

Electronic Supplementary Material: The computational model

Title:

Is airway damage during physical exercise related to airway dehydration? Inputs from a computational model.

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The core numerical results are based on the computational tool previously developed by Karamaoun et al. [1]. This tool, focused on the computation of the heat and water transfers in the bronchi, is based on several input parameters i.e., minute ventilation \dot{V}_E , temperature and relative humidity of air at the trachea during inspiration, respectively T_T and RH_T . To connect this bronchial model with the external environment, adaptations of the computational tool are required. Indeed, T_T and RH_T depend on the environment and on the individual subject. In order to obtain the numerical results presented in this work, a new computational scheme has been designed and is presented in four steps in this supplementary material. This scheme allows to automatically compute the bronchial transfers for each subject, according to each individual's lung properties, knowing the room air conditions and the average minute ventilation.

The first step consists in the derivation of several correlations for the ventilation parameters, as well as a correlation that links the room air temperature T_{room} with the tracheal temperature T_T . From that, the second step describes the derivation of a new complementary model of the transfers in the upper airways, which allows for the calculation of the tracheal relative humidity RH_T . In the third step, we describe briefly the core computational model at the basis of our work and its central equations. Finally, in step four, we describe the adaptation of the bronchial geometry to each subject, the influence of the bronchial blood circulation on the

transfers and the numerical scheme used. These four steps allow to calculate automatically, for each individual subject, the heat and water transfers dynamics in the bronchi. The main aspects of the workflow are presented in Figure ESM1.

Step 1 of the computational scheme – derivation of ventilation parameters and correlation for the tracheal temperature T_T from the minute ventilation \dot{V}_E .

The simulations conditions are built using three input parameters: (1) the relative humidity of the inspired air (RH_{room}), (2) the temperature of the inspired air (T_{room}) and (3) the minute ventilation (\dot{V}_E , in $l \cdot min^{-1}$) (Table ESM1). First, based on previous findings [2], a correlation between \dot{V}_E and breathing frequency (f_b , in s^{-1}) is derived as follows: $f_b = \frac{0.28 \dot{V}_E + 10.7}{60}$. Tidal volume (VT, in l) is then derived as $VT = \frac{\dot{V}_E}{60 f_b}$. For any given \dot{V}_E , we derive the inspiration duration $t_i = \frac{1}{f_b} \times (0.0009 \dot{V}_E + 0.39)$ from the total time of the ventilation cycle ($t_{tot} = t_i + t_e$) and inspiratory ratio [$t_i/(t_i + t_e)$], which depends on \dot{V}_E (see Table 1 of the article). Finally, the correlation between the air temperature at the entrance of the trachea T_T (in K) and \dot{V}_E is obtained based on McFadden's *et al.* data [3], giving $T_T = -0.033 \dot{V}_E + 305.50$. According to McFadden's data, T_T values are obtained for constant T_{room} and RH_{room} of 26.7 °C and 34%, respectively. This correlation is established based on experimental measurements averaged over 6 subjects and performed at rest and exercise, with \dot{V}_E ranging from 15 to 100 $l \cdot min^{-1}$ [3]. A linear model is appropriate for fitting the experimental data, which deviate only slightly from the linear regression over the range of \dot{V}_E here considered. Thus, this model brings good predictions for the range of \dot{V}_E of McFadden's data [3]. This is consistent with our experimental measurements, which are performed at \dot{V}_E values that lie in this range. Although these atmospheric conditions differ from the experimental conditions of this work,

they induce only a slight deviation of the resulting correlation for the temperature of the trachea.

Step 2 of the computational scheme – derivation of a new phenomenological model for the calculation of relative humidity at the entrance of the trachea RH_T based on minute ventilation \dot{V}_E .

Next, we derive an expression for the relative humidity at the entrance of the trachea during inspiration (RH_T). General heat and mass balance equations are established over a control volume representing the upper airways, with \dot{V}_E , RH_{room} and T_{room} as input parameters. Output parameters are RH_T , T_T and the flow at the entrance of the trachea, which is equal to \dot{V}_E , as it remains constant along the upper airways. RH_T , combined with \dot{V}_E and T_T (Step 1) will be input parameters for the bronchial heat and water transfers model described in the Step 3.

Equation (1) water mass balance: $\dot{V}_E RH_{room} C_{sat}(T_{room}) + F_{H_2O} = \dot{V}_E RH_T C_{sat}(T_T)$,

Equation (2) heat balance: $\dot{V}_E \rho c_p T_{room} + F_{heat} = \dot{V}_E \rho c_p T_T$,

with F_{H_2O} the total flux of water exchanged between the tissues and the air in the upper airways and F_{heat} the total flux of heat exchanged between the tissues and the air in the upper airways. ρ and c_p are the volumetric mass and heat capacity of the humid air, respectively. The thermodynamic parameter $C_{sat}(T)$ is the saturation concentration of water in air at the temperature T . The first equation is the water mass balance established over the upper respiratory region. It states that the flux of water vapor entering the upper airways $\dot{V}_E RH_{room} C_{sat}(T_{room})$ plus the flux of water vapor evaporated in the upper airways F_{H_2O} is equal to the flux of water vapor entering the trachea $\dot{V}_E RH_T C_{sat}(T_T)$. The second equation is the heat balance established over the same control region. Similarly, this equation writes the balance of heat between the inspired air $\dot{V}_E \rho c_p T_{room}$, the air extracted from the upper airways F_{heat} and the air entering the trachea $\dot{V}_E \rho c_p T_T$.

The heat and water fluxes can be physically connected, as the total energy flux transferred from the tissues to the air during the inspiration F_{tot} is the sum of the sensible heat F_{heat} directly transferred between the compartments and of the latent heat related to the evaporation/condensation flux $F_{\text{H}_2\text{O}}$ of the water in the tissues. It can be written as $F_{\text{tot}} = F_{\text{heat}} + \mathcal{L} F_{\text{H}_2\text{O}}$, where \mathcal{L} is the latent heat of vaporization of water. Moreover, the latent heat transferred can be written as a fraction of the total energy transferred i.e., $(1 - \beta) F_{\text{tot}} \simeq \mathcal{L} F_{\text{H}_2\text{O}}$, where β is the fraction of the sensible heat of the total energy transferred. In previous works, we estimated and derived numerically that β is approximately equal to 0.15 [1, 4]. Then, it comes that:

$$F_{\text{H}_2\text{O}} = \frac{1 - \beta}{\beta} \frac{F_{\text{heat}}}{\mathcal{L}}. \quad (3)$$

Solving the system of equations (1) and (2) using equation (3) allows writing an analytical expression for the relative humidity of the air at the entrance of the trachea RH_T , depending on the ventilation and atmospheric parameters:

$$\text{RH}_T = \frac{\text{RH}_{\text{room}} C_{\text{sat}}(T_{\text{room}})}{C_{\text{sat}}(T_T)} + \frac{1 - \beta}{\beta} \frac{1}{C_{\text{sat}}(T_T)} \frac{\rho c_p}{\mathcal{L}} (T_T - T_{\text{room}})$$

Thus, this analytical expression links directly the relative humidity at the entrance of the trachea with the inspired air conditions and with the temperature at the entrance of the trachea, previously derived (see Step 1). The major interest of the analytical model of RH_T lies in its versatility and its ability to connect, in a compact manner, the room and ventilation conditions with the tracheal environment.

It is to be noted that this phenomenological model does not take fully into account the complex physics of water and thermal transfers in the upper airways. Indeed, it is known that these transfers present a great level of complexity, namely due to the intricate geometry of the upper respiratory tract. This complexity leads to elaborate air flow dynamics, and thus

complex heat and water transfers. The use of general balances allows to generalize the modelling approach without considering a more comprehensive approach, that could lead to high complexity and expensive calculations.

Interestingly, we observed during numerical simulations that, at high air flows, the temperature profile of the air in the bronchial tree deviates from the expected profile from McFadden's experiments (see Figure ESM2) [3]. Thus, we introduced an *ad hoc* fitting factor γ that corrects the effective value of the relative humidity depending on the air flow \dot{V}_E . By integrating the complex physics of the transfers, γ allows that the qualitative behavior of the temperature profile in the bronchi is coherent with the experimental data available in the literature.

As described, this phenomenological model is based on several physical assumptions that need to be highlighted.

First, the value of the parameter β has been determined from its average value calculated in the bronchi in [1, 4]. However, an accurate value of β in the upper airways has not been determined precisely in this work. Indeed, its determination would require the development of a comprehensive model of the transfers in these airways. As said before, this model would have to take into account the precise geometry of the upper airways and the fluid dynamics of the airflow. This modelling would then be out of the scope of this work and deviate from the compact and practical approach presented here, for which an approximate value of β is sufficient.

Second, the question of the magnitude of the water transfer in the upper airways, from and to the mucosa, needs to be discussed. Indeed, a potential dehydration of the mucosa in case of high \dot{V}_E , and thus important water transfers, cannot be excluded. However, this question requires a complex analysis, as the magnitude of the transfers varies depending on \dot{V}_E , but

also on the air temperature – and thus its saturation concentration – and its relative humidity. Furthermore, as previously demonstrated (see for example [5]), the mucosa possesses a certain capacity of replenishment of the mucus layer. The extent of this replenishment in the upper airways has to be evaluated, as it counteracts the potential effect of dehydration. Several studies bring interesting insights in this question, as for example the work from Tabka *et al.* [6]. They observed experimentally that the relative humidity of the expired air diminishes during the first minutes of exercise, after what it increases up to rather normal values [6]. This demonstrates that the mucosa seems to be subject to dehydration at the start of exercise, but also demonstrates an adaptative capacity of replenishment of the mucus layer by the tissues (see also the work from Boucher [7]). In addition, Tabka *et al.* [6] also showed that the water content of the expired air is dependent on the relative humidity of the inspired air: as expected, the dryer the inhaled air, the lower the exhaled air relative humidity. These results support our experimental approach, as the inspired ambient air is not excessively dry. Furthermore, the subjects perform a 10-min warm up period followed by a 5-min rest period [8], in coherence with the adaptation period observed experimentally [6].

Finally, the use of the fitting factor γ should be evaluated in light of the complexity of the transfer mechanisms. From our analyses and numerical simulations, it appears that the behavior of the relative humidity in the bronchi is not fully described by our computational approach, especially at high airflows (not presented here). As for the upper airways, the physical mechanisms underlying the transfers in the intricate bronchial environment should require extensive modelling and numerical simulations to be fully apprehended. Obviously, the approach would be far beyond the scope of this study. Thus, the introduction of the γ correction allows to maintain the level of modelling as compact as possible, while improving the fitting of our computational results with the experimental data, especially at high \dot{V}_E .

Step 3 of the computational scheme – implementation of the core computational model of bronchial transfers

The computational model on which the present simulations are based upon has been described previously in details in [1]. The model consists in a mathematical description of the transport and exchange of heat and water in the bronchi. It consists in a set of equations in the air in the bronchial lumen, in the ASL and in the surrounding tissues. Our algorithm takes advantage of the framework of the Weibel's model of the lung [9]. More specifically, it accounts for three main hypotheses about the idealized bronchi: 1/ The idealized bronchi are considered as straight cylinders with circular section; 2/ The physics in each idealized bronchi is assumed axisymmetric; 3/ The idealized bronchi with the same generation index have the same geometry and physics. Thus, for each generation, the heat and water transport and exchange equations are solved only for one cylinder and the results are extended to the whole bronchial tree based on the model hypotheses. To solve the equations, the input parameters \dot{V}_E , T_T and RH_T are injected in the model in the first generation that mimics the trachea. Then, computations are run from the trachea to the peripheral airways at inspiration, and from the peripheral airways to the trachea at expiration. The output parameters are the profiles of temperature and relative humidity in each generation (see Figure ESM2) and the magnitude of the evaporation/condensation flux at the air/ASL interface (J_{evap}). As detailed in Step 4, the model is adapted to each subject in terms of morphology and of magnitude of the heat and water exchanges with the tissues, which depend on the cardiac output – and thus on \dot{V}_E .

Step 4 of the computational scheme – adaptation of the morphometry and the exchanges with the tissues; numerical scheme

The bronchial tree is reconstructed by assembling the idealized bronchi in a tree-like structure that mimics the inner lung, following a validated procedure previously presented in [1, 10]. The morphometry of the tree is adjusted to each individual functional residual capacity (FRC, in l), before solving the set of equations of our model. The FRC of each subject is first

estimated by using the correlation proposed by Quanjer *et al.* [11] i.e., $FRC = 2.34 H + 0.009 A - 1.09$, with H the height (in m) and A the age (in years) of each participant. The morphometry of Weibel's lung model [9, 10] is then adjusted to fit the FRC of each subject, by modifying the lengths and diameters of the bronchi in each generation. More precisely, the cubic root of the ratio of the FRC of each subject to the average FRC from Weibel's model is used as a correcting factor for the lengths and diameters. This yields to a model adapted to each subject's lung geometry. Thus, the sum of the inner volume of the modified bronchial tree and the alveolar compartment – also adapted but not considered in the bronchial simulations – corresponds to the FRC of each participant. In this way, our model takes into account the bronchial geometry of each subject, on which the heat and water transfers values are dependent (see the work of Karamaoun *et al.* [1]).

Another aspect of the model consists in the estimation of the thermal transfers in the bronchi based on local blood supply from the bronchial circulation [1], adjusted to each participant. The parameters describing this dependency are grouped in a dimensionless number Ξ that includes all the characteristics of energy exchange between the mucosa and the blood circulation. Thus, any change in this dimensionless number reflects the changes in the thermal properties of the bronchial mucosa, epithelium and ASL, and of the gradients between air and tissues. This parameter Ξ arises from the equation of heat transport in the mucosa proposed by Karamaoun *et al.* [1], with $\Xi = \frac{Q_b}{V_{cap}} \frac{c_{p,b}\rho_b}{c_{p,l}\rho_l} t_i$. Q_b is the blood flow rate in the bronchial circulation and V_{cap} is the volume of the connective tissue surrounding the bronchial environment and impacted by heat exchange with the lumen, as defined in [1]. The quantities c_p and ρ are the heat capacity and the density of blood (index b) and liquid water (index l), respectively. Furthermore, we know that $\frac{Q_b}{V_{cap}} \approx cst \frac{1}{\delta_{cap}}$, with $\delta_{cap} = \sqrt{\alpha_l t_i}$, and cst a constant independent of the ventilation parameters. The quantity δ_{cap} is the thickness of the connective

tissue involved in the heat transfer towards the lumen and α_l is the thermal diffusivity of liquid water. Thus, Ξ can be written as $\Xi = \text{cst} \sqrt{t_i} Q_b$. During exercise, $\Xi^{\text{ex}} = \Xi^{\text{rest}} \sqrt{\frac{t_i}{t_i^{\text{rest}}} \frac{Q_b}{Q_b^{\text{rest}}}}$.

To connect the value of Ξ with the ventilation of each participant, a relation between \dot{V}_E and Q_b is derived based on the work of Morris *et al.* [12]. In this work, the authors studied the link between the cardiac output in the respiratory system with the parameters of ventilation. Based on their results and our previous model, the adapted relation of Ξ with the minute ventilation is written

$$\Xi = \Xi^{\text{rest}} \sqrt{\frac{1}{2f_b} \frac{\dot{V}_E + 40}{t_i^{\text{rest}} \dot{V}_E^{\text{rest}} + 40}}$$

The relationship between the energy exchange parameter (Ξ) and \dot{V}_E is presented in Figure ESM3.

The computational tool presented in Karamaoun *et al.* [1] can be adapted and used for any given \dot{V}_E , RH_T , T_T and Ξ , in the limits of ventilation and atmospheric conditions previously highlighted. The computations consist in solving numerically the transport and exchange equations of the model in the idealized geometry of the bronchial tree previously described and adapted. The numerical resolution takes advantage of the finite difference method, which is applied over a discretization grid of 30 x 30 intervals per idealized bronchus. The boundaries of the grid are the entrance and exit of the bronchus, the axis of symmetry of the bronchus, and the air-ASL interface, at which the boundary conditions of heat and water exchange are applied. The detailed numerical approach is extensively presented in [1].

In conclusion, this 4-steps workflow allows to determine several outputs, namely the magnitude of the evaporation flux J_{evap} in each generation of the bronchial tree, which is at the basis of the comparison with the replenishment rate of the tissues. In addition, the heat and

water vapor profiles can be computed, in each generation, for any subject, minute ventilation and air room conditions.

References

1. Karamaoun C, Sobac B, Mauroy B, Van Muylem A, Haut B (2018) New insights into the mechanisms controlling the bronchial mucus balance. *PloS One* 13:e0199319
2. Haverkamp HC, Dempsey JA, Miller JD, Romer LM, Eldridge MW (2005) Physiologic response to exercise. In: *Physiol. Basis Respir. Dis.* p 17
3. McFadden ER, Pichurko BM, Bowman HF, Ingenito E, Burns S, Dowling N, Solway J (1985) Thermal mapping of the airways in humans. *J Appl Physiol Bethesda Md* 1985 58:564–570
4. Sobac B, Karamaoun C, Haut B, Mauroy B (2019) Allometric scaling of heat and water exchanges in the mammals' lung. *ArXiv191111700 Phys.*
5. Widdicombe JH. Regulation of the depth and composition of airway surface liquid. *J Anat.*;201(4):313-8.
6. Tabka Z, Ben Jebria A, Guénard H (1987) Effect of breathing dry warm air on respiratory water loss at rest and during exercise. *Respir Physiol.*;67(2):115-25.
7. Boucher RC (2002) Molecular insights into the physiology of the 'thin film' of airway surface liquid. *J Physiol.*;516 (Pt 3)(Pt 3):631-8.
8. Combes A, Dekerle J, Dumont X, Twomey R, Bernard A, Daussin F, Bougault V (2019) Continuous exercise induces airway epithelium damage while a matched-intensity and volume intermittent exercise does not. *Respir Res.*;20(1):12.
9. Weibel ER (1963) *Morphometry of the human lung.* Springer Verlag and Academic Press, New York.
10. Karamaoun C, Van Muylem A, Haut B (2016) Modeling of the Nitric Oxide Transport in the Human Lungs. *Front Physiol* 7:255
11. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC (1993) Lung volumes and forced ventilatory flows. *Eur Respir J Suppl* 16:5-40
12. Morris NR, Ceridon ML, Beck KC, Strom NA, Schneider DA, Mendes ES, Wanner A, Johnson BD (2008) Exercise-related change in airway blood flow in humans: relationship to changes in cardiac output and ventilation. *Respir Physiol Neurobiol* 162:204–209

Table ESM1: Correlations used as input parameters in the computational model.

Parameter	Unit	Correlation
f_b	s^{-1}	$\frac{0.28 \dot{V}_E + 10.7}{60}$
TV	l	$\frac{\dot{V}_E}{60 \times f_b}$
t_i	s	$\frac{0.0009 \dot{V}_E + 0.39}{f_b}$
T_T <i>temperate conditions</i>	K	$-0.033 \dot{V}_E + 305.50$

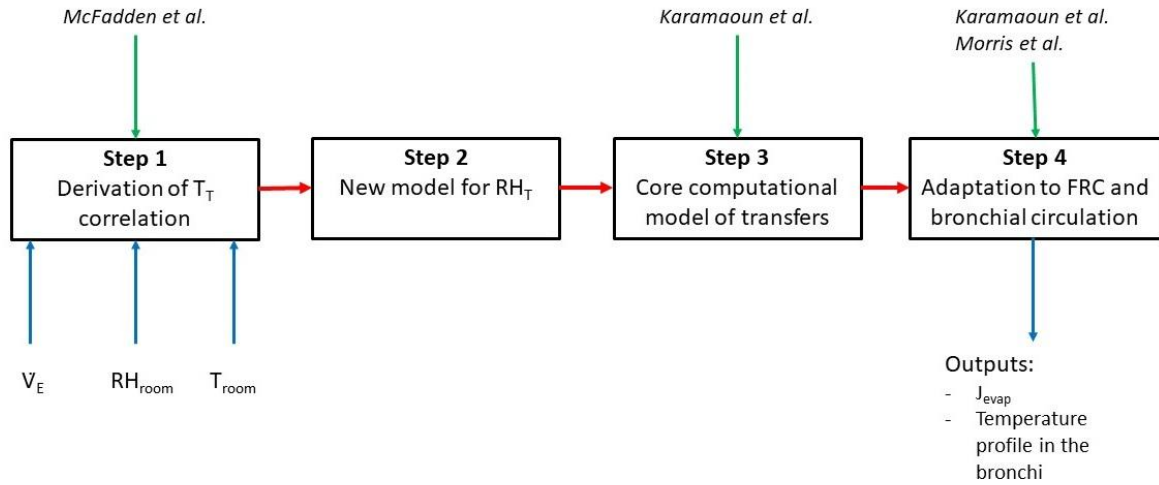


Figure ESM1: Schematic representation of the four-steps workflow used in this work for computing the heat and water transfers in the bronchial tree.

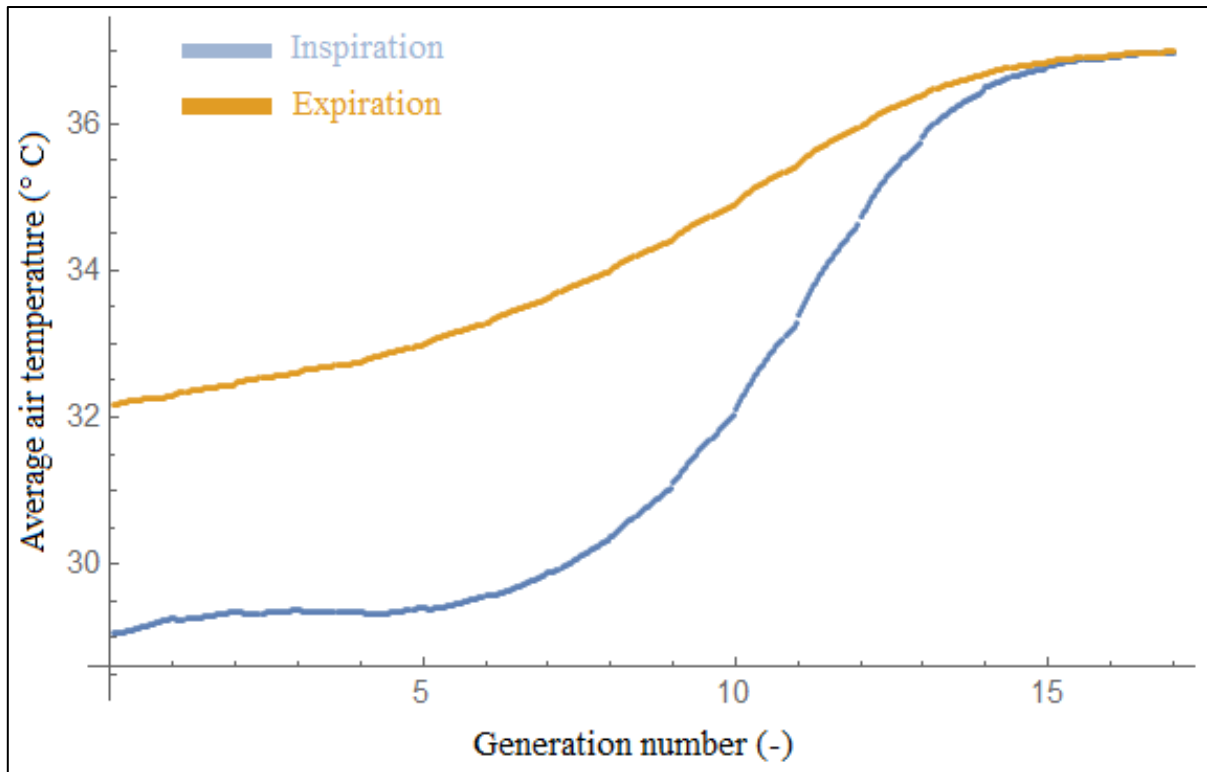


Figure ESM2: Temperature profile of the bronchial air based on numerical simulations at high air flow ($\dot{V}_E = 100 \text{ l}\cdot\text{min}^{-1}$). The profile agrees well qualitatively with the experimental results from McFadden *et al.* [3].

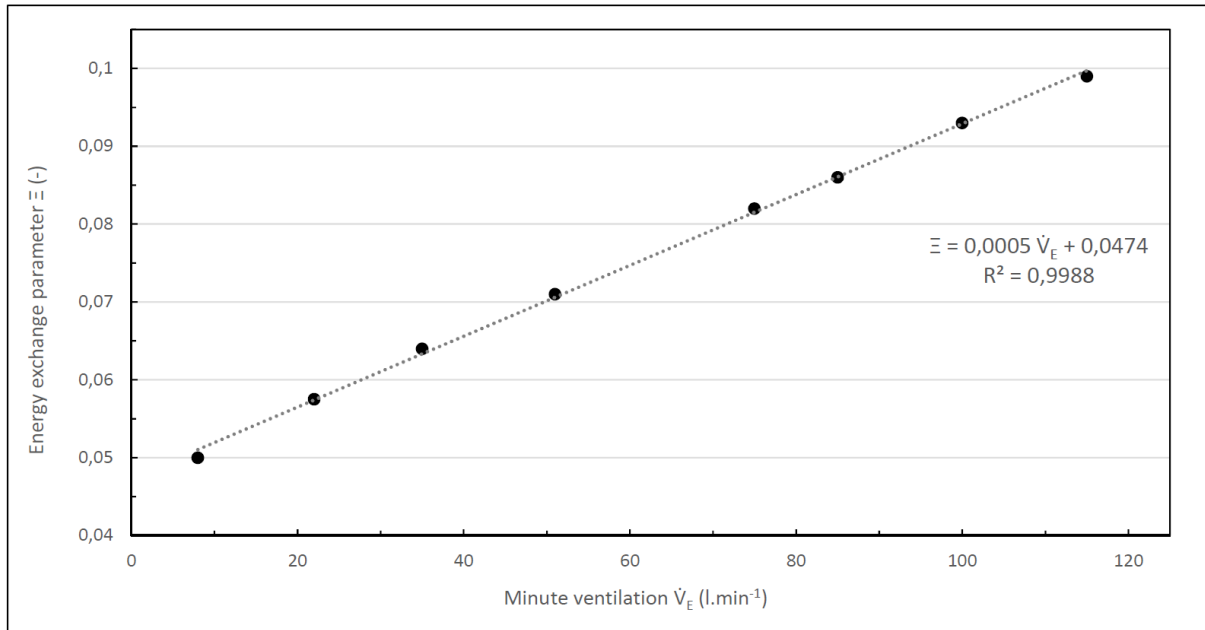


Figure ESM3: Relationship between the energy exchange parameter (Ξ) and the minute ventilation \dot{V}_E .

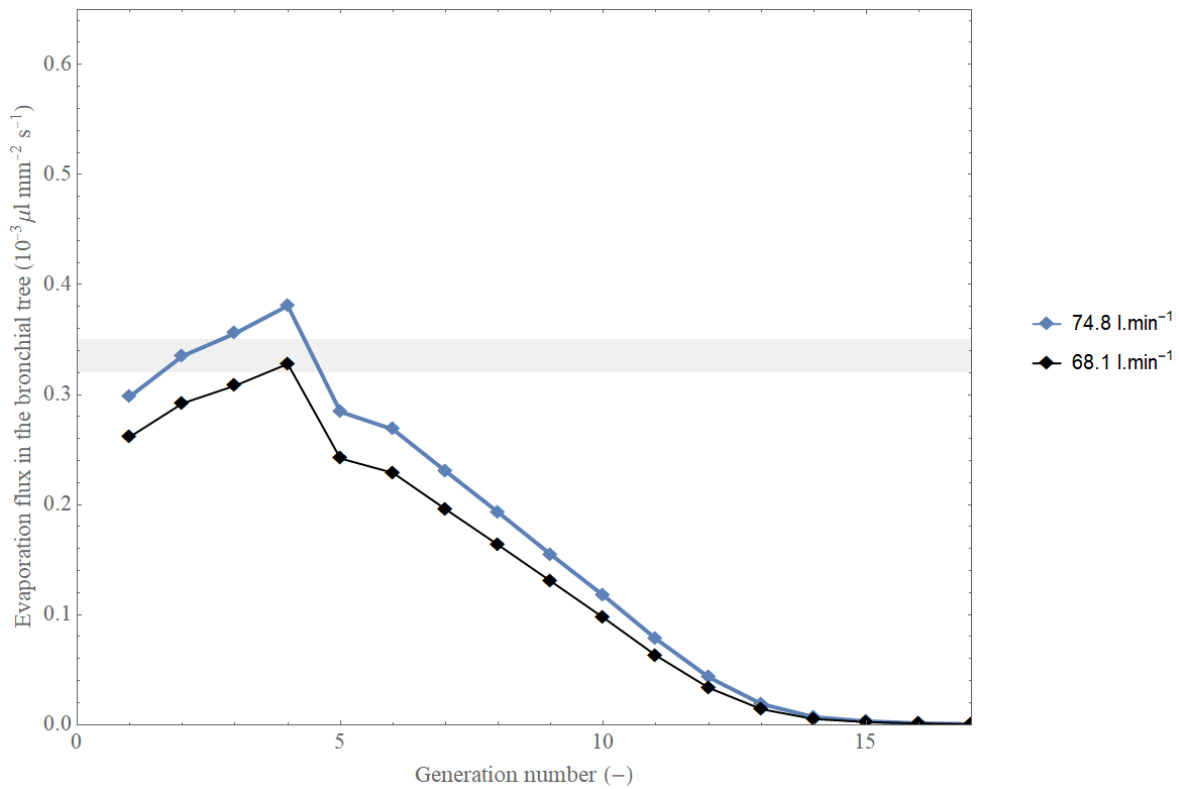


Figure ESM4: Evaporation flux in models of the bronchial tree of two participants, at $T_{\text{room}} = 8\text{ }^{\circ}\text{C}$ and $\text{RH}_{\text{room}} = 24\%$. The blue line represents the evaporation flux in the subject who ventilated at a rate of $74.8\text{ l}\cdot\text{min}^{-1}$ during the 30-min exercise. The black line represents the evaporation flux in the subject who ventilated $68.1\text{ l}\cdot\text{min}^{-1}$ during the 30-min exercise.

The dehydration threshold of $0.32\text{ to }0.35 \times 10^{-3}\text{ }\mu\text{l}\cdot\text{mm}^{-2}\cdot\text{s}^{-1}$ (10) is represented by a horizontal grey zone. The first generation represents the trachea.