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Gas and Aerosol Mixing in the Acinus

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Abstract

This review is concerned with mixing and transport in the human pulmonary acinus. We first examine the current understanding of the anatomy of the acinus and introduce elements of fluid mechanics used to characterize the transport of momentum, gas and aerosol particles. We then review gas transport in more detail and highlight some areas of current research. Next we turn our attention to aerosol transport and in particular to mixing within the alveoli. We examine the factors influencing the level of mixing, review the concept of chaotic convective mixing, and make some brief comments on how mixing affects particle deposition. We end with a few comments on some issues unique to the neonatal and developing lung.

1. Introduction

The lung is a remarkable organ. It is the body's major exchange site with the environment, processing over 10,000 liters of air per day. The lung is light in weight, being composed mainly of extremely thin, fragile septa, but it is also surprisingly resilient: if we take a deep breath the lung more than doubles in volume and if we exhale fully the lung volume reduces to half its resting value. In extreme cases (e.g., breath-hold deep diving) the lung can reduce to as little as one twentieth of its total lung capacity.

There are roughly 17 million ducts (trachea, bronchi, bronchioles, and alveolar ducts and sacs) in the human lung with a combined length of the order of nine kilometers but the ducts are arranged in such a way that the average path from mouth to alveolus is 20–40 cm (Weibel et al, 2005). Oxygen in the ambient air reaches the gas exchange surfaces of the alveoli through a combination of convective and diffusive transport, diffuses through the enormously large surface area of the alveolar walls (130 m², Gehr et al., 1978 - comparable to the size of a tennis court) but extremely thin air-blood tissue barrier (0.62 μm, Gehr et al., 1978 – 100 times thinner than a human hair), and is collected by a quantity of blood (194 ml, Gehr et al., 1978) that could fit into a wine glass (P. Gehr, personal communication).

Another remarkable feature of the lung is that there is only one entry/exit pathway, the trachea, through which air enters and leaves the lung, and the same ducts are used for both inhalation and exhalation. This means that the airflow has to come to a stop and reverse. A significant amount of air generally remains in the lung at the end of exhalation. The

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reversing nature of the air flow and the appreciable amount of residual air in the lung suggest that the basic mechanism of gas transport is neither simple nor trivial.

The main focus of this paper is to examine the transport mechanisms that are responsible for exchanging O₂ and CO₂, supplying and maintaining the body's needs, and to point out the mechanistic differences operating for aerosol mixing.

2. Anatomy and Fluid Mechanics in the Pulmonary Acinus

Acinar and alveolar anatomy

The pulmonary acinus is the area of the lung in which gas exchange takes place. While it is customary to talk of acinar ducts, these passageways are really formed by entrance rings of alveoli all opening into a common passageway (Fig. 1). It is through the surface of the alveoli that gas enters the blood stream. The ducts are arranged and interconnected in such a way as to make optimum use of the volume available. This complex structure makes a precise description of the acinar anatomy a difficult task (e.g., Mandelbrot, 1982).

While others (e.g., Pump, 1969; Boyden, 1971; Parker et al., 1971; Schreider and Raabe, 1981) have made significant contributions to the understanding of the anatomy of the acinus, it is the works of Hansen et al. (1975), Hansen and Ampaya (1975), and Haefeli-Bleuer and Weibel (1988) that are most often referenced. Both groups conclude that irregular branching (a parent duct producing daughters with unequal numbers of descendants) is the norm in the acinus. However, some differences exist between the two groups. For instance, Hansen et al. (1975) report trichotomous branching to be relatively common whereas Haefeli-Bleuer and Weibel (1988) found only one instance of trichotomy. As we have used the data of Haefeli-Bleuer and Weibel (1988), modified by Weibel et al., (2005) in our own studies, we will discuss this data set in a little more detail.

While Haefeli-Bleuer and Weibel (1988) give no explicit estimate of the size or shape of the average alveolus they note that the outer diameter of the functional unit, which they define as including the sleeve of alveoli, is constant at about 700 μm . As the average duct diameter in the acinus is approximately 300 μm , the depth of the average alveolus is 200 μm . Hansen and Ampaya (1975) classified the alveoli into six shapes with the 3/4 spheroid being the most common and give the mean depth of the 3/4 spheroidal alveolus as 174 μm , which scales to 192 μm at TLC. It is noted that due to the volume-filling structure of the acinus, the shape of alveoli in-vivo must be more polyhedral than spherical.

The total number of alveoli in an average lung has been traditionally taken to be 300 million (Weibel et al., 1963). However, Ochs et al. (2004) in a study of six adult human lungs found the mean number to be 480 million (range: 274-790 million). Ochs et al. (2004) point out that as the size of a single alveolus is reasonably constant, larger lungs have considerably more alveoli. Another interesting estimate they make is that approximately 170 alveoli would fit in one cubic millimeter. However, in formulating geometric models for e.g. computational fluid dynamic calculations, it could be argued that estimates of total surface area within, say, an acinus, together with nondimensional shape factors associated with the fractionation of acinar volumes into ducts and alveoli, as well as the serial disposition of alveolation, is more important than any estimate of the total number of alveoli in the lung. Total areal estimates are relatively robust in this context (which we may call a "good" number), much more so than either a mean area per alveolus or the number of alveoli (whose product is good, but individually may be called "bad" numbers). Indeed, the rapidly increasing number of branches (and terminal units) in bifurcating models implies a large variation in estimates of alveolar number depending on generation assumptions, and this is markedly exacerbated by the known asymmetries within the airway tree.

Dimensionless parameters governing fluid flow, diffusion, and unsteady flow

To quantify gas and aerosol mixing and transport processes we need to introduce some basic concepts of fluid mechanics. Flows of all common fluids are governed by the same set of equations (the Navier-Stokes equation), which are derived from Newton's second law of motion. These equations describe mathematically the balance between the forces (pressure, viscous, gravitational, etc.) on a fluid element and its temporal and spatial acceleration. What distinguishes flow in the lung from, say, flow over an aircraft's wing, apart from obvious differences in geometry, is the relative magnitude of the various forces. In fluid mechanics, dimensionless parameters are used to characterize which force dominates in a particular flow. Dimensionless parameters also help to identify similarities in seemingly different flows and are used to construct models that when studied produce results that can be used to predict the behavior of a full-scale prototype. For meaningful comparison, model and prototype have to be geometrically, kinematically, and dynamically similar. This is true whether we are constructing a physical or a numerical model.

Geometric similarity requires that the model and prototype be identical in shape but differ only in size. Denoting the subscripts p and m to refer to prototype and model, respectively, the scale ratio of linear dimensions $L_r = L_p/L_m$ must be the same for all corresponding pairs of dimensions for the prototype and the model. Thus, the streamlines in the model and prototype flows must be geometrically similar. Kinematic similarity requires that the ratio of velocities at all corresponding points in the model and the prototype flows be the same; i.e., the ratio $V_r = V_p/V_m$ must be constant throughout the two flows. Dynamic similarity requires that the ratio of forces (or pressures) at all corresponding points in the model and prototype flows be the same; i.e., the ratio $F_r = F_p/F_m$. The force, F , can represent a single type of force or a combination of types of force. These may include inertial, pressure, viscous, elastic, gravitational, and surface tension forces. Hence, it is possible to construct various force ratios.

In lung flow, the significant forces are those due to flow inertia (due to both temporal and spatial acceleration) and those due to the fluid viscosity, balancing the driving force (pressure). The inertial force in a steady flow can be shown to be proportional to $\rho L^2 V^2$, where ρ is the fluid density, and L and V are a characteristic length and velocity. The viscous force is proportional to μVL , where μ is the fluid viscosity. The ratio of inertial to viscous forces is known as the Reynolds number, $Re = VL/\nu$, where $\nu (= \mu/\rho)$ denotes the kinematic viscosity. The Reynolds number can also be thought of as a measure of the strength of momentum transport due to convection compared to that due to viscous diffusion. If instead of the transport of momentum we consider the transport of a scalar, such as concentration or heat, then we define this ratio as the Péclet number; i.e., $Pe = VL/D$, where D is the molecular diffusivity of the scalar in the carrier fluid. In acinar flow, in most situations, $Re \ll 1$, which means that viscous forces dominate. Also, for gas transport in the acinus, $Pe \ll 1$, which means that diffusional transport dominates. However, in the case of aerosol particulates it is usual for $Pe \gg 1$; i.e., convective transport dominates.

If the flow under consideration is unsteady then we need to consider the force due to temporal acceleration which can be shown to be proportional to $\rho L^3 V/T$, where T is the characteristic time of the flow. The ratio of this force to the force due to spatial acceleration ($\propto \rho L^2 V^2$) is called the Strouhal number, $St = L/TV$. If $St \ll 1$, then the flows can be considered quasi steady. However, in the relatively slow flows found in biomechanics it is customary to consider the ratio of the temporal acceleration force to that due to fluid viscous forces ($\propto \mu VL$). The square root of this ratio is essentially the Womersley number, α ; i.e.; $\alpha^2 \propto St \cdot Re = L^2/\nu T$. The usual definition of α^2 includes a factor of 2π , which occurs naturally in the solution of the flow originally considered: that of oscillating pipe flow

(Womersley, 1955). In most of the acinus, we find that $St \ll 1$ and $\alpha \ll 1$; i.e., acinar flows are basically quasi steady.

Geometric model: Weibel's lung model

The basic structure of the airway tree of the human lung is encapsulated by the windpipe, or trachea, splitting into two mainstem bronchi, and each subsequent airway splits into two daughter airways (Fig 2). This dichotomous branching structure occurs, on average, for 23 generations (the trachea being generation 0). Various groups (see for instance Horsfield et al., 1971 and Phalen et al., 1985) have shown that the branching is irregular and asymmetrical and the number of generations in a particular pathway (from trachea to terminal alveolar sac) is quite variable. However, much can be understood of gas and particle transport in an idealized, regular, symmetric, model. Such a model was proposed some forty years ago by Weibel (1963) and has since become a standard.

Weibel (1963) presented diameters and lengths of each generation in an average adult lung. There were 23 generations in this model lung, termed Model "A", of which the last seven were populated with alveoli. Estimates of the total number of alveoli in each generation were also given. The lung volume was 4800 ml when inflated to approximately three fourths of TLC. Haefeli-Bleuer and Weibel (1988) reconsidered the acinus and presented a revised model acinus with ten generations (designated 0-9). Generations 0-3 were termed respiratory bronchioles, 4-8 alveolar ducts and 9, a blind-ending duct, an alveolar sac. Later, Weibel et al. (2005) modified the data of Haefeli-Bleuer and Weibel (1988) to a nine generation acinus (designated 0-8) with the acinus starting at generation 15, thus retaining the original 23 generation model of the airway tree. Haefeli-Bleuer and Weibel (1988) found the average volume of an acinus to be 187 mm^3 (at total lung capacity, TLC). Hansen and Ampaya (1975) found a similar value when scaled to TLC (the data of Hansen and Ampaya (1975) was reported at three fourths of TLC).

The acinar data of Haefeli-Bleuer and Weibel (1988), modified by Weibel et al. (2005) is at approximately full inflation (TLC) and the conducting airway data of Weibel (1963) is at three fourths TLC. Hence in order to construct a consistent set of data one set has to be scaled to fit the other. In our work we have chosen to scale up the conducting airway data to TLC. Also, we chose to use only the first 10 generations of the conducting airway data of Weibel (1963), along with the acinar data of Weibel et al. (2005), and fit smooth regression curves through the data to determine the values of length and diameter for generations 11-14. The distribution of alveoli per generation was determined, following Weibel et al. (2005), by assuming that the fraction of the total number of alveoli per generation is proportional to the fraction (f) of the total ductal surface area in that generation. Adjustments were made for the first three acinar generations to account for the fact that the ducts in these generations were not fully alveolated. The resulting 23-generation data set is given in Table 1.

3. Gas Mixing

Phenomenology and historical perspective

The first step in the exchange of the respiratory gases, O_2 and CO_2 , with the ambient environment is the gas phase transport between room air and alveolar gas. It is clear that during the course of breathing, alveolar gas is therefore some mixture of inspired gas and resident alveolar gas together with a metabolic sink for O_2 and a source for CO_2 ; this concept has been debated for over a century, with important foundations laid by the seminal work of Krogh and Lindhard (1917). The phenomenology of this mixing can be appreciated by a simple inspection of, for example, a single breath washout curve of N_2 concentration as a function of expired volume, following a tidal inspiration of pure O_2 . This classic curve

consists of an initial phase (I) of essentially zero N_2 , a rapidly rising phase (II) to an approximate plateau (III). This suggests that the gas mixing mechanism can be well approximated by a simple serial arrangement of a pure conducting tube with a well-mixed reservoir. Equivalently, this picture involves pure bulk transport in the conducting airways serving an alveolar or gas exchanging space wherein diffusive transport is dominant. These ideas lead to an equally simple set of measurements that distinguish these two regions as dead space and an alveolar or resident space, the dead space in particular being defined as the expired volume required to wash out the inspired gas, in the sense of replacing the sharply rising phase II by a mass conserving step function. This concept underlies the classic work of Fowler (1948), whose ideas are still current. Further phenomenologic observations of this type reveal that the dead space thus calculated is only weakly dependent on lung volume, respiratory flows, and even gas composition, which in turn leads to the more fundamental question of why the lung should behave in this manner. This is discussed in more detail in the sections below, where the physics behind this phenomenon is treated semiquantitatively, with the aim of elucidating the essential mechanisms.

We are thus led to investigate the nature of gas exchange in the face of both convective movement and diffusive transport. The interaction of convection and diffusion is enormously complex, with a wide variety of manners in which this interaction can occur. Here we will discuss a few of these, with attention to issues that remain open. However, it must be stated at the outset that the ideas outlined above, despite their simplicity, in fact capture a very large percentage of the real mechanism behind gas exchange. In particular, the extension to the concept of alveolar ventilation rests in large measure on the notion of that fraction of the tidal volume which participates significantly in gas exchange, and alveolar ventilation (and its distribution) in turn has long been known to be an essential component of the overall gas exchange picture, through its matching (or mismatching) with the distribution of pulmonary perfusion (West, 1965).

From the conduction to exchange zone

Why, then, should the lung display such a sharp demarcation between a conducting zone of bulk transport and an exchange zone of diffusive transport? The answer here lies in a semiquantitative assessment of the relative magnitudes of these mechanisms throughout the bronchial tree and distally to the alveoli. For this, the Péclet number ($Pe = VL/D$) is a useful parameter which we have seen reflects the importance of bulk transport to diffusive transport. Here V is the local bulk velocity of gas within an airspace (bronchial, ductal, or alveolar), L is a characteristic linear dimension of the bounding surfaces, and D is the molecular diffusivity of the gas species in question. (For O_2 or CO_2 , both D and ν are on the order of $0.2 \text{ cm}^2/\text{sec}$.) For normal respiration in humans, and using any of the classical models of the structure of the bronchial tree, together with morphometric measurements down to the extreme periphery of the lung, one finds that Pe (or Re) is $\gg 1$ in the major airways, consistent with bulk domination of transport, and falls to values $\ll 1$ in airways and airspaces peripheral to sites somewhere in the vicinity of the terminal bronchioles, consistent with diffusive domination of transport. The important point here is that the transition from very high Pe to very low Pe , and hence the transition from bulk to diffusive transport, occurs very sharply as a function of axial distance down the bronchial tree; this is due to the extremely rapid rise in cross sectional area of the segments with generations of the bronchial tree (taken in parallel). These simple ideas account in large measure for the presence of essentially pure inspired gas in the initial expirate (phase I) and the sharply rising phase II in a washout curve. The approximate alveolar plateau requires a bit more than simple diffusive domination of transport, insofar as O_2 and CO_2 are continuously being consumed from and evolved into the alveolar gas. For this, we can estimate a characteristic time τ for diffusive equilibration; this is given by $\tau = L^2 / D$, which for alveolar dimensions on the order of 100

μm , leads to τ less than 1 msec. Since this is much less than any breathing period times, one concludes that there is approximate equilibration within the alveolar gas space, justifying the idea of it being a well-mixed region, which in turn is reflected in the approximate alveolar plateau (phase III) in the washout curve.

Alveolar ventilation

This remarkably sharp transition is the origin of how one disambiguates the various definitions of alveolar ventilation. Unlike pulmonary perfusion, which both globally and regionally, can be clearly defined by the volume flow of blood into and out of either the whole lung or a region of interest, the nature of cyclic breathing does not admit such ease in defining alveolar ventilation. Indeed, the notion of it being that gas which participates in gas exchange is misleading insofar as all gas is at all times participating to a greater or lesser extent in gas exchange. But if, as is the case, the transition from greater to lesser is relatively sharp, then such an idea defining alveolar ventilation does in fact make sense. Similarly, another idea is that alveolar ventilation is related to the volume of inspired gas entering the alveoli, forming a kind of morphometric basis for the concept. But here, too, there is an unavoidable ambiguity in what constitutes alveoli for the purposes of relating alveolar ventilation to gas exchange. Thus, the effective ventilation contributing to gas exchange might be more adequately characterized by the volume of inspired gas entering some proper subset of an acinus but larger than individual alveoli, or even the volume of inspired gas entering an entire acinus. But this ambiguity as well is largely ameliorated by the sharpness of the boundary between bulk transport and diffusive transport, the site of which determines the functional volume where “alveolar” ventilation takes place in its role as a determinant of gas exchange. Note, however, that this transition site moves distally and proximally, cyclically over time in parallel with the cyclic nature of breathing, and consequently there does not exist a specific, time-invariant, volume for this fractionation of ventilation into a dead space and alveolar (or exchange) component.

Beyond a single dead space/ alveolar space

It is less clear what the most important issues are in progressing beyond the two compartment picture described above. In the first place, there is a marked regional variability in local ventilation, and secondly, there exists some degree of axial or serial inhomogeneity of gas concentrations. The former is intimately connected to the distinction often made between the Fowler type dead space referred to above, and a functional or physiologic dead space that is computed on the basis of a dilution argument: the ratio of alveolar concentrations to mixed expired concentrations involves the reduction of tidal volumes by an effective dead space diluting a resident volume. In normals, such “Bohr” type or physiologic dead spaces are similar quantitatively to the Fowler type, but in diseases wherein the regional variation in ventilation is more marked, and in addition is compromised by ventilation/perfusion abnormalities, there can be a large discrepancy between the two measures. At the level of specific measurement, the regional distribution of ventilation has been studied with a variety of techniques, including radioactive tracers (Milic-Emili, 2005), PET scans (Musch, 2002) and, more recently, MRI techniques utilizing hyperpolarized noble gases (Butler et al., 2002; Kauczor, 2002; Patz, 2008). This, coupled with corresponding measurements of the distribution of pulmonary perfusion, has led to wide applications and an enormous literature on ventilation/perfusion relationships as functions of health and disease, species differences, posture, and even in spaceflight; these issues however are far beyond the scope of our remarks here.

The degree of axial or serial inhomogeneity of gas concentrations most likely has less ultimate impact on issues of health and disease compared with parallel ventilation/perfusion mismatching, but speaks to the more fundamental issue of how convection and diffusion

interact serially beyond the step-like approximation discussed above. This requires a more detailed look at the foundations of this interaction, to which we now turn.

The convection-diffusion equation

In its simplest form, and sufficiently general for the ideas we wish to raise here, the convection-diffusion equation results from combining two ideas. The first is the equation of continuity, expressing conservation of mass. This may be written

$$\partial c / \partial t = - \nabla \cdot \vec{j}$$

where c is the concentration of some molecular species such as O_2 or CO_2 , or perhaps a tracer (dimensions number per unit volume), and $\vec{j}$ is the flux density of that species (dimensions number per unit area per unit time crossing a surface normal to $\vec{j}$). In words, it states that the time rate of change of mass in any small volume element is equal to the net rate of mass entering that element. The second idea is to relate the flux density to the concentration; this is where the two components of convection and diffusion arise. The convective flux density is $\vec{u}c$, where $\vec{u}$ is the local velocity of the air—this is simply the rate at which mass crosses any unit area per unit time due to bulk translation of the carrier gas. The diffusive flux density is given by Fick's first law, $-D\nabla c$, where D is the molecular diffusivity. The latter states that diffusive mass transfer is proportional to the concentration gradient, by analogy with Fourier's observation of heat flux being linearly related to a temperature gradient. We thus find, ignoring any interaction terms between molecular species, the classical convection-diffusion equation,

$$\frac{\partial c}{\partial t} = D\nabla^2 c - \nabla \cdot \vec{u}c = D\nabla^2 c - \vec{u} \cdot \nabla c$$

the second form following if the velocity field is essentially divergenceless (as is the case for air; it is essentially incompressible in applications to the lung).

This form is deceptively simple. With appropriate boundary conditions, which we address below, it would seem a simple matter to solve this. Unfortunately, no solutions are known for this equation except in the simplest possible circumstances, which do not include features necessary to include in any realistic lung model. Thus, there is a large literature on attempts to reduce this equation to one that is more manageable, and in particular to reduce its dimensionality from three to one. For example, diffusion coupled with even simple Poiseuille flow in a tube of constant radius is not trivial. An approximate solution to this was given by Taylor, 1953, who found that radial diffusion coupled with a parabolic profile led to a net axial flux, in coordinates moving with the mean fluid velocity, which was proportional to the mean concentration gradient. This is precisely the form of Fick's law of diffusion, but the prefactor which would otherwise have been the molecular diffusivity is replaced by a new prefactor, ever since known as the effective diffusivity D_{eff} , which was quadratic in the mean velocity but, counterintuitively, inverse with the molecular diffusivity D . To what extent such Taylor-type diffusion (including its extension to turbulent flow in the upper airways (Taylor, 1954), and oscillatory flow (Watson, 1983)) is important in pulmonary gas exchange remains an open question, it has been argued that it is not likely to be highly significant (Worth, 1977), although it may play a role in intermediate level bronchi (Wilson and Lin, 1970). By contrast, there is evidence (Kvale, 1975) that CO uptake is significantly enhanced in the presence of SF_6 as a carrier gas, suggesting that at least in some circumstances, Taylor-type diffusion may play a large role.

A more serious issue arises from the rapidly expanding area cross section. Here the reduction of the convection-diffusion equation to one dimension requires recasting both the conservation law and the fluxes in terms of their area-mean equivalents. For example, with overbars denoted areal averages over cross sectional areas S at axial coordinate z , the equation of continuity reads

$$\frac{\partial}{\partial t} S \bar{c} = - \frac{\partial J}{\partial z} - \alpha$$

where α is the mass lost per unit axial distance per unit time. This term arises from the necessary inclusion of radial boundary conditions at the airspace walls, and involves additional approximations over a simple area integration. This mass loss term may be safely taken to be negligible in the major airways, but is surely significant in any realistic model of the acinus. The area integrated flux, denoted J , is defined as the net mass transfer per unit time across a given cross section (here typically over the cross section of an airway at axial coordinate z). Just as the local flux density is the sum of a diffusive and convective term, the area integrated flux is similarly given by such a sum. In general the form of the diffusive and convective terms is complex, but they are often approximated by writing

$$J = - D_{eff} S \partial \bar{c} / \partial z + \bar{u} S \bar{c}$$

assuming the average of the product uc can be fractionated into a product of the separate averages and with molecular D replaced by D_{eff} (this is in fact the origin of Taylor-type diffusion). It is further assumed here that a Taylor-type diffusivity can simply be substituted throughout for the molecular diffusivity, but this has not been confirmed in expanding geometries. Substituting this area weighted flux into the one dimensional reduced equation of continuity then results in a reduced convection-diffusion equation,

$$\frac{\partial \bar{\rho}}{\partial t} = D_{eff} \frac{\partial^2 \bar{\rho}}{\partial z^2} - \frac{\partial}{\partial z} \bar{u} \bar{\rho} + \frac{1}{S} \left(\frac{\partial}{\partial z} D_{eff} S \right) \frac{\partial \bar{\rho}}{\partial z} - \frac{1}{S} \frac{\partial \alpha}{\partial z}.$$

The first two terms on the right hand side resemble the fundamental convection-diffusion equation, but there are additional terms: those associated with the (strong) axial dependence of the cross sectional area, the dependence of D_{eff} (if indeed this is an appropriate approximation) on z , and the axially changing mass loss or gain at the radial boundaries, especially at the level of the acinus. We note here that in addition to whatever Taylor-type diffusivity D_{eff} has on the local velocity (and hence on z), an additional feature is the fact that D_{eff} is sensitive to the velocity profiles even at the same overall flow rate; thus kinematic irreversibility associated with different profiles between e.g. inspiration and expiration necessarily imply a different D_{eff} during these phases of breathing. This is the origin of early work by Scherer, 1975, which has been widely used in gas exchange models incorporating both phases of respiration. Despite the difficulties noted above, however, significant progress has been made here, especially using trumpet models of the expanding cross section (Scherer, 1972, Paiva, 1973) as well as multinode models of the branching bronchial and acinar trees, as exemplified in Dutrieue, 2000 and Tawhai & Hunter, 2001.

Finally, it is especially important to consider the fact that the conduit boundaries themselves are moving with regular expansion and contraction during the course of breathing. Indeed, as noted elsewhere in this paper, there are major difficulties in computing either analytically or even numerically, what the relevant velocity profiles are in conduits where the walls are

moving. This is traceable to ‘the fact that the common no-slip condition, while elementary in principle to implement in rigid geometries, presents formidable complications when the zero velocity condition is replaced by a velocity equal to the material velocity of the moving boundary. As very little is known about the effects of such boundaries on the velocity fields, so too is even less known about the fundamental interaction of convection and diffusion in this circumstance. In short, the very foundations of the one dimensional reduction of the convection-diffusion equation in expanding and contracting conduits are not well understood and bear further examination, particular for those models which rest on such an approach.

Boundary conditions, proximal: the stationary front

Besides the governing differential equation, it is necessary to consider the appropriate boundary conditions. This turns out to be a rather delicate question for a number of reasons. First, we return to the ideas presented at the beginning regarding the interface between serially arranged regions dominated respectively by convection and diffusion. Considering a typical N₂ washout experiment, one finds that during inspiration, there is an axial site at which the convective flux of N₂ distally is exactly balanced by its diffusive flux proximally; at this point the concentration of N₂ remains constant, and represents the so-called “stationary front” for gas transport (Engel, 1983). Because of its constancy, many models of gas transport focusing on the periphery of the lung have used a constant value at the model proximal end. This is problematic for a number of reasons, among them because the concept itself is limited to only half the respiratory cycle, and because such a front is in fact not stationary but evolves in time during variations in inspiratory flows. These difficulties are not likely to influence numerous results found on single breath washin-washout studies, but are potentially more serious in analyzing either multi-breath washout experiments or steady state respiratory gas exchange.

For steady state problems, setting the airway opening boundary condition to the concentration of room air is clearly fine, but it is not obvious that any boundary condition is appropriate at the airway opening during expiration, for the following reasons. Clearly, setting a fixed value there would imply a boundary layer development axially as the expired gas is trying to rise or fall convectively to its approximate alveolar concentration level. Similarly, the very high Peclet number proximally might suggest simply setting the diffusive flux at the airway opening to zero. But this too implies a boundary layer (though less extreme than that secondary to a Dirichlet condition). By contrast, one approach is to extend the airway opening during expiration to either a finite distance axially (a “buffer” zone), sufficiently far away such that regardless of boundary condition the “back” effect of the boundary layer is negligible (Pack, 1977), or even infinitely far away, in which case the boundary condition is completely irrelevant (Butler, 1977).

Boundary conditions, distal: the alveolar surface

Here we must carefully distinguish between analyses of transient transport problems, and steady state exchange problems. Due to the enormous surface area in the far distal regions of the parenchyma, it follows that diffusive gradients are correspondingly small, even for respiratory gases. Indeed, we argued above that due to the characteristic diffusive mixing times associated with alveolar and ductal dimensions, the alveolar gas should be essentially in equilibrium throughout the alveolar region. This is true, and leads to the idea that setting the normal gradient ∇c to zero at an alveolar surface termination is appropriate. For washin-washout transient analyses, this is a fine approximation, but the departure from complete equilibrium, though immeasurably small, is nevertheless important in analyzing steady state transport. That is, the metabolic needs of the body are set by factors independent of the lung, and in steady state, one must have

$$\dot{V} = -D \int d\vec{S} \cdot \nabla c$$

where $\dot{V}$ represents either O_2 consumption or CO_2 production. Writing this in terms of areal averages $\langle \cdot \rangle$ and averaging over a respiratory cycle, we have $\dot{V} = -DS \langle \nabla c \rangle$. In this form we see that in very far distal portions of any kind of trumpet model of the lung wherein the area S increases very fast with axial distance z , as the convective term tends towards zero, the only meaningful quantity that remains is the product of the (very large) surface area S and the (very small) mean concentration gradient $\langle \nabla c \rangle$, and that if the source/sink term $\dot{V}$ is fixed (as it is physiologically), then the independent values for area and mean gradient are not important except insofar as their product satisfies the overall metabolic needs of the body. In short, we may call the extremely large morphometrically determined S and the (unmeasured) mean gradient both as “bad” numbers, whereas their product $\dot{V}$ is a “good” number. Phrased differently, if in any realistic lung model, the alveolar surface area were to be doubled or halved, we would argue that there would be an insensibly small effect on alveolar gases. This observation is in striking contrast to the intuitive notion that ultimately distal gas transport (i.e. at the alveolar gas/liquid interface) ought to be at least approximately proportional to the surface area. This is not true; the intuition rests on the assumption that a reduction of the diffusion equation to one dimension preserves a fixed concentration gradient, from which it would follow that diffusive flux is extensive in the area. But this dimensional reduction must preserve not the gradient, but the total flux, and this can be accomplished by appropriate variations in the gradient with changes in area. Without going into arguments about the potential fractal nature of the alveolar surface area, we note simply that estimates of area may be significantly affected by field magnification in microscopic morphometry, but that such variations are unlikely to correspondingly change alveolar gas composition. To be sure, in the extreme case of severe emphysema where substantial area is lost, the entire argument above breaks down, but suggests a reason why individuals with moderate emphysema and loss of parenchymal surface area may be asymptomatic, with completely normal exercise tolerance and arterial blood gases.

Convection and diffusion within the acinus

Despite the difficulties described above, there has been enormous progress in our understanding of the nature of gas exchange at the level of the pulmonary acinus. Here one of the major issues is to include diffusive flux at the walls of some serial model of alveolation progressing down an alveolar duct. Note that this leads to a division in modeling between those approaches which utilize a dimensionally reduced convection-diffusion equation, for which a nonzero flux condition at the walls reappears as a sink or source term in the reduced equation of transport, versus those approaches which retain the full three dimensional sourceless transport equation, but with boundary fluxes explicitly included as boundary conditions. Early work by Chang et al. (1973) deals with diffusive transport in a variety of models of the acinus, seeking insight into the potential of stratified inhomogeneity within the ductal/alveolar architecture. This prefigures more recent work within the acinus associated with the potential for “screening”, introduced by Sapoval et al. (2002) in the detailed analysis of the interaction of convection and diffusion within the branching acinus.

Serious progress has been made especially in the context of more detailed analyses of the progression of e.g. the slope of phase III in multiple breath washout studies. Pioneering work by Paiva (1975) exemplifies this, wherein it is possible to dissect the interaction of convection and diffusion into components that are effectively conductive in nature representing intra-acinar inhomogeneity of emptying versus those lumped into an acinar

zone representing inter-acinar stratified inhomogeneity. A lucid example of this is found in Verbanck et al. (1997).

Summary

First, we have argued that the classical fractionation of gas transport into zones dominated by conduction and diffusion, despite its simplicity, captures much of the essence of the physics of gas exchange, and have tried to illustrate the most important features that contribute to this strikingly good description. Second, we have focused on what we believe to be some of the fundamental issues that remain open, including the nature of the conduction/diffusion transition, the dimensional reduction of the convection-diffusion equation, and the importance of boundary conditions especially in the case of cyclic wall motion during the course of breathing.

4. Aerosol Mixing

Historical prospective

Contrarily to gas mixing phenomena in the acinus described above, very little attention was paid to aerosol mixing. As diffusivity of aerosols is significantly smaller than diffusivities of gases, aerosol particle transport in the acinus is dominated by convection. An interesting question arises as to how such particles mix with acinar residual gas and deposit on the alveolar surface. This is because those particles, penetrating deep into the acinus, must follow the streamlines of the airflow, presumed to be kinematically reversible because the flow Reynolds number is less than unity in the acinus.

Classical theories, adapted from convection-diffusion gas transport theory, describe aerosol transport as a dispersion process (e.g., Taulbee and Yu, 1979; Egan, 1989; Darquenne and Paiva, 1994; Edwards, 1994). These theories are based on the following two key assumptions: (i) acinar flow is basically kinematically reversible (i.e., during expiration each fluid particle retraces the path taken during inspiration) (Davies, 1972; Watson, 1974), and (ii) all processes (including the coupling of Brownian diffusivity with the convective flow field and any kinematical irreversibility that may be present) that contribute to irreversible aerosol bolus spreading can be characterized as axial mixing with an effective longitudinal diffusivity, D_{eff} . The first assumption is based on classical fluid mechanics (Taylor, 1960) and the second assumption is substantially equivalent to Taylor dispersion (Taylor, 1953). As most aerosol studies are currently interpreted in the framework of these dispersion theories, experimental data are often reduced and analyzed through the use of some D_{eff} (e.g., Rosenthal et al., 1992), and many of the theoretical research efforts are focused on refining D_{eff} for better fit to experimental data, through which new insights into acinar transport mechanisms are sought.

Kinematic flow irreversibility: chaotic mixing

By contrast to the above foundation, we have argued (Tsuda, et al., 1995, 2002; Butler and Tsuda, 1997; Haber et al., 2000, 2006; Henry et al., 2002, 2008) that the fundamental characteristic of acinar flow and the one responsible for aerosol mixing; i.e., recirculating flow in the expanding alveoli, cannot be modelled by an effective diffusivity. The character of the flow in an individual alveolus depends crucially on its generational position. As each alveolus expands at approximately the same rate, the rate of flow entering the alveolus, Q_A , is roughly the same throughout. However, the flow in the duct passing by the alveolar opening, Q_D , is a function of the expanding lung volume distal to the alveolus of interest. As the Reynolds number is everywhere small (less than unity), it is the ratio Q_A/Q_D that chiefly defines the character of flow in the individual alveoli, consequently conditioning aerosol

mixing and deposition. That is, whether or not recirculation occurs in an alveolus depends on the value of Q_A/Q_D , not on Re .

The acinar geometry expands in a fashion approximating geometrical similarity (Gil & Weibel 1972; Ardila, Horie & Hildebradt, 1974; Gil et al. 1979; Weibel 1986; but note that Miki et al. 1993 found a small but significant amount of geometric hysteresis); that is, all lengths change as $l=l_0R(t)$ where the subscript 0 represents the mean value, thus $Q_A/Q_D = V_A/V_D$, where V_A is the volume of a typical alveolus and V_D the volume distal to the generation of interest. Hence, Q_A/Q_D is only a function of geometry. It is not, therefore, affected by breathing rate or tidal volume. Estimates of Q_A/Q_D are given in Table 2.

We have examined the role of recirculating flow in the rhythmically expanding alveoli on acinar flow irreversibility (Tsuda, et al., 1995). We solved numerically quasi-Stokes flow in an axisymmetric alveolated duct model and found that the flow in an expanding/contracting alveolus exhibits a characteristic recirculating flow inside the alveolus, providing Q_A/Q_D is sufficiently low (Fig. 3). We found, that if recirculation occurs then the flow must exhibit a stagnation saddle point near the proximal corner of alveolar flow field (Fig 4). We demonstrated that in such a flow the motion of fluid particles is not kinematically reversible, resulting in highly complex twisted/tangled Lagrangian trajectories. These results suggest that flow in the alveolated duct is chaotic. In parallel with this axisymmetric study, we solved Stokes flow in a fully three-dimensional alveolus model with rhythmically expanding/contracting walls (Haber et al, 2000), confirming the basic features of alveolar flow with a characteristic vortex and an associated stagnation saddle point in the alveolar flow field. In a subsequent study (Henry et al., 2002), we simulated the behavior of a tracer bolus (i.e., a cloud of fluid particles) in an axisymmetric acinar model with multiple alveoli and showed that a bolus evolved into fractal-like patterns after a few cycle (Fig 5). We also showed (Henry et al., 2008) that chaos can exist in the flow of a rigid model alveolus (Fig 6). Most recently, we provided theoretical explanation for the role of alveolar recirculation in triggering chaotic mixing (Tsuda and Laine-Pearson). In animal model experiments, we also demonstrated substantial alveolar flow irreversibility with stretched and folded fractal patterns (Tsuda et al., 2002). These animal experimental data together with theoretical findings support our idea that chaotic alveolar flow governs flow kinematics in the pulmonary acinus, and hence the transport/deposition of inhaled fine particles.

Brief comments on aerosol deposition

This paper is focused primarily on the transport and mixing mechanisms within the acinus. However, in the case of aerosols, we are ultimately interested in the rate at which particles deposit on the airway and alveolar surfaces. Hence, we make a few brief remarks on this subject below.

For a fine particle, which generally follows the airflow streamline, to deposit on the alveolar surface, it must, at some point, deviate from the streamline. This occurs via a number of different mechanisms. For instance, if the particle has sufficient momentum, it will deviate from the airflow streamlines and may deposit by impaction. If the particle has sufficient mass, it will be affected by gravity and may deposit by sedimentation. If the particle is sufficiently small, it will be affected by stochastic Brownian movement and may deposit by diffusion.

There is a range of biologically important particles (e.g., cigarette particles), centered around $0.5\ \mu\text{m}$, that are too small to be significantly affected by gravity or inertia but too large to be affected by diffusion. It is these particles whose fates are largely dictated by kinematically irreversible acinar airflow and chaotic mixing discussed above. Our experimental and theoretical findings (Tsuda, et al., 1995, 1999, 2002; Butler and Tsuda, 1997; Haber et al.,

2000, 2006; Henry et al., 2002, 2008) support our idea that chaotic alveolar flow governs flow kinematics in the pulmonary acinus, and hence the transport and deposition of inhaled fine particles. What remains to be established is the particle size range over which chaotic mixing is important. Further, studies are also needed to ascertain the importance of the combined effects of chaotic mixing and diffusion and chaotic mixing and gravity.

5. Issues unique to the developing lung

Anatomy

In recent years, the anatomy of the infant acinus has been the subject of much study. It is now generally accepted that structural alveolation in the postnatal lung development period is achieved by the formation of new secondary septa from the shallow primary septa that are present at birth (Burri et al., 1974, 2006) but the number of generations and the distribution of alveoli in the infant acinus are largely unknown. On a global scale, Zeltner et al. (1987) presented measurements of parenchymal air volume, V_P and alveolar surface area, S_A , with body weight in infants. These data show that S_A/V_P grows with age.

Towards an infant airway model

It is conceptually more difficult to generate an infant model acinus comparable to the adult model of Weibel et al. (2005), because in the infant case the elements of the model, including the number of generations, the average length and diameter of a typical airway in each generation, and the distribution of alveoli, are all strong functions of age or body weight. What is immediately clear, however, just from the observation that that S_A/V_P increases with body weight (Zeltner et al., 1987), is that the infant lung is not a scaled version of the adult lung.

Unfortunately, there are not yet sufficient data to build a model acinus even for one particular age. There are data for average dimensions of the trachea (Butz, 1968) and the upper airways (Horsfield et al., 1987) but little for the acinar airways. Hislop et al. (1986) gave average values of alveolar diameter and alveolar duct diameter in infants up to 18 weeks old but gave no information on duct length or the number of generations. Dunnill (1962) gave estimates of the number of alveoli and generations with age but, more recently, Burri (2006) presented data that seem to contradict many of Dunnill's findings. Also, Hislop et al. (1986) found that at birth the human lung had an average of 150 million alveoli but Burri (2006) states that at birth the human lung contains between zero and about 50 million alveoli.

One vital piece of information currently missing concerns the structure of the infant acinar airways. While in the major airways, it is known that branching occurs by successive bifurcations arising at fetal buds, it is unclear whether the ontogeny of neonatal acinar development proceeds by radially inward secondary septation associated with myofibroblast activity contracting new ductal rings, or by radially outward expansion of the acinar unit from a pre-existing ductal architecture leaving secondary septation in its wake. In any event, the geometric characterization of this acinar structure as it evolves during development presents new and formidable problems in morphometry. Clearly, further studies utilizing classical and robust estimators of e.g. surface area, volume densities, and even curvatures are both possible and needed. But beyond this, we need new parameters describing the complexity of the evolving structure. An example of this is found in the tortuosity limit of apparent diffusion coefficients probing at least one new aspect of the distribution of characteristic length scales (Sen, 2004). But as we now know, structural aspects of acinar alveolation are critically important to the gas exchange efficiency of the lung as well as to aerosol transport and deposition, and identifying those features of structural geometry that

are most pertinent and important as the lung develops from birth to adulthood remains an exciting and open area of research.

Flow in the infant alveolus

Although the rate at which the depth of the alveolus increases remains uncertain, it is clear that the depth of the alveolus increases as new secondary septa grow from the primary septa (Burri, 2006). As the flow pattern in the alveolus is a strong function of alveolar wall geometry (e.g., Tsuda et al., 1995; Karl et al., 2002), acinar fluid mechanics in the developing lung must be strongly age-dependent.

To show this, we have computed airflows in a rhythmically expanding/contracting alveolar model with 3 different alveolar depths. For very shallow alveoli, representing the alveolus at birth, alveolar flow pattern is simple with no recirculation (Fig. 7a). As the alveolus grows deeper, a small recirculation region appears (Fig. 7b). Eventually, the alveolus grows to its mature shape, and the recirculation region fills the cavity (Fig. 7c). These results imply that alveolar flow mixing and subsequently aerosol deposition may be strongly conditioned by age-dependent change of alveolar structure. This emphasizes the different mixing mechanisms occurring in the developing lung to those in adult lung. We predict that acinar fluid mechanics change dramatically during lung development, influencing flow mixing and deposition in an age-dependent fashion. This is an important area that requires further research.

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Figure 1. Scanning electron micrograph of an alveolar duct surrounded by alveoli. From Gehr et al., by permission.

Figure 2.
Model human airway system. From Weibel et al., 2005, by permission.

Figure 3.

Instantaneous streamlines at peak inspiration in expanding alveolated duct with fixed alveolar shape for three different values of Q_A/Q_D . From Tsuda et al., 1995, by permission.

Figure 4. Instantaneous streamlines in expanding (A) and contracting (B) duct. Inset: expanded view of flow near proximal wall shown a stagnation saddle point. From Tsuda et al., 1995, by permission.

Figure 5.

Lower panel and inset: distributions of massless (fluid) particles at the end of cycle 1 (green), cycle 2 (blue), and cycle 3 (red). Approximately 16,000 particles are shown for each cycle. Top left: box-counting analysis. A linear relationship on $\log[\text{coefficient of variation (CV)}]$ vs. $\log[\text{edge length } (E^2)]$ with a slope of -0.2 shows that the pattern of particle distribution is fractal with a fractal dimension D 1.2. Flow conditions in the 9-cell model: $0.040 < Q_A/Q_D < 0.069$, $0.092 < Re_{RMS} < 0.053$. From Henry et al., 2002, by permission.

Figure 6. Poincaré sections for a flow in a rigid alveolus model with $Re = 1.0$ and Womersley number, $= 0.096$ ($T = 3s$). Upper panel; full view of all orbits computed. Lower panel; an expanded view of the orbits with islands and their neighbours. From Henry et al., 2008, by permission.

Figure 7. Instantaneous streamlines at peak inspiration in an expanding alveolated duct with fixed Re and three different alveolar depths. From Tsuda et al., 1995, by permission.

Table 1

Adult data at TLC Derived from Weibel (1963) and Weibel et al. (2005)

Gen. Z	<i>D</i> (mm)	<i>l</i> (mm)	<i>f</i>
0	18	120	0
1	12.2	47.6	0
2	9.14	20.9	0
3	6.17	8.37	0
4	4.96	13.99	0
5	3.86	11.79	0
6	3.08	9.91	0
7	2.53	8.37	0
8	2.05	7.05	0
9	1.70	5.95	0
10	1.43	5.07	0
11	1.16	3.92	0
12	0.94	3.03	0
13	0.76	2.34	0
14	0.62	1.81	0
15	0.50	1.40	0.2
16	0.50	1.33	0.4
17	0.49	1.12	0.7
18	0.40	0.93	1
19	0.38	0.83	1
20	0.36	0.70	1
21	0.34	0.70	1
22	0.31	0.70	1
23	0.29	0.70	1

Estimates of the variation of flow Reynolds number, Péclet number for 5nm and 500nm particles, Strouhal number, Womersley number and flow ratio Q_A/Q_D in the acinus.

Table 2

Gen.	Re	Pe (5nm)	Pe (500nm)	St	α	Q_A/Q_D
15	1.606	126	3.28×10^7	0.0001	0.04	0.0003
16	0.798	62.5	1.63×10^7	0.0003	0.04	0.0006
17	0.393	30.8	8.03×10^6	0.0006	0.04	0.0011
18	0.192	15.03	3.92×10^6	0.0012	0.04	0.0023
19	0.092	7.20	1.88×10^6	0.0026	0.04	0.0048
20	0.043	3.37	8.77×10^5	0.0055	0.04	0.0103
21	0.019	1.46	3.80×10^5	0.0126	0.04	0.0238
22	0.007	0.53	1.38×10^5	0.0349	0.04	0.0657
23	0.001	0.10	2.56×10^4	0.1872	0.04	0.3525

Characteristic velocity, V = maximum velocity; Characteristic length, L = duct radius, taken to be 0.125mm (at FRC) throughout; T = 4s; tidal volume = 500 ml; lung volume at FRC = 2500 ml; Q_A = flow into a ring of alveoli surrounding the duct; alveolar width = depth = 0.13 mm. Values of Re , Pe , St and α were computed using the geometry data (Table 1) and defining the function $\tilde{R}(\theta)$ to be a simple sinusoid. It is seen that $St < 1$ and $\alpha < 1$, which confirms that the flow is quasi-steady. Also, as expected, $Re < 1$ for all but generation 15, which confirms that the flow in the acinus is dominated by viscous force. It is also seen from the values of Pe that convection dominates the transport of 500-nm particles throughout the acinus and is also significant for 5-nm particles except for the last few generations.