency 
of the pattern of distribution amongst individuals 
of differing habitus further suggests the results 
are not artifactual.

Deposition of airborne particles in the res-
piratory tract is influenced by the sedimentary, 
inertial and diffusional characteristics of the 
inhaled particle [10, 11]. The airways consist of a 
series of tapering cylinders with multiple bi-
furcations, with the nose and the dead space 
being the site of deposition of most larger 
particles above 7 $\mu$m [23]. The effects of particle 
size and shape, hygroscopicity, the rate of 
breathing, of tidal volume and other factors have 
been investigated in an attempt to predict particle 
deposition in the lungs [10, 11, 23, 24]. As 
such, most studies of particle deposition have 
failed to take into account the marked regional 
differences in ventilation [1-5], and much 
the same can be said for most mathematical models 
designed to predict deposition [23, 25-28], with 
one recent exception [29].

It was assumed for many years that the 
regional distribution of inspired gas was similar 
from apex to base, an assumption that was based 
on the fact that quantitative studies of large areas 
of excised lung had shown relatively even 
distribution of inspired gas per lung unit volume 
[30, 31]. Studies from the Montreal group [2, 3, 
32, 33] and from West and colleagues [5] have 
shown that there are significant differences 
between apex and base for both ventilation and 
perfusion. These disparities depend on the in-
trapleural pressure gradient that exists between the 
top and the bottom of the lungs [1, 2, 4]. At 
functional residual capacity, in the sitting and 
erect positions, the alveoli are larger in the apical 
region than they are at the base because of the 
vertical gradient in intrapleural pressure. Because 
of regional differences in alveolar expansion, 
basal ventilation exceeds that of the apical 
regions. In the supine subject, the intrapleural 
pressure gradient lessens, and ventilation 
becomes more evenly distributed from base to 
apex [33]. Particle deposition should therefore be 
influenced by regional ventilation, since the best 
ventilated areas of the lung would receive the 
greatest number of particles [6]. Our studies 
show that, no matter whether the subject is sitting 
or supine, aerosol deposition is closely related to 
ventilation.

Breathing at a HRR resulted in an increase in 
the relative proportion of both xenon and aerosol 
going to the upper lobes, but did not change the 
horizontal distribution of ventilation to the 
central, middle and outer portions of the lung. 
This finding is not unexpected since Bake et al. 
[34] showed that at high inspiratory flow rates, 
regional ventilation became more uniform. In 
contrast, during breathing at HRR, relatively 
more aerosol was deposited in the central regions 
of the lung, especially in smokers. Two possible 
mechanisms for this phenomenon of increased 
central deposition exist. First, if tidal volume were 
to decrease, then a greater proportion of each 
breath would remain in the dead space and there 
would be relatively more deposition in the 
proximal airways [35]. However, both increases 
and decreases in $V_T$ occurred. Furthermore, $V_T$ 
varied between the beginning and the end of the 
aerosol administration and this explanation there-
fore cannot entirely account for the greater 
central deposition. Secondly, the higher flow rates 
at the HRR would lead to more deposition from 
inertial impaction in the proximal airways. 
Probably both of these mechanisms played a role. 
Smokers showed significantly more central depo-
sition than did non-smokers, presumably because 
the excess mucus leads to a decrease in the 
cross-sectional area of the airways, an increased 
linear velocity, and hence greater impaction. In 
addition, smokers showed less upper-zone venti-
lation and deposition than did non-smokers. This 
is likely a consequence of early anatomical 
changes which have been reported in 
asymptomatic subjects [36, 37]. Such early 
changes affect predominantly the respiratory 
bronchioles of the upper lobes of the lung. 
Clearance of radioactive particles was occasion-
ally delayed in smokers and was sometimes 
associated with areas of increased radioactivity.

The observation that silicosis and coal wor-
kers' pneumoconiosis initially involve the upper 
zones of the lungs, and that as the disease 
progresses the predominant upper-lobe involve-
ment persists [8] cannot be explained by dis-
parities in regional deposition. Although the 
particles we used are smaller than those generally 
considered responsible for the development of the 
pneumoconioses, there is excellent evidence that 
small particles between 0-5 and 1-0 $\mu$m are 
particularly hazardous [38]. Our studies indicate 
that those regions which are subject to the
greatest particle deposition are the least involved in silicosis and coal workers’ pneumoconiosis. However, we have carried out further studies of particle deposition during moderate exercise and have shown that the apex to base gradient for particle deposition lessens significantly (unpublished observations). Even if one assumes that most subjects who are exposed to silica and coal dust are involved in fairly heavy activity, and thereby to more uniform deposition, this still does not explain the predominant upper-lobe involvement in silicosis and coal workers’ pneumoconiosis and another explanation must be sought. Thus it may be that particle clearance from the non-ciliated regions of the upper lobes is slower and that this results from the reduced perfusion of these regions. Whether there are also regional variations in lymph flow is, to our knowledge, unknown, but here again such differences might influence parenchymal clearance of deposited particles.

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