Convective Dispersion during Steady Flow in the Conducting Airways of the Human Lung

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Abstract

The adverse health effects of inhaled particulate matter from the environment depend on its dispersion, transport, and deposition in the human airways. Similarly, precise targeting of deposition sites by pulmonary drug delivery systems also relies on characterizing the dispersion and transport of therapeutic aerosols in the respiratory tract. A variety of mechanisms may contribute to convective dispersion in the lung; simple axial streaming, augmented dispersion, and steady streaming are investigated in this effort. Flow visualization of a bolus during inhalation and exhalation, and dispersion measurements were conducted during steady flow in a three-generational, anatomically accurate in-vitro model of the conducting airways to support this goal. Control variables included Reynolds number, flow direction, generation, and branch. Experiments illustrate transport patterns in the lumen cross-section and map their relation to dispersion metrics. These results indicate that simple axial streaming, rather than augmented dispersion, is the dominant steady convective dispersion mechanism in symmetric Weibel generations 7-13 during normal respiration. Experimental evidence supports the branching nature of the airways as a possible contributor to steady streaming in the lung.

Keywords: respiratory airway, bifurcation, secondary flow, aerosol transport, dispersion, drug delivery
Introduction

Atmospheric pollutants are capable of causing diseases such as pneumoconiosis, lung cancer, bronchitis, emphysema, and asthma. Inhalation of ambient aerosols is also a conduit for infectious diseases (measles, influenza, anthrax, tuberculosis). Indeed, analysis of the health effects of particulate matter in the environment has estimated an approximate two-year shortening of lifespan [1]. Conversely, from a therapeutic viewpoint, both respiratory (asthma) and systemic diseases (diabetes, growth deficiency, pain) may be addressed via delivery of pharmaceutical aerosols [2]. In addition to the aerosol’s chemical or biological composition, its actual deposition site within the lung greatly influences its effect on human health. Thus, a variety of human health concerns have driven a need for understanding the dispersion, transport and eventual deposition of aerosols in the respiratory tract.

Convective mixing axially disperses passive tracer in the human respiratory tract [3]. A host of mechanisms have been offered to explain convective dispersion. The primary focus of this effort is simple axial streaming and augmented dispersion; steady streaming is also addressed to a lesser extent.

A bolus introduced at the entrance of a given passage of the lung transports downstream according to the flow field. The advection of mass in the lung by a radially and azimuthally varying axial (i.e., primary) velocity is known as simple axial streaming. As Reynolds number (Re) decreases for deeper generations of the conductive airways the flow may become more Poiseuille-like. Reynolds number is defined as $Re = \frac{ud}{\nu}$, where $u$ is the local average velocity, $d$ is the local diameter and $\nu$ is the kinematic viscosity.

Augmented dispersion arises in the respiratory system due to secondary flows. Flow in curved tubes exhibit a pair of counter-rotating vortices mirrored about the plane of symmetry
arising from centrifugal effects (Dean instability). Depending on Re and curvature in the particular airway, secondary flows due to the Dean instability may be present. Secondary currents alter transport by mixing the bolus in the cross-section. Redistribution of mass by secondary flows in the respiratory system is termed augmented dispersion.

Steady streaming is the drift in species for oscillating flows. Haselton and Scherer [4] confirmed the existence of steady streaming in the lung from dye experiments with oscillating flows in bronchial models. Differences in velocity profiles on inspiration and expiration were cited as the reason for steady streaming in bifurcations. This explanation can be further investigated, because, as previously discussed, Eulerian arguments (i.e., velocity profiles measured at specific locations) may not fully elucidate Lagrangian phenomena (i.e., steady streaming). Velocity profiles, especially at low Re, may be reversible on inspiration and expiration forcing an alternative explanation of steady streaming.

Another study concerned with steady streaming [5] simulated cyclical transport in a multi-generation model. Lee and Lee [5] found that a no-slip boundary condition develops at each bifurcation on inspiration as the bolus impacts the carina. Basically, higher velocity regions near the tube centerline advect mass ahead of lower velocity regions near the lumen. This distribution, upon arrival at the tri-section of the three tubes on inspiration, undergoes a complicated splitting. Tracer from the high velocity region of the parent tube is decelerated in the tri-section region and eventually falls to zero velocity on meeting the carinal ridge. This tracer remains behind anchored near the carina, as the two daughter streams proceed away from the tri-section, only to repeat these actions in the next generation. The degree to which this tracer delivered to the carinal regions during inspiration remains there after expiration due to the no-slip boundary condition, and the overall affect on steady streaming, is not fully understood.
Regardless of the transport mechanism, measurements in both ex-situ models and on human subjects have assessed dispersion. In general, these experiments record response curves of an injected tracer after passing through some series of idealized or real bifurcating passages. Some studies (including the present work) assume that the response curves (and therefore dispersive mechanisms) obey a one-dimensional convection-diffusion equation and use the solution to obtain an effective diffusivity [6]. Scherer et al. [7] used different velocity profiles on inspiration and expiration to explain the difference in effective diffusivity between flow directions. It is unclear from these results whether this dependence on flow direction in effective diffusivity magnitude still holds at the lower end of the Re range investigated (symmetric Weibel generation 5-13 during normal respiration).

The current effort investigates convective dispersion mechanisms (simple streaming, augmented dispersion, and steady streaming) in the conducting region of the lung. Laser-induced fluorescence (LIF) measurements provided both qualitative and quantitative information regarding the Lagrangian nature of the flow. The Eulerian flow fields have been examined in detail in a companion study [8]. In the present work, flow visualizations on inspiration and expiration elucidate passive tracer deformation patterns at various generations and branches for a range of Re. Concentration distributions from the same set of experiments allowed the determination of effective diffusivities. Combining these data permits an understanding of convective dispersion in the conducting airways.

**Experimental Model and Methods**

The geometry of the experimental model matched that for a typical symmetric bifurcation in the conducting airway given in Pedley [9]. Figure 1 presents the geometry of a single bifurcation
The diameter ratio (ratio of daughter-to-parent diameter) is 0.78, resulting in a net increase in cross-sectional area of 20% from parent tube to both daughter branches. Branch angle is $70^\circ$ and the length-to-diameter ratio is 3.5. The radius of curvature of the bifurcation is 7.5 times the parent tube radius. Finally, the airway features smooth changes everywhere, including a rounded carinal ridge. The geometry described above was rendered as a virtual solid model and written (as a negative) to a stereolithography file.

While the process to manufacture the physical model has been given elsewhere [8], a brief description is provided here. The stereolithography file was input to a rapid-prototyping machine (Z-Corp). Using a simple scale factor to create bifurcations representing the different generations, a total of seven bifurcation units representing the three generations were produced in consolidated cornstarch. These were each coated with water-soluble glue, and assembled by joining the daughter end of one generation with the parent end of the next with water-soluble tape (3M). Assembly was in-plane, meaning the plane containing the daughter tube axes of each bifurcation unit (bifurcation plane) was the same for all units. A box incorporating carefully oriented facets (in order to allow orthogonal viewing of desired cross-sections during LIF recording) was built and the three-generational bifurcation tree was suspended within it. Next, a transparent elastomer (Dow Sylgard 184) was poured into this box, which was then placed in a vacuum chamber to remove air bubbles. The box was separated after the elastomer cured, and the cornstarch pattern was removed by dissolving it in water. At this point, a transparent positive of the airway geometry was obtained.

A schematic of the three-generation model is shown in Figure 2. The nomenclature corresponds to inspiration (right half of tree) and expiration (left half of tree). Generation (G) is numbered based on the number of bifurcations the flow has traversed (i.e., numbering scheme
A comprehensive illustration of the geometry and nomenclature with respect to particular S and O cases is given in the right half of Figure 2 for inspiration. Expiration, however, necessitates the two insets shown on the left half of Figure 2 to distinguish between the S and O cases at a given generation. For example, the upper inset for two-generation experiments shows the path of branches taken by the tracer when the center of curvature remains on the same side of the bifurcation (G2-S) and when center of curvature flips to the other side (G2-O). The lower inset for three generations follows the same logic.
Refractive index of the working fluid must be matched to the elastomer model for accurate measurements. This procedure has been explained elsewhere [8]. In short, mixtures of glycerol and water were varied until optical distortion of a grid was removed.

Flexible tubing connected the model to a reservoir on one end and to a set of syringe pumps (one for each terminal daughter tube) on the other. The syringes were mounted to a translation stage, coupled with a programmable stepper motor to drive the flow. This arrangement is shown in Figure 3.

LIF experiments were conducted in cross-sections of the model at locations given in Figure 2. Illumination was provided by Continuum Surelite II Nd:YAG pulsed lasers (120 mJ/pulse at 532 nm). Sheet-forming optics were used to deliver a plane of laser illumination to the desired measurement planes. Images were recorded on a LaVision Imager Intense (10 bit, 1376 x 1040 pixels) camera oriented perpendicular to the light sheet. Rhodamine 6G was used to dye the working fluid; a long-wave pass filter was placed in front of the camera lens to block elastic scattering of the incident laser light by the apparatus. The Peclet number \( \text{Pe} = \frac{ud}{D_{\text{mol}}} \), where \( D_{\text{mol}} \) is the species molecular diffusivity, is a measure of the relative importance of convection to molecular diffusion. A high Peclet number (~1000) for this dye molecule, along with careful selection of the time-scale for experiments, ensured that the tracer faithfully followed the flow streamlines. A few different methods of injecting dye were investigated. The highest degree of control was obtained by introducing a slug of dye directly into the tube via a single, small-bore hole in the sidewall. Experiments were conducted with two bolus sizes, small and large. The volume of the smaller bolus was equal to a two-diameter long cylinder. The larger bolus corresponded to six diameters in axial length.
For all experiments, a bolus was injected into the desired tube, the flow was turned on, and LIF measurements were obtained at a particular downstream cross-section as a function of time. In this manner, the temporal evolution of the bolus is captured. Multiple realizations, with a common set of experimental variables, were performed to build ensemble statistics. Flow visualizations, presented later, yield representative tracer deformation patterns. Quantitative information is also possible from the same set of experiments since for sufficiently small dye concentration the intensity of dye fluorescence is varies linearly with concentration. Preliminary testing of the intensity of various concentrations of dye in the working fluid ensured that Rhodamine 6G concentrations employed here met the condition for linearity. Thus, averaging the magnitude of dye intensity over the cross-section for each image represents the cross-sectionally-averaged concentration at that instant. The average concentration as a function of time can be used to assess the effective diffusion of the bolus due to steady convective mixing (i.e., interaction between primary and secondary flows).

The metric of interest in calculating effective diffusivity is the axial stretching of the bolus, which can be represented by the standard deviation of the concentration vs. time response curve. Response curves were first normalized by the peak value and analysis was performed only on data with magnitude greater than 15% of the maximum value [10]. Next, the standard deviation of the response curve was computed over multiple runs for a given set of experimental parameters. The average standard deviation ($\sigma$) is then entered into the following form of the equation given in [6] to obtain the effective diffusivity.

$$D = \frac{1}{8} u \frac{V}{A} \left[ \sqrt{8 \left( \frac{\sigma}{Q/V} \right)^2 + 1} - 1 \right]$$  \hspace{1cm} (1)
Here, $V$ is the volume between the injection location and interrogation station, $A$ is the summed cross-sectional area at that generation of the model, and $Q$ is the volume flow rate. Quantifying effective diffusivity via Equation 1 assumes that convection disperses solute in accordance with a one-dimensional convection-diffusion process. The number of realizations for a given set of experimental parameters (up to 14 total) was selected by limiting the uncertainty in the mean of the standard deviation of the response curve, estimated using standard statistical methods. More specifically, the theory of confidence intervals at a 95% level was applied to determine the relative uncertainty ($\varepsilon$) in the experiments via the following formula: $\varepsilon = \left( \frac{1.96\sigma}{\mu N} \right)^2$. Here, $\sigma$ is the standard deviation of the dispersion metric, $\mu$ is the average of the dispersion metric and $N$ is the number of samples. This procedure was also used to determine error bars for results. A sample response curve is shown in Figure 4. The line denotes the average curve of the associated data points from multiple trials of one experimental case; 95% confidence intervals are also included.

We describe results from a Poiseuille flow experiment conducted for calibration purposes using an identical setup (Rhodamine dye bolus injection and laser/camera interrogation) in a separate paper [11]. This exercise also serves as a validation of the experimental methods. LIF results from this calibration study demonstrate that our experimental setup is able to consistently measure the expected response curve for Poiseuille flow.

The set of independent experimental variables included: $Re$, flow direction, generation, and branch. Measurements were taken for $Re = 10$ and 100. These $Re$ represent a wide range of physiological interest, approximately generations 7-13 of the symmetric Weibel model for normal respiration. In contrast, a majority of past research has focused on higher $Re$. Flow direction, as discussed, comprises inspiration and expiration. Experiments have been performed
for the flow through one, two, and three generations, respectively. Finally, measurements at selected branches or with different branch histories at a common generation allow investigation of the effect of secondary flows on mixing.

Results and Discussion

Flow Visualization - Introduction. Poiseuille flow can be employed to introduce the flow visualization results. The deformation of a thin disc of dye is dictated by the parabolic velocity profile. Viewed side-on, the disc of dye would stretch axially by an amount proportional to the flow duration and assume a paraboloid shape. Now consider the head-on view at a prescribed downstream cross-section. As the tip of the paraboloid surface reaches the cross-section, a circular region of dye centered on the tube centerline first appears. The circular region grows radially by an amount decided by the thickness of the original disc, followed by a change into an annulus. Over time, the annulus increases in radius and decreases in thickness due to the development of the parabolic transport profile.

Similar to this Poiseuille flow example, flow visualizations in Figures 5-8 capture the cross-sectional deformation pattern of an initial bolus at a prescribed axial distance from injection. Instead of circles and rings of dye seen for Poiseuille flow, however, these experiments reveal more complex structures associated with flow through bifurcations. Rather than displaying the entire time history of the bolus, Figures 5-8 provide representative frames. In these figures, the dark is the undyed fluid or background and the light represents the dyed fluid. A dotted circle is included to show the location of the lumen. Images are displayed on the bifurcation tree at the corresponding interrogation location (i.e., generation, branch). This allows a concise presentation of the convection through the tree on inspiration or expiration for varying
Re. Figure 2 may be consulted for the orientation and nomenclature of measurement locations within the bifurcation tree. Images were recorded at the mid-point between bifurcations and the camera was always oriented to look upstream (flow is always directed out-of-the-page).

Flow Visualization - Inspiration. Figure 5 depicts flow visualizations at Re=10 during inspiration. The six images within this figure are discussed in order from bottom (G0) to top (G3). This order of discussion (G0-G3) is maintained throughout. After injection, the bolus streams through a straight tube according to Poiseuille flow before encountering the first bifurcation; Poiseuille flow is confirmed by the annulus of dye in image G0 in Figure 5. Proceeding now to the G1 frame located slightly above and to the right of the G0 frame, a slight skewing of the annulus away from the center of curvature, is apparent. Evidence of secondary currents is absent. The effect of a single bifurcation on inspiration at Re=10 is to split the stream from G0 and create a Poiseuille-like structure of tracer which features a peak skewed due to the peak from G0 being intercepted by the carina. Contrasting G2 results (S and O) in this figure reveals the consequence of this skewed volume of revolution in G1. G2-S indicates that the skewed structure from G1 remains skewed, again, because of impaction of the upstream formation on the carina. A more central placement of the tracer pattern is shown at G2-O. Biasing due to anchoring of fluid near the carina region is somewhat alleviated due to a peak from G1 that is predisposed toward the daughter branch corresponding to G2-O. Flow visualization at G3-S-O and G3-O-O support this finding; both images show relatively central dye patterns due to the manner in which the upstream structure has been intercepted by the carina. Secondary currents were not detected for all measurement locations on inspiration at
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Re=10. In summary, low Re inspiratory flow visualizations suggest transport patterns follow those for a Poiseuille flow with some differences due to history effects.

Inspiratory flow visualizations at Re=100 (Figure 6) exhibit one main difference from the low Re case; the presence of secondary velocities. Since the kinematics of Poiseuille flow do not vary with Re, the same result from Re=10 (centered annulus) is presented in Figure 6 for G0 at higher Re. After traversing the first bifurcation, the kidney bean shape at G1 indicates Re is high enough in this geometry to trigger the Dean instability and create secondary currents. Fluid is displaced away from the center of curvature by centrifugal forces producing the kidney bean at G1. Because the sense of curvature is maintained at G2-S, so is the sense of secondary flow, leading to an expectation of amplified cross-sectional mixing. Indeed, this is the case as evidenced in the image for G2-S. Tracer elements undergoing distortion and mixing in G1 are further displaced and wrapped by centrifugal forces in the same direction. The opposite effect is seen in G2-O where local centrifugal effects in G2-O are opposite of G1. As a result the kink in the G1 profile is removed and the overall distribution resembles G0. A minor compression of the annulus in the bifurcation plane, possibly owing to the splitting of the G1 structure at the bifurcation, is noticed for G2-O.

Proceeding now from G2-O to G3-O-O, the similarity in dye pattern with the G0-G1 sequence is unmistakable. Again, a relatively centered volume of revolution in G2-O is acted on by centrifugal forces upon arrival in G3-O-O to generate the kidney bean shape. The explanation for the image in G3-S-O is less straightforward. Despite the presence of “restoring” secondary currents, once the dye is well-mixed as in G2-S, it cannot be unraveled as seen in G3-S-O. This result highlights the difficulty in coherently describing transport for a more complex model (e.g.,
one with greater generations). Thus, inspiratory flow visualizations at higher Re reveal the role of secondary currents and history on the deformation of passive tracer.

Common to both low and high Re inspiratory flow visualizations is evidence of the no-slip boundary condition near the carina region. While Lee and Lee [5] noted this effect in the course of simulations, the present effort lends some experimental confirmation. The images for inspiration show that as solute from the previous generation splits at the junction, some mass remains at the carina. This is evident in the presence of dye at an azimuth of the cross-section which is related to the carina. For example, take the G1 result for Re=10 in Figure 5. Tracer at the left-most portion of the circular pattern emanates from solute that was intercepted at the previous carina. This solute originally belonged to the centerline in G0; as the flow penetrates deeper into the model the centerline concentration diminishes, but the dye intercepted by the carina becomes a source of dye for the next generation. A similar event occurs at each bifurcation. On flow reversal, even if Poiseuille flow theoretically existed in each airway, some amount of solute remains anchored at every bifurcation encountered such that the original bolus cannot exactly recombine. Some axial stretching of the initial distribution of mass after an integer number of cycles is inevitable. Steady streaming, therefore, is impacted by this mechanism. While different velocity profiles on inspiration and expiration (especially at high Re) may influence the summary transport profile of passive tracer to produce steady streaming, another contributing cause may be the retention of mass near each carina due to the no-slip boundary condition as described above.

**Flow Visualization - Expiration.** Figures 7 and 8 show expiratory flow visualizations at Re=10 and 100, respectively. Again, results are discussed from G0-G3; for expiration the order
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progresses from top (G0) to bottom (G3) in the figures. Due to symmetry it is sufficient to examine only four of the eight G0 branches. Of these four, we track the two extreme cases corresponding to the O family (G2-O, G3-O-O) and the S family (G2-S, G3-S-S). Accordingly, the two stations are tracked at G0 by placing annuli of dye corresponding to Poiseuille flow. The merging nature of flow on expiration makes it redundant to probe both branches at a particular generation. Thus, it is appropriate to insert identical images for the two stations at G1. At G2, separate images for G2-S and G2-O have been superposed during post-processing to simulate the effect of simultaneous injection. The image given for G3 also represents a superposition of separate G3-S-S and G3-O-O measurements created for the same reason. The overall pattern allows a more succinct depiction of expiratory flow visualization.

Figure 7 depicts flow visualizations for expiration at Re=10. The Poiseuille flow result was placed in the figure for the S (right-most image in Figure 7) and O (top-most image in Figure 7) injection case in G0. The G1 image is also repeated for the S and O case as previously discussed. In G1, a semi-circular shape is apparent due to the tagging of only one stream during the merging of two daughter flows from G0. Such a well-defined semi-circle in G1 reveals that secondary motion is absent.

After traversing two generations on expiration, a total of four streams have merged in the cross-section at G2 (two streams from G1 each with two streams from G0). The image shown for G2 in Figure 7 represents the first instance of superposing (via post-processing) separate measurements for S and O in a single frame. The result illustrates tracer patterns at G2 given simultaneous injections with S and O histories. Thus, two separate regions of dye are obvious in the G2 frame. To the right, characterized by an elliptical shape, lies the tracer pattern which has traversed the bifurcations with the S branch history (G2-S). The more vertically elongated
structure on the left has passed through two bifurcations with the O branch history (G2-O). Note that the plane of symmetry separating daughter streams from G1 is exactly on the right side of the G2-O dye pattern. Thus, if dye were simultaneously injected into all G0 tubes at the start of the experiment then a structure identical to that shown for G2-O would be positioned between it and the G2-S tracer pattern. Similarly, the G2-S pattern would also appear on the left of the G2-O structure. The net result would be four individual structures in the following order from left to right: G2-S, G2-O, G2-O, G2-S.

The location of both G2-S and G2-O patterns in the cross-section is indicative of the point of origin. At G2 for low Re, an S branch history keeps tracer further away from the symmetry plane and an O branch history keeps tracer closer to the symmetry plane. G2-S and G2-O interact in such a manner as to smoothly fill the cross-section. This produces the rounded shape for G2-S and the elongated structure for G2-O. As for G1 expiration at low Re, secondary currents also do not occur at G2.

Eight streams have merged for expiration at G3. Due to symmetry we focus on a half cross-section. Four unique structures appear in this domain. Of these four structures (G3-S-O, G3-O-O, G3-O-S, G3-S-S), two have been measured: G3-S-S and G3-O-O. Again, these have been superposed in the G3 image given in the figure. For orientation within this frame, the order of structures within the half cross-section, from symmetry plane to the right is: G3-S-O (undyed), G3-O-O (dyed), G3-O-S (undyed), G3-S-S (dyed). Findings at G3 match those observed for G2. Placement of dyed regions for G3-S-S and G3-O-O within the cross-section is representative of their point of origin. Patterns suggest a smooth fill of the cross-section upon entering G3 and secondary motions are absent.
Flow visualizations for expiration at Re=100 presented in Figure 8 are marked by more complex features due to the action of centrifugal forces. Again, the bifurcation tree has both G0 (Poiseuille flow) and G1 images repeated at appropriate locations to adhere to the S and O format of the study. Recall the half-circular shape taken by the dye for G1 at low Re. At high Re, a noticeable bow has developed in the pattern along the bifurcation plane. As explained for the high Re measurements for inspiration, centrifugal forces displace fluid away from the center of curvature in the bifurcation plane.

G2-S and G2-O expiration measurements, as before, are combined in a single image for high Re. Four streams have merged at G2, however, by symmetry, only two of the four dye patterns are unique. The G2 frame at high Re illustrates a striking difference from the G2 results at low Re. Secondary motions have deformed the bolus into C-shaped regions in the cross-section. These C-shaped transport patterns for G2-S are open to the right and those for G2-O are open to the left. The open end of the “C” depends on the local curvature in each half of the cross-section. The plane of symmetry lies to the right of the G2-O structure. If the G2-O pattern were flipped about this plane of symmetry so that all information were given in the same half cross-section then the larger G2-O “C” would be found to hug the smaller G2-S “C”. Inertial effects have become so pronounced that the tip of the bolus cannot instantly turn upon entering the tube. Rather, the bolus from G2-S impacts the plane of symmetry in the cross-section, pushing the bolus from G2-O ahead of it, and both boluses grow the arms of the C-shape as the walls of the tube are encountered. As a result, mixing by secondary currents takes place over a majority of the cross-section. This is contrary to the result at low Re where cross-sectional mixing by secondary vortices was absent.
G3 results for high Re expiration also contain two superposed measurements. Here again, of the four streams merging in a half cross-section (G3-S-O, G3-O-O, G3-O-S, G3-S-S) two (G3-S-S, G3-O-O) have been measured. It becomes relatively difficult to distinguish between G3-S-S and G3-O-O dye patterns in the frame due to the amount of mixing by secondary currents. For G3-S-S, a smaller, well-defined C-shape, similar to that realized for G2, is produced. G3-O-O features more complexity. In fact, the open end of the “C” from G2-S has been flipped in G3-O-O due to a reversal of the direction of local secondary currents. This effect creates more interface (evident in complicated pattern of G3) as tracer is repeatedly folded on transiting generations on expiration with different secondary current directions.

Flow Visualization - Summary. Contrasting the low and high Re flow visualizations for both inspiration and expiration establishes some guidelines on the extent of simple streaming and augmented dispersion. Evidently, simple streaming dominates augmented dispersion at Re=10 (approximately symmetric Weibel generation 13 during normal respiration). The lack of secondary mixing indicates streamlines are mainly parallel to the local tube axis. At Re=100 (approximately symmetric Weibel generation 7 during normal respiration), flow visualizations suggest augmented dispersion may act along with simple streaming to disperse mass in the respiratory tract. Mixing in the cross-section for high Re illustrates an interaction between primary and secondary velocity components. Discussion of effective diffusivity measurements further addresses these findings.

Effective Diffusivity. As discussed earlier, dye intensity data from flow visualizations were also used to determine effective diffusivity. Statistics on the standard deviation from multiple
concentration vs. time response curves for a given experimental condition were used in tabulating the ensemble-averaged data and associated experimental uncertainty (error bars at 95% confidence level). Effective diffusivities have been nondimensionalized \( (D^*) \) by the product of average bulk flow velocity and tube diameter. Results for all twenty experiments are shown in Figure 9. The plot is separated into inspiratory (to the left) and expiratory (to the right) results. Each experimental condition is given along the \( x \)-axis; nomenclature adheres to the format followed in this effort. For example, “L3SO” corresponds to inspiration with low Re (L) at G3-S-O.

Averaging small and large bolus tests yields the results given in the figure. Most data are in the range of 0.3-0.7. Only one case, H1 for expiration, is above 1.0. This is likely due to an outlier for the small bolus set of experiments at this condition. The small bolus featured larger uncertainty (28%) and an average value almost three times higher than that for the large bolus. For this reason, results for the small bolus on expiration at high Re are excluded from the subsequent discussion. The amount of information provided in the figure prohibits analysis; results can be re-expressed in terms of the independent experimental variables. To this end, results were grouped in the following three categories: generation (one, two, and three), flow direction (inspiration and expiration), and Re (low and high). This facilitates characterizing the behavior of convective dispersion for the parameter space examined in this effort.

Figure 10 presents the effective diffusivity and corresponding uncertainty as a function of generation. Results given in the figure at a particular generation were obtained by averaging across all experiments (different branch histories, inspiration and expiration, low and high Re) at that generation. To within experimental uncertainty, the dispersion does not appear to vary with generation. This suggests that, for the geometry of this model and parameter space investigated,
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dispersion measurements for one generation may contain all the essential features of multiple
generations. Local steady flow dispersion may not depend on the history of the tracer. This
finding is slightly unexpected given different flow visualization observations for varying
generations, especially at high Re. Results are not shown as a function of branch at a particular
generation because effective diffusivity was also insensitive to this independent variable.
Scherer et al. [7] also probed various tubes in a generation at higher Re and found no differences
in effective diffusivity.

Effective diffusivity measurements are recast in terms of flow direction in Figure 11.
Results indicate that convective dispersion is independent of inspiration and expiration. This can
also be compared with the flow visualizations. At low Re, both inspiration and expiration
structures illustrated a more simple streaming type mechanism. Secondary activity, however,
was encountered for high Re on inspiration and expiration. Furthermore, the particular patterns
were influenced by the number of secondary vortices (two for inspiration and four for
expiration). Mixing of passive tracer due to the presence of none, two, or four secondary
vortices, however, does not significantly impact the bulk dispersion measurements.

Figure 12 gives effective diffusivity for the low and high Re. Dispersion measurements
also do not appear to depend on the magnitude of Re for the range inspected in this model.
Again, while flow visualizations indicate mixing by secondary currents at high Re, overall
dispersion measurements remain mostly unaffected. The interaction between primary and
secondary momentum must not be vigorous enough to significantly alter the distribution of
passive tracer from that for the simple streaming mechanism.

Conclusions and Implications
Simple Streaming and Augmented Dispersion. While measurements quantifying mixing suggest bulk dispersion is unaffected by history, flow visualizations support unique trajectories for individual parcels of passive tracer sampling different branches, generations, flow directions, and Re. Transport was found to be mainly parallel to the tube axis at low Re. Some degree of cross-sectional mixing by secondary currents was observed at high Re. Thus, flow visualizations suggest simple streaming dominates steady convective dispersion through a typical conducting airway at Re=10 (approximately symmetric Weibel generation 13 during normal respiration) and augmented dispersion may also begin to play a role at Re=100 (approximately symmetric Weibel generation 7 during normal respiration).

Evaluating the dispersion through the usage of an effective axial diffusivity, however, further elucidates the roles of simple streaming and augmented dispersion in the conducting airways. When interested in the overall assessment of mixing, comparison of effective diffusivity at various generations indicates local conditions dominate any history effects. Dispersion results also expound on flow visualizations by suggesting simple streaming dominates augmented dispersion in this model for both inspiration and expiration at $10 \leq Re \leq 100$ since effective diffusivity lacks dependence on flow direction and Re (i.e., none, two, or four secondary vortices).

The independence of effective diffusivity with branch and generation also supports simple streaming as the dominant mechanism since, regardless of location in the bronchial tree, the same phenomenon produces dispersion. Asymmetries associated with sufficient secondary flows during augmented dispersion may be expected to result in different effective diffusivities at different locations in the bronchial tree.
These results may be interpreted with respect to Scherer et al. [7]. In terms of the nondimensional effective diffusivity implemented in the present work, Scherer et al. advocate a value of 1.08 for inspiration and 0.37 for expiration. These results of Scherer et al. primarily derive from measurements at Re~1000 (corresponding to symmetric Weibel generations 0-5 during normal respiration). Inertial effects at Re~1000 increase centrifugal forces in the bifurcation to produce more vigorous secondary currents; this supports the argument given by Scherer et al. to explain a higher effective axial diffusivity for inspiration than expiration. Greater cross-section mixing due to four secondary vortices on expiration inhibits axial dispersion with respect to that for inspiration. Dispersion in a bifurcation may be expected to feature less dependence on secondary currents for Re orders of magnitude less than Re~1000. Indeed, measurements in the present work at various generations and branches for Re=10 and Re=100 yield $D^* = 0.50$ for inspiration and $D^* = 0.55$ for expiration. Effective diffusivity values derived herein for lower Re (10-100) lie between those given for inspiration and expiration at higher Re (~1000) based on the influence of secondary action. At higher Re, pointed axial velocity profiles on inspiration, produced by the presence of two secondary vortices in a bifurcation, advect mass with a similarly pointed transport profile (relatively greater effective axial diffusivity). More blunted axial velocity profiles due to a quadruple vortex on expiration at high Re, alternatively, result in more blunted transport profiles (relatively lesser effective axial diffusivity). When Re decreases, secondary activity becomes minimal enough to ensure similar axial velocity profiles on inspiration and expiration generate likewise similar transport profiles (relatively similar effective axial diffusivity). This regime, captured in the experiments of this effort, can be expected to yield effective diffusivity values between those given by Scherer et al. for higher Re.
Thus, simple streaming appears to be a dominant steady convective dispersive mechanism for the conducting airways at $10 \leq \text{Re} \leq 100$, corresponding to normal respiration in symmetric Weibel generations 7-13. It is interesting to note that this finding exists despite the observation of some secondary activity in flow visualizations at Re=100. Evidently, a threshold lies somewhere in the range $100 < \text{Re} < 1000$ that dictates the manner in which the strength of interaction between primary and secondary momentum influences convective dispersion in the conducting airways.

Effective diffusivity has been applied to help analyze the dose-response relationship of inhaled particulates. Specifically, models of aerosol transport and deposition employ effective diffusivity to account for axial convective dispersion. The most frequently used forms of effective diffusivity in these models is either that derived for Poiseuille flow [10] or found from the bifurcation network experiments of Scherer et al. [7] for inspiration and expiration [12, 13]. Results of the present work suggest that $D^* \approx 0.50$ for both inspiration and expiration in symmetric Weibel generations 7-13 during normal respiration. Since this value of $D^*$ is comparable to that for Poiseuille flow in a bifurcation with length-to-diameter ratio of 3.5 ($D^* \approx 0.54$) applying the formulae derived mainly at higher Re in [7] throughout the respiratory tract may not be warranted. Rather, it may be more appropriate to use a Poiseuille-type effective diffusivity as found in this study for generations corresponding to Re<100 and that derived in [7] for Re>1000 in models of aerosol transport. Note that implementing a steady convective diffusivity in these models assumes independent dispersion on inspiration and expiration whereas in reality some amount of the original bolus may reassemble after a breath.
Steady Streaming. Flow visualizations help reveal the efficacy of steady streaming in dispersing mass within the respiratory tract. Different tracer patterns at a particular Re and generation/branch combination on inspiration and expiration illustrate that the initial bolus cannot reassemble after an integer number of breathing cycles. This has also been experimentally confirmed by Haselton and Scherer [14] for approximately $1 < \text{Re} < 1000$. Different velocity profiles, owing to secondary vortices, on inspiration and expiration were posited to explain steady streaming in the bifurcation model.

Indeed, flow visualizations at high Re support different transport structures on inspiration and expiration due to secondary currents. Low Re flow visualizations, however, did not detect mixing by secondary vortices. Steady streaming in the respiratory tract, therefore, may be driven purely by the branching nature of the airways at low Re. Oscillating flow in a network of branching tubes possesses two features which may contribute to steady streaming: taper and the action of a bolus impacting the carina on inspiration and anchoring in this region for subsequent cycles by the no-slip boundary condition. Tapering systems produce dissimilar transport profiles depending on flow direction. Gaver and Grotberg [15] measured the steady streaming for oscillatory flow in tapered channels. Previous discussion of flow visualizations indicated the manner in which the no-slip boundary condition at carinal ridges traps portions of a bolus over multiple cycles. Both of these phenomena, under certain conditions, advects solute in regions of the cross-section closer to the tube centerline more distally and that nearer the peripheral walls more proximally. This agrees with observations in [14]. Thus, at low Re, steady streaming may be driven by these mechanisms associated with branching. Further study must be undertaken to verify that branching contributes to steady streaming.
At high Re, flow visualizations indicate steady streaming takes place by branching (i.e., taper and no-slip boundary condition) and possibly secondary activity. Transport patterns containing features related to secondary currents ensure that parcels of passive tracer sample different radial positions while traversing multiple generations of an inspiration-expiration cycle. As a result, the original bolus cannot exactly reassemble.

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Nomenclature

\( A \) = summed cross-sectional area at that generation of the model

\( D \) = effective diffusivity (m\(^2\)/s)

\( D_{mol} \) = species molecular diffusivity (m\(^2\)/s)

\( G \) = generation

\( H \) = high Re

\( L \) = low Re

\( O \) = opposite secondary velocity direction

\( Pe \) = Peclet number

\( \mathcal{R} \) = radius of curvature

\( Re \) = Reynolds number

\( S \) = same secondary velocity direction

\( Q \) = volume flow rate

\( V \) = volume between the injection location and interrogation station

\( d \) = tube diameter (m)

\( u \) = flow velocity (m/s)

Greek symbols

\( \nu \) = kinematic viscosity (m\(^2\)/s)

\( \sigma \) = average standard deviation of bolus response curve (s)

Superscripts

\(*\) = nondimensionalized
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- $d_1 = 1.28$ cm
- $d_2 = 1.0$ cm
- $\mathcal{R} = 4.76$ cm
- $35^\circ$
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