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Breath tests and airway gas exchange

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Abstract

Measuring soluble gas in the exhaled breath is a non-invasive technique used to estimate levels of respiratory, solvent, and metabolic gases. The interpretation of these measurements is based on the assumption that the measured gases exchange in the alveoli. While the respiratory gases have a low blood-solubility and exchange in the alveoli, high blood-soluble gases exchange in the airways. The effect of airway gas exchange on the interpretation of these exhaled breath measurements can be significant. We describe airway gas exchange in relation to exhaled measurements of soluble gases that exchange in the alveoli. The mechanisms of airway gas exchange are reviewed and criteria for determining if a gas exchanges in the airways are provided. The effects of diffusion, perfusion, temperature and breathing maneuver on airway gas exchange and on measurement of exhaled soluble gas are discussed. A method for estimating the impact of airway gas exchange on exhaled breath measurements is presented. We recommend that investigators should carefully control the inspired air conditions and type of exhalation maneuver used in a breath test. Additionally, care should be taken when interpreting breath tests from subjects with pulmonary disease.

Keywords: Bronchial circulation; Endogenous; Soluble; Mathematical modeling; Alveoli

1. Introduction

The primary function of the lung is as a gas exchange organ. Most notably, the lung assists in exchanging oxygen and carbon dioxide between the atmosphere and the blood. However, the lung exchanges many more gases than simply the respiratory gases. Many non-respiratory gases that exchange in the lung are soluble inert gases such as ethane, ether, toluene, acetone and ethanol. Many times, these gases can be found circulating in the blood as a result of environmental exposure, ingestion and metabolic production. When blood enters the lung, these gases diffuse into the lung air and subsequently appear in the exhaled breath.

Because the lungs transport soluble gas from the blood to the exhaled air, the exhaled breath is frequently used as a non-invasive surrogate for a blood sample. It is thought that the partial pressure of a soluble gas in the exhaled breath represents the partial pressure of that gas in the blood. In this sense, the lungs are thought to provide a window into the blood and, by inference, the body. Because of its non-invasive nature, measurement of the exhaled breath is becoming increasingly common in many professions to infer soluble gas concentrations in the blood and by analogy to determine a medical condition or legal status of the subject. Industrial hygienists sample exhaled breath to estimate a worker's exposure to chemical solvents such as toluene and methyl ethyl ketone. Toxicologists and law enforcement agents depend on measurements of ethanol in the end-exhaled breath to estimate blood alcohol content in workers and automobile drivers. Currently, clinical scientists have become interested in sampling the end-exhaled breath for endogenous gases such as ethane, isoprene and acetone. Recent literature suggests that absolute blood levels of these gases may indicate common disorders such as lung cancer [1], acute myocardial infarction [2], and congestive heart failure [3].

Although sampling the exhaled air is relatively simple, the relationship between partial pressure of soluble gas in the breath and blood can be complex depending on where gas exchange occurs. Location of gas exchange, airway versus alveoli, depends primarily on the blood solubility of

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the gas as described by the blood–air partition coefficient, $\lambda_{b:a}$. Low blood-soluble gases like oxygen ($\lambda_{b:a} \approx 0.7$) and carbon dioxide ($\lambda_{b:a} \approx 3$) exchange in the alveoli while high blood-soluble gases like ethanol ($\lambda_{b:a} \approx 1756$) exchange in the airways. For low blood-soluble gases, the relationship between the breath and blood is relatively simple and depends predominately on two factors: the blood solubility of the gas, $\lambda_{b:a}$, and the distribution of ventilation-to-perfusion in all gas exchange units. For these gases, the partial pressure of soluble gas in the end-exhaled air depends on the breathing maneuver. For a tidal breath, the partial pressure of soluble gas in the end-exhaled air is equal to alveolar air. For these gases, the partial pressure of soluble gas in the alveolar air is not equal to that in the blood. However, the partial pressure of soluble gas in this alveolar sample can be converted to an approximate blood value by estimating the ventilation-to-perfusion distribution in the lung and using the Farhi kernel [4]. For a single-exhalation breath test (i.e. the subject inhales to total lung capacity and exhales at a slow constant rate to residual volume), the partial pressure of soluble gas in the end-exhaled air is larger than the alveolar air but generally smaller than that in the blood. This difference between the end-exhaled and blood partial pressure decreases as $\lambda_{b:a}$ increases for these low blood-soluble gases.

For high blood-soluble gases, gas exchange occurs in the airways and the relationship between end-exhaled breath measurement and blood is complex. Airway gas exchange depends on multiple factors such as airway temperature, bronchial blood flow and blood–air partition coefficient. For a particular gas, the specific airway generations participating in gas exchange affect the exhaled partial pressure. Additionally, the diffusion gradient for soluble gas exchange with the airways reverses from inspiration to expiration. As a result, the partial pressure of these soluble gases in the breath is always less than that in the blood and the relationship between the two is difficult to precisely quantify.

In this paper, we focus on airway gas exchange. First, we discuss the gross differences between gases that exchange in the alveoli versus those that exchange in the airways. Second, we discuss the specific mechanisms of airway and alveolar gas exchange and show where soluble gases exchange in the lung, alveoli versus airway. Third, we examine factors that most impact airway gas exchange. Fourth, we review how using a classical alveolar gas exchange model can lead to errors in interpreting breath tests involving highly blood soluble gases.

2. Airway versus alveolar gas exchange

The differences between gases that exchange in the alveoli and those that exchange in the airways can be observed in their expirograms. For a gas that exchanges in the alveoli (e.g. carbon dioxide), the partial pressure of gas in the exhaled breath as a function of exhaled volume is schematically shown as the parallel-lines tracing in Fig. 1.

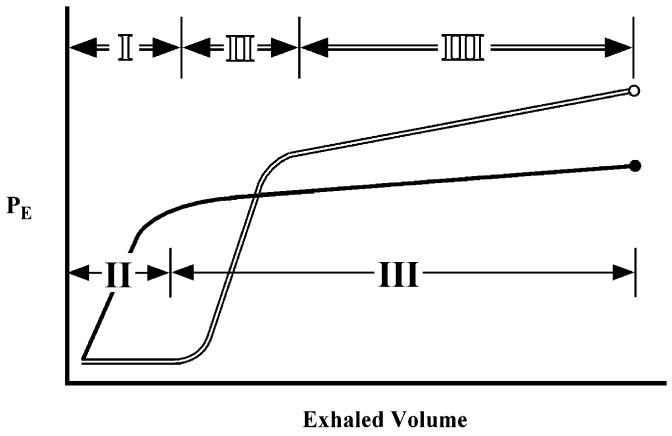

Fig. 1. Schematic identifying the phases of an expirogram from a low blood-soluble gas that exchanges in the alveoli (parallel-lines) and from a high blood-soluble gas that exchanges in the airways (solid line). Phase I represents air emptying the anatomic dead space (i.e. the conducting airways). Air emptying the exchange space, phase III, corresponds to air from the alveoli for low soluble gases and airways for high soluble gases. For gases exchanging in the airways: (1) phase I is not present because the airways participate in gas exchange; and (2) the end-exhaled breath concentration (solid circle) is always less than that in the alveoli.

The initial volume of air does not contain soluble gas and is labeled as phase I. This volume of air is considered to represent air residing in the anatomic dead space (i.e. conducting airways). The rapidly rising phase of the expirogram is labeled as phase II and represents the transition from air residing in the dead space to alveolar air. Soluble gas appearing at the mouth during phase III comes from the alveoli where gas exchange occurs. Thus, the final volume of air that exits the mouth represents alveolar air and measuring this end-exhaled breath provides an estimate of alveolar gas partial pressure (open circle). We contrast the expirogram of a gas that exchanges in the alveoli (parallel-lines curve) with a gas that exchanges in the airway (solid curve). For a gas that exchanges completely in the airways (e.g. ethanol), phase I is not present in the expirogram because the airways participate in gas exchange [5,6]. Therefore, an anatomical dead space cannot be defined for these gases. Phase III does not represent air coming from the alveoli but rather air emptying the exchange space. For these highly soluble gases, the exchange space is the conducting airways. In contrast to gases exchanging in the alveoli, the partial pressure of soluble gas in the end-exhaled breath (solid circle) is always less than that in the alveoli.

The differences between these expirograms for these two types of pulmonary gas exchange result from the different mechanisms underlying their exchange. For alveolar gas exchange, fresh air is inspired, fills the conducting airways, and then enters the alveoli. Once in the alveoli, low blood soluble gas present in the blood moves into this inspired air. This movement of gas from the blood into the alveolar air continues throughout the entire breathing cycle, inspiration and expiration. On expiration, gas in the

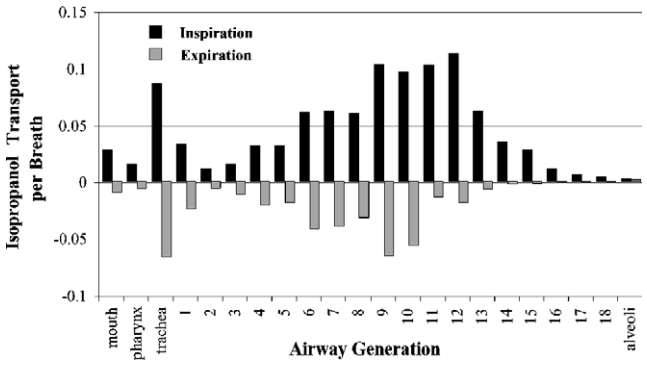

Fig. 2. The axial distribution of gas transport during inspiration (black columns) and expiration (gray columns) for a tidal breath of isopropanol ($\lambda_{b:a} = 848$) shows that almost 100% of isopropanol exchanges occurs in the airways. Each flux has been normalized by the total inspiratory soluble gas flux.

conducting airways leaves the lung first causing the phase I seen in the expirogram. Afterwards, alveolar air, containing high partial pressures of low blood soluble gas, exits the lung via the conducting airways and appears as phase III in the expirogram. The mechanisms of airway gas exchange are markedly different [5,7,8]. High blood-soluble gases are present in large concentrations in the airway tissue and mucus as compared with low blood-soluble gases for a given partial pressure. Thus, as fresh air is inspired, it absorbs high blood-soluble gas from the mucus lining the airway wall (Fig. 2) thereby depleting the concentration of soluble gas in the airway wall. Because of the small bronchial blood flow and the significant tissue barrier between the bronchial circulation and mucus layer, the airway wall is not replenished with soluble gas before expiration begins. By the time the inspired air reaches the alveoli, the air is saturated with soluble gas and no additional gas exchange occurs within the alveoli. During expiration, the air, saturated with soluble gas, encounters a lower partial pressure of soluble gas in the mucus and therefore a large driving force for the deposition of soluble gas on the mucus. This large air-to-mucus gradient promotes recovery of soluble gas by the mucous layer and delays the rise in soluble gas partial pressure at the mouth, thus accounting for the rising slope of phase III. These absorption–desorption phenomena cause the partial pressure of soluble gas in the end-exhaled breath to always be less that that in the alveoli (i.e. saturation) and is the major mechanism of pulmonary gas exchange for any gas with a blood–air partition coefficient greater than 100 [7].

3. Location of soluble gas exchange in the lung

To determine the appropriate method of interpreting a breath test, it is important to understand where a particular soluble gas exchanges within the lung. To determine location of gas exchange, we simulated pulmonary gas exchange using a mathematical model of the airways and alveoli of the lung [7]. The model has a symmetrically bifurcating structure through 18 generations. The upper respiratory tract and intraparenchymal airways are divided into 480 axial control volumes. Radially, the airways are divided into six layers (see Fig. 1 in [7]): (1) the airway lumen, (2) a thin mucous layer, (3) connective tissue (epithelium and mucosal tissue), (4) the bronchial circulation, (5) the adventitia, and (6) the pulmonary circulation. Cartilaginous airways (generation < 10), functionally, only have the first four layers. The respiratory bronchioles and alveoli are lumped together into a single alveolar unit. The concentration of soluble gas in the alveolar air is allowed to vary with time and depends on the pulmonary blood flow, ventilation, blood solubility, and concentration of soluble gas in the incoming blood as described by a mass balance on the alveolar compartment. Within each radial layer, concentration and temperature values are bulk averages for the entire layer. 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. Transport of water and soluble gas between layers occurs via filtration (from bronchial circulation to mucus) and diffusion (Fick's law). Mass and energy balances around a control volume produce three partial- and 9 ordinary-differential equations that are solved simultaneously in time and space. The solution of the mathematical model yields axial profiles of partial pressure within the airway lumen and airway wall (and all other layers as well) for any desired time during inspiration and expiration.

From these axial profiles of soluble gas partial pressure, the flow of soluble gas (mol/s) from the airway wall to the airway lumen for a given axial position (e.g. the trachea) and period of time can be calculated. For a given axial position such as an airway generation, these flows of soluble gas can be summed together over all time points throughout an inspiration and/or expiration. As an example of airway gas exchange, we simulated the exchange of isopropanol ($\lambda_{b:a} = 848$ from [9]) during steady breath-to-breath tidal breathing and calculated the mass flows of isopropanol at each airway generation. The sum of these isopropanol flows from airway wall to lumen over an inspiration and expiration is plotted in Fig. 2 and represents the axial distribution of isopropanol transport from the airway wall to the lumen (positive flow). The axial distribution of isopropanol transport on inspiration shows a bimodal distribution with a peak in the trachea and the 12th generation. After the 12th generation, isopropanol flows during inspiration decrease per generation and approach zero in the alveolar region. For isopropanol and other gases that exchange in the airways, almost 100% of exchange occurs within the airways. For low blood-soluble gases ($\lambda_{b:a} < 10$), their axial distribution of flow shows a concentrated spike in the alveoli. As the blood solubility of gas increases from low to high, the distribution shifts from a sharp concentrated peak in the alveolar region to a wider distribution that spreads throughout the airways as seen for isopropanol (see Fig. 5 in Anderson et al. [7]).

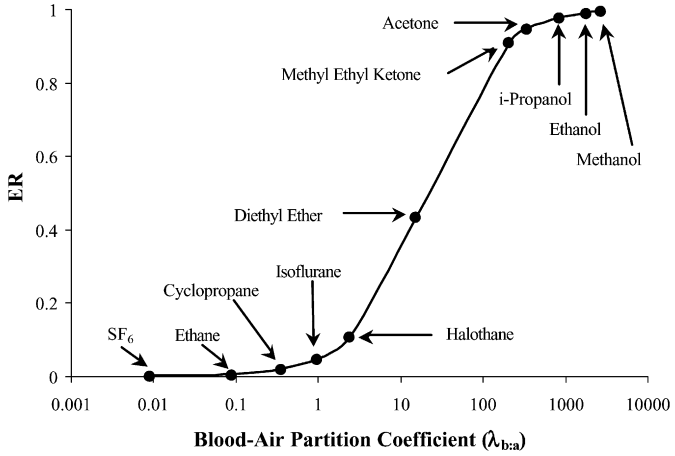

Fig. 3. The exchange ratio (ER) is the ratio of airway gas exchange to total pulmonary (airway + alveolar) gas exchange and is plotted versus $\lambda_{b:a}$ for eleven soluble gases as calculated from the airway–alveolar gas exchange model during tidal breathing. Gases with $\lambda_{b:a} < 10$ such as ethane and cyclopropane exchange predominately in the alveoli. Diethyl ether exchanges equally between the airway and alveoli. Gases with $\lambda_{b:a} > 100$ such as acetone and ethanol exchange almost exclusively in the airways (figure adapted from Anderson et al. [7]).

In Anderson et al. [7], we constructed axial distributions of gas transport during tidal breathing for eleven gases with $\lambda_{b:a}$ ranging from 0.88 to 2709. To determine where the majority of gas exchange occurs, either airways or alveoli, we defined an exchange ratio (ER) to be the ratio of airway gas exchange to total pulmonary (airway + alveolar) gas exchange. From the axial distribution, we calculated an ER for each gas and plotted ER against $\lambda_{b:a}$ (Fig. 3). Fig. 3 was adapted from Anderson et al. [7] and indicates where the majority of gas exchange occurs for a gas with a given blood–air partition coefficient. When ER = 0 or ER = 1, 100% of gas exchange occurs in the alveoli or airways, respectively. Thus, soluble gases with a blood–air partition coefficient less than ten ($\lambda_{b:a} < 10$) exchange almost solely with the alveoli whereas gases with a blood–air partition coefficient greater than 100 ($\lambda_{b:a} > 100$) exchange almost exclusively with the airways. Gases in between these two extremes ($10 < \lambda_{b:a} < 100$) exchange partially with the airways and partially with the alveoli. Although only eleven soluble gases were identified in Fig. 3, many more soluble gases exchange in the lung. The blood–air partition coefficients for some of these gases have been summarized [10] and can be used to estimate where in the lung these gases exchange.

4. Factors influencing airway gas exchange

Perfusion. It is known that an increase in bronchial blood flow increases the amount of blood soluble gas in the exhaled breath. This relationship has been shown for many soluble gases in the following experimental animal preparations: (1) a unidirectionally ventilated, in situ, isolated canine trachea [11]; (2) an intact, split lung sheep model with bronchial blood flow controlled via an aortic pouch preparation [12]; and (3) a sheep model where the left pulmonary artery was ligated for a period of weeks to years and caused the bronchial circulation to hypertrophy [13]. Because of this correspondence between blood flow and exhaled concentration, pathologies and drugs that increase bronchial blood flow will affect breath tests involving highly soluble gases. A many-fold change in bronchial blood flow has been seen in some pathological conditions such as asthma (100% change) [14], bronchiectasis (500–1000% change) [15], smoke inhalation (500% change) [16], and cystic fibrosis [17].

Diffusion. Soluble gas diffusion through the airway wall has been shown to affect airway gas exchange. Swenson et al. [18], using a unidirectionally ventilated, in situ, isolated canine trachea, demonstrated that gas exchange in the trachea is strongly dependent upon the diffusion of the gas from the bronchial vasculature to the airway lumen. Schimmel et al. [12] showed that excretion from the bronchial circulation was inversely affected by molecular weight (MW), demonstrating a dependence on diffusion. From modeling experimentally measured exhalation profiles in healthy subjects, George et al. [5] found that ethanol diffusion through the airway wall affected the exchange of ethanol with the airways. This diffusion dependence is best understood by examining the diffusing capacity of the airway tissue

$$D_L = \frac{D_t \Phi_c A_s}{\ell_t}.$$

This diffusing capacity is a function of the molecular diffusion coefficient through tissue, D_t, the surface area for diffusion between the bronchial capillary and tissue, which is represented by the capillary area fraction, Φ_c, multiplied by the airway surface area, A_s, and divided by the mucosal tissue thickness, ℓ_t. The diffusion coefficient of soluble gas through tissue is generally assumed to be 33% of its value in water [19]. The capillary surface area, $\Phi_c A_s$, and mucosal tissue thickness, ℓ_t, can change as a result of disease or inflammation as might occur with asthma. These changes could impact exhaled measurement of soluble gas. For example, if the mucosal tissue thickness increases as a result of airway wall remodeling, then the diffusing capacity decreases. A diminished diffusing capacity hinders the speed at which the airway wall can be replenished with soluble gas from the bronchial circulation. Thus, during exhalation, more soluble gas will be deposited on an airway wall from the airstream than would deposit on an airway wall with a normal diffusing capacity. As a result the soluble gas partial pressure in the exhaled air would be less than that in a normal healthy lung.

Temperature. We know that $\lambda_{b:a}$ of a soluble gas is the most important factor for determining the location of pulmonary gas exchange. However, $\lambda_{b:a}$ depends strongly on temperature [7], which can vary from 23 °C in the mouth during inspiration to 37 °C in the alveoli. Over this range, the blood–air partition coefficient can vary considerably. For example, methanol's temperature coefficient

for $\lambda_{b:a}$ is $-5.9\%/^{\circ}C$ [20]. As a result, $\lambda_{b:a}$ for methanol at the mouth during inspiration ($T = 23\,^{\circ}C$) can be 120% larger than $\lambda_{b:a}$ for ethanol in the alveoli ($T = 37\,^{\circ}C$). The dependence of $\lambda_{b:a}$ on temperature primarily affects soluble gas exchange occurring in the first 10 airway generations. These airways heat and humidify the inspired air and, as a result, a large axial temperature gradient is present that will change the value of $\lambda_{b:a}$. When breathing room air at rest, this dependency will most likely only affect soluble gases with $\lambda_{b:a} > 800$ like isopropanol that primarily exchange in the first ten airways' generations (Fig. 3). However, during exercise or breathing cold-dry air, a greater number of airway generations participate in heating and humidifying inspired air. As a result, the exchange of soluble gases with much lower $\lambda_{b:a}$ ($T = 37\,^{\circ}C$) values than isopropanol will be significantly influenced by the axial temperature gradient. Because of the large impact airway temperature (via airway energy exchange) can have on soluble gas exchange, it is important to control the inspired conditions and exertion of a subject when sampling the exhaled breath for soluble gas that interacts with the airways.

4.1. Exhalation maneuver

Breath testing commonly requires either a tidal exhalation [21–23] or a prolonged exhalation [3,6,24]. During a tidal exhalation, subjects passively exhale ~500 ml of air. The flow rate varies over the exhalation. During a prolonged exhalation, subjects inspire to total lung capacity and exhale ~5000 ml at a slow constant rate (~200 ml/s) to residual volume. Between of the different exhaled volumes and exhalation times, the type of exhalation maneuver affects the location of gas exchange. If we examine an inspiration as a sequence of small volumes of fresh air, the first volume of air absorbs soluble gas from the airway wall and decreases the concentration of soluble gas in the wall. Subsequent volumes of fresh air must each travel deeper into the lung than the preceding volumes to become saturated with soluble gas. Thus, compared to a tidal breath, a prolonged exhalation maneuver will shift gas exchange deeper into the lungs (i.e. towards the alveoli). For example, during a tidal breath 96% of acetone exchange occurs in the airways (Fig. 3) but during a prolonged exhalation maneuver 73% of acetone exchange occurs in the airways [6]. In addition to the volume of the exhalation maneuver, the speed of the maneuver may affect the end-exhaled concentration. Recently, we found that the normalized end-exhaled acetone concentration was dependent on flow and was 0.79 ± 0.04 and 0.85 ± 0.04 for the slow (~200 ml/s) and fast (~350 ml/s) exhalation rates, respectively [6]. For these reasons, it is important to control the volume and speed of the exhalation maneuver to reduce systematic errors in breath testing within and between subjects.

5. Potential errors from neglecting airway exchange

Model predictions of highly soluble gas exchange demonstrate that the concentration of high soluble gas in a volume of air increases (decreases) as this volume travels from the mouth (alveoli) to the alveoli (mouth). The increase (decrease) in concentration is caused by absorption (desorption) from (into) the airway mucosa. To understand how these absorption–desorption kinetics affect classic predictions of soluble gas exchange, we examined the exchange of 19 soluble gases with $\lambda_{b:a}$ ranging from 0.88 to 12382. We simulated gas exchange during tidal breathing using our model of airway and alveolar gas exchange. Each gas was assumed to originate in the blood. For each gas, we normalized the end-exhaled partial pressure by the venous partial pressure and plotted these data (open circles) on a semi-log plot against $\lambda_{b:a}$ (Fig. 4). This plot of soluble gas excretion is a reflection of a plot from Kumagai et al. [25] that summarized uptake data from the literature (Excretion = 1−Uptake). Included on this plot are similar predictions from the classic model of gas exchange (solid line). This classic model [4] describes gas exchange in an alveolar unit, excludes airway gas exchange, depends on the ventilation–perfusion ratio and $\lambda_{b:a}$, and is used to interpret end-exhaled breath measurements. For $\lambda_{b:a} < 1$, gas exchange occurs exclusively in the alveoli and thus, classic alveolar predictions accurately reflect pulmonary gas exchange. An algebraic transformation from Farhi [4] allows conversion of this end-exhaled measurement to an alveolar value. As $\lambda_{b:a}$ exceeds 100, the classic alveolar model assumes that the end-exhaled concentration represents the blood and alveolar value. However, our airway–alveolar model predicts that the end-exhaled partial pressure for gases with $\lambda_{b:a} > 100$ is always less than the blood value. The *difference* between the end-exhaled and blood partial pressures is a non-linear function of $\lambda_{b:a}$ that reaches a maximum at $\lambda_{b:a} \sim 800$. Currently,

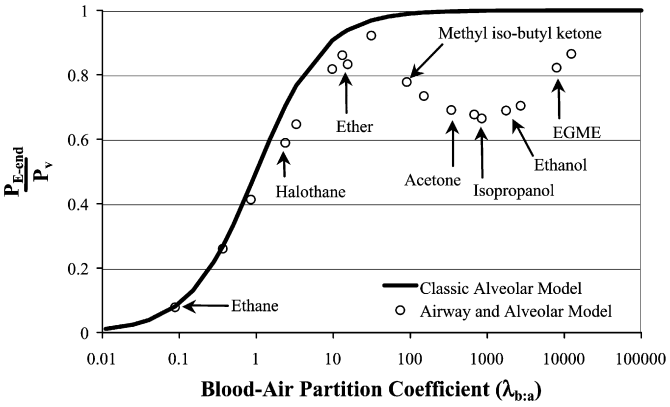

Fig. 4. End-exhaled inert gas partial pressure normalized by venous partial pressure versus blood–air partition coefficient during elimination of soluble gases during tidal breathing. Predictions from two models are presented: (1) the classic alveolar gas exchange model [4] that excludes airway gas exchange (solid line); and (2) a model of gas exchange in humans [7] that includes both airway and alveolar gas exchange (open circles). When $\lambda_{b:a} > 100$, airway gas exchange dominates and the predictions from the two models deviate. The vertical difference between the solid line and each circle represents the underestimation of alveolar air if airway exchange is neglected. EGME, ethylene glycol monobutyl ether.

a simple transformation is unavailable to adjust the end-exhaled concentrations to blood values for gases with $\lambda_{b:a} > 100$. Thus, end-exhaled concentrations of gases with $\lambda_{b:a} > 100$ should be interpreted as an estimate of blood concentration that may be 30% less than the true blood value.

6. Conclusion

Airway gas exchange significantly impacts the interpretation of breath tests, particularly for gases with a blood–air partition coefficient greater than 100. The absorption–desorption kinetics of airway gas exchange cause the end-exhaled gas concentration to be less than the blood value by up to 30%. Additionally, factors such as airway perfusion and diffusion that govern airway gas exchange are intrinsic to the lung and affected by lung disease. Other factors like inspired air temperature and breathing maneuver should be carefully controlled to ensure accurate and repeatable breath measurements.

Acknowledgments

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