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1           **Effect of dead space on breathing stability at exercise in hypoxia.**

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30 **Abstract**

31 Recent studies have shown that normal subjects exhibit periodic breathing when submitted to  
32 concomitant environmental (hypoxia) and physiological (exercise) stresses. A mathematical  
33 model including mass balance equations confirmed the short period of ventilatory oscillations  
34 and pointed out an important role of dead space in the genesis of these phenomena. Ten  
35 healthy subjects performed mild exercise on a cycloergometer in different conditions:  
36 rest/exercise, normoxia/hypoxia and no added dead space / added dead space (aDS).  
37 Ventilatory oscillations ( $\dot{V}_E$  peak power) were augmented by exercise, hypoxia and aDS  
38 ( $P < 0.001$ ,  $P < 0.001$  and  $P < 0.01$ , respectively) whereas  $\dot{V}_E$  period was only shortened by  
39 exercise ( $P < 0.001$ ), with an 11-second period. aDS also increased  $\dot{V}_E$  ( $P < 0.001$ ), tidal volume  
40 ( $V_T$ ,  $P < 0.001$ ), and slightly augmented  $PETCO_2$  ( $P < 0.05$ ) and the respiratory frequency  
41 ( $P < 0.05$ ). These results confirmed our previous model, showing an exacerbation of breathing  
42 instability by increasing dead space. This underlines opposite effects observed in heart failure  
43 patients and normal subjects, in which added dead space drastically reduced periodic  
44 breathing and sleep apneas. It also points out that alveolar ventilation remains very close to  
45 metabolic needs and is not affected by an added dead space.

46 Clinical Trial reg. n°: NCT02201875

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## 52 **Introduction**

53 Since the 19<sup>th</sup> century and its first description by Drs Cheyne and Stokes (Naughton,  
54 1998), periodic breathing has been the center of numerous studies on ventilatory stability  
55 among normal subjects and patients. This dysfunction of respiration control is mainly  
56 observed in patients suffering from chronic heart failure (CHF) (Javaheri, 1999) or sleep  
57 apneas, from central (Javaheri and Dempsey, 2013) (SACS), mixed or obstructive (Pham and  
58 Schwartz, 2015) (SAOS) origin, but also in healthy subjects at high altitude, mostly in sleep  
59 state (Ainslie et al., 2013). The pathophysiology of these manifestations involves a decreased  
60 cardiac output ( $\dot{Q}_c$ ) (Agostoni et al., 2015) and/or a hypersensitivity of peripheral and central  
61 chemoreceptors to  $O_2$  and  $CO_2$  stimuli (Chua et al., 1996; Francis et al., 2000; Giannoni et al.,  
62 2008; Ponikowski et al., 2001; Solin et al., 2000). However, recent studies (Hermand et al.,  
63 2015b, 2015a; Latshang et al., 2013) have paradoxically underlined a similar phenomenon in  
64 normal subjects submitted to concomitant metabolic (exercise) and environmental (hypoxic)  
65 stresses. In these conditions, the amplitude of periodic breathing is positively related to both  
66  $\dot{Q}_c$  and ventilation ( $\dot{V}E$ ), as opposed to the observations in CHF and SACS/SAOS patients  
67 whereas its period, much shorter (between 11 and 13 seconds), is inversely related to  $\dot{Q}_c$  and  
68  $\dot{V}E$ .

69 Several methods to treat periodic breathing and sleep apneas are being used or  
70 experimented, with a variable efficiency: CPAP and oxygen therapy (Pearse and Cowie,  
71 2016), acetazolamide (Javaheri, 2006; White et al., 1982) and  $CO_2$  inhalation (Szollosi et al.,  
72 2004; Wan et al., 2013). An alternative approach is the use of an additional external dead  
73 space, which has proven to be effective by drastically reducing periodic breathing during in  
74 patients (Khayat et al., 2003; Sharma et al., 2011; Xie et al., 1997) and in subjects at high  
75 altitude (Lovis et al., 2012; Patz et al., 2013). By maintaining a relatively high arterial partial  
76 pressure in  $CO_2$  ( $PaCO_2$ ) combined with a higher  $\dot{V}E$ , this device prevents its fall below the  
77 apnea threshold and the consequent genesis of a central apnea cycle. Augmented dead space  
78 also alters the breathing pattern when increasing  $\dot{V}E$ , as respiratory rate remains stable while  
79 tidal volume ( $V_T$ ) augments (Agostoni et al., 2008; Khayat et al., 2003; Xie et al., 1997). This  
80 underlines the additional contribution of low tidal volume in central sleep apneas in patients,  
81 besides cardiac output and chemosensitivity.

82 In exercise conditions, scarce studies highlight a similar inhibiting effect of added dead  
83 space on periodic breathing in CHF patients (Agostoni et al., 2008).

84 However, in a previous work, we developed a model in order to evaluate the respective  
85 influence of various factors on breathing stability during moderate exercise in hypoxia. Our

86 model predicted that a decrease in alveolar ventilation / minute ventilation ratio ( $\dot{V}_A/\dot{V}_E$ ),  
87 therefore an increase in dead space, would increase breathing instability and ventilatory  
88 oscillations (Hermand et al., 2016), regardless of cardiac output and chemosensitivity.  
89 Therefore, we aimed to validate our mathematical model in normal subjects at moderate  
90 exercise in hypoxia, by adding dead space in the breathing circuit and we hypothesized that  
91 this intervention would promote breathing instability.

92

## 93 **Subjects and methods**

94

### 95 **Subjects.**

96 Ten healthy non-smoking male subjects volunteered for the study and were given  
97 complete information about the successive tests. All were in good physical condition, with a  
98 medium to high level of regular physical activity (from 2 to 10 hours per week). A  
99 preliminary medical examination showed no evidence of cardiovascular or pulmonary  
100 disease. Subjects' characteristics are presented in table 1. The protocol was approved by the  
101 Ile-de-France Ethics Committee (CPP-IDF2) and an individual written informed consent has  
102 been collected from all subjects. The study was registered as Clinical Trial reg. n°:  
103 NCT02201875.

104

### 105 **Procedure.**

106 All subjects were first asked to perform a standard ramp test protocol on a  
107 cycloergometer to be familiarized with calibrated breathing apparatus and determine their  
108 maximal aerobic power (MAP, Table 1): after a 3-minute warm-up at 60 watts, power output  
109 was increased by 30-watt steps every two minutes until exhaustion.

110 Four tests were then randomly conducted, in normoxia and hypoxia (fraction of inspired  
111  $O_2$ ,  $FIO_2 = 14,5 \%$ ), in accordance with previous work (Hermand et al., 2015a), with and  
112 without a 500 mL added dead space (aDS), consisting in a cylindrical tube (diameter 5 cm)  
113 clipped on the mouthpiece. This volume was determined accordingly with our predictive  
114 model (Hermand et al., 2016) and with the existing literature (Khayat et al., 2003; Lovis et al.,  
115 2012; Patz et al., 2013).

116 After one minute rest for material habituation and cardiorespiratory parameters  
117 stabilization, subjects were first asked to keep a resting sitting position on the ergometer for 6  
118 min, and then to pedal for 6 min at around 65 rpm pedaling cadence at an exercise intensity of  
119 30 % of MAP (Hermand et al., 2015a).

120  $\dot{V}E$  (L.min<sup>-1</sup>) and heart rate (HR, bpm) were measured through a metabograph (Vmax  
121 Encore, SensorMedics, Yorba Linda, CA). VT (L), O<sub>2</sub> consumption ( $\dot{V}O_2$ , L.min<sup>-1</sup>), CO<sub>2</sub>  
122 production ( $\dot{V}CO_2$ , L.min<sup>-1</sup>), total respiratory cycle time (T<sub>tot</sub>, s) and inspiratory time (T<sub>i</sub>, s)  
123 were derived from the ventilation signal. Pulse O<sub>2</sub> saturation (SpO<sub>2</sub>, %) was measured by  
124 transcutaneous oximetry (Nellcor N-595, Nellcor, Pleasanton, CA) on a pre-warmed ear lobe.  
125 End tidal PCO<sub>2</sub> (PETCO<sub>2</sub>, mmHg) was measured by infrared thermopile (Vmax Encore,  
126 SensorMedics, Yorba Linda, CA). During the whole test,  $\dot{V}E$ , SpO<sub>2</sub> and PETCO<sub>2</sub> were  
127 recorded breath-by-breath (Fig. 1). Data were transferred to a computer for further variability  
128 analysis. A Fast Fourier Transform (FFT) was then applied to the breath-by-breath ventilation  
129 signal, extracted from the raw data, in sequences of 128 points (one point per second) of a  
130 steady state interval at the end of each phase of the test. This method allowed us to detect the  
131 presence of peaks in the frequency domain of the ventilation signal (Fig. 2) (Hermand et al.,  
132 2015b). Two main parameters were derived from the FFT: the frequency in hertz (or period in  
133 seconds) of the larger peak and its power estimated as the area under the peak at  $\pm 0.02$  Hz  
134 around the peak (in L<sup>2</sup>.min<sup>-2</sup> for  $\dot{V}E$  spectrum). Thus, a high peak power translates into greater  
135 ventilatory oscillations. This method allowed us to precisely quantify the presence of  
136 oscillations in the signals that are not observable in a standard protocol routinely used where  
137 the signals are averaged every 20 seconds (Bourdillon et al., 2014; Canouï-Poitrine et al.,  
138 2014; Lhuissier et al., 2012; Richalet et al., 2012). Finally, alveolar ventilation was assessed  
139 from the values of end tidal CO<sub>2</sub> pressure, as a surrogate of alveolar CO<sub>2</sub> pressure (P<sub>A</sub>CO<sub>2</sub>)  
140 and CO<sub>2</sub> production rate ( $\dot{V}CO_2$ ), which anatomical dead space (VD), alveolar / total  
141 ventilation ratio ( $\dot{V}A/\dot{V}E$ ) and dead space / tidal (VD/VT) are derived from (Whipp and  
142 Ward, 1998):

$$\dot{V}A = \frac{\dot{V}CO_2}{K.P_ACO_2}$$

143 where K is the constant to adapt standard temperature and pressure dry (STPD) to body  
144 temperature pressure and saturation (BTPS) conditions;

$$VD = \frac{(\dot{V}E - \dot{V}A)}{FR}$$

145 where FR is the respiratory frequency (min<sup>-1</sup>)

146

147 **Statistical analysis.** Results are presented as mean  $\pm$  standard deviation. Regarding the  
148 expected difference in mean period (3 seconds), the standard deviation (2.4 seconds), a level  
149 of significance at 0.05% and a statistical power at 80%, the minimum number of subjects to

150 be included was 7 for each protocol. Since spectral peak power showed a high standard  
151 deviation and a non-normal distribution, we performed a logarithmic transformation of raw  
152 data, and calculated a minimum number of subjects of 10 to include. Normality of data on  
153 each condition (rest/exercise, normoxia/hypoxia, without/with aDS) was verified by a  
154 Shapiro-Wilk normality test. Thus, a three-way analysis of variance (ANOVA) with repeated  
155 measures were done, including interactions between factors. A post-hoc paired Student's test  
156 was used when applicable. As exercise is associated with a concomitant variation of multiple  
157 variables, we performed a multivariate regression analysis in order to evaluate the  
158 independent influence of each cardiorespiratory variable on period and peak power of  $\dot{V}E$   
159 spectrum. This approach, for example, will allow us to assess the specific influence of  $\dot{V}E$   
160 and/or  $\dot{Q}c$  on peak power and period of  $\dot{V}E$ .

161

## 162 **Results**

163 Values of measured cardiorespiratory variables and post-hoc tests in subgroups are presented  
164 in table 2 and in figures 3, 4, 5 and 6.

165

### 166 **Effect of exercise vs rest**

167 As expected,  $\dot{V}E$ ,  $\dot{V}O_2$ ,  $\dot{V}CO_2$ ,  $PETCO_2$ ,  $V_T$ ,  $HR$ ,  $\dot{V}A$  and  $\dot{V}A/\dot{V}E$  increased with exercise ( $P <$   
168  $0.001$ ) whereas  $SpO_2$ ,  $T_{tot}$  and  $VD/V_T$  decreased ( $P < 0.001$ ).  $\dot{V}E$  peak power was greater ( $P$   
169  $< 0.001$ ) and its period shorter ( $P < 0.001$ ).

170 In hypoxia,  $O_2$  desaturation was accentuated by exercise for both aDS condition ( $P < 0.01$ ).

171

### 172 **Effect of hypoxia vs normoxia**

173 Hypoxia increased  $\dot{V}E$  ( $P < 0.01$ ),  $HR$ ,  $\dot{V}A$  ( $P < 0.001$ ),  $\dot{V}A$ ,  $\dot{V}A/\dot{V}E$  ( $P < 0.05$ ) and decreased  
174  $SpO_2$  and  $PETCO_2$  ( $P < 0.001$ ) and  $VD/V_T$  ( $P < 0.05$ ) whereas  $T_{tot}$ ,  $VD$  and  $V_T$  were not  
175 modified, except a trend for a rise in  $V_T$  ( $P = 0.06$ ).  $\dot{V}E$  peak power was augmented by  
176 hypoxia ( $P < 0.001$ ) and period of  $\dot{V}E$  oscillations remained unchanged.

177 During exercise,  $\dot{V}E$  was not modified by hypoxia at aDS = 0 but significantly increased with  
178 a 500 mL aDS ( $P < 0.001$ ).

179

### 180 **Effect of added dead space**

181  $\dot{V}E$ ,  $V_T$  and  $\dot{V}O_2$  increased with the aDS ( $P < 0.001$ ) whereas  $T_{tot}$  was shortened ( $P < 0.05$ ).  
182  $PETCO_2$  was very slightly increased (+ 1.8%,  $P < 0.05$ ). Added dead space had no effect on

183 SpO<sub>2</sub> and  $\dot{V}A$ . However, it enhanced  $\dot{V}E$  peak power ( $P < 0.001$ ), period remaining  
184 unchanged.

185 In most conditions, despite large increases in  $\dot{V}E$  due to aDS (+ 42 %, all values pooled, fig. 4,  
186 upper left),  $\dot{V}A$  remains stable and is not affected by aDS (Fig. 4, upper right).

187 In hypoxia, aDS increased  $\dot{V}A$  and  $\dot{V}E$  peak power during exercise in hypoxia ( $P < 0.05$ ,  $P <$   
188  $0.01$  and respectively, fig. 4 and 5).

189

### 190 **Interactions between factors**

191 The ANOVA showed that exercise accentuated, respectively, the effect of aDS on  $\dot{V}E$ ,  $\dot{V}O_2$   
192 and on  $\dot{V}A/\dot{V}E$ , the effect of hypoxia on O<sub>2</sub> desaturation, the effect of hypoxia on decreased  
193 PETCO<sub>2</sub>, the effect of aDS on increased  $\dot{V}E$  peak power.

194

### 195 **Multivariate regression analysis: factors influencing $\dot{V}E$ peak power and** 196 **period**

197 Among various cardiorespiratory parameters,  $\dot{V}E$  peak power was positively correlated to  $\dot{V}E$   
198 and PETCO<sub>2</sub> (Fig. 6,  $P < 0.001$ ), with a trend for  $\dot{V}A/\dot{V}E$  ( $r = 0.67$ ,  $P = 0.073$ ).  $\dot{V}E$  period was  
199 strongly positively correlated to T<sub>tot</sub> (Fig. 6,  $P < 0.001$ ) and, in a lesser extent, negatively  
200 correlated to  $\dot{V}A/\dot{V}E$  ( $P < 0.01$ ).

201

202

### 203 **Discussion**

204 Two main conclusions might be drawn from these original data. First, this study confirms the  
205 mathematical simulations of the impact of added dead space on ventilatory instability in  
206 healthy subjects, during exercise in hypoxia (Fig. 1). Second, unlike the observations made in  
207 CHF/SAS patients and normal subjects during sleep at high altitude, an increased dead space  
208 promotes respiratory instability and ventilatory oscillations.

209 As observed in patients and normal subjects (Ainslie et al., 2013; Khayat et al., 2003), the  
210 breathing pattern with aDS was mainly affected by VT swings (Fig. 3, lower panels). In  
211 addition, respiratory frequency was equally shortened by added dead space at rest and  
212 exercise (-8% and -7%, respectively): as the added dead space induces a higher alveolar  
213 PCO<sub>2</sub>, the ventilatory control system in a normal subject quickly adjusts  $\dot{V}E$  to eliminate CO<sub>2</sub>  
214 by augmenting both VT and respiratory rate, although in a lesser extent, as opposed to what is  
215 observed in CHF patients (Khayat et al., 2003). This illustrates a fully functional respiratory



216 output in a normal subject. On a side note, the slight metabolic increase of  $\dot{V}O_2$  with aDS  
217 (+9%, all conditions, fig. 5), along with a similar trend for  $\dot{V}CO_2$  ( $P = 0.075$ ), could be  
218 attributed to the additional workload of respiratory muscles (Lorenzo and Babb, 2012), due to  
219 a substantial increase of  $\dot{V}E$ , mainly through a large rise in VT. However, the increase of  $\dot{V}E$   
220 did not modify  $SpO_2$  as it does in patients and normal subjects at high altitude (Khayat et al.,  
221 2003; Lovis et al., 2012; Xie et al., 1997) (Fig. 3).

222 This study confirms that the ventilatory control is destabilized when the system is submitted  
223 to a double concomitant, physiological and environmental, stress, at exercise in hypoxia  
224 (Hermant et al., 2015b, 2015a). Thus, amplitude of ventilatory oscillations are correlated to  
225 ventilation level and cardiac output (not shown) and their period, inferior to 11 seconds at  
226 exercise and therefore shorter than those observed in CHF and SAS patients (Francis et al.,  
227 2000)(Fig. 2), is strongly correlated to  $T_{tot}$  (Fig. 6).

228 This striking difference may have an origin in the regulatory system of arterial  $CO_2$  pressure.  
229 A well-known mechanism preventing a CHF/SAS patient from starting an apnea/hyperpnea  
230 cycle is to keep  $PaCO_2$  above an apnea threshold (Xie et al., 2002) using  $CO_2$  inhalation or  
231 external dead space device, even though the ventilation is augmented by the respiratory  
232 command via a central  $CO_2$  chemoreflex activation. This explains why, in this context, the fall  
233 of apnea/hypopnea index (AHI) is systematically associated with a large increase in  $PaCO_2$   
234 and an inadequate response to hypercapnia due to an augmented ventilatory response to  $CO_2$ ,  
235 leading to successive  $CO_2$ -threshold crossings and apnea cycles (Khayat et al., 2003; Xie et  
236 al., 1997). The opposite phenomenon takes place in normal subjects: a slight change in arterial  
237  $PCO_2$  induces an immediate and appropriate ventilatory response to bring the system back to  
238 a homeostatic equilibrium. For instance, in CHF patients at rest, a ~15% rise in  $PETCO_2$ , from  
239 37 to 42 mmHg, elicits a ~50% increase in  $\dot{V}E$ , from 6.4 to 9.6  $L \cdot min^{-1}$  (Khayat et al., 2003)  
240 whereas a mere 3%  $PETCO_2$  gain, from 37.9 to 39.1 mmHg, in healthy subjects induces a  
241 67% rise in  $\dot{V}E$ , from 11.1 to 18.5  $L \cdot min^{-1}$  (the  $\dot{V}E$  response is even greater at exercise). In the  
242 latter, a well-functioning  $CO_2$  control system limits the aDS-induced  $CO_2$  rise to a very low  
243 range, but nevertheless drastically augments the ventilation level which is associated to  
244 increased breathing instability at exercise (Hermant et al., 2015a, 2015b) (Fig. 5). In that  
245 perspective, the same remarkable mechanism was recently pointed out in obese patients with  
246 and without obstructive SAOS, in which progressive aDS-induced variations of  $PETCO_2$  were  
247 kept within a 2 mmHg margin by rises of  $\dot{V}E$  (Bernhardt et al., 2017).

248 It is interesting to note that the oscillatory pattern enhanced by adding dead space might be  
249 explained by the difference between the input and the output of the control system: the values

250 of blood gases ( $\text{PaO}_2$  and  $\text{PaCO}_2$ ) are determined by alveolar ventilation ( $\dot{V}_A$ ), while these  
251 blood gases act on total ventilation ( $\dot{V}_E$ ) via the chemoreceptors and control centers. Thus,  
252 any difference between  $\dot{V}_A$  and  $\dot{V}_E$  will promote instability in blood gases and therefore in  
253 ventilation.

254 These systemic properties unveiled a second and noticeable mechanism: a stable  $\dot{V}_A$  despite  
255 large swings of  $\dot{V}_E$  in most conditions underlines a remarkable adaptation of ventilatory  
256 control system, in order to maintain the “effective” respiration,  $\dot{V}_A$ , close to the metabolic  
257 needs of the organism, under environmental and physiological stresses, regarding the dead  
258 space status (VD, fig. 4, lower right). Assuming that the ratio ventilation-perfusion is optimal  
259 in healthy subjects at rest and at mild exercise (Moinard et al., 2004), we suggest that the  
260 “extra” ventilation with aDS (Fig. 3 and 4) is then attributed to the sole action of  $\text{CO}_2$   
261 chemoreflex, combined from peripheral and central chemoreceptors.

262 Central sleep apneas exhibited by normal subjects at high altitude are also greatly reduced by  
263 added dead space (Lovis et al., 2012; Patz et al., 2013). However, underlying mechanisms are  
264 different from patients. A broad consensus point out that an augmented activity of peripheral  
265 chemoreceptors in hypoxia is involved into the genesis of periodic breathing (Ainslie et al.,  
266 2013; Hermand et al., 2015b; Kumar and Prabhakar, 2012; Lahiri et al., 2006), in a subtle  
267 interplay with central chemoreceptors through peripheral afferences into the nucleus tractus  
268 solitarii (NTS) (Smith et al., 2013). A higher  $\dot{V}_E$  by aDS-induced central  $\text{CO}_2$  stimulation will  
269 maintain a higher  $\text{O}_2$  saturation (Patz et al., 2013), lowering carotid bodies activity and its  
270 subsequent effect on periodic breathing. In the present work, aDS did not enhance  $\text{SpO}_2$  in  
271 spite of a large increase in  $\dot{V}_E$  especially in hypoxia, maintaining a higher peripheral  
272 sensitivity and therefore a greater tendency to develop periodic breathing. This may explain  
273 the oscillatory exacerbation observed in hypoxia, even more at exercise, during which  $\text{O}_2$   
274 desaturation is worsened. Furthermore, the prompt response of ventilatory control system to a  
275 higher aDS-induced  $\text{PaCO}_2$  within a narrow range points out the role of  $\text{CO}_2$   
276 chemosensitivity, enhanced in hypoxia (Masuyama et al., 1989), leading to greater ventilatory  
277 oscillations than those observed without added dead space. Whereas the latter points require  
278 further studies to quantify the involvement of central and peripheral chemoreceptors in this  
279 matter, other potential actors could come into play, such as the action of lung stretch receptors  
280 which could be activated by an augmented VT with aDS.

281 Lastly, we confirmed the tight relationship existing between  $\dot{V}_E$  period and  $T_{\text{tot}}$  (Hermand et  
282 al., 2015a, 2015b) (Fig. 6, right), suggesting the existence of an intrinsic oscillator modulating  
283 the activity of the central pattern generator (Forster et al., 2014). The theoretical limit of  $\dot{V}_E$

284 period, when  $T_{tot}$  tends towards zero (i.e. respiratory frequency is infinite), is around 6  
285 seconds.

286

287 In conclusion, these findings confirm the destabilizing role of added dead space in the  
288 ventilatory control system of normal subjects at exercise in hypoxia, as anticipated by a  
289 mathematical model. It also points out the discrepancy of the effect of  $CO_2$  between healthy  
290 subjects on one hand, and CHF/SAS patients and normal subjects asleep in altitude on the  
291 other hand, counteracting or promoting breathing stability. This study, in an original manner,  
292 confirmed that total ventilation adapts to external constraints by maintaining adequate  
293 alveolar ventilation for metabolic needs of the organism.

294

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401

402 **CAPTIONS**

403

404 **Figure 1.** Example of breath-by-breath ventilation recordings in hypoxia, without and with  
405 added dead space (respectively upper and lower panels). Ventilatory instability is noticeably  
406 increased with added dead space.

407

408 **Figure 2.** Means of power spectral densities of the ventilation signal at exercise in 3  
409 conditions: normoxia and hypoxia without added dead space (aDS), hypoxia with aDS (plain,  
410 dot and dashed lines, respectively). Peak power is higher when aDS is combined to both  
411 exercise and hypoxia.

412

413 **Figure 3.** Mean ( $\pm$  SD) values of O<sub>2</sub> saturation (SpO<sub>2</sub>), end-tidal CO<sub>2</sub> pressure (PETCO<sub>2</sub>),  
414 tidal volume (VT) and respiratory frequency. Exercise vs Rest: #,  $P < 0.05$ ; ##,  $P < 0.01$ ; ###,  
415  $P < 0.001$ . Hypoxia vs normoxia: \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . aDS 500 vs aDS  
416 0: †,  $P < 0.05$ ; ††,  $P < 0.01$ ; †††,  $P < 0.001$

417

418 **Figure 4.** Mean ( $\pm$  SD) values of minute and alveolar ventilation ( $\dot{V}_E$  and  $\dot{V}_A$  respectively),  
419 the  $\dot{V}_A/\dot{V}_E$  ratio and the assessed total dead space (VD). Exercise vs Rest: #,  $P < 0.05$ ; ##,  $P <$   
420  $0.01$ ; ###,  $P < 0.001$ . Hypoxia vs normoxia: \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . aDS  
421 500 vs aDS 0: †,  $P < 0.05$ ; ††,  $P < 0.01$ ; †††,  $P < 0.001$

422

423 **Figure 5.** Ventilation peak power ( $\dot{V}_E$  peak power, left) and period ( $\dot{V}_E$  period, right).  
424 Exercise vs Rest: #,  $P < 0.05$ ; ##,  $P < 0.01$ ; ###,  $P < 0.001$ . Hypoxia vs normoxia: \*,  $P <$   
425  $0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . Exercise vs Rest: #,  $P < 0.05$ ; ##,  $P < 0.01$ ; ###,  $P <$   
426  $0.001$ . Hypoxia vs normoxia: \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . aDS 500 vs aDS 0: †,  
427  $P < 0.05$ ; ††,  $P < 0.01$ ; †††,  $P < 0.001$

428

429 **Figure 6.**  $\dot{V}_E$  peak power (left) and period (right) as a function of  $\dot{V}_E$  and T<sub>tot</sub>, respectively.  
430 Rest and exercise values have been pooled in all conditions.

431

432

433 **Table 1.** Characteristics of the subjects

	<b>n</b>	<b>Age (yrs)</b>	<b>Body weight (kg)</b>	<b>Height (cm)</b>	<b>Maximal Aerobic Power (MAP, W)</b>
<b>Dead Space (DS)</b>	10	29.0 ± 9.5	71.8 ± 9.1	175.1 ± 7.5	231.0 ± 31.1

434 Mean ± SD.

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439 **Table 2.** Summary of three-way analysis of variance and interactions between factors.  
440

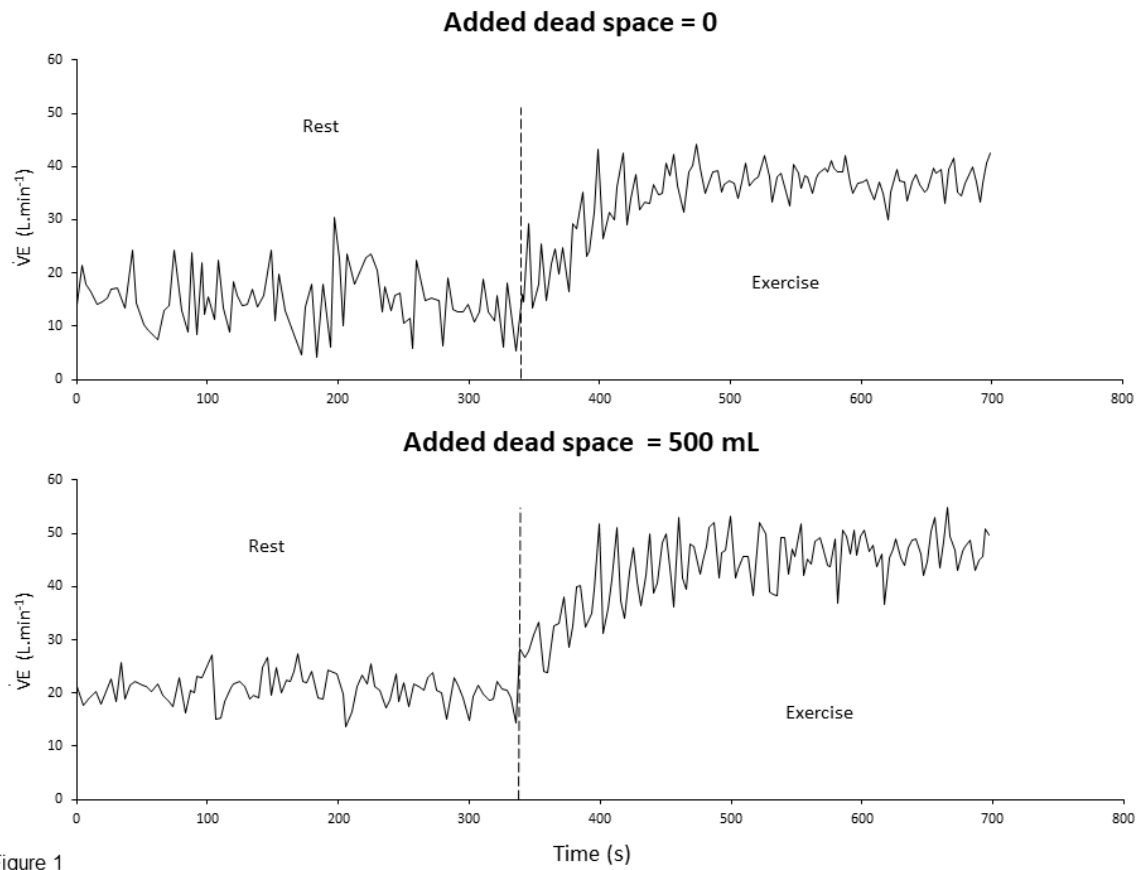
	Effect of Exer. vs. Rest	Effect of Hx vs. Nx	Effect of aDS	Interaction Rest / Exer. – Nx / Hx	Interaction Rest / Exer. – DS	Interaction Nx / Hx – DS
$\dot{V}E$	***	**	***	ns	*	ns
SpO <sub>2</sub>	***	***	ns	**	ns	ns
PETCO <sub>2</sub>	***	***	*	**	ns	ns
VT	***	<i>P = 0.0629</i>	***	ns	ns	ns
Ttot	***	ns	*	ns	ns	ns
HR	***	***	ns	<i>P = 0.07</i>	ns	ns
$\dot{V}A$	***	***	ns	ns	ns	ns
$\dot{V}E$ peak power	***	***	**	ns	*	ns
$\dot{V}E$ period	***	ns	ns	ns	ns	ns

441 Nx: normoxia; Hx: hypoxia; Exer.: Exercise; aDS : added dead space ;  $\dot{V}E$ : minute  
442 ventilation; SpO<sub>2</sub>: pulse O<sub>2</sub> saturation; PETCO<sub>2</sub>: end-tidal PCO<sub>2</sub>; VT: tidal volume; Ttot: total  
443 respiration cycle time; HR: heart rate;  $\dot{V}A$ : alveolar ventilation.

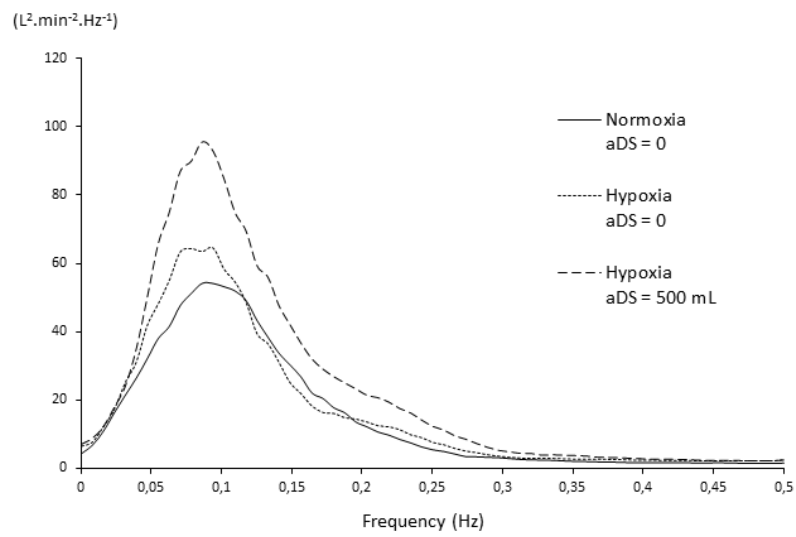
444 \*, *P* < 0.05; \*\*, *P* < 0.01; \*\*\*, *P* < 0.001; ns, non-significant.

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452 Figure 1



453 Figure 2

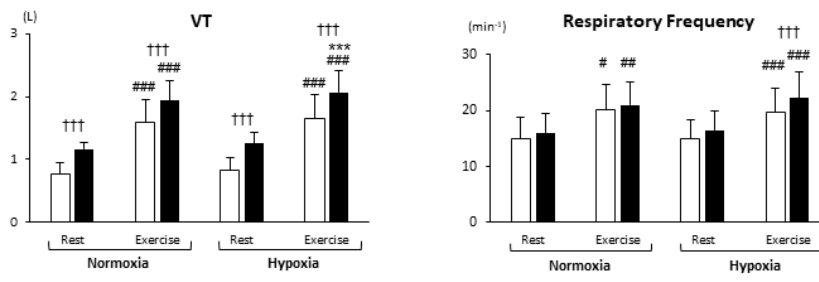
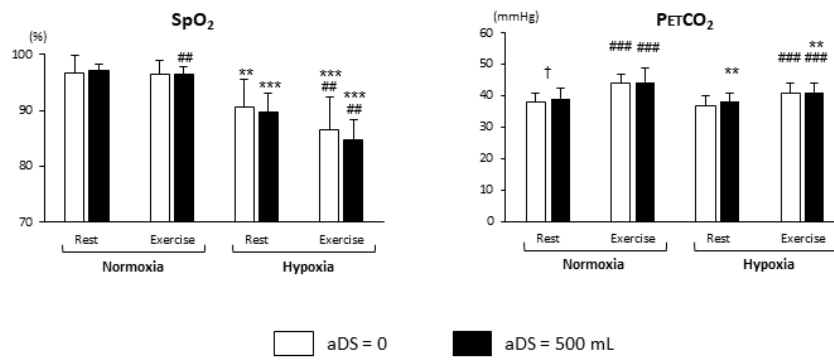


Figure 3

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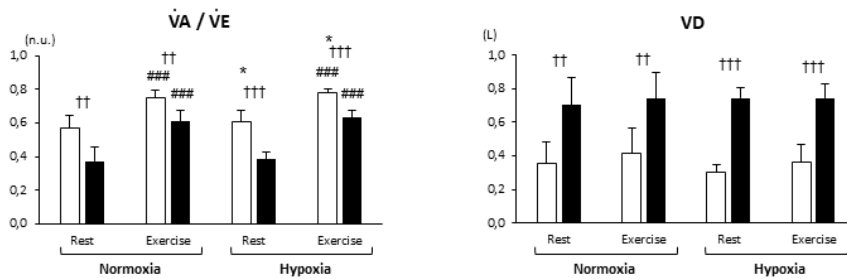
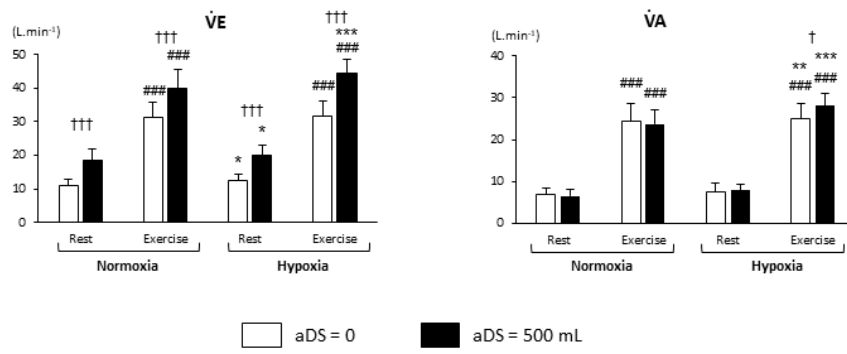
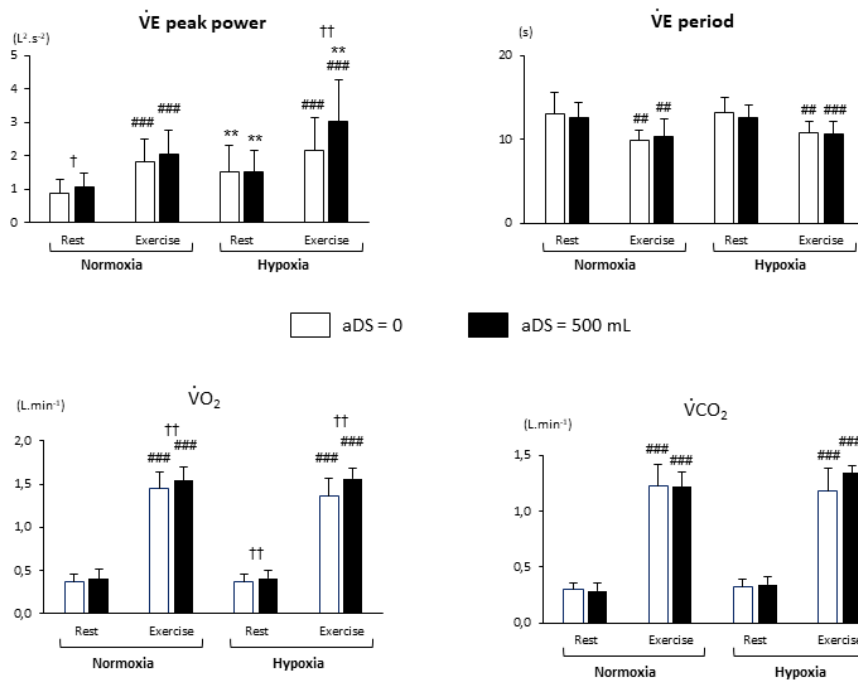
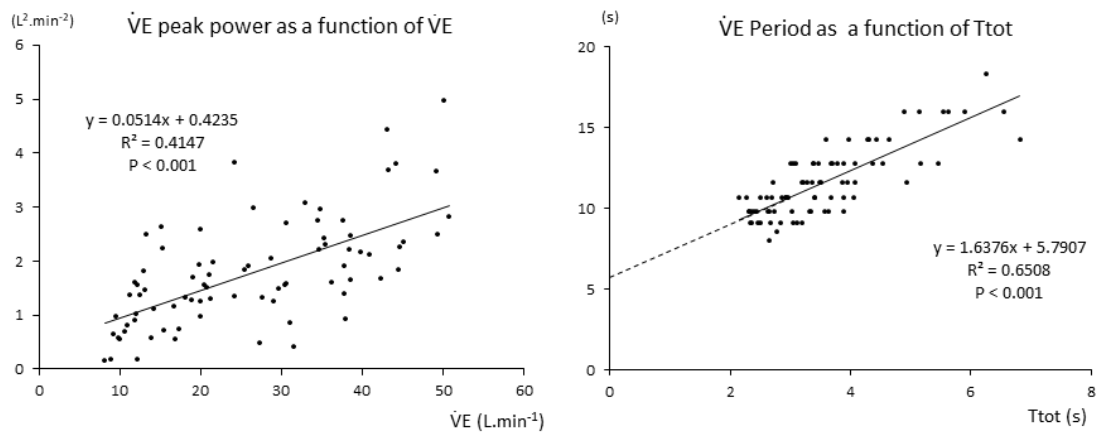


Figure 4

455



456 Figure 5



457 Figure 6