RELATIONSHIPS BETWEEN INHALED AEROSOL DEPOSITION IN THE LUNGS AND HUMAN LUNG PHYSIOLOGY IN CHILDREN AND ADULTS

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Inhaled Therapeutic Aerosols: Relevant Principles

Human lungs, because of their primary function of gas exchange, are brought into intimate contact with inhaled particles. In every environment, particles enter the lungs. We do not live in a sterile environment. Only in recent centuries have we emphasized air pollution particles and exposures in the work environment. Infectious aerosols have always been present. The mechanisms which are pertinent to particle deposition and clearance will now be described and the relationship of these mechanisms to aerosol retention will be presented.

Deposition

Deposition is the process that determines the fraction of the inspired particulates that will be caught in the respiratory tract and thus fail to exit with the expired air. Several distinct processes operate to move particles suspended in the inspired air toward the surface of the respiratory tract: inertial forces, sedimentation, Brownian diffusion and interception. It is likely that all particles deposit after touching a surface; thus the site of initial deposition is the site of contact.

Inertia refers to the tendency of moving particles to resist changes in direction and speed. Repeated branching in the airways cause sudden changes in the direction of air-flow; however, because of inertia, particles tend to continue in their original direction, crossing air-flow streamlines and eventually impacting on the airway walls. Gravity accelerates falling bodies downward, and terminal settling velocity is reached when viscous resistive forces are equal and opposite in direction to gravitational forces. Respirable particles reach this constant terminal or sedimentation velocity in less than 0.1 msec. Thus, particles are removed as their terminal velocity causes them to strike the airway walls or alveolar surfaces. Aerosols also undergo Brownian diffusion, a motion caused by collisions of gas molecules with particles suspended in the air; this motion causes the particles to cross streamlines and thus increases the probability they will deposit.

The effectiveness of these deposition mechanisms depends on: (1) the anatomy of the respiratory tract, (2) the effective aerodynamic diameters of the particles, and (3) the pattern of breathing. These factors determine the fraction of the inhaled particles that are deposited as well as the site of deposition.

The anatomy of the respiratory tract is important since it is necessary to know the diameters of the airways, the frequency and angles of branching, and the average distances to the alveolar walls. Furthermore, along with the inspiratory flow rate, airway anatomy specifies the local linear velocity of the air stream and the character of the flow. A significant change in the effective anatomy of the respiratory tract occurs when there is a switch between nose and mouth breathing. There are inter- and intra-species differences in lung morphometry; even within the same individual, the dimensions of the respiratory tract vary with changing lung volume, with aging, and with pathological processes.

The effective aerodynamic diameters of the particles affect the magnitude of forces acting on them. For example, while inertial and gravitational effects increase with increasing particle size, diffusion produces larger displacements as particle size decreases. Effective aerodynamic diameter is a function of particle size, shape, and density. In order to predict deposition patterns, it is essential to
describe the distribution of aerodynamic diameters of aerosols as well as the mean of the aerodynamic diameter.

The remaining factor affecting deposition is the breathing pattern. Minute volume defines the average flow velocity of the aerosol-containing air in the lung and the total number of particulates to which the lung will be exposed. Respiratory frequency will affect the residence time of aerosols in the lungs and hence the probability of deposition by gravitational and diffusional forces. Changing lung volume will alter the dimensions of the airways and parenchyma.

The ICRP lung model of 1966 provides some predictions for the deposition fraction (collection efficiency) of particles for an adult human breathing a 1,450 ml tidal volume, 15 times a minute. Deposition in the nasopharynx ranges from 50.2% of the inspired particles with 2.0 um MMAD to 95.6% of 20 um particles. Deposition in the tracheobronchial compartment decreases from 3.61 to 1.03% as the MMAD increases from 2.0 um to 20 um and finally, deposition in the pulmonary compartment decreases from 21 to 2.6% as MMAD increases from 2.0 um to 20.0 um.

**Clearance**

Clearance refers to the dynamic processes that physically expel particulates from the respiratory tract; it is the output of particulates previously deposited. Highly soluble particles dissolve rapidly and are absorbed into the blood from the respiratory tract. Their metabolism and excretion resemble that of an intravenously injected dose of the same material.

Although some of this discussion applies to bioaerosols, we also emphasize unique aspects of respiratory defense mechanisms which are critical to keeping our lungs clean and sterile. Some secretions of the upper respiratory tract such as airway mucus may have bactericidal or antiviral properties. Especially, the ability of phagocytic cells looms large. Their ability to migrate, bind, and ingest deposited bioaerosols is critical. After phagosomes containing pathogens are created, preformed lysosomes fuse to create a phagolysosome. Within that “intracellular stomach” pathogens are killed by reactive oxygen species. After pathogens are killed, they are then digested by lytic enzymes. Ultimately, their constituents are recycled or metabolized. Clearance can refer to the disappearance of materials which are measured because of their physical or chemical properties. It also describes *in situ* mechanisms where pathogens are killed, digested, and gradually disappear.

**Ciliated Regions**

Less soluble particles that are deposited on the mucus blanket covering pulmonary airways are moved toward the pharynx by the cilia. Also present in this moving carpet of mucus are cells and particles which have been transported from the non-ciliated alveoli to the ciliated airways. Similarly, particles deposited on the ciliated mucus membranes of the nose are propelled toward the pharynx. There, mucus, cells, and debris coming from the nasal cavities and the lungs meet, mix with salivary secretions, and enter the gastrointestinal tract after being swallowed.

A number of factors can affect the speed of mucus flow. They may be divided into two categories: those affecting the cilia themselves and those affecting the properties of the mucus. The following aspects of ciliary action may be affected: the number of strokes per minute, the amplitude of each
stroke, the time course and form of each stroke, the length of the cilia, the ratio of ciliated to non-ciliated areas, and the susceptibility of the cilia to intrinsic and extrinsic agents that modify their rate and quality of motion. The characteristics of the mucus may become critically important. The thickness of the mucus layer and its rheological properties may undergo wide variations; for example chronic exposure to cigarette smoke or to irritant gases in the work place can induce significant changes in airway mucus.

Non-Ciliated Regions

Particles deposited in the non-ciliated portion of the lungs are either moved toward the ciliated region, primarily within alveolar macrophages, or they enter the alveolar wall and accumulate in connective tissue, especially lymph nodes. Particles remaining on the surface are cleared with a biological half-time estimated to be twenty-four hours in humans, while particles that have penetrated into "fixed" tissues are cleared with half-times ranging from a few days to thousands of days. Therefore, the probability of particle penetration is critical in determining the clearance of particles from the non-ciliated regions of the lungs.

Particles removed by alveolar macrophages show a variety of patterns and half-lives which are dependent upon particle number, size, shape and surface reactivity. However, generally alveolar macrophages act to decrease the probability of particle penetration, thereby aiding clearance. These free cells, ultimately derived from the hematopoietic system, play the primary role in removal of dust particles and potentially pathogenic micro-organisms from the alveoli. Most free cells containing the deposited particles eventually reach the ciliated region of the lungs and are eliminated into the pharynx and swallowed.

Pathophysiology of Pulmonary Macrophages

In addition to a variety of protective postures that help the host, macrophages may also participate in the pathogenesis of lung disease. Inhaled cytotoxic, radioactive, or carcinogenic particles become concentrated in pulmonary macrophages because macrophages are actively phagocytic. What begins as a diffuse and uniform exposure becomes highly localized and nonuniform. Macrophages may also metabolize chemicals and change them to more toxic forms.

Another way in which macrophages may be involved is through diminution or failure of their defensive role. Macrophage function can be compromised by environmental insults and pathological changes. Such diverse agents as silica, immunosuppressives, ethanol intoxication, cigarette smoke, nitrogen dioxide, ozone, and hyperoxia can depress the ability of pulmonary macrophages to protect their host.

Pulmonary macrophages not only fail but may contribute directly to the pathogenesis of pulmonary diseases. Two important examples involve pulmonary connective tissue. Connective tissue proteins have an essential role in lung structure and function. Collagen and elastin help maintain alveolar, airway, and vascular stability, limit lung expansion, and contribute to lung recoil at all lung volumes. Two groups of lung disease are associated with aberrations of normal collagen and elastin balance: emphysematous and fibrotic disorders.
Release of lysosomal enzymes, particularly proteases, from activated macrophages and leukocytes promotes the development of emphysema. Release is a consequence of cell death, cell injury, exocytosis, or regurgitation while feeding. Increased deposition of particles acts to recruit additional macrophages and thus may reinforce the effect. Oxidant gases which inactivate endogenous anti-proteases may further disturb the normal balance of proteolytic and antiproteolytic forces.

Fibrogenesis also involves macrophage damage. Dead or dying macrophages may release substances that attract fibroblasts and elicit fibrogenic responses. These mediators may be chemotactic for fibroblasts; they also stimulate their proliferation, and their rate of collagen formation. Dust particles which are cytotoxic and durable are retained in the lungs and stimulate persistent production of excess collagen in the alveolar wall. In such diseases as asbestosis and silicosis, progressive fibrogenesis may continue long after inhalation of dust particles has stopped.

The response of the lungs to inhaled antigens and allergens is also emerging as an important area that involves macrophages. Considerable evidence is available showing that inhaled organic chemicals, dusts, molds, and animal proteins can cause a variety of lung responses such as allergic asthma, extrinsic allergic alveolitis, immune complex disease, and other phenomena. Yet, little is known about the degradation of proteins deposited on the respiratory tract surfaces. Probably, in most instances macrophages and mucociliary transport defend the body against excessive antigenic stimulation. However, there may be other circumstances when clearance pathways cooperate with the immune system and preserve and present immunogenic molecules to the immune system. Thus the issue of how and when pulmonary macrophages suppress or enhance the immunogenicity of antigens must be confronted.

In conclusion, macrophages serve as a key element in the defense of the respiratory tract. They are also capable of injuring the host while exercising their defensive role. Investigations should continue into the ultrastructural and biochemical features of normal pulmonary macrophages as well as their alterations after exposure to physical, chemical, and infectious agents.

**Retention**

The actual amount of a substance in the respiratory tract at any time is called the retention. When the exposure is continuous, the equilibrium concentration (achieved when the clearance rate matches the deposition rate) is also the retention. Thus, the relative rate constants of deposition and clearance determine the equilibrium levels; it is the equilibrium level, or retention integrated over time, and the properties of the particle that are presumably related to the probability of a pathological or therapeutic response. For nonliving particles, clearance results in decreasing amounts of material. Retention as a function of increasing time is a decreasing fraction of the amount initially deposited. In contrast, many pathogens are capable of replicating within the respiratory tract. Thus, sometimes following deposition of bioaerosols, the number of pathogens which can be cultured from the lung may actually exceed the number initially deposited.
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