Effect of lung function and mode of inhalation on penetration of aerosol into the human lung

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Pavia, D., Thomson, M. L., Clarke, S. W., and Shannon, H. S. (1977). *Thorax*, **32**, 194–197.
Effect of lung function and mode of inhalation on penetration of aerosol into the human lung.
The method using radioactive tracer particles has been applied to study the effect of the mode of
inhalation of aerosols on the depth of deposition in the lungs of 50 patients with airways
obstruction. The findings show that the penetration of particles is directly related to: (1) volume
inspired per breath (V_I); (2) forced expiratory volume in one second (FEV_1); and inversely
related to (3) flow rate during inhalation ($\dot{V}$). In mathematical terms, alveolar deposition (%) =
$40\cdot3 (V_I) + 10\cdot98 (FEV_1) - 0\cdot75 (\dot{V}) + 40\cdot4$; for this regression $F = 4\cdot41$ and $P < 0\cdot01$.

Topical administration of drugs into the bronchial
tree by inhalation of aerosol often has advantages
over the oral and parenteral routes, particularly in
patients with reversible airways obstruction. The dose
is relatively small (Lal *et al.*, 1972) and response may
be more rapid (Plit *et al.*, 1972). The main benefit of
this route, however, is that high levels of the drug are
concentrated at the site of action in the lung, giving
the desired therapeutic action while minimising
undesired systemic side effects.

The efficacy of topical therapy depends on the
proportion of the inhaled drug which is deposited in
the lung (Blackwell *et al.*, 1974) and, for certain
drugs, that proportion that is retained in the more
peripheral parts (Godfrey *et al.*, 1974). Some of the
factors which determine penetrance of aerosol have
long been known to particle physicists (Hatch and
Gross, 1964). Recent findings indicate the import-
ance of the technique of inhalation (Booker *et al.*,
1967; Goldberg and Lourenço, 1973) and the effect
of lung and especially airway abnormality (Thomson
and Short, 1969; Pavia *et al.*, 1977) in reducing
the penetrance of aerosol.

We report a study on 50 patients with varying
degrees of airways obstruction who inhaled mono-
disperse 5 μm aerodynamic particles in a controlled
manner. The mode of inhalation was based on that
suggested for inhaling therapeutic pressurised aero-
sol. Predicted values have been obtained of the
tracheobronchial/alveolar partition ratios for those
particles deposited in the lungs, taking into account
the mode of inhalation and the degree of airways
obstruction.

Method

The tracer technique used here to assess depth of
deposition and clearance of inhaled particles in
humans has been fully reported by Thomson *et al.*
(1974). Polystyrene particles ($5 \pm 0\cdot7$ μm) were
generated by a spinning disc (May, 1949) and
inhaled via the mouth of the patients seated upright.
The particles were tagged unleachably (Few *et al.*,
1970) with the gamma-emitting radionuclide tech-
netium-99m (^{99m}Tc). The volume inspired in a
single breath (V_I), 0·11, 0·30, 0·50, 0·75 or 0·88 litre
was randomly allocated to each patient and deter-
mined by an automatic valve. After inspiration
there was an obligatory 3-second breath-holding
pause before exhalation. The average flow rate
during inhalation was measured by a pneumotacho-
graph. The mean, range, and standard deviation
(SD) of the flow rate during inhalation ($\dot{V}$) for the 44
patients for whom measurements were available
were 25·4 (13·3 – 50·4; SD ± 7·9) l/min. Immediately
after inhalation the patients washed out their
mouths and then swallowed some water to remove
radioaerosol from the oropharynx and oesophagus.

Immediately afterwards and six hours later gamma
radiation from the patients' lungs was counted by

two horizontally opposed scintillation detectors, one in contact with the midpoint of the sternum anteriorly and the other against the spine axially opposite to the first. The degree of collimation was such that the field of view of the detectors included most of both lungs but virtually excluded the stomach. In all runs the first count was normalised to 100% to adjust for unavoidable differences in the initial radioactive lung burden; the burden did not exceed 30 μCi in any one run. The initial and six-hour counts were corrected for radioactive decay and background, and the second was expressed as a percentage of the initial count after inhalation. It is estimated that in 90% of the population (Thomson and Short, 1969; Foord *et al.*, 1975) the mucociliary clearance phase (tracheobronchial clearance) will be over or nearing completion after six hours and the percentage of the particles remaining in the lung at six hours (6 h % Ret) is used here as a measure of alveolar deposition.

The forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC) of the patients were measured by a dry bellows spirometer (Vitalograph®) before the inhalation of the tracer particles. The patients were under continuous observation and did not smoke for one hour prior to the inhalation of the tracer particles nor during the six-hour experimental period.

Patients

Fifty male patients with varying degrees of airways obstruction volunteered for the study. All but two of these were smokers. Their mean age was 65·3 years (range 43–85; SD±8·9), mean height 1·68 metres (range 1·51–1·83; SD±0·08), and tobacco consumption 47·8 pack-years (range 3·5–255·1; SD± 42·1). The Table gives the ventilatory capacities of the 50 patients.

Table   *Means, ranges, and standard deviations of the ventilatory capacities for 50 patients*

	FEV$_1$		FVC		FEV$_1$/FVC Obs (%)
	Obs.	% Pred.	Obs.	% Pred.	
Mean	1·07	38·6	2·38	64·2	45·0
Range	0·44–2·32	16–88	1·07–3·93	26–115	23–73
SD	0·49	17·8	0·73	17·8	12·8

Results

There was a significant relationship between the percentage of particles retained at six hours and three variables, namely, V$_I$, FEV$_1$, and $\dot{V}$. V$_I$ and FEV$_1$ accounted for 19% of the variation in the

regression and $\dot{V}$ for a further 6%. The way in which these three variables affect the 6 h % Ret is given by the equation 6 h % Ret = 40·3(V$_I$) + 10·98(FEV$_1$) − 0·75($\dot{V}$) + 40·4; F = 4·41, p < 0·01.

Thus for the ranges of variables investigated alveolar deposition will increase by 40% for every 1 litre increase in V$_I$ and by 11% for every 1 litre increase in FEV$_1$ but will decrease by 0·75% for every 1 litre/min increase in flow rate. (The *t* values for the regression coefficients of V$_I$, FEV$_1$, and $\dot{V}$ were 3·18 (p < 0·005), 1·94 (p ≈ 0·05), and 1·92 (p ≈ 0·05) respectively.)

The Figure shows a nomogram for estimating the effect of V$_I$ and FEV$_1$ on alveolar deposition for single breaths of aerosol inhaled at a normal flow rate of 30 l/min.
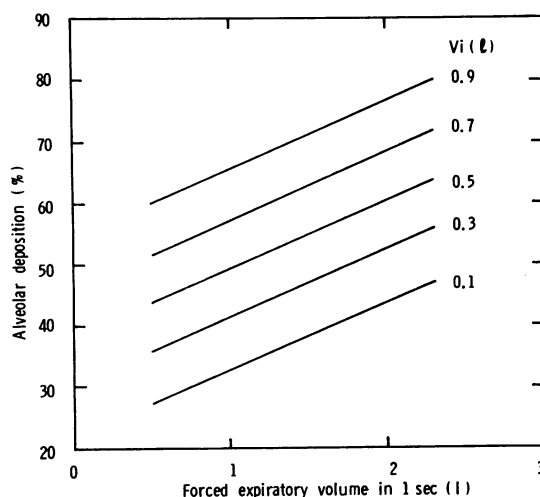

Figure   *Nomogram for predicting alveolar deposition of 5 μm particles as a percentage of total lung deposition (SD±18·5%) for various inspired volumes (V$_I$) taken at a flow rate of 30 l/min.*

Discussion

In our experience, sex, age, height, and long-term tobacco smoking do not affect mucociliary clearance rates as measured by the above method (Pavia *et al.*, 1970; Pavia and Thomson, 1970; Thomson and Pavia, 1973).

The figures quoted above are for the alveolar deposition as a percentage of the total deposition in the lung which is about 85% of that inhaled for the monodisperse particles used here. For heterodisperse aerosols from pressurised canisters total deposition is much lower, amounting to about 10% for isoprenaline (Blackwell *et al.*, 1974). However, the

factors controlling penetration within the lung will be similar for both types of aerosol.

The site of deposition of inhaled aerosols in the human lung depends on the physical characteristics of the aerosol, the mode of inhalation, and the degree of abnormality of the airways. In general, the bigger the aerodynamic diameter (diameter $\times$ density$^{1/2}$), the nearer to the mouth will the deposition of the aerosol be (Lippmann and Albert, 1969; Pavia and Thomson, 1976). The main inhalation variables that affect the depth of deposition are the flow rate during inhalation, which, if high, reduces penetrance by impaction (Lippmann and Albert, 1969; Goldberg and Lourenço, 1973), and the tidal volume, which, if increased, will increase penetrance provided the flow rate is constant (Pavia et al., 1977). A breath holding pause after inhalation of the aerosol favours gravity settlement of a small proportion of particles which would otherwise remain airborne during expiration. It has recently been shown that airways obstruction and, to a lesser degree, restrictive defect cause premature deposition during inhalation; this is presumably due to increase in impaction caused by disturbed flow in these conditions (Thomson and Short, 1969; Lippmann et al., 1970; Goldberg and Lourenço, 1973; Thomson and Pavia, 1974; Dolovich et al., 1976).

However sophisticated the technique of administration, aerosol deposition while maximum in one zone will spread along the airways on either side. Thus it is not possible to deposit drugs in the fine airways without some deposition in the alveoli and in the large airways.

The effect of particle size and flow rate on lung penetration has been known for years but appears to have been neglected in makers' recommendations for therapeutic aerosol administration. For example, patients may be advised to direct the aerosol jet from pressure nebulisers towards the pharynx while inhaling. This results in impaction of most of the heterodisperse aerosol on the mouth and pharynx so that only the smallest particles (10–20% of the dose) are likely to reach the lung. Of that which reaches the lung much may then be deposited in the large airways and be ineffective if the site of action is deeper in the lung. Godfrey et al. (1974) have demonstrated that sodium cromoglycate is more effective in controlling exercise-induced asthma when administered in 2 as compared to 10 μm particle sizes, presumably because more of the smaller particles reach the site of action of the drug: this is assumed to be in the small airways.

In the same way the efficacy of topical steroid administration may well depend on the aerosol reaching the small airways. Some of the steroid preparations found to be unsuccessful for topical

administration may have failed for no other reason than that the depth of deposition in the lung was inadequate.

The above results suggest that to enhance depth of deposition of therapeutic aerosols in the lungs full breaths of the aerosol should be inhaled slowly followed by a breath-holding pause which 'freezes' some particles at the furthest point of penetration. For pressure nebulisers total deposition will be enhanced if the bulk of the aerosol is in small particles (2–7 μm) and is dispersed in a container in which the particles lose their momentum before being inhaled. Control of the distribution of aerosols in the lung is likely to become increasingly important as more information is obtained about the site of action of drugs.

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