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Project FM203

BIOFLUID MECHANICS

Respiratory Biofluid Mechanics

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Problems

→ Problem 1: Dimensionless Numbers in Respiration

The following table refers to convective and diffusive gas transport and mixing in the airways. Under which circumstances does turbulence occur in the pulmonary system? Also, recalling that the Peclet number is a ratio of the intensity of mass transport by convection to transport by diffusion, discuss which type of transport predominates across the tracheobronchial tree.

Table 3: Convective and diffusive gas transport and mixing in the airways between trachea and alveoli.

		Resting ventilation = 6 l/min			Exercise ventilation = 100 l/min		
Generation	Airway*	Peak flow‡ cm/s	Peclet number	Reynolds number	Peak flow‡ cm/s	Peclet number	Reynolds number
0	Trachea	131.23	6151.5	1408.5	1968.5	92273.6	21128.8
6	Bronchus	84.17	295.9	140.5	1262.6	4438.92	2108.1
16	TB	1.852	1.194	0.663	27.778	17.904	9.938
17	RB1	0.967	0.533	0.311	14.509	7.991	4.672
18	RB2	0.467	0.214	0.139	7.011	3.204	2.090
19	RB3	0.211	0.082	0.059	3.166	1.224	0.887
20	AD1	0.078	0.025	0.021	1.176	0.381	0.316
21	AD2	0.035	0.010	0.009	0.530	0.145	0.136
22	AD3	0.016	0.004	0.004	0.240	0.055	0.059
23	AS	0.008	0.002	0.002	0.120	0.023	0.029

→ Problem 2: The Diffusing Capacity of the Lung

Problem 2A

The idea of measuring the specific diffusing capacity of the lungs for carbon monoxide, $D_{L_{CO}}$, as an index of the condition of the "alveolar-capillary membrane" was introduced in 1915 by M. Krogh. She showed that during short periods of breath-holding with the glottis open the removal of carbon monoxide, CO, from alveolar gas by the hemoglobin was a first order reaction, and proposed that the time constant of the exponential decay of alveolar CO during breath-holding be used as a measure of the size of the "alveolar capillary membrane."

The single-breath diffusing capacity test is the most common way to determine the CO diffusing capacity, $D_{L_{CO}}$. The test is performed by having the subject blow out all the air that they can, leaving only the residual lung volume of gas. The person then inhales a test gas mixture rapidly and completely, reaching the total lung capacity as nearly as possible. This test gas mixture contains a small amount of carbon monoxide and a tracer gas that is freely distributed through the alveolar space but which doesn't cross the alveolar-capillary membrane. Helium and methane are two such gases. The test gas is held in the lung for about 10 seconds during which time the CO (but not the tracer gas) continuously moves from the alveoli into the blood. Then the subject exhales.

The anatomy of the airways means inspired air must pass through the trachea, bronchi, and bronchioles before it gets to the alveoli where gas exchange will occur; on exhalation, alveolar gas must return along the same path, and so the exhaled sample will be purely alveolar only after a 500 to 1,000 mL of gas has been breathed out. Thus, the first 500 to 1,000 mL of the expired gas is disregarded and the next portion, which contains gas that has been in the alveoli, is analyzed. By analyzing the concentrations of carbon monoxide and inert gas in the inspired gas and in the exhaled gas, it is possible to calculate $D_{L_{CO}}$.

The diffusing capacity of the lung for carbon monoxide is commonly recognized as an indicator of the gas exchange function of the lungs. The $D_{L_{CO}}$ is useful in a variety of clinical settings, including distinguishing emphysema from chronic bronchitis and asthma; evaluating diseases of the pulmonary vasculature and interstitium; screening for tolerability of lung resection surgery; and establishing criteria for disability benefits. The $D_{L_{CO}}$ has also been used to predict exercise desaturation in patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease, and in unselected patients.

The process of CO uptake can be simplified into two transfer or conductance properties: membrane conductivity (D_M), which reflects the diffusion properties of the alveolar capillary membrane; and the binding of CO and Hb. The latter can be represented as the product of the CO-Hb chemical reaction rate (θ) and the volume of Hb in alveolar capillary blood (V_c). Since these are conductances in series, these properties are related by

$$\frac{1}{D_{L_{CO}}} = \frac{1}{D_M} + \frac{1}{\theta V_c}$$

This equation has had a significant impact on pulmonary research since it was published in the paper by Roughton & Foster in 1957. Provide two aspects that illustrate the impact of this equation in physiological investigations.

Problem 2B

A number of pathological states can affect D_M, θV_c, or both, and thereby affect $D_{L_{CO}}$. Measurement of $D_{L_{CO}}$ is indicated when such abnormal processes are suspected or need to be ruled out. Moreover, measuring changes in $D_{L_{CO}}$ over time in some of these processes is a useful way of following the course of disease. Name two physiological conditions that increase $D_{L_{CO}}$ and two conditions that decrease $D_{L_{CO}}$.

Problem 2C

Let us consider some technicalities of the single-breath CO diffusion capacity test. In 1949, Ward Fowler suggested an important modification to the original single-breathing Krogh technique: the addition of helium as an inert reference gas to the inspired mixture so that sample A (the first round of expiration) could be omitted, and calculated instead by gas dilution from the inspired CO concentration and the dilution ratio of helium (expired/inspired) sampled *after* the breath-holding period. This became known as the *modified Krogh single-breath* $D_{L_{CO}}$. It is remarkable that this was one of only a few modifications of substance required to Krogh's 1915 description of the single-breath technique. Comment on the need for an inert reference gas in the $D_{L_{CO}}$ measuring procedure.

Furthermore, experience has shown that there is a requirement for specific provisions when performing the test in individuals with higher-than-normal concentrations of blood carbon monoxide, CO. Who are these individuals? What are the adjustments in the normal test protocol for these individuals?

Problem 2D

Although some have proposed that the $D_{L_{CO}}$ be normalized with respect to alveolar volume V_A, thus producing the so-called transfer coefficient $K_{CO} = D_{L_{CO}} / V_A$, experience has shown that the relation between these two quantities is far from ideal. Discuss.

Problem 2E

In the 1980s, a new technique for evaluation of lung diffusing capacity was devised, in which nitrogen oxide (NO) is employed instead of CO in the single-breath test. In this new procedure, the diffusing capacity of the lung for nitric oxide, $D_{L_{NO}}$, is obtained instead of the $D_{L_{CO}}$. The corresponding transfer factor $T_{L_{NO}}$ is often obtained as well. This test variation is being widely studied and has now become a viable alternative or complement to its CO-based counterpart. Hughes et al. state that "*physiologically, $T_{L_{NO}}$ acts as a surrogate for the membrane diffusing capacity (D_M)*" in the Roughton-Forster equation. Explain why this is so. Also, explain what are the settings for the gas mixture and the equipment required for the single-breath $D_{L_{NO}}$ test. Finally, noting that the $D_{L_{NO}}/D_{L_{CO}}$ has been increasingly used as a diagnostic tool in pulmonary research, elaborate on the variation of this parameter with exercise and certain diseased states.

→ Problem 3: Respiratory CFD

Problem 3A

Computational and mathematical models solve equations to predict or study function of the lungs. Certain classes of model may consist of a few relatively simple equations that can be solved analytically. Simulating fluid flow necessitates solving the Navier-Stokes and mass continuity equations. These are nonlinear partial and differential equations, which cannot be solved analytically in their generalized form. Solving these intricate equations requires approximations to cope with flow in complex geometries and potentially turbulent conditions. The use of numerical methods and parallel computing to obtain simulation results within a reasonable timeframe, and methods for defining the shape and discretization of the domain in which the equations are solved, all become essential. The field of research that handles these tasks is termed computational fluid dynamics, or CFD. CFD analysis is well established in many areas of engineering and design, but its use in physiology is considerably more difficult because biological structures are typically deformable and complex in shape. Nevertheless, CFD is now becoming a viable tool for simulation of airflow and particle deposition in the human respiratory tract, and has been pursued by a number of research groups for a while.

The interest of scholars has been devoted to questions such as the study of flow physics and airways resistance, improving drug delivery, or investigating which populations are more susceptible to inhaled pollutants. CFD allows bioengineers to predict a number of flow characteristics at the local level, including pressure, velocity profiles, and wall shear stresses. In the field of particle transport, for instance, this enables prediction of agent transport in an airway (lung structure) model that is specific to the geometry of an individual, and to understand how inter-subject variation in airway geometry, normal or pathological, influences the conveyance and deposition of particles. In a systems biology approach, these local flow characteristics can be further integrated with epithelial cell models for the study of mechanotransduction. At the global (organ) level, in turn, one would like to match regional ventilation (lung function) that is specific to the individual, thus ensuring that the flow that transports inhaled particles is appropriately distributed throughout the lung model.

One important aspect of CFD studies is the imposition of representative boundary conditions, which are essential to match regional ventilation phenomena. In particulate flow studies, exemplary BCs are critical in studying preferential deposition of inhaled aerosols in subpopulations, e.g., normal versus asthmatics, which exhibit different ventilation patterns. Regional ventilation computations define flow distributions and characteristics in airway segments and bifurcations, which, in particle deposition studies, determine the transport and deposition of aerosols in the entire lung.

Indeed, patient-specific models of the lung, lobes, airways, and pulmonary vascular trees has become the state-of-the-art approach in most current CFD applications to respiratory function. The application of engineering analyses of fluid mechanics to image-based subject-specific models has the potential to provide new insight into structure-function relations in the individual. Now, answer: what advantages can CFD offer over existing modeling

and measuring techniques? Provide three aspects that justify the use of CFD simulations as a valuable research tool in respiratory physiology.

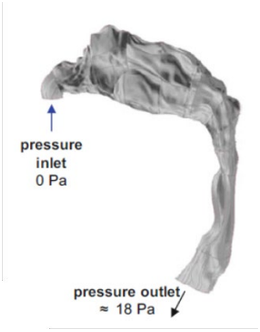

Figure 1 3D model of the nasal cavity with inlet and outlet boundary conditions.

Problem 3B

One of the main difficulties associated with the simulation of specific flows in the central airways is the allocation of outlet flow boundary conditions. One method, termed functional respiratory imaging (FRI), has the ability of countering this limitation and turning CFD into an even more powerful bioengineering method. What is FRI?

Problem 3C

Consider the excerpt of the study *Validation of Computational Fluid Dynamics in CT-based Airway Models with SPECT/CT*, authored by J.W. de Backer et al. circa 2010. The abstract of the study contains the following excerpts:

Purpose: To compare the results obtained by using numerical flow simulations with the results of combined single-photon emission computed tomography (SPECT) and computed tomography (CT) (...)

Materials and Methods: (...) In this study, six patients with mild asthma (three men and three women; overall mean age 46 years ± 17 [standard deviation]) underwent CT at functional residual capacity and total lung capacity, as well as SPECT/CT. CT data were used for segmentation and computational fluid dynamics (CFD) simulations. A comparison was made between air flow distribution, as derived with (a) SPECT/CT through tracer concentration analysis, (b) CT through lobar expansion measurement, and (c) CFD through flow computer simulation. (...)

Results: Good agreement was found between SPECT/CT, CT, and CFD in terms of airflow distribution and hot spot detection. The average difference for the internal airflow distribution was less than 3% for CFD and CT versus SPECT/CT. Heterogeneity in ventilation patterns could be detected with SPECT/CT and CFD. (...)

What do these results say about the viability of FRI, i.e., the combination of CT imaging with CFD simulations?

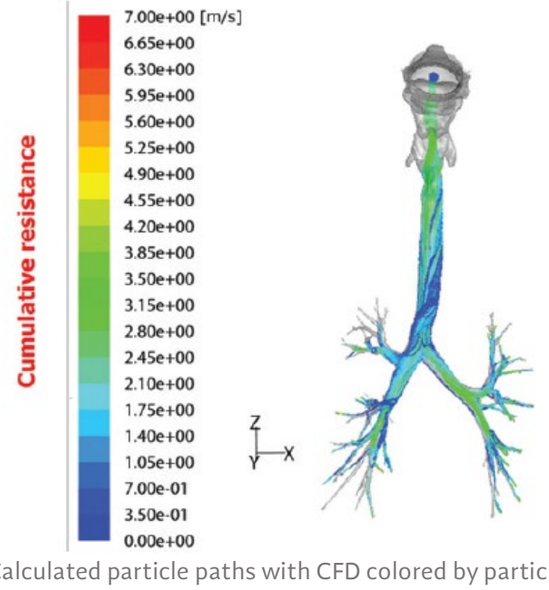

Figure 2 Calculated particle paths with CFD colored by particle velocity (in meters per second) for the 2010 study by de Backer et al.

Problem 3D

While the overall correlations between conventional parameters, such as FEV_1, and image-based endpoints are good in general, the image-based parameters obtained from FRI have been shown to provide superior performance in certain contexts. Indicate circumstances in which FRI may produce better results than conventional endpoints.

Problem 3E

In 2007, Ching-Long Lin and his collaborators employed a CFD technique to understand the relative importance of the upper and intra-thoracic airways and their role in determining central flow patterns, with particular attention paid to the importance of turbulence. The geometry they used was derived from volumetric scans of a volunteer imaged via multidetector-row computed tomography. Two computational geometries were prepared: Geometry 1 consisted of a mouthpiece, the mouth, the oropharynx, the larynx, and the intra-thoracic airways, while Geometry 2 comprised only the intra-thoracic airways. Suppose you were one of the researchers in Lin's team. Explain how you would prepare the initial settings for the simulation, including boundary conditions and highlighting differences between the two cases. What differences in flow patterns would you expect to obtain with geometries 1 and 2? Then, answer: excluding the intricacies of the nose and mouth, what is the first structure in the respiratory tract that normally displays a significant level of turbulence? What are the implications of this phenomenon to flow variables in the airways?

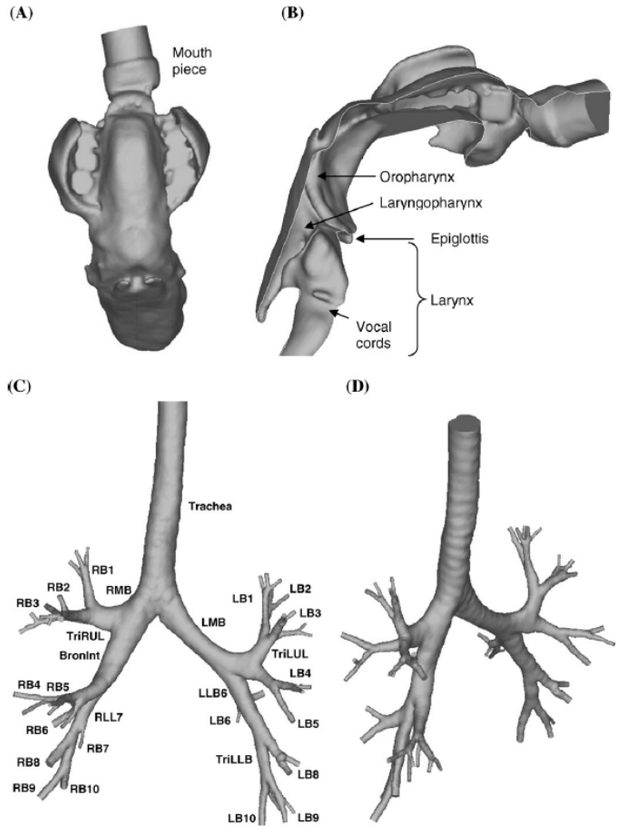

Figure 3 The upper respiratory tract for a human subject: (a) top view of the mouth, (b) inside oblique view of the previous scan, (c) front-view of the CT-based human airway, and (d) oblique view of the previous scan.

Solutions

▸ Problem 1

We observe that, under most normal breathing patterns, the small airways convey low Reynolds number flows; indeed, Re at the level of the alveolar sac is of the order of 10^{-3}. Under normal breathing conditions, turbulence is relatively missing in the portion of the respiratory tract located beyond the trachea. However, there is transitional flow in the bronchus and sustained turbulence at the level of the trachea under exercise ventilation conditions.

The relative importance of convective and diffusive transport in different generations of airways can be estimated with the Peclet number (*Pe*). In the present case, we see that *Pe* for flow entering the trachea is relatively high, but drops quickly from the bronchus forward; physically, this implies that, at first, transport by convection is quite pronounced, but diffusion quickly becomes important as flow partitions into the lower airways. Diffusion has markedly superseded convection by generation 19. The situation is somewhat different under conditions of exercise ventilation, which raises the Peclet number across all of the tracheobronchial tree; as a consequence, convection predominates for a longer portion of the lower airways than it would with resting ventilation.

▸ Problem 2

P.2A ➡ *Solution*

The Roughton-Fowler equation was of great significance for several reasons: (1) it provided a convenient separation of the effect of diffusion conductance from alveolar gas up to the red cell, represented by D_M, and the diffusion conductance from the red cell membrane to the hemoglobin molecule, represented by the product θV_c; (2) gas dynamically, it emphasized that there was a P_{CO} gradient from pulmonary capillary plasma to the red cell interior that might be as great as or greater than the P_{CO} gradient from alveolar gas to plasma; (3) it led a method, based on in vitro kinetics of CO uptake by red cells, for using $D_{L_{CO}}$ measurements at different alveolar values of P_{O_2} to obtain the membrane (D_M) and red cell (θV_c) conductances; and (4) it allowed for the possibility of test hypotheses such as the effect of alveolar expansion on D_M, of anemia on θ, and of exercise on V_c.

P.2B ➡ *Solution*

Conditions that affect $D_{L_{CO}}$ are listed below.

Conditions that increase $D_{L_{CO}}$	Conditions that decrease $D_{L_{CO}}$
Diseases that increase θV_c and thus increase $D_{L_{CO}}$ • Polycythemia • Left-to-right shunt • Pulmonary hemorrhage (not strictly an increase in θV_c, but effectively an increase in lung Hb) • Asthma Other conditions that increase θV_c and thus increase $D_{L_{CO}}$ • Supine position (in addition, possibly a slight increase in D_M) • Exercise (in addition, possibly a D_M component) • Obsesity (in addition, possibly a D_M component) • Muller maneuver	Diseases that decrease θV_c and thus decrease $D_{L_{CO}}$ • Anemia • Pulmonary embolus Diseases that decrease D_M and θV_c and thus decrease $D_{L_{CO}}$ • Emphysema • Pulmonary edema • Pulmonary vasculitis • Pulmonary hypertension • Interstitial lung disease (e.g. IPF, sarcoidosis) • Lung resection (however, compensatory recruitment of θV_c also exists) Other conditions that reduce θV_c and thus reduce $D_{L_{CO}}$ • Valsalva maneuver • Hb binding changes (e.g. HbCO, increased F_{l,O_2})

P.2C ➡ *Solution*

The tracer gas that accompanies the test gaseous mixture is designed to facilitate the measurements of the initial alveolar CO concentration and the

alveolar volume (V_A) from which CO uptake is occurring. For this reason, the gaseous diffusivity of the gas should be similar to that of CO. The tracer gas should not ordinarily be present in alveolar gas or else be present at a known, fixed concentration (e.g., argon). Commonly used tracer gases are helium (He) and methane (CH_4). While He has been the dominant choice for a while – it does meet the aforementioned criteria quite well – it should be noted that its gaseous diffusivity is considerably higher than that of CO. CH_4 is commonly used as a tracer gas for systems that continuously sample expired gas. Its gaseous diffusivity is closer to CO, but it has a slightly higher liquid solubility than He. Needless to say, as new tracer gases are introduced, manufacturers should demonstrate that they produce V_A and $D_{L_{CO}}$ values equivalent to those measured using He, as this is the tracer gas that is used to derive most of the available reference equations.

One of the assumptions of the single-breath $D_{L_{CO}}$ determination technique is that capillary blood does not contain CO. As a consequence, corrections are needed for patients who have significant carboxyhemoglobin (COHb). The main population of subjects that possess this feature is that of regular smokers. COHb produces an acute and reversible decrease in $D_{L_{CO}}$, largely due to the effects of CO back pressure, which reduces the driving pressure for CO transport from alveolar gas to capillary blood; and the "anemia effect" from decreased Hb binding sites for CO from the test gas. As cigarette smoking is the most common source of COHb, subjects should be asked to refrain from smoking on the day of the test. The time of the last cigarette smoked should be recorded and noted for interpretation. A correction for CO back pressure should be made for recent or heavy cigarette smoking. In short, corrections are needed for patients who have significant COHb. It deserves mentioning, finally, that small increases in COHb also occur in nonsmokers when CO is inspired in the $D_{L_{CO}}$ test; investigators found that there is a ~0.7% increase with each single-breath diffusing capacity test.

P.2D ➡ *Solution*

Like any clinical test, the $D_{L_{CO}}$ has limitations and must be interpreted carefully. One of the most important considerations is the effect of lung volume on the $D_{L_{CO}}$. The $D_{L_{CO}}$ is usually reported both as an absolute number ($D_{L_{CO}}$) as well as a value that has been divided by alveolar volume (V_A), the $D_{L_{CO}}/V_A$, also known as the transfer coefficient (K_{CO}). Since the $D_{L_{CO}}/V_A$ appears to account for differences in lung size, it might be thought to represent a more accurate expression of the intrinsic gas exchange function of the lung. However, in normal subjects, the $D_{L_{CO}}$ increases and the $D_{L_{CO}}/V_A$ decreases with V_A, so clearly the expression does not correct or standardize for lung volume. In fact, the $D_{L_{CO}}/V_A$ is the transfer coefficient for the diffusion of CO into the blood, and is an essential part of the equation used to calculate the $D_{L_{CO}}$. The global diffusing capacity is calculated as $D_{L_{CO}}/V_A$ multiplied by the overall lung volume, V_A.

In disease states, the $D_{L_{CO}}$ and $D_{L_{CO}}/V_A$ are often discordant. For example, in patients of low lung volumes, including interstitial lung disease and patients with extra-parenchymal restrictive disease (e.g. kyphoscoliosis), the $D_{L_{CO}}/V_A$ often exceeds the $D_{L_{CO}}$ when expressed as a percentage of predicted values. While some authors interpret these findings as relating to underlying lung disease states, others believe that the discrepancies can be largely explained by the inadequacies of the predicted equations. These predicted equations are usually improved by incorporating lung size into the formula used.

P.2E ➡ *Solution*

For CO, the two resistances that occur in the Roughton-Forster equation, $1/D_M$ and $1/\theta V_c$, are approximately equal. For NO, the total resistance to alveolar-capillary transfer is much less, ~20-25% of that of CO, thus the transfer factor $T_{L_{NO}}$ is four to five times greater than $T_{L_{CO}}$, and the resistance resides mostly in the D_M component. This occurs because (1) the physical diffusivity of NO is approximately twice that of CO and its resistance ($1/D_M$) is half; and (2) the rate of combination of NO with blood *in vitro* is considerably faster than for CO. This second aspect merits a bit further discussion. The chemical reactions of NO and CO with blood are different. NO reacts directly with the oxygen of

oxyhemoglobin to form a nitrate plus a deoxygenated form of Hb called methemoglobin (metHb) in which the iron atoms of the heme ring are oxidized from the ferrous (Fe^{++}) to the ferric (Fe^{+++}) form,

$$NO + Hb(Fe^{++})O_2 \rightarrow metHb(Fe^{++}) + NO_3^-$$

CO does not react with O_2 but rather competes with oxygen for the Fe^{++} site on the heme ring,

$$CO + Hb\left(Fe^{++}\right)O_2 \rightarrow Hb\left(Fe^{++}\right)CO + Hb\left(Fe^{++}\right)O_2$$

Both NO and CO are tightly bound to Hb through their extremely slow dissociation constants. NO, however, reacts directly with hemoglobin, instead of competing with oxygen for Hb binding sites. Thus, investigators have cited the rapid reaction of NO with Hb (250 times faster than CO), i.e. the very low blood cell resistance to NO, as a reason for considering $T_{L_{NO}}$ as a surrogate for D_M.

The ERS-ATS Task Force has reviewed a series of exercise studies and verified that $D_{L_{NO}}$ and $D_{L_{CO}}$ increase linearly as cardiac output and oxygen consumption increase, but with more scatter for the $D_{L_{NO}}$ relationship. With exercise, pulmonary vascular pressures increase and more alveolar surface is available for gas exchange from the recruitment of capillary units in the alveolar septa and dilatation of already patent vessels. The recruitment and dilation increases $D_{M_{NO}}$ and $D_{M_{CO}}$ as "more membrane" now takes part in NO and CO transfer. In addition, $D_{L_{CO}}$ (representing the term $1/\theta V_c$) will increase as capillary volume increases. As a result, the $D_{L_{NO}}/D_{L_{CO}}$ ratio decreases linearly with increasing power output.

For a note on the variation of the $D_{L_{NO}}/D_{L_{CO}}$ ratio in abnormal state, check the end of the document.

The standard $D_{L_{NO}}$ system is basically a single-breath $D_{L_{CO}}$ system with the addition of NO in the inspiratory gas mixture and the presence of an NO analyzer. The mixture used in the $D_{L_{NO}}$ test is essentially the same as that of the single-breath $D_{L_{CO}}$ test, the difference being that NO is added is to the inspiratory gas at a concentration of 40 – 60 ppm; the remaining components of the gas are the same as those for the $D_{L_{CO}}$ test, namely, a CO level close to 0.3% and a tracer gas such as He or CH_4 for measuring V_A; also, there should be the addition of 21% oxygen with nitrogen as balance.

Two major subtypes of gas storage configurations can be defined: the first type is characterized by an inspiratory reservoir, such as a balloon, for the storing and measurement of the inspiratory gas mixture; the second type has a mixing chamber in which the inspired gases are mixed, from different sources, before each inspiration. Importantly, NO is reactive with oxygen to form NO_2 (O_2 + 2 NO → 2 NO_2); NO_2 is formed at a rate of ~0.02 ppm s^{-1} in a gas mixture containing close to 21% oxygen and 60 ppm NO; < 3 ppm of NO_2 is produced in 2 min when ~60 ppm NO gas is mixed with ~21% oxygen. Were that mixture to be left in the inspiratory bag for 2 min before testing, $D_{L_{NO}}$ would be overestimated by ~1%. As such, NO gas (along with nitrogen, N_2) is stored in a separate gas cylinder (that is, apart from oxygen) containing NO in a high concentration in N_2, i.e. ranging from 400 to 1200 ppm NO in N_2. Since NO reacts with certain plastics, polytetrafluoroethylene (Teflon) tubing should be used. The connections and regulators should be made of stainless steel in order to prevent reaction of the NO with metals. Two types of NO analyzers are available: one is the highly sensitive but expensive chemiluminescence analyzer, with a detection limit of 0.5 ppb, and linear to the upper detection limit of 500 ppm and with a reaction time of ~70 ms. Because chemiluminescence analyzers are exceedingly expensive, the much cheaper NO electrochemical cells are often used instead. This type of equipment has a lower sensitivity, with a detection range of 0 – 100 ppm, and a response time of < 10 s, hence the reason why they are only suitable for the standard single-breath test.

▸ Problem 3

P.3A ➡ *Solution*

Given the literature published since the beginning of the century, it's become easy to make a case for CFD in respiratory research. To name a few reasons: (1) the combination of structural information from CT with CFD provides a method to obtain very meaningful functional imaging measurements without the need for more expensive imaging and measurement techniques; (2) CFD may provide a number of useful mechanical measurements, including velocity, pressure, wall shear stress, frictional resistance, temperature, humidity, and drug (particle or droplet) distribution; (3) another major advantage is the significant level of detail inherent to CFD simulations, which allow the physician to obtain values for parameters such as pressure and velocity in every point of the computational domain; (4) a fourth positive aspect of CFD modeling is the possibility of easily comparing changes before and after an intervention simply by modifying flow conditions, rather than using real-life, invasive procedures.

P.3B ➡ *Solution*

The FRI methodology combines high-resolution low-dose CT, taken at both full inspiration (total lung capacity, TLC) and expiration (functional residual capacity, FRC), along with CFD. The methodology involves adjusting pressures at the airway outlets, uniformly within each lobe, to match the lobar ventilation as determined by the CT-based lobe expansion. CT images on their own provide an accurate assessment of anatomical structures such as the lung, lobe, airways and their volumes, blood vessels and their characteristics, and airway wall thickness; when combined with CFD, however, the spatiotemporal data obtained with imaging is provided with dynamic information such as regional resistance measures and aerosol deposition characteristics. Thus, the FRI technique provides not only image-based measurements, but also some additional functional representation in the form of resistance and flows stemming from CFD methods.

P.3C ➡ *Solution*

The results show that patient-specific CFD simulations yield information that is similar to that obtained with functional imaging tools, such as SPECT/CT, provided the adequate configurations and boundary conditions are applied (as the authors most certainly have specified).

P.3D ➡ *Solution*

Parameters obtained from FRI have the advantage of revealing regional changes in the lungs that are often smaller in signal, and therefore harder to detect with FEV_1, but may nonetheless be clinically relevant. FRI has also produced better results in the understanding of aerosol deposition characteristics, leading, for example, to better evaluation of drugs and of their capacity to reach areas of the lung that may not be adequately tracked with other techniques.

FRI has also been used in cystic fibrosis, generating valuable data on the dynamics of inhaled antibiotics, including concentration distributions that would have been impractical or simply impossible to obtain with older techniques. Such studies led to the conclusion that concentration distributions are highly patient-specific.

A third area where the lack of regional lung information has resulted in challenging clinical trials is that of bio-equivalence. for a generic drug to obtain market authorization, it must be demonstrated that it has as intense an effect as a reference product, including the proof that the substance is capable of reaching the same areas in the lung (i.e., it has the same regional exposure). A group of investigators has used FRI to show that two formulations for asthma had the same deposition patterns and, consequently, the same *in vivo* response to the substance in terms of changes in airway volumes and resistances.

P.3E ➡ *Solution*

Because of the complexity of the geometry of the upper airways (oral or nasal cavity to larynx), many airway CFD studies neglect this region and instead initiate flow at the trachea. Although this greatly simplifies the geometry and the computational cost of the simulation, it does have its inherent difficulties, such as imposing on the engineer the need to provide an accurate inlet boundary condition at the tracheal opening. If the entrance of the flow is in the mouthpiece, a uniform pressure can be easily provided therein. In turn, a guessed uniform velocity may be the ideal choice of BC for Geometry 2. Thereafter, the engineers should ensure that both geometries are given the same conditions at the outlets of the terminal branches; we assume uniform ventilation and specify uniform velocity. This allows the air to produce comparable velocity profiles at the mouthpiece and the trachea for cases 1 and 2, respectively. After all, the study aims to set side by side the two geometry cases. The outlet velocity can be derived from the volumetric flow rate at a reference condition, such as a flow of 320 mL/s at the peak inspiratory phase, along with the average diameter of a reference airway structure; in Case 2, the obvious choice would be the trachea.

The earliest structure of the respiratory tract that has turbulent features under healthful conditions, excluding the mouth and nose, is the larynx. Instabilities are induced into an airstream as it passes through the constricted vocal aperture and vocal folds. The so-called laryngeal jet and vocal fold disturbances have pronounced effects on airstream motion in the tracheobronchial tree and forward. The disturbed flow that enters the trachea is likely to not reach developed conditions, leading to a relatively flat tracheal velocity profile. Furthermore, the presence of turbulence in the subglottic space will possibly increase the localized tracheal wall shear stress.

A note on Problem 2E

In a 2017 review of most of the clinical studies available prior to that date, Hughes & Dinh-Xuan inferred three patterns for observed $D_{L_{NO}}/D_{L_{CO}}$ ratios: a high range ($\geq$ 110% predicted), a normal range ($<$ 110% $>$ 95%), and a low range ($\leq$ 95%). They verified that a high $D_{L_{NO}}/D_{L_{CO}}$was associated with pulmonary vascular disease, whereas a low $D_{L_{NO}}/D_{L_{CO}}$ had been linked to alveolar destruction (as in emphysema and fibrosis). The pattern of changes in $D_{M_{CO}}/V_c$ and red cell resistance to CO transfer as percent of total resistance to CO transfer, $R_{\mathrm{rc}}/R_{\mathrm{tot}}$, both mirror the changes in $D_{L_{NO}}/D_{L_{CO}}$; but $D_{L_{NO}}/D_{L_{CO}}$ is prioritized, being a directly measured variable rather than a computed one. Because of the early stage of $D_{L_{NO}}$ research and correlation studies, it should be noted that these findings are all quite debatable.

References

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