Lung Physiology and How Aerosol Deposits in the Lungs

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1. Physiological and Anatomical Background

Weibel's morphologic data has been referred to not only for predicting aerosol deposition in the lungs but also lung physiology [1]. During breathing the volume of air passes all through the mouth, the larynx, the trachea and the conductive airways into the alveolar space. When the airflow is not laminar and disturbed at the bifurcation or the irregular airway surface, eddies and turbulence occur there to result in deposition of aerosol by impaction or sedimentation. At high flow rates, there are more chances for turbulence to occur at these sites. Because the cross-section and volume of the subsequent airways increase, the flow rate decreases. It is worthwhile to remember that the pressure drop and resistance do not necessarily follow Poiseuille's law even in the large airways, and that with the turbulent flow the density of a gas plays an important role. If Poiseuille's law is applied, the resistance becomes sixteenfold when the radius of the airway segment is halved. When we breathe quietly, the flow in the trachea and the intermediate conductive airways is laminar and in very small conductive airways including the terminal bronchioles the airflow becomes so slow in velocity that the axial diffusion becomes more prominent, especially distal to the terminal bronchioles the cross-sectional area increases so much that molecular diffusion becomes more important. For gas transfer to occur, molecules of oxygen should pass through the surfactant layer, the alveolar epithelium, the basement membrane, the endothelium of the capillaries, and the plasma to get to the red blood cell to combine with hemoglobin.

2. Physiological Factors to Determine Aerosol Deposition

The physiological factors determining aerosol deposition in the lungs are; lung volumes, flow rates, airflow obstruction, and regional ventilation determined by gravity [2,3].

1) Anatomical Compartment

Inhaled aerosol deposits in the conductive airways and the gas exchanging space

of the lungs. The former consists of the trachea, the bronchi and partly the bronchioli and the latter, partly the respiratory bronchioles and the alveolar space. The luminal surface of the former is covered with mucus under which lie the cilia protruding from the columnar epithelia of the conductive airways. The cilia of the latter are either poorly developed or nonexisting. From the standpoint of respiratory lung function or gas exchange, the former and a small portion of the latter, more specifically the terminal bronchioli and the non-alveolated respiratory bronchioli are equivalent to the anatomical dead space which serves only for gas transfer to and from the respiratory space of the lungs and most of the latter is a functional space where gas exchange takes place. From the standpoint of non-respiratory lung function, however, mucociliary clearance mechanisms are operative only in the former.

2) Physical Factors

Inhaled aerosol is carried in and out of the lungs with ventilation. Aerosol deposits both in the conductive airways and the functioning space by impaction, sedimentation and diffusion. In the functioning lung space or the alveolar space, diffusion takes place. For relatively low inhalation flow rates like in tidal breathing, the distribution of inhaled air normally depends in roughly equal measure on airway resistance and lung compliance [4]. Here airway resistance is defined as the pressure difference between the mouth pressure and the alveolar pressure divided by the airflow rate, when the airflow is laminar. When the laminar flow is disturbed and a turbulent flow occurs, airway resistance further increases and chances of aerosol deposition on the airways increase. Reynolds number (Re) is a useful index in this regard;

$$\mathrm{Re} = 2\mathrm{RF}\rho/\eta$$

where R is diameter of an airway, F, mean flow rate, ρ and η, density and viscosity of air, respectively. Roughly speaking, when Re exceeds 2,000, the flow becomes turbulent. In other words, inhaled aerosol has more chances of impaction and sedimentation. Compliance is a measure of how compliant the lung is, or in other words, reverse of elasticity. When the lungs lose elastic recoil as in pulmonary emphysema, they become more compliant or more difficult to return to their original resting level of the lung volume before pulmonary emphysema develops and the functional residual capacity (FRC) increases. Therefore, when the lungs become more compliant and when the airway resistance increases, the distribution of inhaled aerosol in the lungs becomes disturbed.

3. Particle Deposition in the Lung

1) Upper Airways

For particles to penetrate to the lung, they pass through the nasal vibrissae. The deposition fraction on the nasal cavity varies between different people and between breathing patterns. In order to eliminate the factor of nasal deposition we usually inhale radioaerosol through the mouth using a mouth piece with the nose clipped.

2) Lower Airways

Deposition of particles, especially of 1 - 50μm in diameter is governed by physical phenomena, such as inertial impaction and gravitational sedimentation and diffusion. The former plays a bigger role as either the particle size or the velocity of the airflow becomes larger. The latter becomes important when the particle size is bigger but the velocity is less. Deposition due to Brownian motion is most important for particle size between 0.1 - 0.5 μm. Particles with a diameter of about 0.5 μm would be expected to show minimal deposition, e.g. 90 % of inhaled 0.5 μm diameter aerosol appears in the exhaled gas under quiet breathing conditions [5].

Other factors like growth of hygroscopic aerosols inside the airways and electric charge of aerosols are considered to affect the aerosol deposition but our understanding of these factors is still limited.

4. How to Quantify Inhaled Aerosol Deposition in the Lungs

When a radioaerosol is inhaled, radioactivity deposits in the extrapulmonary ciliated airways (A), intrapulmonary ciliated airways (B), in the poorly ciliated or non-ciliated airways and/or the alveoli (C), or by being swallowed in the stomach and/or the GI tract (D), as shown diagramatically in Fig. 1 [6]. Disregarding the radioactivity in the compartment D, the radioactivity in each compartment at time zero or immediately at the end of inhalation can be written as follows;

$$A_0 + B_0 + C_0 = T_0 \qquad (1)$$

where A, B, and C represent the compartments as shown in Fig. 1, and T, the total radioactivity in all three. At time t, radioactivity at each compartment would be

$$A_t + B_t + C_t = T_t \qquad (2)$$

If radioactivity is corrected for physical half-life, the equation (2) can be rewritten as

$$A_{tc} + B_{tc} + C_{tc} = T_{tc} \quad (3)$$

Because radioactivity in the compartment C is not cleared, if radioactivity remaining in the lungs at 24 hrs is defined as the alveolar deposition, C_0 should be equal to Ctc at 24 hrs.

$$C_{tc} = C_0 \quad (4)$$

Practically speaking, it is extremely difficult to measure A without its being contaminated by swallowed radioactivity remaining in the mouth and the esophagus. In the actual calculation the radioactivity in the compartment A should not be taken into consideration by obviating measurement of radioactivity in the mediastinal portion. In this case the equations become:

$$B_0 + C_0 = T_0 \quad (1')$$
$$B_{tc} + C_{tc} = T_{tc} \quad (2')$$
$$B_{tc} + C_0 = T_{tc} \quad (3')$$

When considering mucociliary transport the radioactivity in the compartment C should be eliminated, because there is no ciliary function in this compartment.

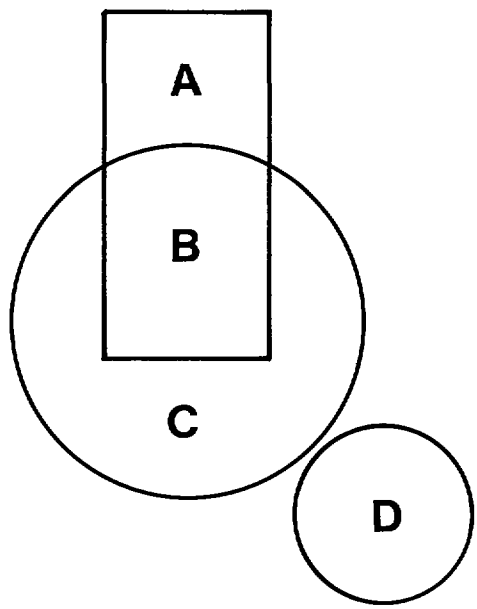

Fig. 1. Diagram of inhaled aerosol deposition sites. (A) extrapulmonary ciliated airways, (B) intrapulmonary ciliated airways, (C) nonciliated distal airways and/or alveolar space, and (D) mouth, stomach or GI tract in general.

5. Parameters to Quantitate Mucociliary Clearance

1) Lung Retention Ratio (LRR) (%) = T_{tc}/T_0 x 100

This ratio expresses the amount of radioactivity remaining in the lungs at time t relative to the total radioactivity initially deposited. c indicates corrected for physical decay.

2) Airway Deposition Ratio (ADR)(%) = B_{tc}/T_0 x 100 = $(T_{tc} - C_0)/T_0$ x 100

This ratio indicates what percentage of radioactivity initially deposited on the ciliated airways has already cleared by time t.

3) Airway Retention Ratio (ARR)(%) = B_{tc}/B_0 x 100 = $(T_{tc} - C_0)/(T_0 - C_0)$ x 100 = (LRR - ALDR)/(100 - ALDR) x 100

This ratio indicates what percentage of radioactivity initially deposited on the ciliated airways has already cleared by time t.

4) Airway Clearance Efficiency (ACE)(%) = $(B_0 - B_{tc})/B_0$ x 100 = 100 - ARR

This ratio indicates what percentage of the radioactivity deposited on the ciliated airways has already cleared by time t.

5) Alveolar Deposition Ratio (ALDR)(%) = C_0/T_0 x 100

This is the percentage of the total initial radioactivity deposited in the non-ciliated alveolar space relative to the total radioactivity deposited in the lungs.

All 5 parameters can be calculated by measuring T_{tc} and C_0. By sequential measurement of radioactivity and measuring radioactivity at 24 hrs, the LRRt (LRR at time t) and the ALDR are calculated. The smaller the size of aerosol, the larger the LRR and the ALDR and the larger the size of aerosol, the smaller the ARR, the ADR and the ACE.

The actual values of the above parameters should change as the size of aerosol used changes. In other words, these parameters depend upon the size of aerosol particle.

6. Establishing a Formula to Estimate the ALDR

Repeating measurement of radioactivity at 24 hrs is tedious and cumbersome both to the examiner and the examined. To circumvent the inconvenience an attempt

was made to establish a formula to get the ALDR by calculation. Because $FEV_{1.0}\%$ ($FEV_{1.0}$ divided by FEV in percent) and LRR_{60} (LRR at 60 min) and LRR thereafter showed good correlation with the actual ALDR, a formula was derived using these 2 indices for aerosols whose activity median aerodynamic diameter (AMAD) was 1.92 μm with geometric standard deviation of 1.57;

$$ALDR\ (\%) = -48.08 + 0.47 \times FEV_{1.0}\% + 0.59 \times LRR_{60}$$

As stated above, this formula applies only to aerosols whose size is equal to 1.92 μm in AMAD with geometric standard deviation of 1.57. Such formula should be established at each laboratory for its own use.

By using these parameters quantitative analysis of mucociliary function in the lungs is made as well as qualitative visual analysis by radioaerosol inhalation lung cinescintigraphy [8,9].

7. Concept of Aerosol Penetration in the Lung Parenchyma

It is perceived a priori that the same aerosol can penetrate further into the lung periphery if the airways are more dilated or if the size of aerosol is smaller. This can be expressed as penetration index [10, 11]. If the penetration is better, the ALDR would be larger. This could be well demonstrated in asthmatic patients in remission before and after bronchodilation [11].

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