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Airway exchange of highly soluble gases

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Hlastala MP, Powell FL, Anderson JC. Airway exchange of highly soluble gases. *J Appl Physiol* 114: 675–680, 2013. First published January 10, 2013; doi:10.1152/japplphysiol.01291.2012.— Highly blood soluble gases exchange with the bronchial circulation in the airways. On inhalation, air absorbs highly soluble gases from the airway mucosa and equilibrates with the blood before reaching the alveoli. Highly soluble gas partial pressure is identical throughout all alveoli. At the end of exhalation the partial pressure of a highly soluble gas decreases from the alveolar level in the terminal bronchioles to the end-exhaled partial pressure at the mouth. A mathematical model simulated the airway exchange of four gases (methyl isobutyl ketone, acetone, ethanol, and propylene glycol monomethyl ether) that have high water and blood solubility. The impact of solubility on the relative distribution of airway exchange was studied. We conclude that an increase in water solubility shifts the distribution of gas exchange toward the mouth. Of the four gases studied, ethanol had the greatest decrease in partial pressure from the alveolus to the mouth at end exhalation. Single exhalation breath tests are inappropriate for estimating alveolar levels of highly soluble gases, particularly for ethanol.

gas exchange; bronchial circulation; alcohol; diffusion; high blood soluble gases; high water soluble gases

IT IS GENERALLY ACCEPTED that the exchange of respiratory gases between the blood and the air in the lungs occurs in the alveoli of the lungs. The relevant gas exchange features of lung anatomy are the very large surface area (~70 m^2) and the thin diffusion barrier (~0.10 μm) between the blood and alveolar gas. However, the lungs have two circulations: bronchial (bringing nutrients to the airway tissue) and pulmonary (bringing deoxygenated blood to the alveolus for oxygenation and elimination of carbon dioxide). This paper addresses the role of the bronchial circulation in the exchange of highly soluble gases by the lungs.

Interest in highly soluble gas interaction with the airways first developed around the events of World War II (11). Further development has continued since that time (2, 9, 12, 14, 15, 17, 36). These studies focused on airway deposition of reactive gases and did not consider the role of the bronchial circulation.

Pulmonary airways are perfused by the bronchial circulation (13). Gas exchange between the respired air and the bronchial circulation was recognized by Wanner et al. (42) who developed a method for measuring bronchial blood flow and airway water volume using dimethyl ether (DME). DME diffused from the inspired air through the bronchial tissue and was taken up by the blood flow. This method was later extended for use in human subjects (43). The exchange of gases between the blood and air was initially studied using an isolated dog trachea preparation. The ventilation to the trachea was isolated, and gases with varying solubility were infused into the circulation. Swenson et al. (37) found that the exchange of gases depended on both their solubility in blood ($\lambda_{b:a}$: blood to air partition coefficient) and molecular weight. Souders et al. (35) found that the exchange of gases with intermediate blood solubility across the trachea also depended on the magnitude of blood flow. These studies were evaluated mathematically by George et al. (18) who found that the diffusive conductance across the trachea tissue increased dramatically for gases with very high $\lambda_{b:a}$. Although the bronchial blood flow represents only ~1% of the cardiac output, the blood can deliver a large amount of very high blood soluble gas and it is easy for the gas to diffuse across the bronchial airway tissue (19). The airway exchange pathway is not available for intermediate or low $\lambda_{b:a}$ gases (8) because only a few molecules dissolve in the watery airway surface layer.

Several studies have used mathematical modeling to demonstrate that highly soluble gases exchange within the lung airways (7, 10, 18, 20, 22, 29–31, 38–40, 46). Airway exchange models have been developed to study the uptake of soluble inhaled toxic gases as well as the elimination properties of soluble inert gases. The models are based on physicochemical principles of gases and show the feasibility of airway exchange of highly soluble gases.

Figure 1 illustrates a model for gas exchange in the airways and alveoli. The pulmonary circulation brings systemic venous blood in close proximity with the alveolar gas where exchange occurs with intermediate and low solubility gases, including O_2 and CO_2. The bronchial circulation perfuses the conducting airways. However, a diffusion barrier minimizes exchange of any gases with low and intermediate blood solubility, including O_2 and CO_2, between the bronchial circulation and the respired air.

Fick's Law quantifies diffusion across both the airway and alveolar gas exchange barriers. The amount that diffuses across a barrier is directly related to the product of the solubility of the gas in the barrier and the diffusivity of that gas in the barrier. In the case of alveolar gas exchange with the pulmonary circulation, the alveolocapillary membrane is ~0.10 μm thick. We have been unable to find any publications with measurements of the diffusion distance between airway lumen and bronchial vasculature in humans. For sheep, an animal of similar size to the human, the diffusion distance varies based on axial position from ~50 μm to 130 μm (4). In addition to the thick tissue barrier, a thin (≤10 μm) mucus layer composed predominantly of water is interposed between the tissue and lumen. Because of this liquid layer's intimate contact with air, the exchange across the airway wall is primarily governed by the solubility of a gas in water ($\lambda_{w:a}$: water to air partition coefficient). In most cases, gases with high $\lambda_{b:a}$ also have a high $\lambda_{w:a}$. However, some gases with high $\lambda_{b:a}$ are not as soluble in water and have a relatively low $\lambda_{w:a}$ (5), presumably because solubility in lipids and other biological substances may

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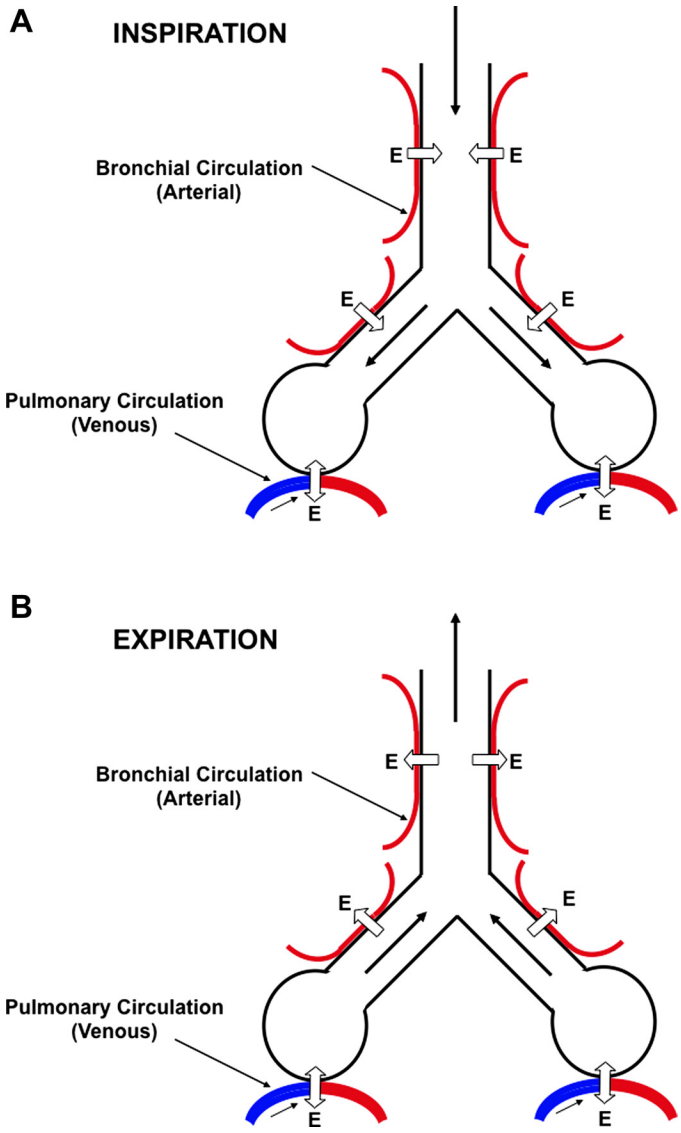

Fig. 1. Schematic illustrating the exchange of gases with both the pulmonary circulation in the alveoli and bronchial circulation in the airways: *A*, inspiration; *B*, expiration. Red indicates arterial blood and blue indicates venous blood. Solid arrows show direction of ventilation. Open arrows indicate direction of highly soluble gas net flux. This schematic shows only the trachea and the first set of bronchi. Airway gas exchange continues throughout the airway tree. E, ethanol diffusion.

exceed that in water (28, 45). For gases with intermediate ($0.10 < \lambda_{w:a} < 10$) and low water solubility ($\lambda_{w:a} < 0.10$), exchange across the airway wall is markedly reduced. However, gases with very high water solubility ($\lambda_{w:a} > 100$), and thus blood solubility, can exchange across the airway tissue. Therefore, although intermediate and low solubility gas exchange takes place in the alveoli with the pulmonary blood, high solubility[1] gases exchange along the airways of the lungs with the bronchial blood.

[1] Intermediate and poorly blood soluble gases exchange in the alveoli in a manner dependent on blood solubility. High water solubility gases exchange in the airways in a manner dependent on water solubility. Typically, a gas' water and blood solubility correlate strongly. However, in some gases the correlation is poor (5).

The focus of this manuscript is to explore the spatial distribution of highly soluble gases throughout the lungs in both the lung tissue and airway gas with mathematical modeling. We evaluate the airway exchange characteristics of four gases whose solubilities span the range of high $\lambda_{b:a}$ and $\lambda_{w:a}$. Methyl isobutyl ketone, acetone, ethanol, and propylene glycol monomethyl ether are typically introduced into the body via endogenous production, chemical exposure, or ingestion.

METHODS

Lung model. A detailed description of the model was published previously (7). Only the salient features will be described here to appreciate how the model is used to systematically explore the effects of solubility on airway exchange. The airway tree has a symmetric bifurcating structure through 18 Weibel (44) generations. The respiratory bronchioles and alveoli are lumped together into a single alveolar unit. Axially, the airway tree is divided into 480 control volumes. Radially, the airways are divided into six layers: *1*) the airway lumen, *2*) a thin mucous layer, *3*) connective tissue layer (epithelium and mucosal tissue), *4*) the bronchial capillary bed, *5*) the adventitial layer, and *6*) the pulmonary capillary bed. Functionally, the upper respiratory tract and cartilaginous airways (generations <10) only have the first four layers.

Within each airway layer, concentration and temperature values are bulk averages for the entire layer. The air in the lumen is considered a mixture of dry air, water vapor, and a single soluble gas. Mass and energy are transported between control volumes by bulk convection and axial diffusion through the lumen. Radial transport between the gas phase and mucous layer is described with heat and mass transfer coefficients. Near the air-mucus interface, local vapor-liquid equilibrium is described by Raoult's law for water and $\lambda_{w:a}$ for each soluble gas. The mucous layer is assumed to have the properties of water and can change thickness depending on local hydration. A minimum mucous layer thickness is maintained by filtration of water from the bronchial circulation through the connective tissue layer and into the mucous layer. Transport of water and soluble gas between these three layers occurs via filtration and diffusion (Fick's law). The connective tissue layer and the adventitial tissue layer are treated as a binary mixture of dilute soluble gas and water. For a soluble gas, the tissue solubility is assumed to be equal to blood solubility. The bronchial capillary bed is modeled as an axial series of annular sheets of perfused blood interposed between the connective and adventitial tissue layers. Adjacent to the adventitial tissue layer, the pulmonary capillary bed is assumed to be at body temperature, and the concentration of soluble gas is assumed to be the average of the soluble gas concentration entering and leaving the alveolar unit via the pulmonary circulation. The concentration of soluble gas in the venous blood entering the pulmonary capillary bed is determined by solving the equation describing mass accumulation in the alveolar unit. Within the alveolar unit, the concentration of soluble gas in the alveolar unit is allowed to vary with time.

The lengths and diameters of the intraparenchymal airways were scaled to ensure the ratio of the airway volume to the vital capacity ($=5{,}000$ ml) was constant and to represent the lung at functional residual capacity ($=2{,}650$ ml).

Mass and energy balances around each control volume produce three partial- and nine ordinary-differential equations in time, *t*, and space, z. The equations are solved simultaneously for the following 12 dependent variables: the mole fraction of soluble gas in the air, mucous, connective tissue, bronchial capillary bed, and adventitial tissue layers; the temperature of the air, mucous, connective tissue, bronchial capillary bed, and adventitial tissue layers; the mole fraction of water in the air; and the mucous thickness. The 12 differential equations are solved numerically using previously published boundary conditions (7). The spatial dimensions are solved by upwind finite

difference, whereas the time derivatives are handled using LSODE, an integration software package developed by Hindmarsh (24). The mass balance around the alveolar compartment is integrated separately from the airway control volumes using LSODE.

Computer simulations. A breathing maneuver was simulated for each soluble gas after the model reached steady state. Breath-to-breath steady-state conditions were achieved by simulating tidal breathing at functional residual capacity. A respiratory rate of 12 breaths/min, a sinusoidal flow waveform, and a tidal volume of 500 ml were used. The thermodynamic state of inspired air was 23°C and 50% relative humidity. Steady-state conditions were reached when the end-exhaled temperature and soluble gas concentration changed by less than 0.1% between breaths. Each prolonged exhalation was preceded by a single inhalation from functional residual capacity to total lung capacity, a volume approximated as 75% of the vital capacity (3,750 ml). The airway volumes were fixed at 3/4 of total lung capacity. Then, a vital capacity exhalation at 200 ml/s was simulated.

By using the model, we simulated the exchange of gases spanning the range of high blood (human) and water solubility: methyl isobutyl ketone, used in solvents [$\lambda_{b:a} = 90$, $\lambda_{w:a} = 79$ (33)]; acetone, which is produced by the body when fat is burned [$\lambda_{b:a} = 341$, $\lambda_{w:a} = 279$ (41)]; ethanol, relevant for breath testing to determine intoxication [$\lambda_{b:a} = 1{,}803$, $\lambda_{w:a} = 2{,}132$ (28)]; and propylene glycol monomethyl ether (PGME), used in lacquers and paints [$\lambda_{b:a} = 12{,}380$, $\lambda_{w:a} = 12{,}280$ (27)]. The temperature for the partition coefficients is 37°C.

RESULTS

Of all the highly soluble gases studied, the most data are available for ethanol (alcohol) because of interest by forensic scientists in evaluation of the alcohol breath test. Ethanol is a highly soluble gas (in both blood and water) similar to water vapor (which has a much greater effective solubility than ethanol). In a complex fashion that is similar to water exchange, ethanol exchanges between the air, airway wall, and bronchial vasculature during both inhalation and exhalation (25, 26).

During inhalation of fresh air, ethanol is transported from the airway mucosal surface and into the respired air. The airway mucous layer is partially replenished by diffusion of ethanol from the bronchial blood vessels through the airway tissue and into the mucous. As the respired air moves peripherally, its ethanol partial pressure increases to an alveolar ethanol partial pressure (that of venous blood) just prior to reaching the alveolus. For ethanol excretion, the partial pressure of ethanol in the wall is always greater than that in the adjacent airspace throughout inhalation.

During exhalation, the respired air leaving the alveoli has a large ethanol partial pressure. On its transit to the mouth, the respired air loses ethanol to the airway wall as the molecule moves toward the lower partial pressure within the airway mucus and tissue. This deposition into the wall causes the partial pressure of ethanol along the airway tract to decrease from the alveoli to the mouth. The same approach can be used to determine the relative role of airway vs. alveolar exchange for gases covering the entire range of solubility (see Fig. 3 in Ref. 8).

Figure 2*C* shows the magnitude of ethanol flux from the airway tissue during inhalation and to the airway tissue during exhalation. The height of each bar represents the amount of ethanol exchanging in any airway generation during the respiratory phase relative to the total amount of ethanol exchanged over an entire inhalation. The downward bars represent the amount of ethanol deposited onto the airways of any airway generation during a full or prolonged exhalation, the maneuver typically used for an alcohol breath test. During inhalation ethanol delivered to the mucus surface by the bronchial circulation and exhalation from the previous breath, is absorbed by the inspired air (Fig. 2, solid columns) as respired air passes from the mouth or nose along the airway tree toward the alveoli. Before reaching the alveolus, the air is saturated with ethanol. During exhalation, air passes from the alveolus along the airway tree to the mouth or nose. During this process, some ethanol is deposited onto the airway surface (Fig. 2, gray columns). The remaining ethanol is exhaled from the mouth or nose. Further information about the model used to determine these flows can be found in prior studies (7, 10, 35, 39).

The relative importance of solubility in determining airway gas exchange distribution can be assessed using mathematical modeling. The distribution of flows between the airspace and airway wall is plotted for gases of varying solubility in the following figures. Methyl isobutyl ketone ($\lambda_{b:a} = 90$) has the lowest solubility of the four gases and hence, less airway exchange (Fig. 2*A*). Methyl isobutyl ketone exchange is shifted more peripherally than ethanol. A large component of the exchange occurs in the alveoli. Acetone ($\lambda_{b:a} = 341$) exchanges more peripherally than ethanol, but more centrally then methyl isobutyl ketone, consistent with its relatively greater blood solubility (Fig. 2*B*). PGME is almost seven times more soluble than ethanol in blood ($\lambda_{b:a} = 12{,}380$). PGME is the most soluble gas used in our analysis (Fig. 2D). It exchanges in the airways more proximal to ethanol because of its greater blood solubility.

Inert gas partial pressure in air within the airways is shown at each airway generation at both end inhalation and end exhalation (Fig. 3). With inspiration, the air picks up high blood solubility inert gases from the airway tissue. As inspired air passes along the airway tree, the inert gas concentration in the airspace and wall gradually increases from zero (at the mouth) to alveolar ethanol concentration as the air reaches the alveolar region. During exhalation, the concentration of inert gas in a bolus of air leaving the alveoli decreases as inert gas is deposited to the airway tissue. The amount of inert gas moving into the air during inspiration exceeds the amount of inert gas deposited during exhalation (see Fig. 2). The degree of gas interaction with the airways depends on water solubility, providing water solubility is similar in magnitude. Increased blood solubility results in a more rapid rise in gas concentration during inhalation and a more rapid fall in gas concentration during exhalation. The exception to this "rule" is PGME at end exhalation. In the case of extremely high solubility gases the vapor partial pressure depends strongly on heat exchange with the airways as changes in temperature alter the solubility of inert gases (23).

DISCUSSION

Alveolar gas exchange. Recent research into the exchange of ethanol in the lungs has shown that the airways play an important role in the exchange of highly soluble gases, like acetone and ethanol (6, 8, 20). Ethanol exchanges in the lungs quite differently from oxygen and carbon dioxide because of ethanol's very high solubility [$\lambda_{b:a}$ (Ostwald partition coefficient) = 1,803 for blood:air at body temperature (37°C or 98.6° F)] (28). Oxygen and carbon dioxide (effective $\lambda_{b:a} = 0.1$ and 3, respectively) exchange in the alveolus (between the alveolar air and the pulmonary blood), whereas ethanol and the

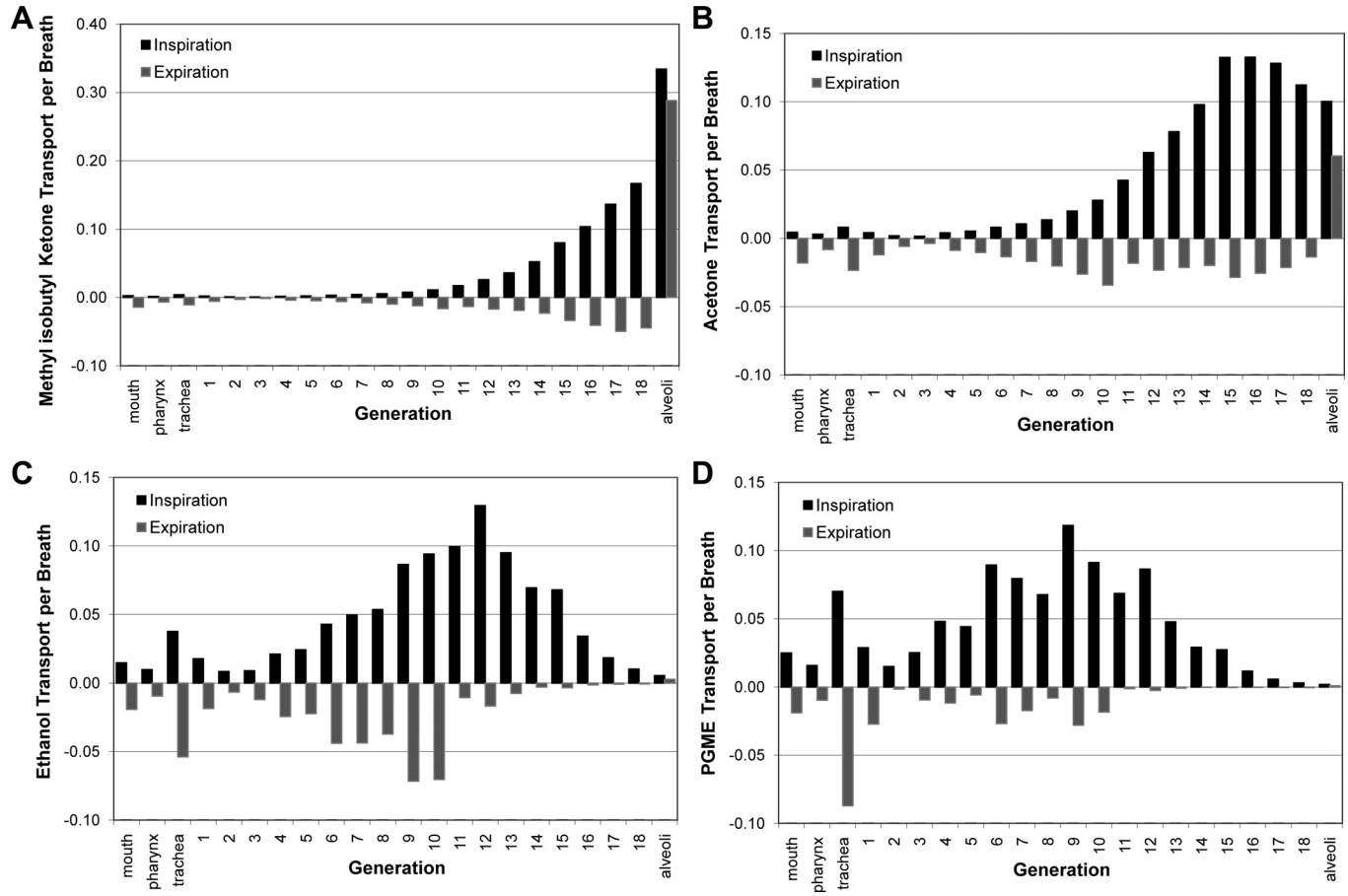

Fig. 2. Radial flow of soluble gas within each airway generation during both inspiration and expiration (flux of gas per generation per breath vs. airway generation). Solid bars show uptake of gas during inspiration. Gray bars show redeposition of gas during expiration. *A*: methyl isobutyl ketone ($\lambda_b = 90$), note the expanded *y*-axis; *B*: acetone ($\lambda_b = 341$); *C*: ethanol ($\lambda_b = 1{,}803$); and *D*: propylene glycol monomethyl ether (PGME; $\lambda_b = 12{,}380$).

other high solubility gases exchange within the airways (between the respired air and the bronchial circulation) (7, 10).

Gas exchange in the alveolus is strongly dependent on the relative balance of alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) to that alveolus and the partition coefficient of the gas exchanging. For an inert gas eliminated from the lungs, this relationship was carefully developed for inert gases eliminated from the lungs by Farhi (16):

$$E = \frac{P_A - P_I}{P_{\bar{V}} - P_I} = \frac{\lambda_{b:a}}{\lambda_{b:a} + \dfrac{\dot{V}_A}{\dot{Q}}} \qquad (1)$$

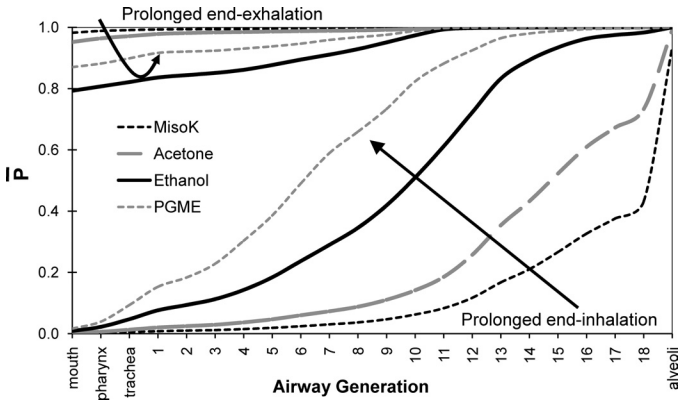

Fig. 3. Axial partial pressure profiles at end-inhalation and end-exhalation after deep inhalation and full exhalation of 4 gases with varying blood solubility: methyl isobutyl ketone (MisoK), acetone, ethanol, PGME [(partial pressure − inspired partial pressure)/(alveolar partial pressure − inspired partial pressure) vs. airway generation]. Arrows indicate increasing blood solubility.

where E is the alveolar excretion of a gas; P_A is partial pressure of the gas in the alveolus; P_I is the partial pressure of the gas entering the alveolus; $P_{\bar{v}}$ is mixed venous partial pressure of a gas; $\lambda_{b:a}$ is the Ostwald partition coefficient (blood/air) and $\dot{V}_A$ is the alveolar ventilation to the alveolus and $\dot{Q}$ is the blood flow to the alveolus. *Equation 1* describes the elimination of inert (linear content vs. partial pressure relationship) gases. For the respiratory gases, the partition coefficient of ~0.01 for oxygen and 3.0 for carbon dioxide means that both oxygen and carbon dioxide exchange efficiently in the normal range of $\dot{V}_A/\dot{Q}$ [0.1 − 10] in alveoli of normal human lungs.

In the case of ethanol, which has a partition coefficient of 1,803 (28) at normal body temperature (37°C), inspired air becomes saturated with ethanol, which is taken up from the airway surface during inspiration. Inspired ethanol partial pressure approaches mixed venous partial pressure. According to *Eq. 1*, as $\lambda_{b:a}$ becomes much greater than $\dot{V}/\dot{Q}$, E approaches 1 and P_A approaches P_v. For ethanol, $\lambda_{b:a} >> \dot{V}_A/\dot{Q}$. Therefore,

alveolar ethanol partial pressure is equal to mixed venous ethanol partial pressure in each alveolus within the lungs.

Path length symmetry. Our mathematical model assumes symmetry of the branching pattern of the pulmonary airway as described by Weibel (44). However, more recent studies have shown that the pulmonary airway branching pattern is fractal in nature, with an asymmetric branching pattern (3). Thus it likely that the linear distance from alveolus to mouth is heterogeneous among the various airways in the lungs. In some cases, there are airway pathways that are shorter and, thus, the respired air may not completely saturate with a high solubility gas before reaching the alveoli. In such a situation, the partial pressure of high solubility gas "inspired" by the alveoli will vary among alveoli. However, *Eq. 1* shows that despite variation in inspired partial pressure, alveolar pressure for very highly soluble gases will be equal to mixed venous partial pressure of that inert gas when exchanging in the alveolus. Even if a high solubility gas has not completely exchanged with inspired air traveling through a shorter path length airway, complete equilibration with venous blood will be achieved in the alveolus. The alveolar partial pressures of a high solubility gas such as ethanol are identical to mixed venous ethanol partial pressure and uniformly distributed throughout all alveoli.

Bronchial circulation. The interaction of highly soluble gases with the airways during respiration has been recognized for several decades (2). However, the exchange of gases through the airway tissue with the bronchial circulation was recognized more recently (13, 19, 21, 34, 35, 37). Exchange between airway gas and the bronchial circulation is limited due to a significant diffusion barrier and the magnitude of the bronchial blood flow is quite small (~1% of the cardiac output) (1). Despite the small blood flow, the high solubility of ethanol and large blood vessel surface area allows the complete exchange of ethanol within the airways. For lower solubility gases, airway exchange is much less in magnitude depending on blood solubility (7, 8), water solubility (5), bronchial blood flow (34, 35), and molecular weight (37).

The microscopic details of the bronchial circulation have not yet been well studied. Our model assumes that each control volume of the model is perfused by capillaries fed by the bronchial artery, but this is only an assumption. In reality, there are anastomoses between the bronchial veins and the pulmonary veins. In the more peripheral airways, the bronchial capillaries may be perfused by blood from the pulmonary venous circulation. However, for highly soluble gases, the pulmonary arterial and pulmonary venous blood has similar soluble gas concentration because only a very small fraction of the gas is eliminated into the respired air. So any perfusion of blood from one system into the circulation of the other should have an insignificant effect.

This paper uses a simple model that functionally separates these two types of exchange at the 10th generation of bronchial branching, which allows us to systematically explore the relationship between solubility and flux of highly soluble gases in the airways. Understanding exactly how overlap and transition between alveolar (pulmonary capillary) and airway (bronchial capillary) exchange may affect the exchange of highly soluble gases is a more complex problem requiring additional modeling.

Ethanol exchange in the lungs. Ethanol exchange in the lungs is temporally and spatially distributed. During inspiration, ethanol exchanges with the airway tissue and the bronchial (arterial) blood through a diffusion barrier that varies in length depending on the airway size and position in the airway tissue. Inspired air received ethanol from the arterial blood. The exchange is made possible by the very high water solubility of ethanol. Once within the alveolar acinar regions, the alveolar air equilibrates with arterialized (for ethanol) blood perfusing the pulmonary capillaries. During exhalation, some alcohol in the air moves back onto the airways.

Alcohol breath test. By far the most studied high blood- and water-soluble gas is ethanol. In the United States each year, there are ~1.5 million arrests for driving while intoxicated. Most of those arrested were given alcohol breath tests. The alcohol breath test is based on the assumption that end-exhaled breath ethanol concentration is always equal to alveolar ethanol concentration (which is presumed to be in equilibrium with mixed venous blood). However, as explained above, models (10, 20, 29) and experimental (20, 32) evidence do not support the alveolar assumption. From the data presented in this paper, it can be presumed that breath ethanol is, on average, about 20% lower in concentration than alveolar air after a complete prolonged exhalation. The relative reduction in breath ethanol concentration (from that in the alveolus) varies with exhaled volume (32). In some instruments, exhaled volume is estimated, but no correction is attempted for variance in exhaled volume. In essence, the lack of adjustment for physiological variation renders the alcohol breath test inaccurate. This problem would persist for a single-breath test for any of the high blood-soluble gases that exchange within the airways with the bronchial circulation.

In conclusion, highly blood soluble gases exchange primarily in the airways. The longitudinal distribution of the airway gas exchange depends on the water solubility of that gas, with the more highly soluble gases exchanging more proximally in the airway tree. Any gas that does not complete its exchange in the airways will do so in the alveoli, providing a uniform alveolar distribution with the partial pressure related to systemic venous blood through the Ostwald partition coefficient. During exhalation, each highly water-soluble gas exchanges with airway wall, which has been partially depleted of inert gas during inspiration. Of the gases studies in this paper, the redeposition of inert gas onto the airways is greatest for ethanol.

DISCLOSURES

All three authors serve as expert witnesses in alcohol-related cases.

AUTHOR CONTRIBUTIONS

Author contributions: M.P.H. and J.C.A. conception and design of research; M.P.H., F.L.P., and J.C.A. interpreted results of experiments; M.P.H. drafted manuscript; M.P.H., F.L.P., and J.C.A. edited and revised manuscript; M.P.H., F.L.P., and J.C.A. approved final version of manuscript; J.C.A. performed experiments; J.C.A. analyzed data; J.C.A. prepared figures.

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