Acinar determinants of the apparent diffusion coefficient for helium-3

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Verbanck S, Paiva M. Acinar determinants of the apparent diffusion coefficient for helium-3. J Appl Physiol 108: 793–799, 2010. First published February 18, 2010; doi:10.1152/japplphysiol.01230.2009.—The apparent diffusion coefficient (ADC) obtained by helium-3 magnetic resonance imaging over several seconds is thought to reflect diffusion impairment due to both intra- and interacinar structure. In this study, numerical simulations of intra-acinar gas mixing and effective diffusion were performed in a multiple-branch-point model of the human acinus. Using a previously described method, we computed the instantaneous effective diffusion resulting from the diffusive impairment imposed by intra-acinar branching for varying times up to 5 s. We also tested the influence on effective diffusion of intra-acinar collateral channels in the fully alveolated intra-acinar airways to mimic the effect of emphysema. Randomly connecting two or four pairs of airways per generation (in generations 19–25) led to a 40 and 142% increase, respectively, in effective diffusion coefficient cumulated over the time interval of 0.2–5 s. Finally, we also used a system of two coupled multiple branch-point models to simulate diffusive attenuation over a 50-s interval in cases of purely acinar tagging (i.e., the initial gas concentration = 1 in one acinus and 0 in the other) and of partial tagging astride on two acini. It is shown that, in the latter case, the decay rate cannot be approximated by a mono-exponential with a several-fold faster decay for times below 10 s due to intra-acinar diffusion. We conclude that both the characteristic biphasic time dependence of simulated effective diffusion and its sensitivity to intra-acinar structural change mimic experimental ADC behavior. Additional simulations of combined inter- and intra-acinar diffusion strongly suggest that neglecting intra-acinar branching would in fact lead to considerable error of simulated ADC.

Magnetic resonance imaging of the lungs via hyperpolarized helium-3 aims to characterize lung structures that are beyond the scale of resolution of direct airway visualization methods available for in vivo imaging in humans (5, 6, 9, 14–19). In particular, an apparent diffusion coefficient (ADC) can be derived by imposing a specific magnetic field profile on a helium-3 equilibrated lung and considering signal attenuations due to the fact that initially tagged helium-3 molecules move away by molecular diffusion. When measuring a so-called “long-range” ADC over several seconds (e.g., 15), time-averaged ADC values derived from the signal attenuation of an initial sinusoidal magnetization profile with a given tag length (λ) in one given direction to then derive an ADC value as the decay rate of the mono-exponential fit to the total magnetic moment of the tags, multiplied by (λ/2π)². The other approach, which is computationally far less challenging, is to not make any assumptions about the 3D arrangement of relevant airway structures. For instance, a SPAMM (spatial modulation of magnization) experiment can be simulated by introducing a sinusoidal magnetization profile with a given tag length (λ) in one given direction to then derive an ADC value as the decay rate of the mono-exponential fit to the total magnetic moment of the tags, multiplied by (λ/2π)². The other approach, which is computationally far less challenging, is to not make any assumptions about the 3D arrangement of relevant airway structures but to solve the diffusion equation numerically along the axes of all interconnected airways within a given volume and compare this to the free diffusion in that same volume without internal branching. This produces a value for an effective diffusion coefficient that is the result of the impairment to free diffusion on which the MRI experiments are based (12). These independent approaches are both confronted with the same problem: Which are the relevant structures that should be included for the computation of effective diffusion reflected in the long-range ADC measurement?

An important clue comes from recent ADC data as a function of MRI measurement time showing a distinct biphasic time-dependence, with ADC markedly decreasing up to 1 s and

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decreasing more slowly beyond 1 s (up to 5 s) (15). The MRI experiment simulations with lumped acini embedded in a bronchial model (1) produced an exponential decrease of the magnetic moment with a time constant of the order of 100 s. This implies no biphasic dependence of simulated ADC in the 5-s time interval corresponding to the MRI experiments, and it is difficult to predict whether the presence of inter-acinar holes that were proposed to produce a more realistic ADC value would elicit a biphasic ADC dependence on time. With the alternative model approach proposed in our previous simulation study (12), a biphasic behavior of effective diffusion can be appreciated retrospectively. In that study, we showed how the coefficient of variation (CoV) of concentration distribution generated by an initial He bolus in different parts of a multi-branch-point model representative of an acinus decreases as a function of time and how instantaneous effective diffusion at each time point could be considered directly proportional to the gradient of the logCoV vs. time curve. Hence, the fact that the logCoV vs. time curves in our previous work showed a biphasic relationship indicated that intra-acinar pathways were at least partly responsible for the diffusion impairment reflected in ADC.

The first aim of the present work is to actually compute the effective diffusion as a function of time for comparison with ADC experimental values obtained for different time intervals by considering gas mixing within an acinar multi-branch-point model (12). The second aim is to test the sensitivity of effective diffusion to intra-acinar collateral pathways representative of early emphysematous lesions, also as a function of time. Finally, in an effort to clarify the exact link between our simulations and the actual MRI experiments, we used the same acinar models to predict the diffusive attenuation observed during MRI experiments, including the condition where tag lengths exceed acinar size. This was done by considering a system of two interconnected acinar models and imposing distances between them that allowed us to mimic tag lengths roughly ranging 1–4 cm.

### MATERIALS AND METHODS

**Model geometries.** The basic model entities we used were a multi-branch-point model of the acinus (MBPM) and a trumpet model of the acinus with no internal restrictions; the trumpet model is obtained by the cumulative cross-sectional area per generation vs. airway length in successive acinar generations 15–26. For the choice of the MBPM internal structure, we first considered 10 acinar structures proposed by Dutrieu et al. (4) based on the anatomical data of Haefeli-Bleuer and Weibel (7) but with 10 alternative intra-acinar branching patterns compatible with acinar gas mixing as assessed by an independent method (washout test); these 10 acinar structures had been shown to quantitatively reproduce average and standard deviation of gas mixing tests in normal human subjects (4). Finally, we chose 1 of these 10 structures as a representative reference model (MBPM*). For the study of the relevance of intra-acinar branching, we also considered a system in which two MBPM*, or two of its corresponding trumpet models, were connected by a branch point in generation 14 but with subtending airways (generation 15) of varying length between 0.16 and 1.6 cm. In this way, we aimed to simulate diffusive mixing between acini that may well be next to each other in the imaging plane but are actually interconnected via a pathway of varying lengths.

All MBPM and trumpet models were discretized to allow for numerical solution of the 1D gas transport equation of diffusion and convection in the lung (10):

\[
\frac{\partial C}{\partial t} = D \left( \frac{\partial^2 C}{\partial z^2} \right) + \frac{S(\partial C)}{S(\partial z)} - \frac{V(\partial C)}{V(\partial z)} - \frac{C(\partial V)}{V(\partial z)}
\]

where \( C \) is gas concentration in each spatial location \( z \) along each axial pathway, \( s \) is internal lumen cross section (of the internal channel that excludes the alveoli), and \( S \) is external cross section (of the envelope cylinder including the alveoli) at each axial distance \( z \) and time \( t \), \( V \) is volume, and \( D \) and \( V \) are the binary diffusion coefficient and respiratory flow, respectively. Note that the second term, \((D/S)(\partial s/\partial z)\), has the dimensions of a velocity and results from the assumption of instantaneous radial diffusion in a geometry with increasing lumen cross section. This enables the study of diffusion in a 3D structure by means of a 1D equation. Since diffusion is studied during a breath-holding phase, the two last terms of Eq. 1 are discarded; acinar volume was scaled to a functional residual capacity of 3 litters.

For a given initial condition of a helium-3 bolus at different locations of the model (with the model entrance closed), diffusive spread was computed as proposed in our previous study (12) with a method briefly summarized here. After an initial tagging (i.e., initial helium-3 conc = 1 and 0 elsewhere), helium-3 concentration values are computed on each model node for each point in time (0–5 s). The time-dependent spread of concentration over the model is then quantified as follows. The volume corresponding to each node is used to compute a volume-weighted average and a volume-weighted standard deviation of all concentrations in the model at each time point. The ratio of this volume-weighted standard deviation and the volume-weighted average is the volume-weighted CoV, which is plotted in semilog scale as a function of time for the quantification of effective diffusion (examples can be found in Fig. 1A). The gradient of the logCoV vs. time plot obtained from a confined space may be considered directly proportional to the diffusion inside. Thus, when enhanced diffusion occurs, concentration differences equilibrate more effectively, i.e., CoV decreases more rapidly, with a doubling in the effective diffusion coefficient leading to a twofold greater gradient of the logCoV vs. time plot.

To obtain an actual value for effective diffusion coefficient from a logCoV plot obtained in a confined space with a given internal structure, this CoV curve needs to be related to free diffusion of that same gas within the same contours but without internal boundaries. For this purpose, a trumpet model is considered with one single path of a length corresponding to the average path length from beginning to end of a MBPM and a cumulative cross section, which is a summation of all airway cross sections of any given MBPM generation. Examples of the logCoV vs. time curves, representing a rapid equilibrium of concentrations for free diffusion in the trumpet model, can be appreciated from Fig. 1A (dashed lines). For any given time point, an instantaneous effective diffusion is then computed as the ratio of the logCoV gradient obtained for the model under study and that obtained in the corresponding trumpet model at the same point in time. Finally, this ratio of gradients is normalized to the free diffusion coefficient for helium-3 (0.88 cm²/s) to obtain an absolute value of effective diffusion for helium-3. Although the logCoV gradient is determined at each time point (0.2–5 s) to obtain a time-dependent plot of instantaneous effective diffusion, we also considered a time-averaged effective diffusion for comparison with experiments. To this end, the instantaneous effective diffusion was averaged over increasingly greater time intervals, leading to a single time-averaged value of effective diffusion similar to a single ADC that is being reported for a given MRI measurement interval.

The effect on effective diffusion of collateral paths in the fully alveolated airway generations of a MBPM to mimic early emphysema was investigated by imposing communications between two airways of the same airway generation (in generations 19–25) that are normally segregated and that do not necessarily share the same parent branch. A communication between any two airways of choice was
done by a merger of these airways over 50% of their average length (and with double the cross section). Two degrees of collateral pathways were considered: either two mergers of two randomly chosen airways per airway generation or four mergers of two randomly chosen airways per airway generation. Even in the latter case, the decrease in surface-to-volume ratio in the affected airway generations is roughly estimated to be only 8%. In the case of four merged airways per generation, we also considered the collateral airway to merge airways over respectively 20 or 80% of their length, which corresponded to a collateral opening of 70 and 280 μm, respectively.

We used the same acinar geometries (MBPM* and its equivalent trumpet model) to investigate the possibility of reducing an acinar branching structure to an acinar unit characterized by a single diffusive exhaust rate for incorporation into a multi-acinar model as suggested by Bartel et al. (1). Similar to what was done by Bartel et al. (1), we first computed diffusive exhaust from an acinar model (trumpet or MBPM*) by considering concentration 0 at the model exit and unity everywhere inside the acinar model. We considered the decrease of total quantity (concentration times volume computed over all acinar model nodes) at different time points in a total time interval of 50 s. This time interval was chosen as approximately double the time constant (23 s) obtained by Bartel et al. (1) for an acinar branching unit.

Finally, we also considered the effect of intra-acinar branching on the description of diffusive mixing between two acini, depending also on the spatial distribution of the initial tagging across the acini. We considered three cases schematically represented in Fig. 2. In case a, one acinar trumpet of a two-acinar trumpet system is tagged entirely. In case b, one acinar MBPM* of a two-acinar MBPM* system is tagged entirely. In case c, the tag is astride on the two MBPM* of a two-acinar MBPM* system, such that the total number of tagged airways is identical to that in case a or b, but each MBPM* has one of its two subunits tagged and the other subunit untagged (and vice versa in the second MBPM*). In all three cases, the tag signal strength at each time point is computed as the total quantity of gas (concentration times volume) summed over all tagged model nodes. The decrease of the initial tag strength is monitored as a function of time in the 50-s time interval that captures all relevant time-dependent effects for the connecting pathway lengths under study (L in Fig. 2). By assuming 0.7 cm as the characteristic acinar size and considering the terminal bronchioles of tagged and untagged acini 0.32–3.2 cm apart (corresponding to L = 0.16–1.6 cm in Fig. 2), the typical tag lengths that are being simulated here roughly correspond to 1–4 cm.

RESULTS

Figure 1A shows the volume-weighted CoV vs. time for one of the 10 MBPM structures (MBPM*), with the corresponding CoV curves for tagged nodes in subsequent generations of the

\[ L \]

\[ \lambda \]

\[ \lambda = 1.4 \text{ cm} \]

\[ \text{where } \lambda = \text{linear distance between middle of a tagged and untagged acinar trumpet or MBPM*}. \]

Fig. 2. Schematic representation of initial conditions for simulation of diffusion in two-acinar systems, where an initial concentration \( \xi_1 \) (tagging) covers one acinus entirely and not the one next to it (case a and b) or where tagging is imposed approximately on one subacinus of the MBPM* and on the complementary subacinus of the MBPM* next to it (case c). Acinar units are connected via airways of varying lengths, where \( L \) ranges from 0.16 to 1.6 cm.
trumpet model also represented (dashed lines). The logCoV vs. time plot obtained with the trumpet model shows a monotonic and much more rapid decrease than in the MBPM*. The effective diffusion curve obtained by the combination of solid and dashed lines in Fig. 1A leads to the closed circles in Fig. 1B. The same procedure was repeated for all 10 MBPM structures, leading to the other 9 ADC curves in Fig. 1B (solid lines). It was based on all 10 effective diffusion curves in Fig. 1B that one representative MBPM* was chosen for all subsequent simulations. As suggested by the gradients in the logCoV vs. time plot obtained for MBPM*, which decrease more markedly for t < 1 s than for t > 1 s (Fig. 1A), the corresponding instantaneous effective diffusion (Fig. 1B) and the effective diffusion averaged over time (Fig. 1C) show a distinct biphasic time dependence comparable to that of experimental ADC.

Figure 3 shows the influence of a merger of intra-acinar airways (over 50% of their length) that are normally segregated by forcing connections between airways of the fully alveolated airway generations 19–25 in MBPM*. When considering effective diffusion averaged over 5 s, the following increases were obtained. When two mergers of two randomly chosen airways per airway generation (in generations 19–25) were imposed, effective diffusion increased by 40%. When four mergers of two randomly chosen airways per airway generation were imposed, effective diffusion increased by 142%. In the latter case, we also tested the influence of the collateral opening size created by the merger by alternatively considering that the merged airways have a common length of 20 and 80% of the originally segregated airways rather than the reference opening of 50% in all other simulations. The 20 and 80% openings increased effective diffusion by 138 and 147%, respectively, with respect to the reference model MBPM* (compared with 142% in the case of 50% opening).

Figure 4 shows the diffusive exhaust rate obtained from a single acinar model, with mono-exponential decay time constants of 31 s (trumpet) and 40 s (MBPM*) when the sink (concentration = 0) is imposed in generation 14. When the sink is imposed in a more proximal location (generation 12), the time constant for MBPM exceeds 100 s. Figure 5 illustrates the impact of the exact location of a tagged area in a two-acinus system. When one acinus (trumpet or MBPM*) is tagged and not the one next to it, the decay rate of the original tag decreases with tag length; decay rates of a mono-exponential fit were 88, 120, 185, and 331 s for simulations with \( L = 0.16, 0.4, 0.8, \) and 1.6 cm, respectively (corresponding A estimates are 1.0, 1.5, 2.3, and 3.9 cm). When the tag is astride the two acini, this leads to a much faster decay, which is relatively independent of \( L \) for the \( L \)-range considered. (In this case, the deviation from a mono-exponential fit makes a single decay constant meaningless.)

**DISCUSSION**

This study indicates that intra-acinar structure is a crucial determinant of the effective diffusion that is being measured by the long-range ADC obtained from MRI experiments spanning several seconds. In particular, the simulated effective diffusion coefficient in a multiple branch point model of the acinus and its dependence on time (Fig. 1C) is only slightly greater than ADC values obtained experimentally for nine normal subjects over the time interval 0.2–5 s (15). Direct comparison with other experimental ADC studies are more difficult because the time over which the reported long-range ADC is being obtained varies, but in general our simulated effective diffusion coefficients averaged over 5 s (ADC values for 5 s in Fig. 1C) are compatible with the reported experimental long-range ADC value of 0.015–0.02 cm/s (9, 17). Using the same acinar models, we have also shown how lumping intra-acinar airways to single acinar units may lead to considerable error when estimating the degree of tag attenuation used in MRI experi-
ments, even when tag length exceeds acinar size (Fig. 5). This is linked to the partial acinar tagging that will most likely occur when a magnetic modulation in one linear direction is imposed on the lung periphery with all its 3D complexity. As a result, intra-acinar branching (and all the tortuous pathways this implies) necessarily comes into play and impairs diffusion such that larger length scales are hardly explored by diffusion during the MRI experiment duration. Hence, the main message from the present work is that intra-acinar branching is a geometrical feature likely playing a pivotal role in the diffusion process underlying ADC measurement.

The simulations in Fig. 5 also elicit the question of how exactly the experimental signal decay curves should be translated into one single ADC value representative of the restriction to diffusion of all the peripheral structures that will be encountered in the time span under study. Each MRI experiment has its own method of generating the diffusion sensitizing gradients and analyzing the resulting signal decay curves. It would be helpful if experimental ADC values obtained with any given combination of experimental condition and analysis method would be reported for different tag lengths and different time intervals (within each set of experimental constraints). Information about time and length scale should then enable us to tease out how exactly the different experimental long-range ADC values relate to each other and to model simulations of effective diffusion.

If intra-acinar structure is a determinant of ADC, one would also expect the simulations of effective diffusion to produce the several-fold ADC increases seen experimentally in emphysematous lungs. Obviously, emphysema as determined morphologically is difficult to translate into a model, as regards the choices of which and how many airways should be merged. Hence, the simulations in Fig. 3 should be regarded as a qualitative result in that several-fold increases in effective diffusion can indeed be generated by randomly selected mergers of normally segregated airways in the fully alveolated lung generations, reminiscent of very early emphysema with loss of surface-to-volume ratio. Although one would generally expect an increase in effective diffusion with increasing degree of emphysema, the relationship is less than straightforward, as has been pointed out by Woods et al. (18) when relating experimental ADC to a histological index of tissue destruction. Since long-range ADC is a measure of interconnectivity of airways that are normally segregated, it is likely that a similar degree of emphysema (e.g., in terms of surface-to-volume ratio) could correspond to multiple combinations of airway connectivity and possibly different long-range ADC. This contrasts with the short-range ADC measurements that can be more directly related to alveolar size or mean linear intercept (6, 19) and are also poorly time-dependent, at least in the time range 1.6–10 ms (6). Surely, the most complete information
(alveolar size and airway connectivity) can be gained from the combination of short- and long-term ADC measurements in the same patients, as was done by Wang et al. (14), showing that asthma patients had increased long-range ADC (intermediate between healthy and COPD lungs) but normal short range ADC values.

Intra-acinar airway connectivity of the healthy human lung has been documented by Haefeli-Bleuer and Weibel (7), but such information is not readily available for the diseased lung, despite being crucial for realistic simulations of effective diffusion and its sensitivity to peripheral tissue destruction. Recently reported micro-computed tomography images of explanted lung lobes from normal and diseased lungs (8) offer a unique potential for obtaining this type of information. Segmenting these images of the acinar space could reveal all disease-induced interconnected pathways, i.e., merger of airways (reminiscent of emphysema) or holes in the alveolar septa (reminiscent of enlarged alveolar pores). In addition, the electron microscopic images of alveolated spaces from normal donor lungs and diseased lungs provides information regarding the magnitude of holes connecting neighboring alveoli (2). Our simulations show that effective diffusion dictated by actual merger of intra-acinar airways over 20% of their length or more is only marginally affected by actual size of the opening between normally segregated airways (Fig. 3). Very much like overall alveolar duct diffusion is hardly hampered by alveolar mouth restrictions in communication with the alveolar duct inner channel (11), overall acinar effective diffusion is scarcely affected by the local rate of diffusion at the level of a single intra-acinar airway merger. The major impairment to effective diffusion at the time scale of long-range ADC indeed resides in the tortuosity of overall intra-acinar airway arrangement. The same reasoning may not hold when smaller connections, such as small pores (≤10 μm), are considered, but until data concerning their number and distribution are available it is almost impossible to realistically incorporate this.

It has been suggested that, in the normal human lung, long-range diffusion through collateral paths would be more important than diffusion along the airways (3) based on computations of diffusive fluxes across small holes (e.g., 5 μm) between acini depleted of internal structure (1). On the basis of the effect of intra-acinar structure shown here, it is expected that, in case of a collateral channel between any two neighboring acini, effective diffusion will again be determined by the internal acinar connectivity of, in this case, any two connected acinar structures. Purely on the basis of the contact surface between intra-acinar airways vs. that between two neighboring acini, one could argue that the probability of connections between intra-acinar alveolated ducts will exceed that of interacinar ones, at least in the case of early lung disease. However, in the absence of any morphometric data, the choice of number and distribution of interacinar connections would seem even more challenging than in the case of intra-acinar collateral channels, as was done here.

In summary, we studied the impairment to diffusion elicited by the intra-acinar airways by simulating effective diffusion as a function of time. We found a good accordance with long-range ADC values as a function of time reported for normal lungs. We also assessed the potential effect of merging intra-acinar alveolar ducts to mimic early emphysema, obtaining increases in effective diffusion that are of similar magnitude to the locally observed ADC increases in emphysematous lungs. We conclude that any future modeling should incorporate intra-acinar branching and that both experiments and simulations should consider time- and length-scale dependencies to better understand the link between long-range ADC measurement and the effective diffusion it is meant to represent.

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