Estimating Alveolar Ventilation for Use in Physiological-based Exposure Models

by

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Abstract

The United States Environmental Protection Agency (EPA) utilizes the Air Pollutants Exposure (APEX) model to estimate exposure to criteria air pollutants such as carbon monoxide (CO), to inform the setting of air quality standards (e.g., US EPA, 2010). The data for estimating alveolar ventilation rates ($\dot{V}_A$) in this model used for modeling CO exposures and dose was last updated over 20 years ago and could benefit from additional information extracted from new studies as well as performing additional data analysis. Specifically, the existing constant value used in the equation to estimate $\dot{V}_A$, 19.63, has been raised by public reviewers of the most recent CO human health risk and exposure assessment as potentially limited in its applicability, particularly at when simulated individuals are high breathing rates (US EPA, 2011). This new study was conducted to increase our knowledgebase of the physiological aspects of ventilation and to further develop an internal alveolar ventilation database that could be used to either support the existing quantitative linear relationship or, where possible, improve the algorithm. This evaluation also explored the relationship of how alveolar ventilation with might be affected by key demographic attributes such as body mass, age, and sex. Two approaches were explored to estimate $\dot{V}_A$ and are linked to key respiratory variables already modeled by APEX. The first, used a direct relationship between $\dot{V}_A$ and oxygen consumption rates ($\dot{V}_{O2}$). The second used the relationship of dead space to tidal volume (V_D/V_T) to $\dot{V}_{O2}$ and expected to be used with total ventilation rate ($\dot{V}_E$) to indirectly estimate $\dot{V}_A$. This study increased the amount of useful data within the internal database by over two-fold, albeit sample size limitations for important population groups remain an issue (e.g., adults > 35 years old). New data analyses using the updated database suggest a linear relationship between $\dot{V}_A$ and $\dot{V}_{O2}$ appears appropriate across all population groups and breathing rates, while differences in the V_D/V_T to $\dot{V}_{O2}$ relationship across

population groups suggests adoption of this latter approach is less likely due to the sample size issues. It is hoped study results assist in the development of a newly refined algorithm to for estimating CO exposure and dose estimations, reduce uncertainties in exposure models that would use such an approach, and provide sound support to air quality regulations.

Acknowledgements

Thank you to Dr. Linda Taylor for her extensive help and correspondence as I prepared myself for entering the Environmental Assessment program. Thank you to Dr. Tamara Pandolfo, Dr. Jennifer Richmond-Bryant, Dr. Linda Taylor, and Dr. Stephen Graham for their welcoming, reassuring, and kind words of support, patience, understanding, and encouragement throughout my journey of returning to academics. Thank you to the NC Department of Health and Human Services' Vocational Rehabilitation program for sponsoring my education. A special thanks to my family without whom this would not have been possible.

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Introduction

The United States Environmental Protection Agency (EPA) is responsible for the creation and maintenance of the primary National Ambient Air Quality Standards (NAAQS), regulations that are designed to reduce human exposure to pollutants that have been identified as criteria pollutants by the Clean Air Act. Human exposure modeling is a particularly useful element in informing the setting of the NAAQS and has been used as the basis for regulating pollutants such as carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (US EPA, 2007, 2008a; 2009; 2010; 2018; 2020). Exposure modeling provides a basis on which health effects in response to exposure to pollutants can be understood on a national basis and has functioned in the decision-making process of the EPA for several decades. One example of an exposure model serving as a useful tool for estimating inhalation exposures is the Air Pollutants Exposure (APEX) model.

Initially, this physiological-based population exposure modeling approach was used in developing the NAAQS for carbon monoxide (CO) and over time, this modeling tool, coined as the probabilistic NAAQS exposure model (pNEM; Johnson et al., 1999) has been refined, improved, and ultimately evolved into the Air Pollutants Exposure (APEX) model (US EPA, 2019a, b). APEX has incorporated numerous functionality improvements (e.g., probabilistic exposure, uncertainty analysis) and is currently able to estimate exposure to several air pollutants simultaneously. APEX is also capable of estimating on an individual basis the chemical exposure and doses in addition to expended energy, ventilation rates, and activity patterns all within a continuous time series (i.e., minute, hourly, daily basis).

It is the nature of models and modeling that after having been applied, over time, inadequacies or inefficiencies become apparent as do areas in which improvements can be made to increase the overall efficacy of the model. The advent of newly collected information can lead to the reduction of uncertainties and assumptions that existed earlier in the model's lifetime. It is also likely that added information and model inputs can serve to adjust previously used equations and algorithms. Such is the case for the APEX modeling methods used for CO.

In the most recent review of the NAAQS for CO there were areas identified as potential candidates for improvement in the estimation of exposures and potential health effects (US EPA, 2010; 2011). There were uncertainties in the exposure assessment regarding anticipating the dose levels of individuals that were simulated, especially considering various physiological characteristics. This is in large part due to the information available at the time of APEX's initial application. The items of particular concern in the review were the presumed linear relationship in the ventilation equation, the age of the studies that were used for data inputs, and the data collection methods used in those historical studies.

This paper seeks to present previously published research findings to improve the understanding of alveolar ventilation rate ($\dot{V}_A$), including ventilatory dead space and ventilatory CO exposure modeling, so that more accurate estimations can be made. In extending the knowledgebase using the existing probabilistic physiological-based approach, it is hoped that human health can be further protected by considering more realistic representations of activity-specific exposures and resulting health effects. Before providing the details for how the algorithm can be updated, we must first possess a reliable understanding of the most foundational aspect of air quality and its effects on human health: breathing. Alveolar ventilation rate and the equation used in its estimation with respect to the variability resulting from activities

performed has the potential to be improved, which would increase the reliability of the estimated exposures and health endpoints used to estimate health risk.

Terminology

Appropriate estimation of ventilation is dependent upon the understanding of the specific functions that take place during respiration (Figure 1). The human lung is not 100 percent efficient in its conversion of the O_2 molecule contained within any puff of air that is inhaled. Thus, it is pertinent to distinguish between the total volume of air that is taken in and the amount of air which actually participates in gas exchange. Furthermore, not all air that is taken into the airway reaches the alveoli of the lungs where gas exchange occurs. The terms used in a few noteworthy respiration resources (e.g., McArdle, 2001; West, 2000) hereafter have since been standardized in their usage by EPA. The entire amount of air that enters the airways is referred to as *total ventilation* or V_E. The *total ventilation rate* ($\dot{V}_E$) is defined as the amount of air taken in or out of the human per minute and is equivalent to breathing frequency (fb, breaths per minute) and tidal volume (V_T, in liters).

To quantify the amount of oxygen that has been taken into the blood (also CO which would also use a similar mode of absorption), it is necessary to measure the amount of air that does not participate in gas exchange. This is referred to as dead space, of which there are two varieties pertaining to our purposes. There is the amount of air that entered the air way that did not reach the alveoli called anatomic dead space, and the amount of air that successfully reaches the alveoli but still does not contribute oxygen to the body distinguished as alveolar dead space. The volume of both dead spaces added together is physiologic dead space. In healthy adults, the amount of alveolar dead space is miniscule therefore, anatomic and physiologic dead space are

treated as though equivalent. In the same fashion as total ventilation, we calculate the amount of dead space in liters per minute as dead space ventilation rate (V_D).

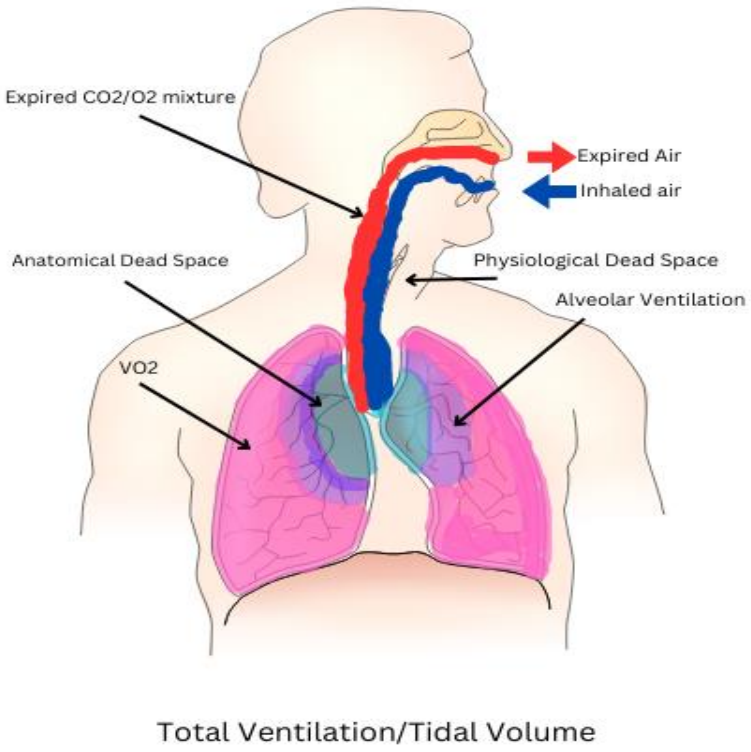

Figure 1 Diagram illustrating terms used for describing human ventilation.

To derive the dead space, one can measure and control the amount of O_2 that is inhaled in studies, inversely we can quantify the amount of carbon dioxide (CO_2) that is expired from the lungs. The amount of CO_2 in the dead space is negligible, so the rate of CO_2 expired from the lungs (V_{CO2}, liters per minute) can be used to estimate the amount of actual gas exchange, alveolar ventilation, that occurred. The expired concentration of CO_2 is comprised of alveolar PA and arterial Pa partial pressures. These values are the CO_2 and O_2 mixtures measured either through blood draw or end of exhalation by which the amount of exchanged gas can be

quantified or approximated. For our purposes these partial pressures are treated as being equivalent, this is because the CO_2 transfer in the lung has been shown to be effective. Fortunately, the partial arterial pressure of CO_2 in the blood (P_{ACO2}, mm-hg) can be measured via direct methods or otherwise reliably approximated. With these terms established we are now able to present the relevant constants, equations and parameters used within the APEX model for estimating $\dot{V}_A$.

Overview of Ventilation Relationships

Following the presentation of the fundamental terminology, key ventilation relationships were explored to create the context for collecting additional data and generating potentially new predictive equations that might be useful for exposure models. As discussed above, total ventilation rate ($\dot{V}_E$) is equal to the breaths per minute or breathing frequency (fb) and the tidal volume (V_T, volume of air per breath in liters).

$$\dot{V}_E = f_B \times V_T \qquad \text{(eq. 1)}$$

It can be exceedingly difficult and impractical to account for the myriad of potential variables that can affect an individual's ventilation rate (activity level, age, body mass, and sex). To facilitate this, one could use a relationship between energy expenditure/activity level and their total oxygen consumption rate ($\dot{V}_{O2}$) (US EPA, 2009). A multiple linear relationship shown in equation 2 was developed to account for age, body mass, and sex (Graham and McCurdy, 2005). Note that, due to discontinuities of the $\dot{V}_E$ response with respect to age, separate regression equation coefficients were developed using the fundamental algorithm below and based on four different age groups. The benefit of this approach is that it allows for the estimation of activity-specific ventilation rate for exposure events ranging from 1 minute to 1 hour, while also

accounting for the most important influential variables of body weight, age, and sex. This approach to estimating the time series of ventilation rates for individuals, select population cohorts (e.g., children ages 5-18), and populations residing in an urban area has been used in the population-based exposure assessments for CO, NO_2, O_3 and SO_2 (US EPA, 2008, 2010, 2018, 2020).

$$Ln(\dot{V}_E/BM) = b_0 + b_1 Ln(\dot{V}O_2/BM) + b_2 Ln(age) + b_3(sex) + e_b + e_w \qquad \text{(eq. 2)}$$

The approach for predicting activity-specific $\dot{V}_E$ was recently updated to a simpler form, while still inherently accounting for the most influential variables that would affect inhalation rates (see Appendix H of U.S. EPA (2018)). First, the new $\dot{V}_E$ algorithms explain variability in ventilation rate by using a new variable, the maximum volume amount of oxygen an individual can use during intense or maximal exercise ($\dot{V}_{O2}$max) as an input. Body weight, height, and sex – as well as fitness level (which is often represented by $\dot{V}_{O2}$max) – influence oxygen consumption for a particular activity. When modeling inhalation rates using APEX, variability for each of these influential variables are already captured in the algorithm used to estimate each simulated individual's resting metabolic rate (RMR), which, combined with estimates of energy expended while performing activities such as sleeping, walking, or running, is used in estimating activity-specific $\dot{V}_{O2}$. As a result, the only input variables needed for this new $\dot{V}_E$ algorithm are $\dot{V}_{O2}$ and $\dot{V}_{O2}$max (eq. 3), both of which are already estimated by APEX.

$$\dot{V}_E = e^{\left(3.300 + 0.8128 \times \ln(\dot{V}_{O2}) + 0.5126 \times (\dot{V}_{O2}/\dot{V}_{O2}max)^4 + \mathrm{N}(0,\mathrm{eb}) + \mathrm{N}(0,\mathrm{ew})\right)} \qquad \text{(eq. 3)}$$

As mentioned in the previous section, we understand that the lungs do not utilize all the oxygen within the entire volume of a breath. As a result, using total ventilation would not be the most appropriate metric to use when estimating an inhaled dose, which would vary based on the

physical-chemical characteristics of the inhaled substance. For instance, respiratory gases such as O_2 and CO_2 (and hence CO) require a different approach to estimate respiratory exchange and inhaled dose when compared to substances such as particles and relatively hydrophobic chemicals, which would likely have a portion of the amount inhaled trapped and removed by the lungs via respiratory elimination mechanisms (e.g., mucociliary escalator). In the same fashion that $\dot{V}_E$ was expressed, the physiologic dead space ventilation (which is the sum of physiological and anatomical dead space) is expressed as the product of breathing frequency and the volume of dead space estimation.

$$\dot{V}_D = f_B \times V_D \quad \text{(eq. 4)}$$

The alveolar ventilation rate ($\dot{V}_A$) is the volume of air, in liters, per minute, that successfully contacts the alveoli and participates in exchange of gaseous substances. Because total ventilation encompasses both the air that enters the airway that is and is not exchanged, the total ventilation rate can be expressed as the sum of the dead space ventilation rate and the alveolar ventilation rate.

$$\dot{V}_E = \dot{V}_A + \dot{V}_D \quad \text{(eq. 5)}$$

After having been rearranged, and by understanding alveolar ventilation to be a fraction of total ventilation, we can use an expression including dead space and tidal volume as ratios to express $\dot{V}_A$ as a function of $\dot{V}_E$.

$$\dot{V}_A = \dot{V}_E \left(1 - \frac{V_D}{V_T}\right) \quad \text{(eq. 6)}$$

As mentioned in the previous section, alveolar ventilation can be estimated in a clinical setting by measuring the amount of expired CO_2. The rate of CO_2 expired from the lungs in liters

per minute is noted by $\dot{V}_{CO2}$. The CO_2 that is expired from the lungs mixes with the CO_2 quantities in the dead space (although negligible). This mixture is a fraction of the volume of alveolar CO_2 (or C_{ACO2}). As such, to yield the rate of the volume of expired CO_2, we observe the product of the rate of alveolar ventilation and the volume of alveolar CO_2.

$$\dot{V}_{CO2} = \dot{V}_A \cdot C_{ACO2} \quad \text{(eq. 7)}$$

Because alveolar and arterial partial pressure contents of CO_2 have been considered equivalent, we can utilize the equation above to include their composite values (P_{aCO2}), where K is a conversion factor equal to 863 mm-hg derived from the ideal gas law.

$$\dot{V}_A = \frac{\dot{V}_{CO2}}{P_{aCO2}} \times K \quad \text{(eq. 8)}$$

Alternatively, we can express alveolar ventilation in terms of $\dot{V}_{O2}$. For this we use the respiratory quotient or RQ, defined as the metabolic gas exchange ratio. For standard diets and lifestyles, the RQ is considered equal to 0.82 (McArdle et al., 2001).

$$RQ = \frac{\dot{V}_{CO2}}{\dot{V}_{O2}} \quad \text{(eq. 9)}$$

The most widely used method for calculating the physiological dead space is Bohr's equation. This is due to the complications involved in taking direct measurements of V_D. Instead, Bohr's equation can be used to indirectly measure V_D by using the partial pressure of arterial CO_2 (P_{aCO2}) (St. Croix et al., 1995) and the mixture of partial expired CO_2 (P_eCO_2) that can be measured after exhalation as above, with arterial and alveolar partial pressures being treated equal (West, 2000).

$$\frac{V_D}{V_T} = \frac{P_{aCO_2} - P_{eCO_2}}{P_{aCO_2}} \quad \text{(eq. 10)}$$

Previously, there were limitations in the data necessary to determine the variables used in some of the above equations, to account for activity-specific $\dot{V}_A$ (Galetti, 1959). Galetti derived a simpler form for estimating alveolar ventilation by using exploring a linear relationship between $\dot{V}_A$ and $\dot{V}_{O2}$. The calculation for this, including a constant C and considering an initial starting condition of $\dot{V}_{O2}$ being equal to zero (and hence $\dot{V}_A$ = 0), is as follows.

$$\dot{V}_A = c \times \dot{V}_{O2} \quad \text{(eq. 11)}$$

Also,

$$1/c = d\dot{V}_{O2} / d\dot{V}_E \quad \text{(eq. 12)}$$

where, d$\dot{V}_{O2}$ = derivative of $\dot{V}_{O2}$, with $\dot{V}_{O2}$ = 0

When taking the quadratic expression including the data used in the source study of the model shown as

$$\dot{V}_{O2} = -55.0 + 51.34\,\dot{V}_E - 0.191\,\dot{V}_E{}^2 \quad \text{(eq. 13)}$$

And implementing the derivate in the previous equation, the following is yielded.

$$d\dot{V}_{O2} / d\dot{V}_E = 51.34 - 0.382\,\dot{V}_E \quad \text{(eq. 14)}$$

Using these equations and data, with $\dot{V}_{O2}$ equaling 0, $\dot{V}_E$ is approximately equal to 1.08. When using this $\dot{V}_E$ value in the last equation gives 50.93. Next, a correction is necessary for the units squared and the reciprocal of the constant C is converted to 0.05093, or 19.63. Having established this relationship, the following has been used for the estimation of alveolar ventilation (Journard et al., 1981).

$$\dot{V}_A = 19.63 \times \dot{V}_{O2} \quad \text{(eq. 15)}$$

It is this singular constant 19.63 and its derivation that are of interest in this study. It might be difficult to represent the wide variety of variables that might influence another with a single constant. Sex, body mass, age, and activity levels are possibly among the influential variables that may be necessary to adequately account for to yield representative estimations. Further, limitations of using this algorithm to estimate alveolar ventilation rate are also in part due to the volume of data commonly used to develop useful predictive equations.

The first step to addressing the potential shortcoming is to compile additional and more recent studies containing measurement values for $\dot{V}_A$, $\dot{V}_{O2}$, V_D, V_T, and $\dot{V}_E$ at various activity levels. The relationships developed because of the newly collected data would also be made stronger if they appropriately represented both sexes and encompassed a wide range of ages and body mass. At the time of this writing, the publication dates from sources in the provided pre-existing data ranged from the early 1900's to 2008. While all applicable and appropriate studies that were found had their measurements recorded in the dataset, a particular focus was given to finding sources from 2008 to present, while also open to older publications to bolster the overall data set.

Background

The estimation of alveolar ventilation rate, and the constant value of 19.63 used has been raised as an important respiratory metric in need of update in exposure modeling. During the proposal of the 2011 Carbon Monoxide NAAQS, comments were received in response to the Quantitative Risk and Exposure Assessment for Carbon Monoxide (REA) by the National Association of Clean Air Agencies (NACAA) and Northeast States for Coordinated Air Use Management, along with twelve other state and local level agencies and ten environmental interest groups and public health organizations and other individuals (see Docket Number EPA-

HQ-OAR-2008-0015). Among the comments received was one directly suggesting the constant value of 19.63 was inadequate for broad use in estimating $\dot{V}_A$. Specifically, the commenter took issue with the frequent assumption of linear relationships between certain variables and the implications and impacts that it would have for estimating the adverse health effect used in the CO REA (i.e., carboxyhemoglobin or COHb).

The spirit of the comment was agreed upon by EPA, as limitations in anticipating the relationships between variables while modeling is to be expected. However, in the case of 19.63 the EPA disputed that for its intents and purposes, while some improvements could be made with added data, the constant was adequate. It was acknowledged that use of 19.63 might cause overestimations of $\dot{V}_A$ at sedentary or low activity levels, however, medium to higher levels of activity were more likely to be underestimated. Yet due to the expected decrease of $\dot{V}_A$ and $\dot{V}O_2$ in older adults, the population group of greatest interest regarding adverse health effects following CO exposures, underestimations of $\dot{V}_A$ during moderate of high activity are possibly limited. The point of contention between the commentor and EPA was primarily concerned with the importance of $\dot{V}_A$ regarding its impact on COHb. The commentor was concerned with a snowballing effect of inaccuracies on exposure estimations as a result of using the constant value of 19.63's in the modeling, however the gravity of 19.63 was not effectively demonstrated. Further review following the REA would go on to show that the concentration of CO, has a much larger impact on COHb estimation than that of $\dot{V}_A$ (US EPA, 2011), further supporting the general conclusion that adjusting the constant may not have a significant impact to the estimated risk.

That said, it is generally understood that a model is made stronger with new data, updated algorithms, and evaluation methods. The NAAQS for CO is once again due for review. In the

interest of lessening some of the uncertainty in estimating $\dot{V}_A$ by exposure models such as APEX and to further account for the relationship between variables, data analysis was conducted which began with the search for additional relevant studies.

Data Collection and Analysis

The literature review aspect of this work was to obtain research publications having ventilation measurements taken at different workloads or activity levels for healthy individuals and add them to the preexisting data collected thus far. Many studies concerning the evaluation of COPD patients were used but only the data for the healthy controls was taken. Some studies accounted for only partially the measurements that were sought. The amount of data for children and infants is still limited, as is the amount of data for individuals over 50 years of age. By far the most represented age group reported in extant literature is 18-35 years. Fortunately, most studies utilized uniform methods of measuring activity levels such as treadmills and ergonomic cycles. Similarly, the methods for taking the measurements are also identical. Unit conversions were mostly only needed for data collected from infants or children.

Eventually the amount of data points in the preexisting data set was effectively doubled. Before adding the new data, the data set contained 109 group mean values from studies conducted between 1957-2004 and taken from 21 original studies. For 5 of these studies, various useful measurements such as $\dot{V}_{O2}$, V_D/V_T, and $\dot{V}_E/\dot{V}_{O2}$ were not reported, but these values were able to be produced using calculations from the data that was available along with a few of the relationships described in equations 1 through 15. Using this newly generated data set, the linear regressions for V_D/V_T and $\dot{V}_{O2}$, and $\dot{V}_A$ and $\dot{V}_{O2}$ were derived. Figures 2 and 3 are the plots showing the pre-existing data set and proposed relationships for estimating $\dot{V}_A$.

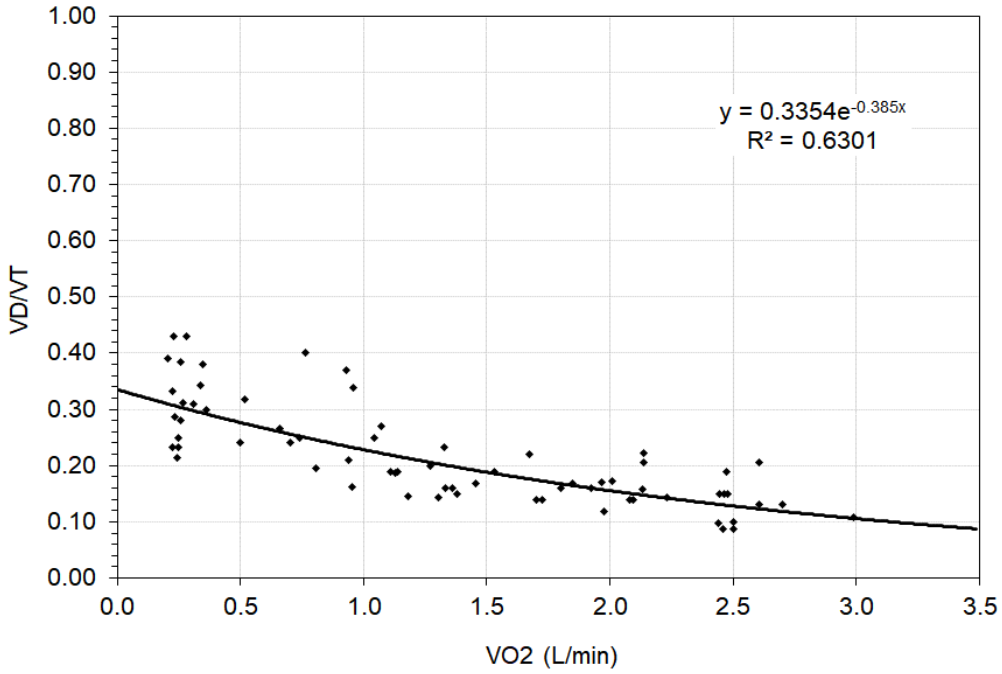

Figure 2. Relationship of V_D/V_T to $\dot{V}_{O2}$ from pre-existing dataset.

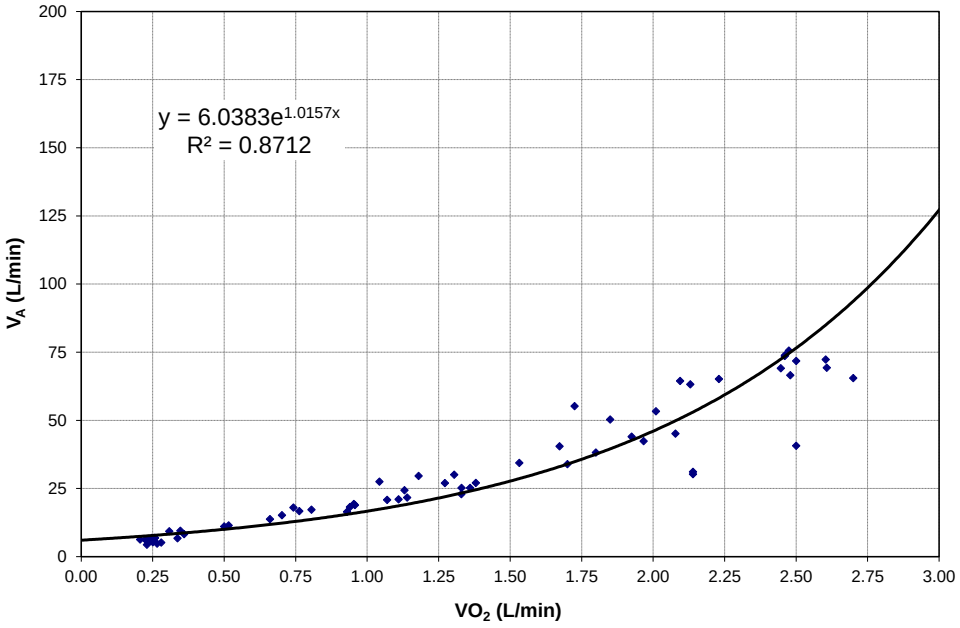

Figure 3. Relationship of $\dot{V}_A$ to $\dot{V}_{O2}$ from pre-existing dataset.

With the process of adding new data complete, there are now a total of 193 group mean values from 38 sources. As was the case previously, only a few sources contained all the relevant measurements needed for the two relationships explored. Many studies on ventilation are not concerned with quantifying dead space. Ventilatory dead space was not measured in 54 of the 193 total data points. V_D alone was not measured most of the time however, a calculated V_D/V_T was commonly provided in the publication. Seventy-one of the 193 measurement collections did not include $\dot{V}_A$. Also, as was the case in generating data for the pre-existing data set, there remains a limited amount of data for individuals younger than 19 years of age, and those older than 35. Nonetheless, with this new data now included, the next step was to understand the statistical distribution for each variable of interest, including a determination of how study subject attributes (i.e., age and sex) may influence the ventilation metrics. The general intent is also to determine if a data transformation is needed prior to their use in the statistical model. Following this determination, the goal was to establish the most appropriate relationships that can be generated between the variables of interest. The following sections present the progression of the distributional analysis and the development of statistical relationships that could be useful in predicting alveolar ventilation.

Distributions of $\dot{V}_{O2}$/BM and $\dot{V}_A$/BM

When comparing physiological variables across different ages and sex, it is common to normalize the variable of interest by the study subjects' body mass (BM). Where data were available across these three parameters ($\dot{V}_{O2}$, $\dot{V}_A$, BM) this calculation was performed. Out of the master dataset, there were 84 entries which contained the necessary information to assess $\dot{V}_{O2}$/BM and $\dot{V}_A$/BM and sex. Of these 84 group mean values, there were 34 females, 40 males, 6 used both male and female subjects, and 4 did not have sex reported (and not used here). Figure

4 shows that for both $\dot{V}_A$ and $\dot{V}_{O2}$ there are differences in the distributions beyond body mass that is related to sex. This is due to physiological differences in lung development and capacity, and musculature. Note that, because of the small sample size for the group not distinguished by a known sex, the distribution deviates from the others.

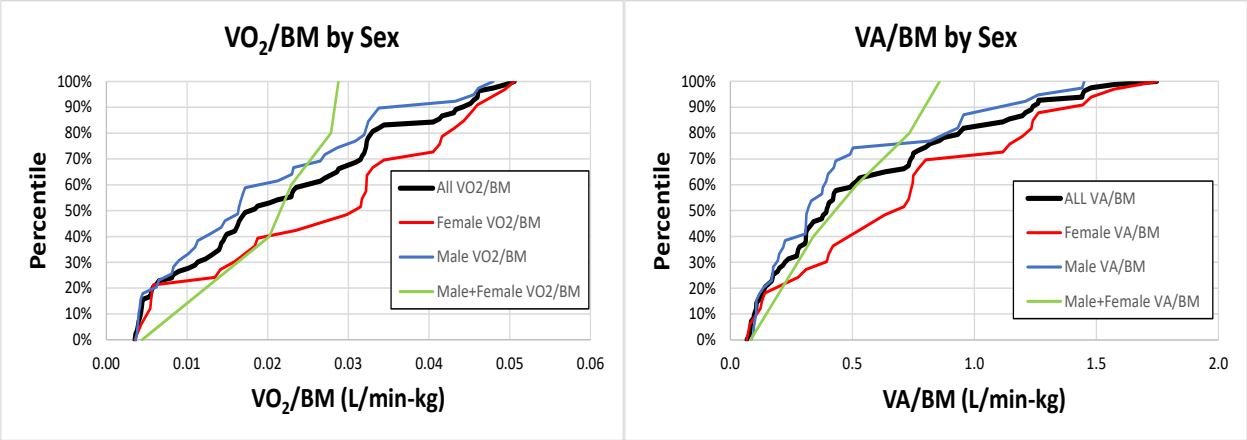

Figure 4. A side-by-side comparison of body mass normalized distributions of $\dot{V}_{O2}$ (left) and $\dot{V}_A$ (right) categorized by age sex.

Distributions of $\dot{V}_{O2}$/BM and $\dot{V}_A$/BM by Age Groups

Within the selected data set there were only 10 data points each for study subjects either under age 19 or over age 35, while there were 64 group mean values for subjects ranging from 18 to 35 years in age. As expected, lung efficiency is shown to increase with age (Figure 5). The distribution of the adults >35 years old could possibly be attributed to difficulty in performing higher workloads during the study, in addition to their having a smaller sample size to construct the distributions shown.

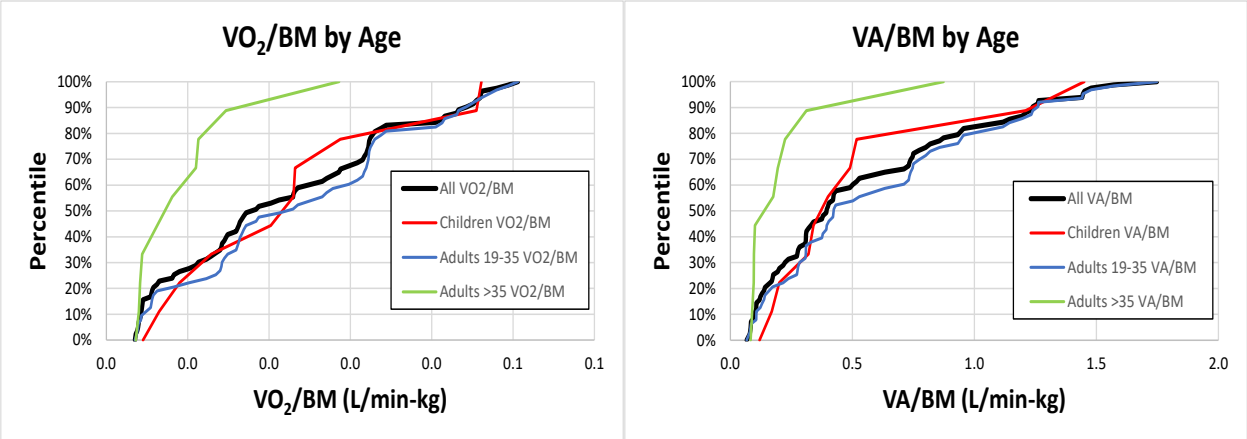

Figure 5. A side-by-side comparison of body mass normalized distributions of $\dot{V}_{O2}$ (left) and $\dot{V}_A$ (right) categorized by age groups.

Distributions of $\dot{V}_A/\dot{V}_{O2}$ by Sex

Ultimately, the statistical model would employ a simple linear regression of $\dot{V}_A$ on $\dot{V}_{O2}$. As a result, the distribution of the $\dot{V}_A/\dot{V}_{O2}$ ratio was evaluated in a similar fashion as was done above using these two individual variables alone (Figure 6). This is because the normalization by body mass is not needed due to the fact that by using a ratio, both variables would have the same exact response and hence would in effect cancel one another out (i.e., $\dot{V}_A$/BM ÷ $\dot{V}_{O2}$/BM = $\dot{V}_A/\dot{V}_{O2}$).

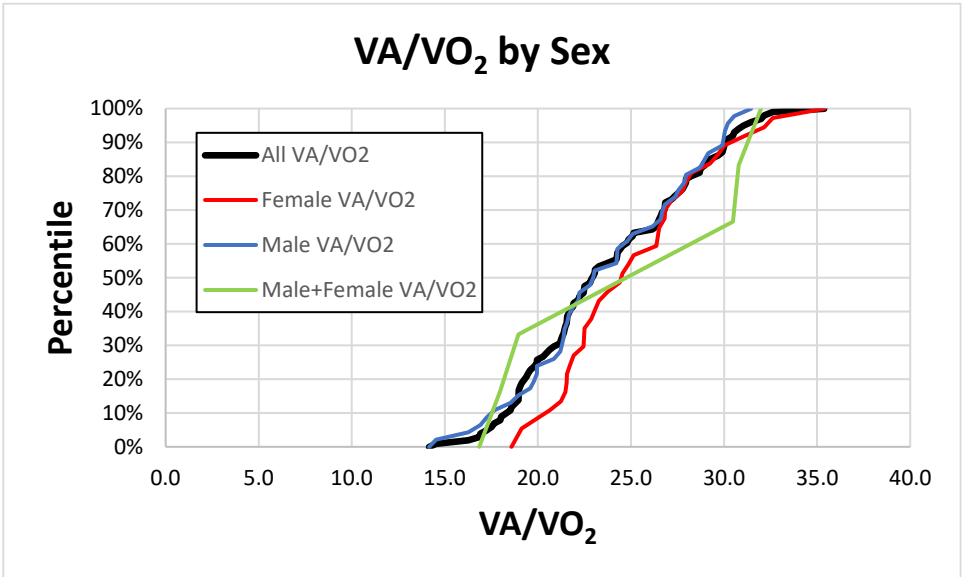

Figure 6. Distributions of the $\dot{V}_A/\dot{V}_{O2}$ ratio categorized by sex.

As shown in Figure 6, the female study participants had a higher minimum $\dot{V}_A/\dot{V}_{O2}$ and converge with males at the 70th percentile. The higher minimum $\dot{V}_A/\dot{V}_{O2}$ in females could be attributed to higher ventilation rates while at rest. In general, however, the distributions for the two are similar and they are expected to have a shared distribution shape that comports well with a simple linear regression.

Distributions of $\dot{V}_A/\dot{V}_{O2}$ by Age Groups

Ventilation efficiency is highest in the age bracket of 19-35 and as expected has lower efficiency in lesser developed lungs (i.e., children) and in older adults (Figure 7). The differences are also possibly related to the peak workloads achieved by study participants, as those are higher also within the 19-35 age group. However, as observed with the $\dot{V}_A/\dot{V}_{O2}$ by sex data, the distributions are similar across all the age groups, supporting a regression analysis that need not include either of these personal attributes as explanatory variables in perhaps a multiple linear regression nor a need for developing separate equations for either sex or age groups.

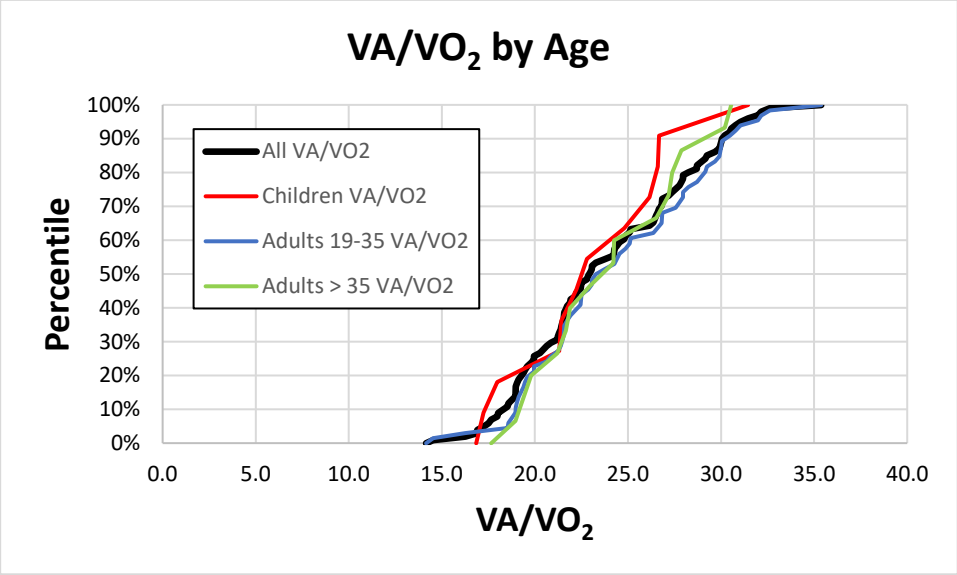

Figure 7. Distributions of the $\dot{V}_A/\dot{V}_{O2}$ ratio categorized by age groups.

Statistical Model for $\dot{V}_A$ and $\dot{V}_{O2}$

Figure 8 presents all study data that reported both $\dot{V}_A$ and $\dot{V}_{O2}$ measurements. Here we observe a considerable linear relationship, supporting the earlier relationship that used a constant value to estimate $\dot{V}_A$ from $\dot{V}_{O2}$. This demonstrates consistent efficiency of the lungs when air (and hence O_2) reaches the alveoli in healthy individuals. The overall statistical model is excellent, having a regression $R^2 = 0.928$, $p<0.001$.

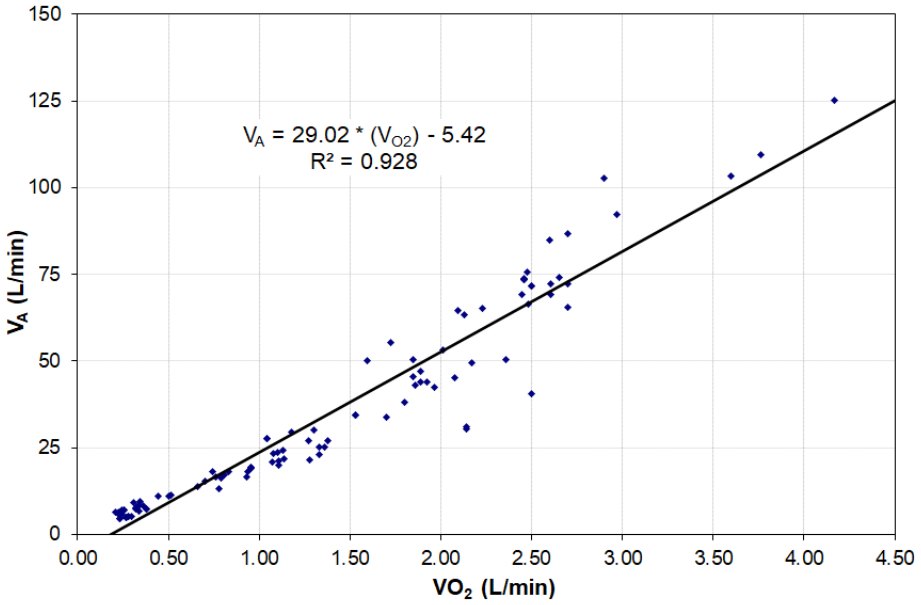

Figure 8. Linear regression model of $\dot{V}_A$ to $\dot{V}_{O2}$ that includes a non-zero intercept.

The overall model fit and predictability of this $\dot{V}_A$ to $\dot{V}_{O2}$ linear regression equation was evaluated. The first approach used a normal probability plot to evaluate the overall distribution of $\dot{V}_A$. As noted above, at times there were features of the distribution that could render it somewhat different than that of a normal distribution, which is one of the general requirements needed when applying statistical techniques such as linear regression.

Figure 9 shows the normal probability plot for the collection of group mean values for $\dot{V}_A$. Data having a normal distribution would have a linear (straight) relationship in this type of plot, and admittedly, there appears to be some curvature and is consistent with the distributional analysis shown above in Figures 4 and 5. However, the relationship shown above in Figures 6 and 7 that incorporate both $\dot{V}_A$ and $\dot{V}_{O2}$ clearly demonstrates a linear relationship, further supporting their use without transformation to make the data more normally distributed.

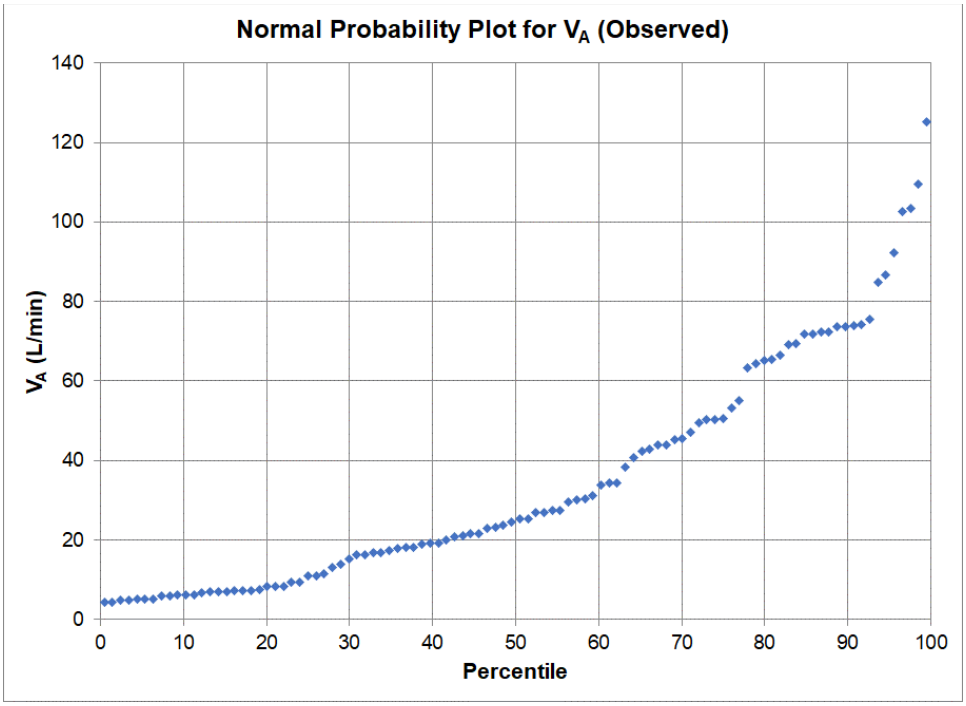

Figure 9. Normal Probability Plot for $\dot{V}_A$ using all data.

It follows that when plotting the original $\dot{V}_A$ to $\dot{V}_{O2}$ data along with the predicted $\dot{V}_A$ using the statistical model, there is good agreement between the two (Figure 10). This is not surprising given the statistical model fit statistics.

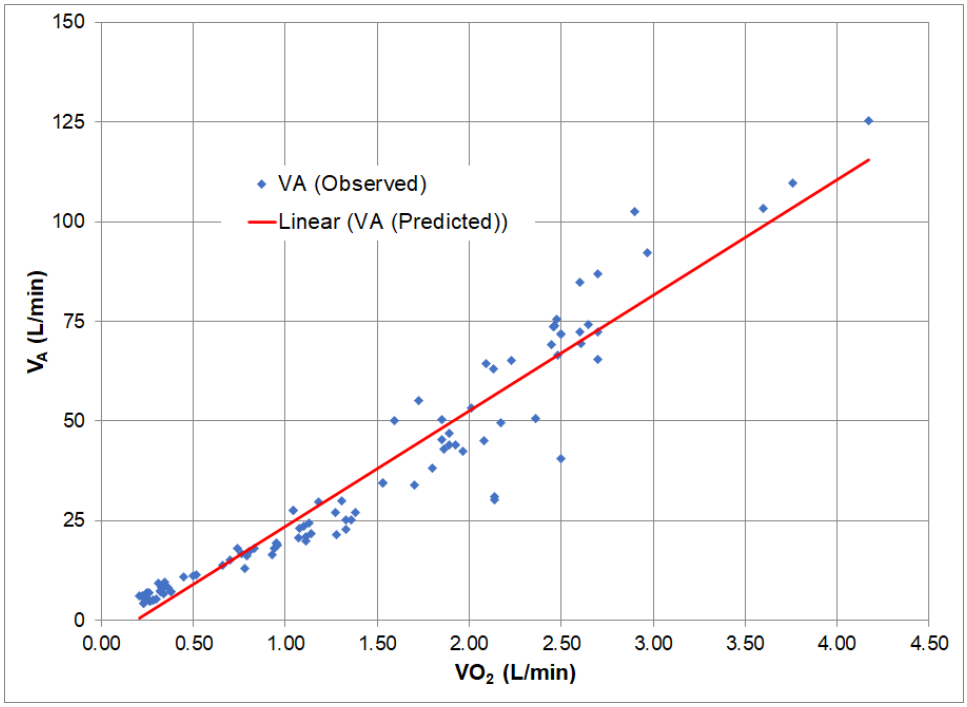

Figure 10. Line fit plot for $\dot{V}_A$ using a $\dot{V}_{O2}$-based regression model that includes a non-zero intercept.

A linear model that uses a non-zero regression intercept might be less than ideal when simulating individuals in an exposure and dose assessment. Given that the measurement data visually appear to be trending towards intersecting with the plot origin and from a practical perspective, one could presume with a measured decrease in $\dot{V}_{O2}$ would also correspond to a relatively similar decrease in $\dot{V}_A$, a linear regression model using zero as the intercept was also developed. Figure 11 shows the relationship as a companion to the earlier linear regression model provided by Figure 8. Again, the model fit is excellent ($R^2 = 0.967$), indicating that the reduction of the equation to a simpler linear regression form $y = ax$ rather than $y = ax + b$ did not dramatically alter the overall relationship between $\dot{V}_A$ to $\dot{V}_{O2}$. This is generally supported by the comparison of the observed vs. predicted values for $\dot{V}_A$ using this simplified relationship and shown in Figure 12 and is consistent with assumptions made by Galletti (1959) and Joumard (1981).

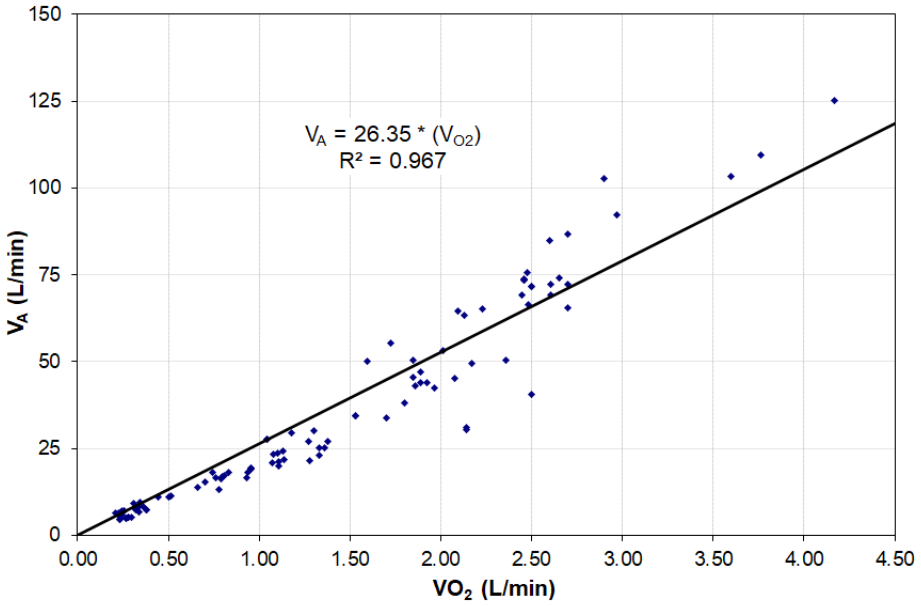

Figure 11. Linear regression model of $\dot{V}_A$ to $\dot{V}_{O2}$ that includes a zero intercept.

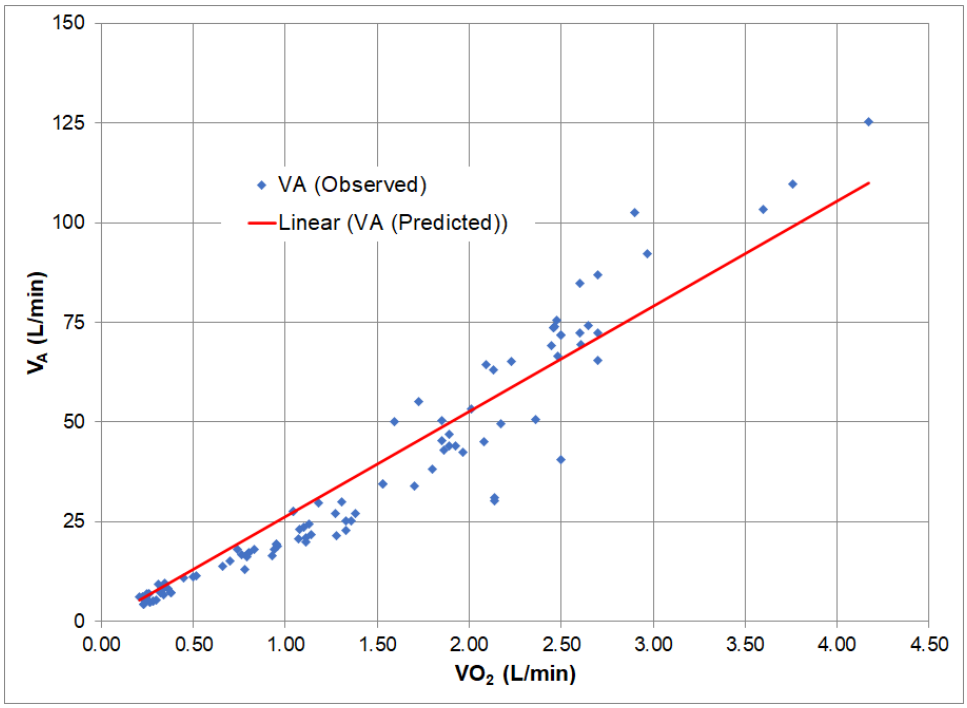

Figure 11. Line fit plot for $\dot{V}_A$ using a $\dot{V}_{O2}$-based regression model that includes a zero intercept.

Approach 2: Use of Dead Space to Tidal Volume

The second approach proposed to estimate alveolar ventilation involved the use of dead space to tidal volume and, when combined with estimates of total ventilation, can be used to estimate $\dot{V}_{O2}$. As described above, distributions of the variables of interest were evaluated, followed by the construction of the most appropriate and best fit statistical models. Even though there may be some differences in the set of studies that included $\dot{V}_{O2}$ in the first approach compared to those that measured $\dot{V}_{O2}$ within the set of studies evaluated here, the number of potentially unique values were considered as likely having a negligible impact to the overall $\dot{V}_{O2}$ distribution and as a result, an additional evaluation was not performed here.

Distributions of V_D/V_T by Sex

The distribution of V_D/V_T ratio for females is somewhat different across the middle portion of the distribution again most likely due to the smaller sample size (Figure 13). These differences in the distribution of the V_D/V_T ratio are a bit concerning as they may not provide support for a single predictive equation as was observed above for the $\dot{V}_A$ to $\dot{V}_{O2}$ model.

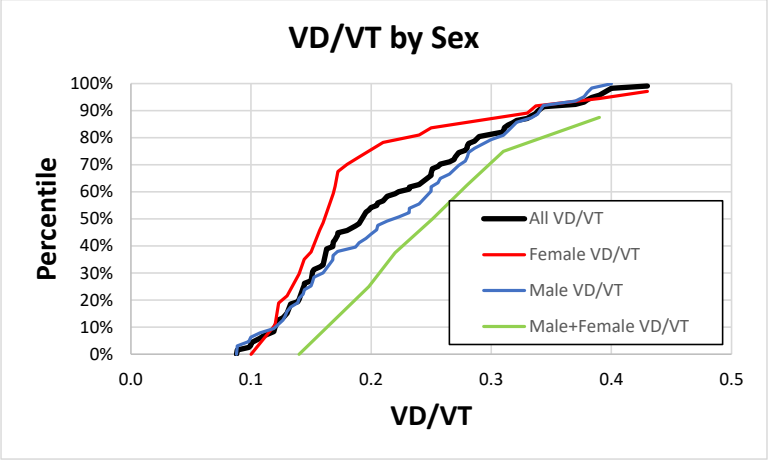

Figure 12. Distributions of V_D/V_T categorized by sex.

Distributions of V_D/V_T by Age Groups

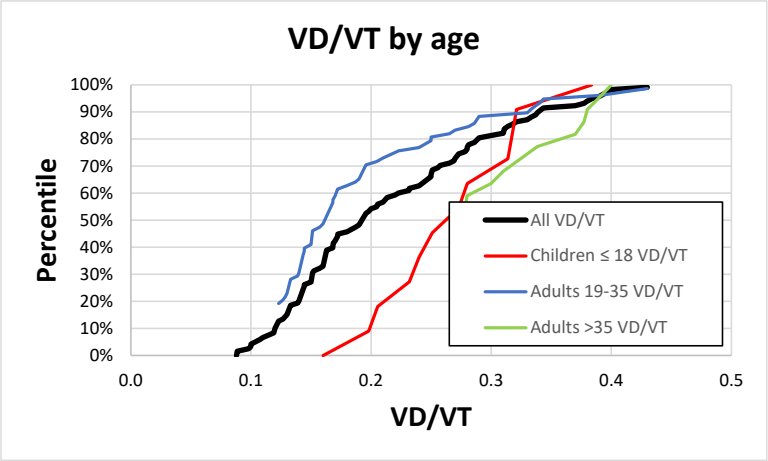

Figure 13. Distribution of V_D/V_T categorized by age groups.

When comparing the distributions of the V_D/V_T ratio by age, there are more dramatic differences than was observed above using the $\dot{V}_A$ variable (Figure 13). Clearly, the distribution for children ≤ 18 and adults >35 are consistently shifted to the right of the distribution for adults 18-35. This is likely a function of their having a larger amount of dead space relative to their tidal volume, which would suggest a potential respiratory inefficiency due to underdeveloped or damaged lung tissue.

Distributions of $(V_D/V_T)/\dot{V}_{O2}$ by Sex

Figure 15 shows there many females having a higher degree of tidal volume relative to dead space, attributed to higher rates of ventilation, and potentially due to their having relatively smaller lung capacity. Also, it is worth noting that a few of the data values were taken from pre- and post-natal mothers which could affect breathing patterns.

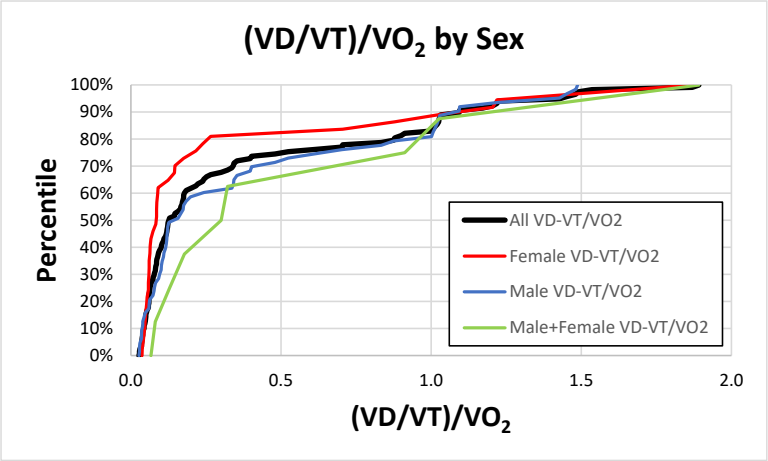

Figure 13 Distributions of the $(V_D/V_T)/\dot{V}_{O2}$ relationship for categorized by sex.

Distributions of VD-VT/$\dot{V}_{O2}$ by Age Groups

Here, as expected based on developmental, health, and body size differences across the three age groups, we observe greater ventilatory efficiency at ages 19-35 (Figure 16). This suggests that it may be necessary to use different formulas or methods for age groups older and younger than the 19-35 group.

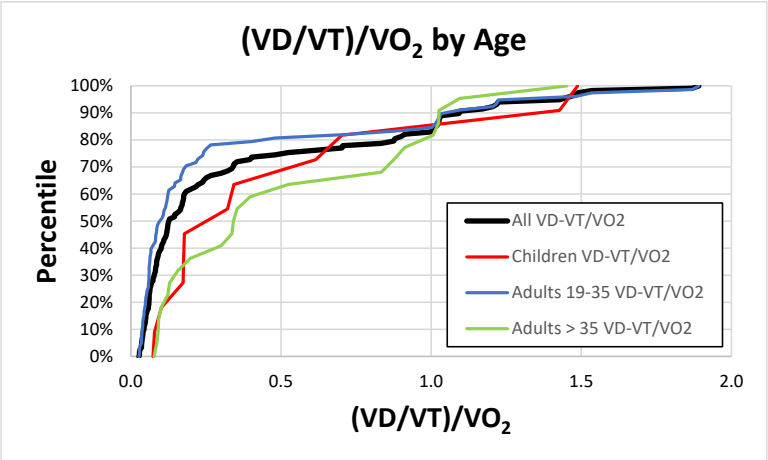

Figure 14. Distributions of $(V_D/V_T)/\dot{V}_{O2}$ relationship categorized by age groups.

Statistical Model for V_D/V_T to $\dot{V}_{O2}$ by Age Groups

The model fit for the V_D/V_T to $\dot{V}_{O2}$ relationship (Figure 17) is not as satisfactory as that of $\dot{V}_A$ to $\dot{V}_{O2}$ (Figures 8 and 11). This is primarily a result of the substantial variability of the V_D/V_T measurements in addition to having a limited sample size for two of the population groups. Yet for the adult age group 19-35, the data added in this project has increased the regression model strength by incorporating $\dot{V}_{O2}$ values that extend beyond previous limits, that still fall within the expected range suggested by the logarithmic relationship.

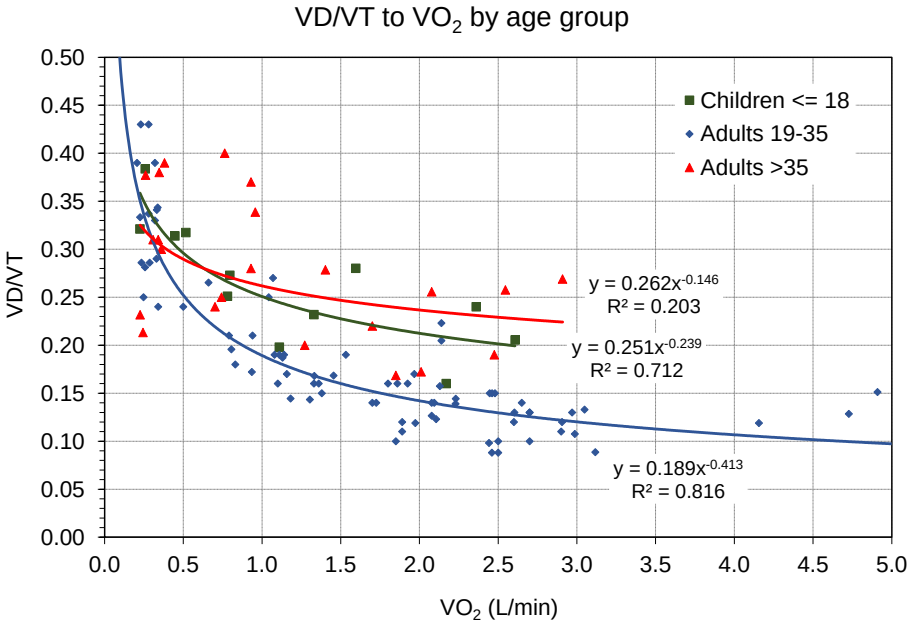

Figure 17. Linear model regressions for the V_D/V_T to $\dot{V}_{O2}$ relationship categorized by age groups.

Discussion

Made apparent throughout this research is the need for a greater level of understanding of dead space quantification. There are too few available data for the under 18 and over 35 age groups to produce meaningful relationships. However, the data for the 19-35 age group is generally strong and yields an equation that could serve as a reasonable alternative to using the

$\dot{V}_A$ to $\dot{V}_{O2}$ approach, although this would have limited application when simulating alveolar ventilation for a broader population.

During the process of collecting data, several articles were encountered that addressed promising advances in the field of Pulmonary MRI imaging. While these articles did not yield data useful for our purposes here, they presented the prospect of another dimension of alveolar ventilation and dead space estimation, in which some measurements may be able to be effectively derived by visual observation. Also, it was clear that there is a high demand for greater variety in the age of ventilatory study participants. However, the inherent difficulties are clear. Data for healthy infants, children, and adults > age 35 are lacking in abundance, especially from studies that would provide a range of activity levels and associated respiratory rates. Nonetheless, additional study data for all population groups will only strengthen simulations and estimations, even when study participants are monitored while at rest.

Conclusion

Ultimately, the most significant product of this work was the generation of a potentially new coefficient of 26.35 to estimate $\dot{V}_A$ from $\dot{V}_{O2}$. The analysis of the updated dataset suggests that the presently used 19.63 could result in underestimation of alveolar ventilation rate, inhaled CO dose, and as a result, modeled COHB levels. Additional research is needed to evaluate the impact of using unweighted mean data taken from individual studies, further evaluating the potential non-linearities in the $\dot{V}_A$ to $\dot{V}_{O2}$ relationship, exploring meta-analysis methods that might be useful in accounting for intra- and inter-study variability, and understanding how the new relationship might impact modeled COHB levels in a population-level exposure assessment.

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