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

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Running title

Airway dehydration threshold determines exercise-induced epithelial damage

Abstract

In healthy subjects, at low minute ventilation (\dot{V}_E) during physical exercise, the water content and the temperature of the airways are well regulated. However, with the increase in \dot{V}_E , the bronchial mucosa becomes dehydrated and epithelial damage occurs. Our goal was to demonstrate the correspondence between the ventilatory threshold inducing epithelial damage, measured experimentally, and the dehydration threshold, estimated numerically. In 16 healthy young adults, we assessed epithelial damage before and following a 30-min continuous cycling exercise at 70% of maximal work rate, by measuring the variation of serum club cell protein (cc16/cr). \dot{V}_E was measured continuously during exercise. Airway water and heat loss were estimated using a computational model adapted to the experimental conditions and were compared to the theoretical threshold of dehydration. Eleven participants exceeded the theoretical threshold for bronchial dehydration during exercise (group A) and 5 did not (group B). The increase in cc16/cr was higher ($p=0.007$, $d=1.40$) in group A (0.50 ± 0.25 ng.l⁻¹) compared to group B (0.10 ± 0.10 ng.l⁻¹). This increase was significant in group A but not in group B ($101\pm 100\%$, $p < 0.001$ and $13\pm 13\%$, $p = 0.28$, respectively). Our findings suggest that the use of a computational model may be helpful to estimate an individual dehydration threshold of the airways that is associated with epithelial damage during physical exercise.

New and noteworthy:

Coupling computational model and experimental data, we estimated for each participant whether they exceeded the theoretical level of airway dehydration. Those who exceeded this threshold demonstrated post-exercise epithelial damage. The computational model might thus be useful to estimate the ventilation level during physical exercise above which airway dehydration occurs and therefore to limit bronchoconstriction bronchial damage due to

dehydration by carefully adjusting exercise intensity. Our results offer interesting clinical perspectives, such as in asthmatic patients for whom the high level of ventilation and associated airway dehydration during physical exercise triggers of asthma.

Keywords

airway dehydration, exercise-induced airway damage, cc16, computational model, exercise, minute ventilation.

Glossary

l: Liquid water

A: Age

ASL: Airway surface liquid

b: Blood

cc16: Club cell protein

c_p : heat capacity at constant pressure of humid air

cr: Creatinine

$C_{\text{sat}}(T)$: Saturation concentration of humid air at a given temperature (T)

f_b : Breathing frequency

FEV₁: Forced expiratory volume in one second

FRC: Functional residual capacity

H: Height

HR: Heart rate

J_{evap} : Evaporation flux in the bronchial tree

MVV: Maximum voluntary ventilation

MVVt: Maximum theoretical voluntary ventilation

Q_b : Blood flow rate in the bronchial circulation

RH: Relative humidity

RH_T: Relative humidity of the air in the trachea

T: Temperature

T_b : Body temperature

T_T : Temperature of the air in the trachea

t_e : Expiration time

t_i : Inspiration time

t_{tot} : Total time of the ventilation cycle

V_{cap} : Volume of the connective tissue involved in thermal transfers

\dot{V}_E : Ventilation

V_T : Tidal volume

δ_{cap} : Thickness of the connective tissue involved in heat transfer towards the lumen

Ξ : Dimensionless parameter of energy exchange between the mucosa and the blood

ρ : Volumetric mass of humid air

Introduction

Under physiological conditions, inspired air is heated and saturated with water vapour as it passes through the nasal cavities and upper airways (1-3). With the increase in ventilatory demand during exercise, breathing becomes mainly oral. The onset of oronasal breathing varies considerably between individuals and averages around 35-45 l/min (4-7). From this oronasal switching point, a dry and cold air is inhaled and rehydrated and warmed by the lower airways (8). At low-level ventilation, a water replenishment mechanism, provided by the epithelium and submucosal glands, allows to maintain the water balance of the mucus (9,10) and compensates for the evaporation in the first generations of airways (11). However, when ventilation is high, as during endurance exercise, a disbalance between water loss and replenishment occurs, known as airway dehydration (8). This phenomenon is considered to be the main stimulus of exercise-induced bronchoconstriction (EIB) (12).

Recent data suggests that exercise ventilation can cause airway inflammation (13-15) and epithelial damage (16-20). While the extent of post-exertion airway inflammation is determined by the presence or absence of EIB or asthma in young adults (14,15), epithelial damage is likely dependent upon the level of ventilation but not EIB (18,19).

The relationship between ventilation, dehydration and airway damage are still misunderstood. It is hypothesized that airway damage is explained by airway dehydration and/or a mechanical stress on the airway when air passes through (21). Therefore, at low level of ventilation during exercise no airway dehydration and airway damage should be observed.

Our aim is to verify this assumption by comparing the epithelial integrity of healthy young subjects after a 30-min endurance exercise that could elicit a level of ventilation high enough in some participants to induce airway dehydration. An original aspect of our study is the determination of an individual theoretical threshold of dehydration using a computational model adjusted to our experimental conditions (11).

Methods

Subjects' description

Healthy active young males (n = 16) aged 24±5 years old participated in the study. None was a current smoker, and all were free of any known cardiac or respiratory disease. None complained of respiratory symptoms during exercise. All had baseline lung function within normal limits. All the participants provided written informed consent prior to participation. The protocol was approved by the University of Brighton Ethics Committee, and the study was conducted according to the 2008 version of the Declaration of Helsinki.

Experimental data

The detailed methodology has been previously described in (22). Briefly, participants performed a maximal and graded exercise test to exhaustion (75W + 25W every 2 minutes) to determine maximal work rate and the first and second ventilatory thresholds (VT₁ and VT₂) were determined. cc16 protein were sampled from the venous blood of the sixteen healthy active young men before and 30-min after a continuous cycling exercise at 70% of the participant's maximal work rate. The maximal increase in cc16 weighted by creatinine from baseline to post-exercise ($\Delta\text{cc16}/\text{cr}$) was as calculated as follow: $((\text{cc16}/\text{cr baseline} - \text{cc16}/\text{cr post-exercise}) \times 100/\text{cc16}/\text{cr baseline})$ and used as a marker of epithelial damage (20). The ventilation (\dot{V}_E) and heart rate (HR) during the 30-min exercise were continuously measured and averaged over the entire duration of the exercise. Spirometric parameters were obtained at rest and at multiple occasions following exercise to confirm subjects had no airway obstruction. Theoretical maximal voluntary ventilation (MVVt) was calculated as forced expiratory volume in one second (FEV₁) × 35.

The room temperature and relative humidity (RH) were kept constant ($19\pm 1^\circ\text{C}$ and $55\pm 3\%$, respectively).

Computational model

To characterize whether each subject has exceeded the theoretical threshold of dehydration, regardless of the location of the latter in the bronchial tree, we used a computational tool, based on a mathematical model of the lung and of the heat and water exchanges in the airways (11). This tool uses a set of parameters as input, which are listed in Table 1. These parameters characterize the ventilation dynamics and the inspired air conditions (11) by using experimental data from Haverkamp et al. (23). These parameters were integrated in the lung model using a correlation between the room temperature (T_{room}) and the tracheal air temperature (T_T) (24). In parallel, the relative humidity at the entrance of the trachea (RH_T) was derived using an original phenomenological model specifically developed for this study (refer to *Supplemental data* steps 1 and 2 for complete methodology). The computational tool was run up for various functional residual capacity (FRC), as described below. The computational model also integrated experimental data such as the controlled temperature and humidity of the room (19°C and 55% RH, respectively), as well as the individual total lung capacity. The individual functional residual capacity (FRC), a central parameter of the model, has been used to determine the bronchial geometry. To estimate the FRC of every participant, the equation of Quanjer et al. (25) was used: $\text{FRC (l)} = 2.34 H + 0.009 A - 1.09$, where H is the height (m) and A the age (years) of the participant. Formulas were then used, using FRC, to obtain the average diameters and lengths of the airways as a function of the stage of a sequence of branches (generations) in our morphometric model (11,26) (*Supplemental data* step 3). This procedure allows obtaining, for each individual FRC, an adapted bronchial geometry – in lengths and diameters of the bronchi – in which the temperature and water content equations of our computational tool were solved, following the numerical procedure described in the *Supplemental data* step 4. This

individual adjustment is a critical aspect, as the geometry of the bronchi *i.e.* their lengths and diameters, has a strong influence on the solving of the equations of the model, and thus on the computation results.

Determination of groups A and B

We used the mean \dot{V}_E during the 30-min steady-state exercise to calculate the corresponding evaporation flux in the bronchial tree for each subject, in the temperature and humidity conditions in which the participants performed the exercise. (19°C and 55% RH). We compared this evaporation flux to the threshold value at which water replenishment of the airway surface fluid is insufficient (dehydration threshold), which is estimated to be around $0.32 - 0.35 \times 10^{-3} \mu\text{l mm}^{-2} \text{s}^{-1}$, based on the value of $120 \mu\text{l cm}^{-2} \text{h}^{-1}$ derived by Widdicombe (10), and taking into account the uncertainty for the last significant digit of this value. According to the individual results of the model, two groups were constituted: participants exceeding the threshold of $0.35 \times 10^{-3} \mu\text{l mm}^{-2} \text{s}^{-1}$ for bronchial dehydration (group A “above”) and those who did not (group B “below”).

Statistical analysis

Data are expressed as mean \pm SD or median [Quartile 1- quartile 3] when data do or do not follow a normal law, respectively. When the conditions of normality and homogeneity of variances were met, a parametric test was used, otherwise the equivalent non-parametric test was chosen. Two ways ANOVAs with repeated measures was carried out to identify significant difference in cc16/cr over time (baseline *vs* post-exercise) and between groups (group A *vs* group B). The Holm-Sidak post-hoc test for multiple comparisons was applied to localize any difference. In two participants (both in group B), the $\Delta\text{cc16/cr}$ ratio was negative and both values were replaced by 0 (but the significance was not different with negative value). The effect size (Cohen’s d) was calculated as [(mean group A-mean group B)/SD], SD being the

standard deviation of the whole group of 16 participants (27). The comparison of the $\Delta c_{16}/cr$ ratio (%) and \dot{V}_E data were analyzed using an unpaired sample t-test or was performed using a Mann-whitney. A p-value < 0.05 was considered as significant. Data was analyzed using Sigmastat (Software version 3.5)

Results

The individual evaporation flux in the bronchial tree relatively to the generation index and \dot{V}_E values are presented in Figure 1. Accordingly, eleven participants constituted the group A and 5 the group B. The mean heart rate (HR) during 30-min exercise was significantly higher in group A (172 ± 8 bpm and $88 \pm 4\%$ of maximum theoretical HR) compared with group B (156 ± 13 bpm and $80 \pm 6\%$ of maximum theoretical HR, $p=0.01$, $d=1.28$).

\dot{V}_E during exercise was significantly higher in group A compared to group B ($p < 0.001$, $d=1.62$ in $l \cdot \text{min}^{-1}$) and averaged $97 \pm 13 l \cdot \text{min}^{-1}$ ($60 \pm 10\%$ MVVt) in group A, ranging from 78.5 to $121.8 l \cdot \text{min}^{-1}$, and $68 \pm 6 l \cdot \text{min}^{-1}$ ($46 \pm 12\%$ MVVt) in group B, ranging from 60.1 to $74.8 l \cdot \text{min}^{-1}$. The \dot{V}_E at VT_1 was $66 \pm 10 l \cdot \text{min}^{-1}$ and $56 \pm 3 l \cdot \text{min}^{-1}$ ($p=0.038$, $d=1.09$), and VT_2 of $105 \pm 11 l \cdot \text{min}^{-1}$ and $78 \pm 10 l \cdot \text{min}^{-1}$ ($p < 0.001$, $d=1.64$) in groups A and B, respectively. Mean \dot{V}_E during 30-min exercise was thus of $147 \pm 16\%$ and $123 \pm 10\%$ of \dot{V}_E at VT_1 ($p=0.005$, $d=1.34$), and of $93 \pm 17\%$ and $89 \pm 12\%$ of VT_2 ($p=0.60$, $d=0.30$), respectively in group A and B.

Individual FRC varied from 3.09 l to 3.54 l in the 16 participants. Hence, we used the computational model to estimate the theoretical ventilation corresponding to the dehydration threshold for every subject, but also for two FRC of 3 l and 3.5 l (Figure 3a and b), to get an idea of the importance of FRC according to various \dot{V}_E on dehydration in our model. For example, the dehydration of the 4th bronchial generation occurs at \dot{V}_E between 70 and 75 $l \cdot \text{min}^{-1}$ and between 75 and 80 $l \cdot \text{min}^{-1}$ for a FRC of 3.1 l and 3.5 l, respectively. The more \dot{V}_E is increased above this ventilation “threshold”, the more bronchial generations are dehydrated.

The Δ cc16/cr ratio of both groups of participants is represented in Figure 2. There was a significant interaction time \times group for cc16/cr ($F=12.80$, $p=0.003$) and the concentration of cc16/cr following exercise was higher in group A (0.50 ± 0.25 ng.l⁻¹) than in group B (0.10 ± 0.10 ng.l⁻¹, $p=0.007$, $d=1.40$). Compared to baseline, this increase in cc16/cr was significant ($101 \pm 100\%$, $p < 0.001$) only in group A but not in group B ($13 \pm 13 \%$, $p = 0.28$) ($d=0.95$). No difference in theoretical MVVt ($p=0.40$, $d=0.48$), or theoretical FRC ($p=0.65$, $d=0.47$) were observed between the groups (data not shown).

Discussion

We used a recently-published computational model in an original way, as it was to assess the level of dehydration in the bronchial tree of healthy subjects, according to their pulmonary capacity and their ventilation level during a 30-min constant workload endurance exercise. Our results showed that the group with the lowest \dot{V}_E did not reach the dehydration threshold during exercise and did not present significant epithelial damage following exercise. The level of ventilation maintained during exercise in this group was at maximum 74.8 l.min⁻¹. The computational simulation of dehydration of the bronchial generations shows that a ventilation rate above 80 l.min⁻¹ would have been necessary to cause dehydration. In contrast, indices of epithelium damage were found in participants whose ventilation level exceeded the ventilatory threshold for airway dehydration. Therefore, the analysis of ventilation during exercise data using a computational model is of significant interest to identify a threshold of dehydration and prevent potential airway damage.

Increase in cc16 at exercise have been found in the literature to occur above 75% of maximum heart rate during 6 min to 90 min of exercise (16,17,20). On the contrary, no change in cc16 have been observed at lower intensities during 90 to 120 min of exercise (28,29), suggesting a

link between exercise intensity and the occurrence of epithelial damage (22). Few studies have linked ventilation to bronchial damage. Previous results from our group showed a correlation between mean \dot{V}_E during a 30-min exercise and $\Delta cc16/cr$ ratio ($r=0.65$, $p=0.006$) (22) and Bolger et al. (19) showed an increase in $cc16/cr$ after a 8-min isocapnic hyperventilation challenge at a mean \dot{V}_E of 87 ± 2 l.min⁻¹ in 31 healthy subjects without exercise-induced bronchoconstriction. The mathematical model of heat and water loss in the human respiratory tract of Daviskas et al. (1990) from 30 years ago showed a link between the level of \dot{V}_E and airway dehydration in the bronchial tree (30), independently of asthma or exercise-induced bronchoconstriction. Therefore, dehydration of the bronchial tree is likely to be concomitant to bronchial epithelial damage during exercise.

In our study, the workload was set at a fixed percentage of each participant maximal capacity, so that the exercise was either intense or moderate, depending on the participant's fitness level. In that sense, \dot{V}_E was higher in the group of participants that exceed the theoretical dehydration threshold, compared with the group for which it was not exceeded. Despite good correlation between \dot{V}_E and heart rate during exercise (31), the use of heart rate is not ideal to assess the dehydration and epithelial damage threshold. While the measurement of \dot{V}_E was mainly limited to laboratory setup, the development of new wearable devices capable to estimate ventilation on the field (32) opens new perspectives in using ventilation to prescribe physical exercise in health and disease. Indeed, the determination of an individual ventilation threshold for airway dehydration and damage could help researchers (and practitioners) to quantify and determine the pathophysiological consequences of chronic exercise training above the threshold. Our results, based on our refined computational model, are thus the first step towards the development of innovative training programs, based on the level of ventilation, and on the level of epithelial damage for both athletes and people with respiratory diseases. In particular, avoiding airway dehydration during exercise in patients with asthma is crucial to prevent

exercise-induced asthma. In addition, our results may help to understand and control the dehydration mechanisms to avoid the development of respiratory disorders in athletes. In healthy endurance athletes, allowing time for the epithelium to regularly repair might prevent the development of exercise-induced bronchoconstriction. To reach this goal, our study suggests controlling the parameters of exercise ventilation in relation to the epithelial damage and dehydration threshold, calculated beforehand by the proposed model. Moreover, monitoring the temperature and humidity content of the inspired air could be a promising tool for the development of specific training methods, especially for highly sensitive athletes such as long-distance runners, cyclists, triathletes or winter sports athletes (33). Indeed, according to the change in atmospheric conditions, the computational model allows to recalculate the maximal possible \dot{V}_E to avoid airway dehydration and damage. However, it has recently been suggested that the atmospheric conditions may not have a strong influence on the evaporation rates (34). Therefore, atmospheric conditions would actually have a minor influence on the hydration status of the airways, and on the magnitude of the evaporation compared to the replenishment threshold. A previous approach to protect the airways of people sensitive to cold dry air or with exercise-induced asthma consisted in wearing a face mask to humidify and warm the inspired air. This approach has focused on the control of inspired air conditions (35-38) to protect the airways. However, the exercise in these studies did not exceed 13 min 15 sec, \dot{V}_E were not reported and to wear a mask during longer periods of time may not be tolerated by every athlete. It would be probably more convenient to monitor the intensity of the effort by measuring \dot{V}_E , being careful not to exceed the dehydration intensity for too long. More generally, our results provide new perspectives on the understanding and control of exercise-induced asthma and on the development of future exercise recommendations to prevent exercise-induced pathologies.

Our computational results are based on several simplification hypotheses on the physical processes involved in the heat and water transfers in the airways. Among those, the physics of the heat and water transfers in the upper respiratory part has been simplified to produce a compact version of the phenomenological model. In addition, the idealized geometry of the bronchial tree does not represent accurately some specific features of the bronchi, namely the branching and size asymmetry of the physiological bronchial tree (39). Hence, the numerical results need to be analyzed in the light of these hypotheses. Nevertheless, our computational approach can reproduce the dynamics and orders of magnitude of heat and water exchanges in the bronchi (11). As the present study constitutes an analysis based on orders of magnitude, our results can be interpreted with a strong level of confidence, in terms of both the dynamics of heat and water exchanges in the airways and of the magnitude of the calculated outputs.

From a physical and modelling point of view, our work highlights the complexity of the transfers in the upper and lower airways, namely due to their complex geometry. This suggests that future works should focus on the development of a more refined geometric description of the airways, allowing to compute accurately the bronchial heat and water transfers while maintaining the models as compact as possible.

Conclusion

Our results show a good correspondence between exceeding the ventilation threshold for airway dehydration and the appearance of epithelial damage. This study is the first step towards the development of innovative training programs, based on the level of ventilation, for both athletes and people with respiratory pathologies. The objective will be to determine the consequences of chronically exceeding or not exceeding this threshold of bronchial dehydration and thus inducing or not epithelial damage during rehabilitation in people with respiratory pathologies.

In addition, our results will help to understand and control the dehydration mechanisms to avoid the development of exercise-induced bronchoconstriction in athletes.

Disclosure of interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Ethics approval

For data on healthy subjects, the exercise protocol had been previously obtained by The University of Brighton Ethics Committee (22).

Code availability

Custom code written in Mathematica® 12. Algorithms and equations are described in text or have been previously published.

Author contributions

CK, VB and BM designed the study; CK, BH and BM designed the computation algorithms and models; CK performed the computations; VB and GB interpreted and processed the experimental data; AB, FD, JD and VB collected and analyzed the experimental data; CK and VB wrote the initial manuscript. All the authors participated in proofreading and correcting the manuscript.

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Table 1 Inputs and outputs of the computational model, depending on the minute ventilation \dot{V}_E , for a room temperature $T_{\text{room}} = 19^\circ\text{C}$ and a room relative humidity $\text{RH}_{\text{room}} = 55\%$. **I**: input data from Haverkamp et al. (23) are compiled as described in Annex I. **II**: from the input data, the values of the tracheal air temperature T_T depending on \dot{V}_E are derived, based on a correlation from McFadden et al. data (24) (see Annex I). **III**: All the input parameters allow for deriving the tracheal relative humidity RH_T , based on our phenomenological model of the upper airways, as described in Annex II. **IV**: Finally, the values of the evaporation in the conducting airways are numerically computed (see Annex IV). Here are only presented the values of the evaporation flux J_{evap} in the trachea, as compared with Fig. 1 where J_{evap} is plotted for all conducting airways. The table is established for $\text{FRC} = 3 \text{ l}$, with $f_b =$ breathing frequency, $V_T =$ tidal volume, $t_i =$ inspiration time, $t_e =$ expiration time. $t_{\text{tot}} = t_i + t_e$ is the respiratory cycle time.

Inputs						Outputs		
I						II	III	IV
\dot{V}_E	f_b	V_T	$t_i + t_e$	t_i/t_{tot}	t_i	T_T	RH_T	J_{evap}
$\text{l}\cdot\text{min}^{-1}$	min^{-1}	l	s	–	s	$^\circ\text{C}$	%	$10^{-3} \mu\text{l}\cdot\text{mm}^{-2}\cdot\text{s}^{-1}$
75	32	2.37	1.89	0.46	0.87	29.9	0.46	0.285
80	33.1	2.417	1.81	0.46	0.837	28.9	0.45	0.304
85	34.5	2.46	1.74	0.47	0.81	29.5	0.43	0.323
100	39	2.58	1.55	0.48	0.74	29.1	0.40	0.379
115	43	2.68	1.40	0.49	0.69	28.6	0.38	0.434

Figures

Fig. 1 Evaporation flux in the bronchial tree modelled for each of the 16 participants.

Each graph represents a participant. FRC: functional residual capacity; VE: minute ventilation during 30-min exercise.

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

Fig. 2 Maximum change in cc16/cr ratio according to the ventilation status in 16 healthy subjects, after a 30-min continuous exercise at 70% of their maximal work rate.

cc16: Club cell protein; cr: creatinine. The median [Q1-Q3] was of 106.9% [42.7-136.6%] in group A and of 15.8% [0-25.7%] in group B. The middle line in the box is the median and upper and lower line of the boxes are respectively Q3 and Q1. The mean is represented by a cross inside the box. The top and bottom bars represent maximum and minimum values, excluding extreme points. The single point is an extreme value.

Fig. 3 Mean evaporation flux by surface unit in the bronchial tree ($J_{\text{evap},i}$) for functional residual capacity of a) 3 l and b) 3.5 l. $J_{\text{evap},i}$ was determined at the level of the trachea (1st generation) up to the last generation of the conducting airways (17th generation). The horizontal dashed zone represents the maximal average replenishment values of the airway surface lining by the tissues (0.32 to $0.35 \times 10^{-3} \mu\text{l mm}^{-2} \text{s}^{-1}$) (10). The first generation is the trachea. Values corresponds to an ambient temperature of 19°C and a relative humidity of 55%.

Figure 1

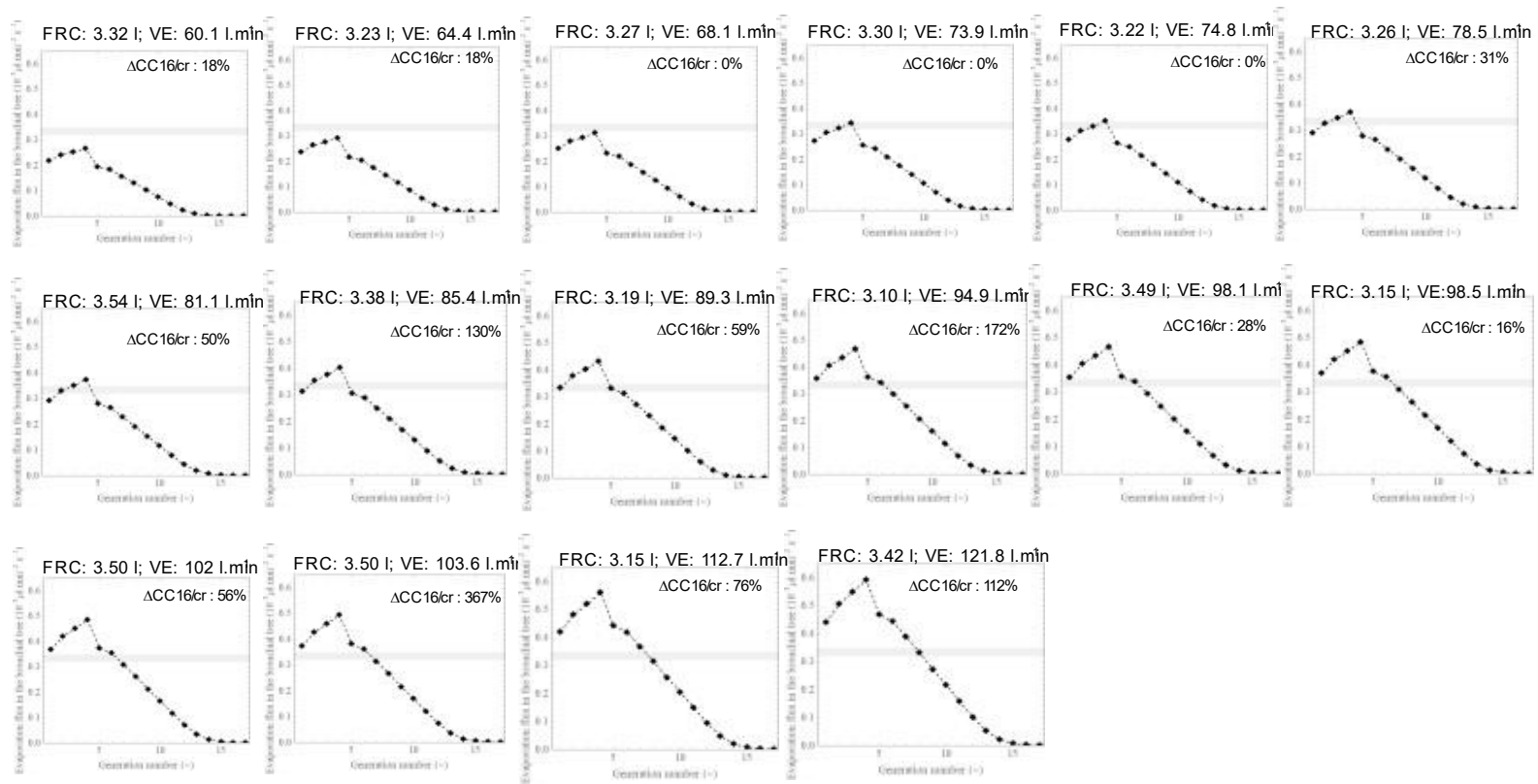


Figure 2

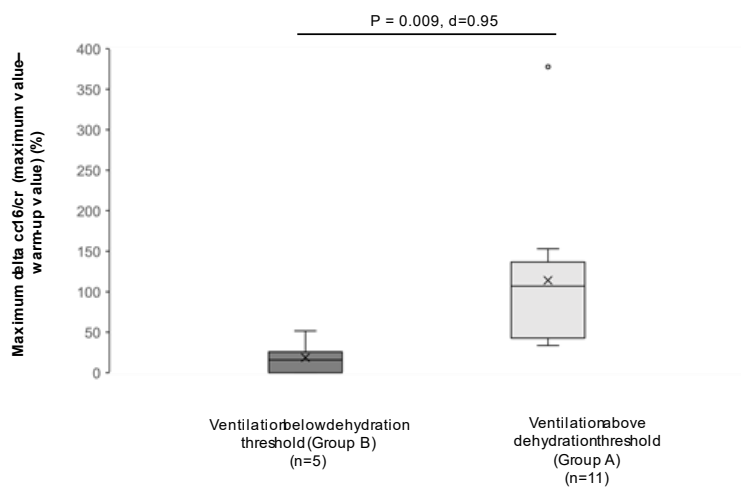


Figure 3

