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# **Ventilatory oscillations at exercise in hypoxia: a mathematical model.**

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## **Abstract**

We evaluated the mechanisms responsible for the instability of ventilation control system under simultaneous metabolic (exercise) and environmental (hypoxia) stresses, promoting the genesis of periodic breathing. A model following the main concepts of ventilatory control has been tested, including cardiovascular and respiratory parameters, characteristics of peripheral and central chemoreceptors, at mild exercise in hypoxia ( $FIO_2=0.145$ ). Interaction between  $O_2$  and  $CO_2$  sensing was introduced following three different modalities. A sensitivity and multivariate regression analyses closely matched with physiological data for magnitude and period of oscillations. Low  $FIO_2$  and long circulatory delay from lungs to peripheral chemoreceptors ( $\Delta T_p$ ) lengthen the period of oscillations, while high peripheral and central chemoresponses to  $O_2$  and  $CO_2$ , low  $FIO_2$  and high  $\Delta T_p$  increased their magnitude. Peripheral and central  $O_2 / CO_2$  interactions highlight the role of  $CO_2$  on peripheral gain to  $O_2$  and the contribution of peripheral afferences on central gain to  $CO_2$ . Our model supports the key role of peripheral chemoreceptors in the genesis of ventilatory oscillations. Differences in the dynamics of central and peripheral components might be determinant for the system stability.

## 2 **1. Introduction**

3 Recent observations showed the existence of ventilatory oscillations in hypoxia during exercise  
4 (Hermand et al., 2015a, 2015b; Latshang et al., 2013). This instability of the ventilatory control system  
5 was related, at exercise, to cardiac output, minute ventilation, ventilatory response to hypoxia and to  
6 hypercapnia (Hermand et al., 2015a, 2015b). A subtle interplay between CO<sub>2</sub> and O<sub>2</sub> sensing seemed  
7 to play a major role in the underlying mechanisms. However, considering the complexity of the  
8 system, we thought that developing a model of ventilatory control in these specific conditions of  
9 hypoxia and exercise would allow us to unravel the factors involved in this instability.

10 The first attempt of modeling the ventilatory control system was developed by Grodins, and was based  
11 on mass balance equation for O<sub>2</sub> and CO<sub>2</sub> (Grodins et al., 1967). Many of the next developed models  
12 followed this approach. Whereas most of them were focused on steady state breathing under hypoxia  
13 and/or hypercapnia, only a few covered the complex topic of stability of ventilation control.  
14 Longobardo (Longobardo et al., 1982) and Khoo (Khoo et al., 1982) developed models describing the  
15 mechanisms of ventilatory oscillations in sleep apnea syndrome (SAS) and chronic heart failure  
16 (CHF). Models became more complex with the addition of numerous cardiorespiratory and neural  
17 inputs, and the technological and computing progress (Fan and Khoo, 2002). These simulations have  
18 brought valuable clinical insights in our understanding of breathing disorders in SAS and CHF  
19 patients, both in their intrinsic mechanisms and in the potential treatments by O<sub>2</sub> or CO<sub>2</sub> inhalation  
20 (Cherniack, 2005).

21 However, to our knowledge, no dynamic model involving both hypoxia and exercise has been built  
22 yet. This double concomitant stress destabilizes the ventilatory control system, enhances the overall  
23 loop gain of the system, leading to the genesis of ventilatory oscillations. This phenomenon, not  
24 characterized until very recently, is not included in nor explained by any of the existing models.  
25 Therefore, in order to deepen our understanding of mechanisms and parameters influencing the  
26 ventilatory system stability under these specific physiological and environmental stimuli, our objective  
27 was to develop a new mathematical model including most of the processes involved in ventilatory  
28 control, and to identify the physiological factors that could account for our recent observations  
29 (Hermand et al., 2015a, 2015b). However, as a rule in modeling physiological processes, we aimed to  
30 find the *simplest* model that could account for the physiological observations (Richalet, 1991).

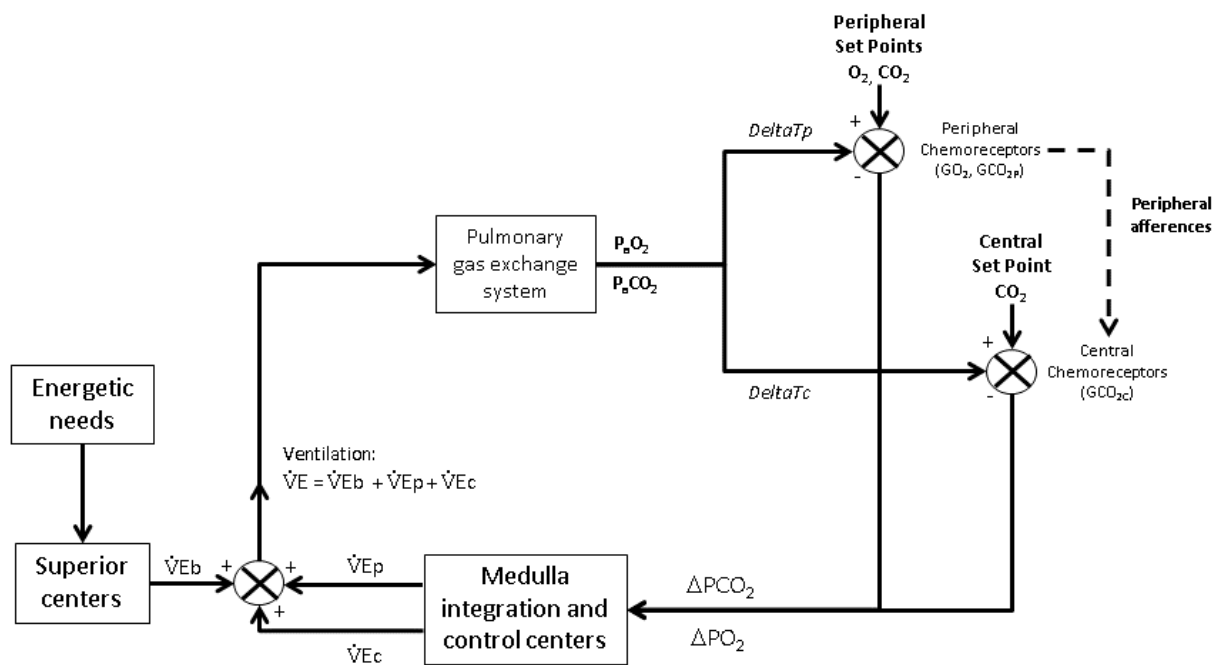
31

## 32 **2. Methods**

### 33 *2.1. Model description*

34 Our model of ventilation control can be described as a pulmonary gas exchange system and  
35 chemoreflex / regulation centers, connected by the cardiovascular system, which transports blood gas

36 information (Fig. 1) (Duffin, 2005; Grodins et al., 1967; Wolf and Garner, 2007). The cardiovascular  
 37 and ventilatory systems are functioning tightly together and are dependent upon each other in a  
 38 complex and time-related way. In existing models, the emergence of oscillations in SAS and CHF is  
 39 conditioned by two main factors: a longer circulation time from lung to peripheral and central  
 40 chemoreceptors, and a higher chemosensitivity to  $O_2$  and  $CO_2$ . Those parameters will be included into  
 41 our model, and their assigned values will vary accordingly to: 1. a metabolic stress, exercise, which  
 42 will impact  $O_2$  consumption ( $\dot{V}O_2$ ),  $CO_2$  production ( $\dot{V}CO_2$ ) and cardiac output ( $\dot{Q}c$ ) in a different way  
 43 than in sleep apneas or heart failure; 2. an environmental stress, hypoxia, with an inhaled fraction of  $O_2$   
 44 ( $FIO_2$ ) varying from a simulated sea level ( $FIO_2 = 0.21$ ) to a 4800 m altitude ( $FIO_2 = 0.115$ ).  
 45  
 46



**Figure 1.** Respiratory control model. Minute ventilation ( $\dot{V}E$ ) is the sum of a basal value represented by the central command adapted to the metabolic needs (rest/exercise), modulated by peripheral and central components. The  $P_aO_2$  and  $P_aCO_2$  gas information is transported to peripheral and central chemoreceptors respectively after a pure time delay of blood convection. The respiratory control center is then stimulated to adjust  $\dot{V}E$  according to  $P_aO_2$  and  $P_aCO_2$  set points.

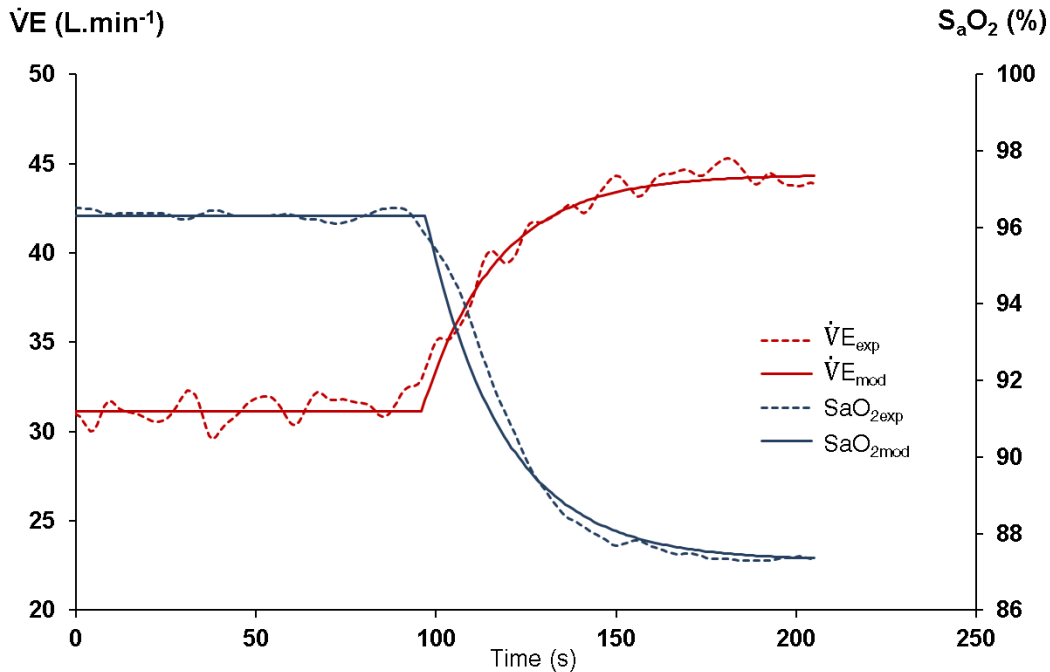
47

### 48 2.1.1. Protocol design

49 In accordance with our previous work (Hermand et al., 2015b), our model consists in two successive  
 50 phases built to simulate similar protocol conditions: rest and mild exercise, either in normoxia or  
 51 hypoxia, the latter obtained by breathing a hypoxic gas mixture, arterial blood  $CO_2$  pressure ( $P_aCO_2$ )  
 52 being free to vary (poikilocapnia).

53 To remain close to physiological behavior, time constants are applied to the basal cardiorespiratory  
 54 parameters ( $\dot{Q}c$ ,  $\dot{V}O_2$ , and ventilation  $\dot{V}E$ ) in the transitions from normoxia to hypoxia and from rest to

55 exercise. We obtained realistic values of these time constants by identifying our experimental data  
 56 with a simple first order system (Fig. 2).



**Figure 2.** Example of identification of transition from normoxia to hypoxia at exercise for the determination of time constants, between physiological data ( $SaO_{2exp}$  and  $\dot{V}E_{exp}$ , dashed lines) and model ( $SaO_{2mod}$  and  $\dot{V}E_{mod}$ , solid lines).

57

### 58 2.1.2. Mass balance equations

59 Mass balance equations are defined for each state variable, per unit of time.

60 Model inputs are  $O_2$  fraction in the inspired air ( $FIO_2$ ),  $O_2$  consumption rate ( $\dot{V}O_2$ ), cardiac output ( $\dot{Q}c$ ),  
 61 ventilatory equivalent for  $O_2$  ( $EVO_2$ ), respiratory quotient (QR), alveolar/total ventilation ratio  
 62 ( $rVAVE$ ), circulation time from lungs to central and peripheral chemoreceptors (see section 2.1.4),  
 63 gains of ventilatory responses to  $O_2$  and  $CO_2$  (see section 2.1.5). Model outputs are minute ventilation  
 64 ( $\dot{V}E$ ), arterial  $O_2$  pressure and saturation ( $P_aO_2$  and  $S_aO_2$ ) and arterial  $CO_2$  pressure ( $P_aCO_2$ ).  
 65 Intrapulmonary and cardiac shunts are negligible at rest and during mild exercise.

66

### 67 2.1.3. Ventilatory control system

68 Two distinct components are included in total ventilation ( $\dot{V}E$ ), in addition to a basal ventilation ( $\dot{V}Eb$ )  
 69 determined by the central command: the ventilatory response from peripheral chemoreceptors ( $\dot{V}Ep$ )  
 70 and the ventilatory response from central chemoreceptors ( $\dot{V}Ec$ ), when activated by hypoxia and/or  
 71 hypercapnia.

$$\dot{V}E = \dot{V}Eb + \dot{V}Ep + \dot{V}Ec$$

72 In case of disturbances in the ventilatory system, the central and peripheral components will act as  
73 negative feedback mechanisms to bring back the system to equilibrium, represented by  $P_a\text{CO}_2$  and  
74  $P_a\text{O}_2$  set points.

75 Ventilatory response to hypoxia at rest shows a biphasic response: first, a rise of ventilation due to the  
76 activation of peripheral chemoreceptors by the decrease of arterial  $\text{O}_2$  pressure; then a progressive  
77 decline, called hypoxic ventilatory depression (HVD), after several minutes (Khamnei and Robbins,  
78 1990), mainly due to prolonged neural hypoxia and central  $\text{CO}_2$  washout caused by an increase of  
79 cerebral blood flow (Ursino et al., 2001). Most models integrate HVD. However, during mild exercise,  
80 HVD is largely blunted (Ward and Nguyen, 1991) and our experimental data confirm that ventilation  
81 remains steady during the entire exercise phase. Therefore, HVD mechanism was not included in our  
82 model.

83

#### 84 *2.1.4. Cardiovascular control: cardiac output, cerebral blood flow and circulation delay*

85 Data from the literature and from our own experimental observations indicate that cardiac output is  
86 increased twofold during mild exercise (30% of maximal aerobic power), compared to rest (Hermand  
87 et al., 2015a, 2015b).

88 In order to facilitate the simulation process and the understanding of the influence of cardiac and  
89 cerebral blood flow, depending on several parameters such as blood velocities and vessel diameters in  
90 the successive arteries, we computed two circulation delays from lungs to peripheral chemoreceptors  
91 ( $\Delta T_p$ ) and from lungs to central chemoreceptors ( $\Delta T_c$ ) respectively. We assume that  
92 circulation delays are reduced when passing from rest to exercise and from normoxia to hypoxia.

93 At the central level, the delay between an instantaneous change of  $\text{O}_2$  and  $\text{CO}_2$  pressure in the lungs  
94 and the corresponding ventilatory response can be split into a circulatory delay and a tissue delay  
95 including the diffusion into the tissue (kinetic of  $\text{H}^+$  ions crossing the blood-brain barrier) and a neural  
96 delay from the chemoreceptors to integration centers and down to ventilatory muscles. Tissue delay is  
97 considered negligible at peripheral chemoreceptors, whereas a significant tissue delay ( $\Delta T_{ct}$ ) will  
98 be added to the central circulation delay (Ogoh and Ainslie, 2009). Therefore, the delay between  
99 changes in  $\text{O}_2$  and  $\text{CO}_2$  pressures in the lungs and the ventilatory response via central chemoreceptors  
100 is the sum

$$\Delta T_{cc} = \Delta T_c + \Delta T_{ct}$$

101

102

103

104

### 105 2.1.5. *Peripheral and central chemoreflex: O<sub>2</sub> and CO<sub>2</sub> gains*

106 The mechanisms of central and peripheral chemoreceptor activation (Grodins et al., 1967; Richalet,  
107 1991) are represented by relations between gas pressure changes and ventilation, with a pure delay,  
108 involving O<sub>2</sub> and CO<sub>2</sub> set points and gains.

109 pH is generally well regulated by the organism at rest and at low intensity exercise, and therefore no  
110 acidosis is observed in the present condition (Sun et al., 2001), and therefore there is no change of  
111 peripheral chemoreceptor activity due to a change in blood pH.

112 The interaction between O<sub>2</sub> and CO<sub>2</sub> stimuli at the level of the peripheral or central chemoreceptors  
113 has been introduced in the model to evaluate its possible implication in the generation of instability  
114 (Blain et al., 2010; Duffin, 2010; Smith et al., 2015). Recent works from the Dempsey group (Blain et  
115 al., 2010; Smith et al., 2015) confirmed and quantified, in a mammal model, the interaction between  
116 peripheral and central chemoreceptors, and between CO<sub>2</sub> and O<sub>2</sub>: the nucleus tractus solitarius (NTS)  
117 receives afferences from the peripheral chemoreceptors and sends projections into the central  
118 respiratory command and, potentially, the central chemoreceptors (Smith et al., 2013).

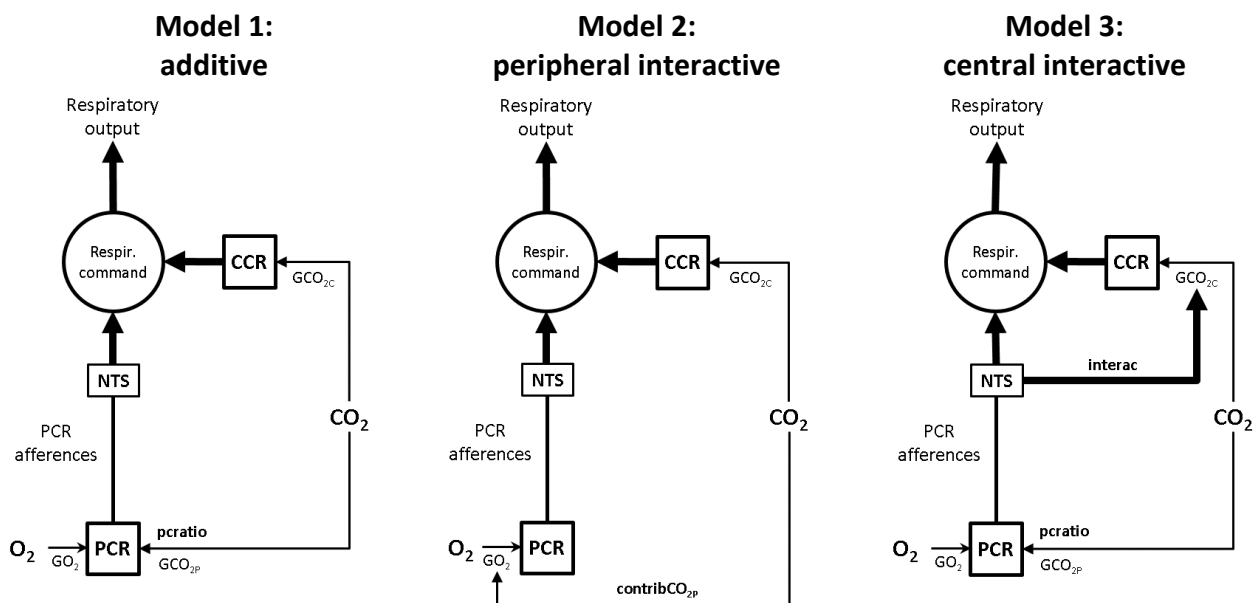
119 This led us to design and test three models of combined effects of O<sub>2</sub> and CO<sub>2</sub> (fig. 3): 1) *Additive*  
120 *model*. additive effects of central response to CO<sub>2</sub> and peripheral responses to O<sub>2</sub> and CO<sub>2</sub>. The latter  
121 ( $G_{CO_2p}$ ) is defined as a ratio (p<sub>ratio</sub>) of the peripheral/central gain to CO<sub>2</sub> ( $G_{CO_2c}$ ) (Wolf and  
122 Garner, 2007); 2) *Peripheral interactive model*: effect of P<sub>a</sub>CO<sub>2</sub> at the peripheral level. The peripheral  
123 gain to O<sub>2</sub> is positively modulated by a coefficient (contribCO<sub>2p</sub>) multiplied by the difference between  
124 P<sub>a</sub>CO<sub>2</sub> and P<sub>a</sub>CO<sub>2c</sub>. 3) *Central interactive model*: interaction between central CO<sub>2</sub> sensing and  
125 peripheral input (O<sub>2</sub> + CO<sub>2</sub>) at the central level. In addition to peripheral action on central respiratory  
126 command, central gain to CO<sub>2</sub> is augmented by peripheral afferences (gain to O<sub>2</sub> and CO<sub>2</sub>) modulated  
127 by the coefficient ‘interac’ (Blain et al., 2010; Smith et al., 2015).

128 Central CO<sub>2</sub> gain is obtained from a modified Read’s rebreathing test (Read, 1967). This test also gives  
129 a value of alveolar CO<sub>2</sub> pressure threshold (P<sub>a</sub>CO<sub>2cth</sub>) under which CO<sub>2</sub> gain is null. Similarly,  
130 peripheral ventilatory response to CO<sub>2</sub>, linear above a peripheral P<sub>a</sub>CO<sub>2</sub> threshold (P<sub>a</sub>CO<sub>2pth</sub>), is  
131 defined as the product of peripheral CO<sub>2</sub> gain by the difference between P<sub>a</sub>CO<sub>2</sub> and P<sub>a</sub>CO<sub>2</sub> set point  
132 (P<sub>a</sub>CO<sub>2c</sub>) (Casey et al., 1987). Exercise does not modify the ventilatory response to CO<sub>2</sub> (Hulsbosch et  
133 al., 1981): therefore, we used the same value for exercise and rest conditions.

134 Peripheral O<sub>2</sub> gain is obtained at rest and exercise from standard tests previously described (Lhuissier  
135 et al., 2012). The O<sub>2</sub> stimulus for peripheral chemoreceptors is tissue PO<sub>2</sub>, derived from arterial PO<sub>2</sub>,  
136 with a hyperbolic response (Weil et al., 1970). However, combining this hyperbolic response and the  
137 sigmoid shape of oxyhemoglobin dissociation curve (approximated by the Hill constant NH and P50),  
138 an empirical linear relationship appears between ventilatory response to hypoxia and arterial O<sub>2</sub>



139 saturation (Steinacker et al., 1996).  $\dot{V}E_c$  is the product of  $CO_2$  gain by the difference between  $P_aCO_2$   
 140 and the  $P_aCO_2$  set point ( $P_aCO_{2c}$ ). Depending on the model used,  $\dot{V}E_p$  is the result of the respective  
 141 contribution of peripheral  $O_2$  and  $CO_2$  gains. See appendix for equations.



**Figure 3.** Diagrams of the three different models: additive, peripheral interactive and central interactive. The central respiratory command receives direct or indirect afferences from peripheral (through nucleus tractus solitaries, NTS) and central chemoreceptors (PCR and CCR, respectively), modulated by  $P_aO_2$  and  $P_aCO_2$ . Details of each model are explained in text.

142

143 *2.1.6. Lungs: dead space, mechanoreceptors, respiratory quotient, alveolar-capillary difference in*  
 144  *$O_2/CO_2$ ,  $O_2$  alveolar-arterial diffusion*

145 As values of alveolar blood gases are determined by alveolar ventilation while the chemosensory loops  
 146 act on total ventilation, it seems important to take into account the dead space by introducing the  
 147 alveolar/total ventilation ratio (rVAVE). This ratio is slightly augmented by moderate exercise  
 148 (Wasserman et al., 1967). During moderate exercise in hypoxia, respiratory quotient (QR) is slightly  
 149 higher than at rest (de Lattre et al., 1969). The activity of pulmonary mechanoreceptors is not modified  
 150 by mild exercise (Fenik, 1992) and therefore will not be included in the present model. The alveolar-  
 151 capillary difference in  $O_2$  ( $DAaO_2$ ) increases with cardiac output from rest to exercise, and with  
 152 hypoxia (Woorons et al., 2007). This variation in  $DAaO_2$  is modulated by a coefficient ( $DlimO_2$ ) of  $O_2$   
 153 diffusion limitation of  $O_2$ . On the other hand, the alveolar-capillary difference in  $CO_2$  ( $DAaCO_2$ ) is  
 154 considered constant in all conditions (see appendix).

155

156 *2.1.7. Alveolar space*

157 Pulmonary alveolar space can be considered as a “mixing box” where  $O_2$  and  $CO_2$  are not instantly  
 158 homogenous when ventilation changes. Alveolar  $CO_2$  pressure ( $P_ACO_2$ ) is determined by the equation  
 159 relating  $\dot{V}E$ , QR,  $\dot{V}O_2$  and rVAVE (see appendix). When submitted to various environmental or

160 metabolic stresses, the value of  $P_A\text{CO}_2$  is not immediately modified by variations of the parameters  
161 cited above. A new equilibrium is reached through a first-order equation involving the level of  $\dot{V}E$  and  
162 the volume of the mixing box (TLC, total lung capacity), from which a time constant  $\text{TaupCO}_2$  is  
163 computed (see appendix).

164

## 165 *2.2. Parameter assignment*

166 All values were obtained from previous research protocols (Hermand et al., 2015a, 2015b) or from the  
167 literature (Duffin, 2010; Pianosi and Khoo, 1995; Saunders et al., 1980; Wolf and Garner, 2007;  
168 Zapata et al., 2012). The time constants for the main cardiorespiratory parameters ( $\dot{V}O_2$ ,  $\dot{Q}c$ ) were  
169 obtained by an identification algorithm from our own data, and in accordance with those found in  
170 literature: values are ranged from 10 seconds for  $\text{FIO}_2$  to 15 seconds for  $\dot{V}O_2$  and cardiac output.  
171 (MacFarlane and Cunningham, 1992; Pedersen et al., 1999; Thamrin and Murray-Smith, 2009).

172

## 173 *2.3. Modeling and sensitivity analysis*

174 The equations describing the various models were translated in a MatLab® script and the ventilatory  
175 output was calculated as a function of time, using 1-second time steps. The pattern of ventilatory  
176 output was analyzed in various conditions, by incrementing from a basal value the different  
177 cardiorespiratory and structure parameters ( $\text{O}_2$  and  $\text{CO}_2$  gains,  $\text{FIO}_2$ , delays, P50, TLC, rVAVE,  
178 pcratio, contrib $\text{CO}_{2P}$ , interac), one by one, in a maximal range of  $\pm 50\%$  around a nominal value or  
179 within realistic physiological range. If an oscillatory pattern of ventilation was observed, the period  
180 and amplitude of oscillations were computed. Then a sensitivity analysis was performed in order to  
181 evaluate the respective influence of each parameter of the model on the period and amplitude of the  
182 oscillatory pattern. Although it may not necessarily capture the general behavior in a multidimensional  
183 space, a single-parameter analysis allows us assessing the relative contribution of each parameter on  
184 the ventilation output.

185

## 186 *2.4. Multivariate regression analysis*

187 A multivariate regression was performed to establish potential correlations between period and  
188 magnitude of ventilatory oscillations on one hand, and model parameters on the other hand:  $\text{FIO}_2$ ,  
189 peripheral chemoresponse to  $\text{O}_2$  ( $\text{GO}_2$ ), central chemoresponse to  $\text{CO}_2$  ( $\text{GCO}_2$ ), delays from lungs to  
190 peripheral and central chemoreceptors ( $\Delta\text{Tp}$  and  $\Delta\text{Tc}$ , respectively), P50, TLC, rVAVE and  
191 interaction parameters (pcratio, contrib $\text{CO}_{2P}$ , interac).

192

193

194 *2.5. Addition of white noise*

195 Finally, in order to verify whether spontaneous variations in the ventilatory command would induce  
196 deeper instability in  $\dot{V}E$ , we added a white noise to  $\dot{V}E_b$ , the profile of which is following a normal  
197 distribution weighted by a 0.015 coefficient, in order to remain as close as possible to physiological  
198 data (Milton and Ohira, 2014). We then performed a paired Student t-test to check if there was a  
199 significant difference between the two simulations (“noise-enriched” and “no-noise enriched”). Values  
200 of period and amplitude of oscillations were also compared in the two conditions. Values of  $p < 0.05$  are  
201 considered significant.

202

203 **3. Results**

204 No significant ventilatory oscillations were found in resting conditions. The following results will  
205 concern only data obtained during exercise in hypoxia.

206

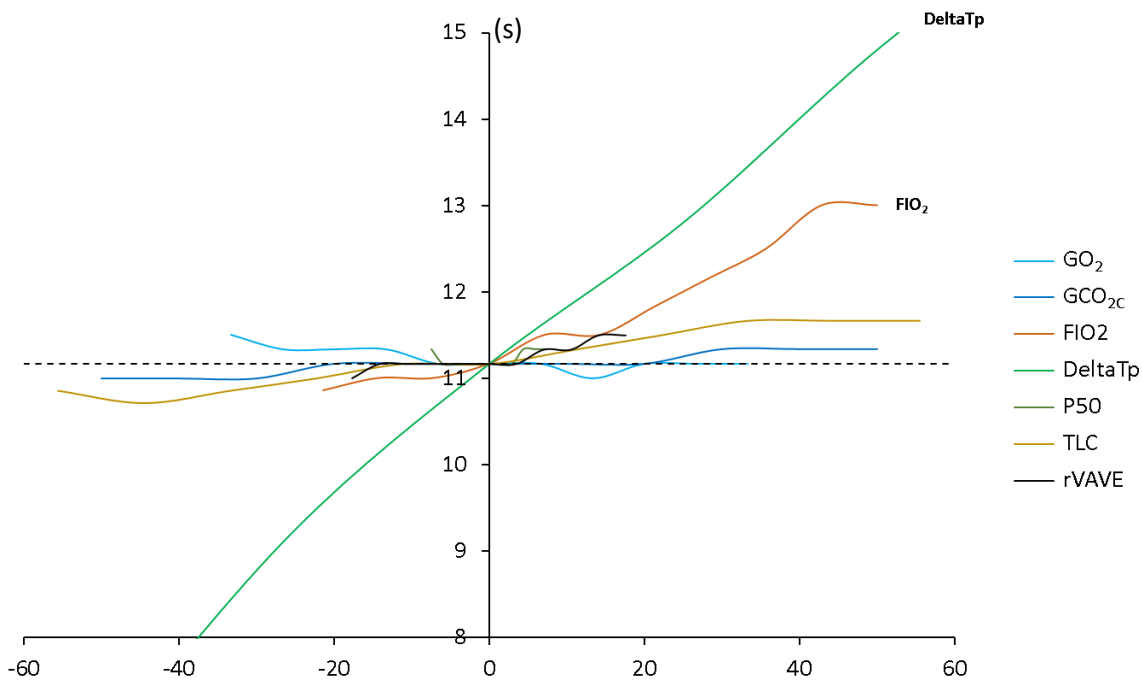
207 *3.1. Sensitivity analysis*

208 The variation of  $\dot{V}E$  magnitude and period during exercise in hypoxia, due to physiological,  
209 environmental and interaction parameters, are presented in figures 4, 5 and 6.

210

211 *3.1.1. Period of ventilatory oscillations (Fig. 4)*

212 Sensitivity analysis showed that the main factors influencing  $\dot{V}E$  period was the time delay between  
213 lungs and peripheral chemoreceptors ( $\Delta t_p$ ): in a range from 2 to 12 seconds, around a 4 s nominal  
214 value, period increased from  $-40\%$  to  $+123\%$  around its corresponding nominal value. In a lesser  
215 extent, the level of hypoxia ( $FIO_2$ ) played a significant role: period steadily increased from  $-3\%$  at  
216  $FIO_2=0.115$  to  $+16\%$  at  $FIO_2=0.21$  (Fig. 7, top). The other parameters induced only minor changes in  
217 period, remaining in a  $[-5\%; +5\%]$  range.

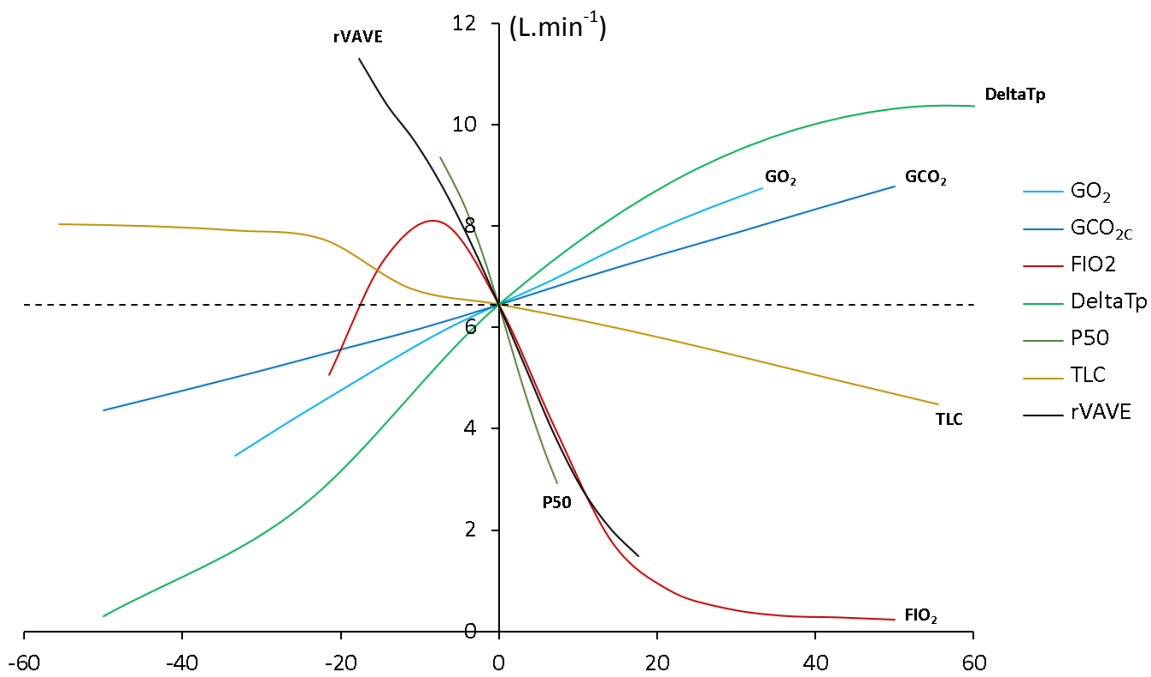


**Figure 4.** Period of ventilatory oscillations according to several cardiorespiratory variables from their nominal values: peripheral O<sub>2</sub> gain (GO<sub>2</sub>), central CO<sub>2</sub> gain (GCO<sub>2c</sub>), inhaled fraction of O<sub>2</sub> (FIO<sub>2</sub>), delay of blood convection from lung to carotid bodies (DeltaTp), arterial O<sub>2</sub> partial pressure at S<sub>a</sub>O<sub>2</sub> = 50% (P50), total lung capacity (TLC) and alveolar / total ventilation ratio (rVAVE). Period is linearly related to DeltaTp and also depends on FIO<sub>2</sub>.

218

219 *3.1.2. Magnitude of ventilatory oscillations (Fig. 5)*

220 Magnitude of ventilatory oscillations was nearly completely blunted, from 0% to -96.5%, when level  
 221 of hypoxia decreased from FIO<sub>2</sub>=0.14 to normoxia (Fig. 7). Peripheral and central gains to O<sub>2</sub> (GO<sub>2</sub>)  
 222 and CO<sub>2</sub> (GCO<sub>2c</sub>) and increased oscillations from - 46% to +35%, and from -32% to +36%,  
 223 respectively. DeltaTp enhanced oscillations from - 95% to +59%. P50 and TLC had a dampening  
 224 effect on oscillations, by decreasing them from +45% to - 54% and from +24% to - 31%, respectively.  
 225 Finally, a decrease in rVAVE (i.e. an increase in dead space) from 1 to 0.7 increased oscillations from  
 226 -77% to +75%. The influence of DeltaTcc is mainly due to the tissue component DeltaTct (fig. 8):  
 227 magnitude of oscillations shows a phasic pattern that can lead to either enhanced or blunted  
 228 oscillations, depending on the tissue component.

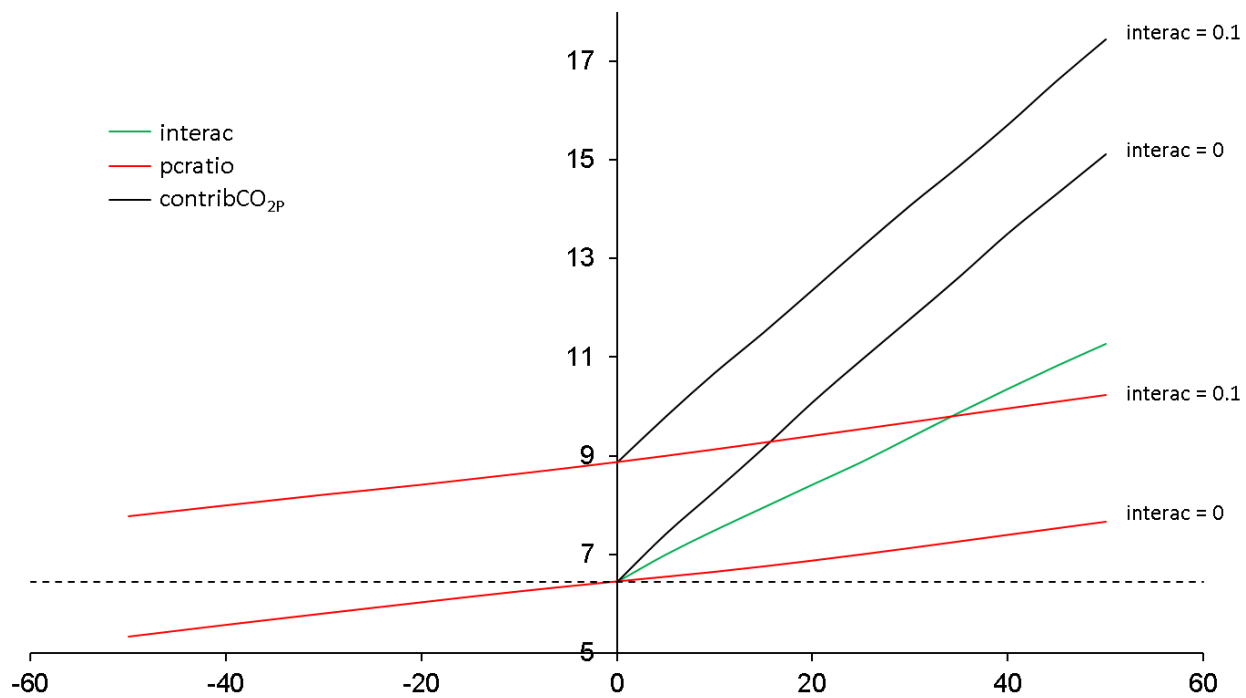


**Figure 5.** Magnitude of ventilatory oscillations according to several cardiorespiratory variables from their nominal values: peripheral O<sub>2</sub> gain (GO<sub>2</sub>), central CO<sub>2</sub> gain (GCO<sub>2c</sub>), inhaled fraction of O<sub>2</sub> (FIO<sub>2</sub>), delay of blood convection from lung to carotid bodies (DeltaTp), arterial O<sub>2</sub> partial pressure at S<sub>a</sub>O<sub>2</sub> = 50% (P50), total lung capacity (TLC) and alveolar / total ventilation ratio (rVAVE). Magnitude mainly increases with GCO<sub>2c</sub>, GO<sub>2</sub> (in a nearly linear manner) and DeltaTp, and decreases with P50, rVAVE, TLC and FIO<sub>2</sub>.

229

230 *3.1.3. Effect of interaction between O<sub>2</sub> and CO<sub>2</sub> at the central and peripheral level (fig. 6)*

231 The effect of contribCO<sub>2p</sub> (effect of CO<sub>2</sub> on O<sub>2</sub> gain in peripheral chemoreceptors) and interac (effect  
 232 of peripheral afferences on central gain to CO<sub>2</sub>) is very low on period values, in a tight range of 0 to  
 233 4.5% (results not shown). In contrast, a significant positive correlation links magnitude of  $\dot{V}E$   
 234 oscillations to contribCO<sub>2p</sub> and interac, from 0 to 134%, and from 0 to 75%, respectively (fig. 6). The  
 235 parameter pcratio (ratio of peripheral/central response to CO<sub>2</sub>) does not impact period and magnitude  
 236 of ventilatory oscillations. The effect of interac and contribCO<sub>2p</sub> are additive.



**Figure 6.** Magnitude of ventilatory oscillations according to interaction parameters: *interac* (effect of peripheral O<sub>2</sub>/CO<sub>2</sub> gain on central gain to CO<sub>2</sub>: *model 3*), *pcratio* (effect of CO<sub>2</sub> on peripheral gain: *model 1*) and *contribCO<sub>2P</sub>* (effect of CO<sub>2</sub> on peripheral gain to O<sub>2</sub>: *model 2*). Contributions of *pcratio* and *contribCO<sub>2P</sub>* are computed at 2 values of *interac* (0 and 0.1) and show an additive effect of the rise from peripheral activity level.

237

### 238 3.2. Multivariate regression analysis

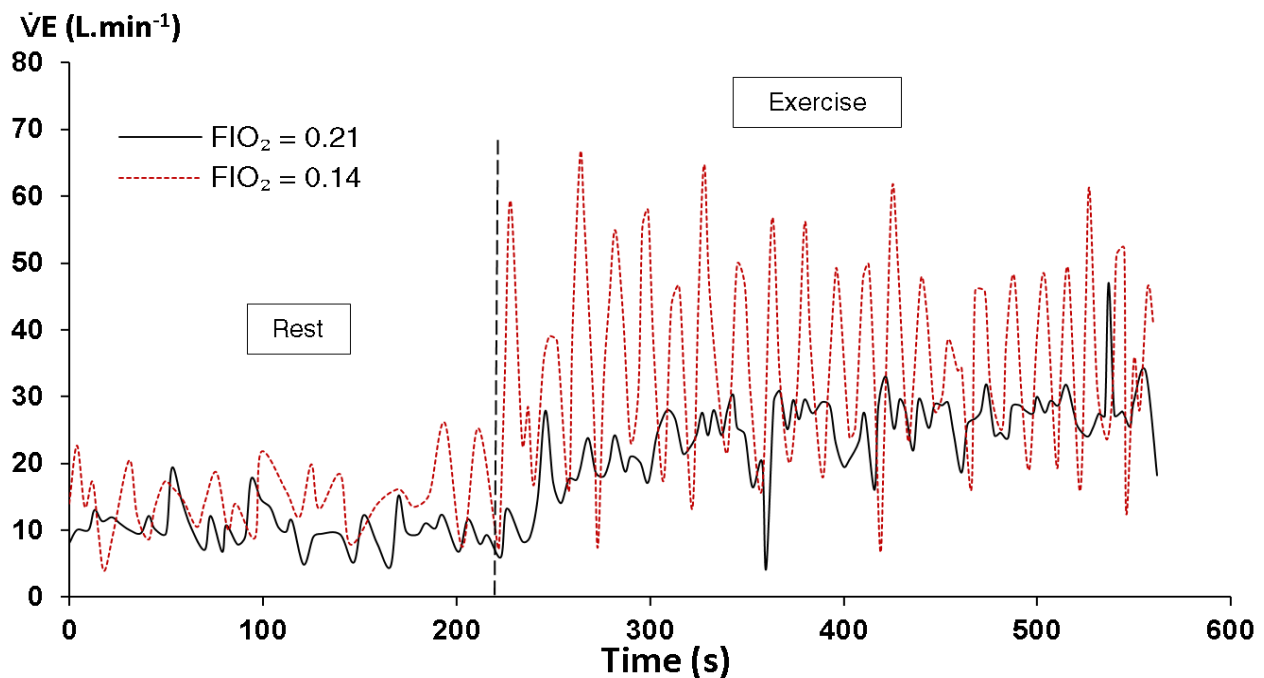
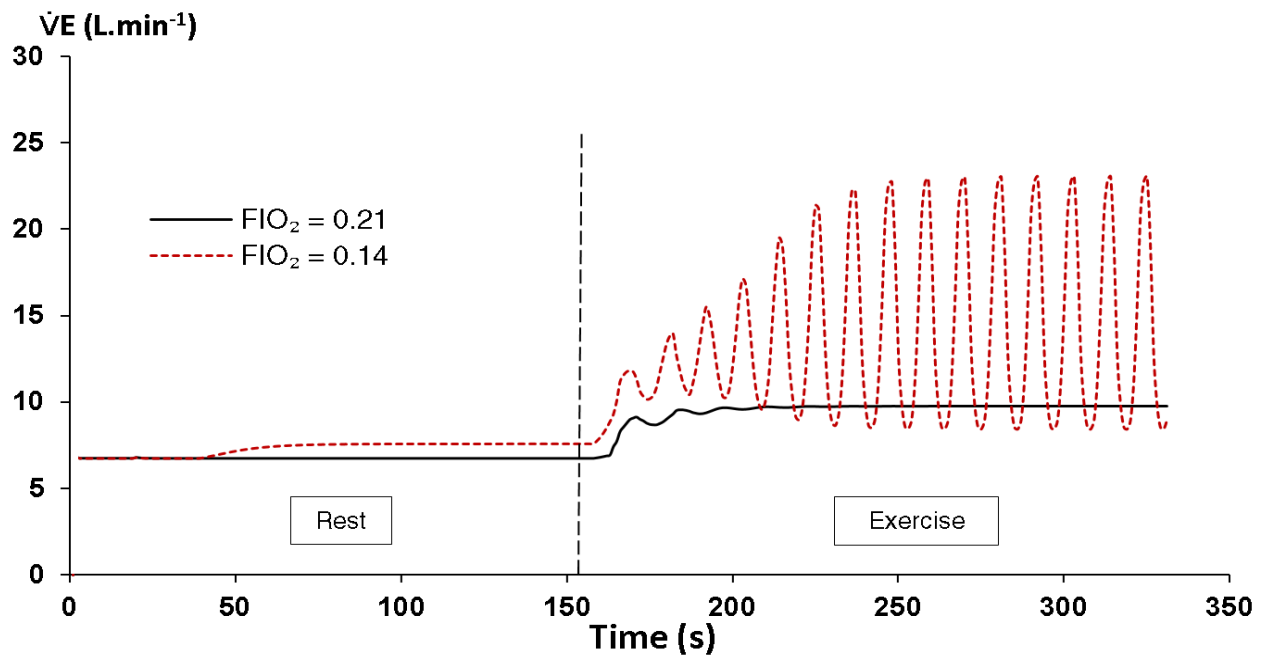
#### 239 3.2.1. Period of ventilatory oscillations

240 The multivariate regression analysis significantly linked  $\dot{V}E$  period to FIO<sub>2</sub>, GO<sub>2C</sub>, DeltaTp, DeltaTc  
 241 and TLC. A trend was observed for GO<sub>2</sub> (p = 0.053).  $\dot{V}E$  period increased when FIO<sub>2</sub>, GCO<sub>2C</sub>, DeltaTp  
 242 and TLC increased (p<0.001, p<0.05 for GCO<sub>2C</sub>) whereas it was shortened when DeltaTc increased  
 243 (p<0.001, respectively).

244

#### 245 3.2.2. Magnitude of ventilatory oscillations

246 Magnitude of oscillations was enhanced when GO<sub>2</sub>, GCO<sub>2C</sub> and DeltaTp increased (p<0.001) but  
 247 decreased when FIO<sub>2</sub>, DeltaTc, rVAVE, P50 and TLC increased (p<0.001).

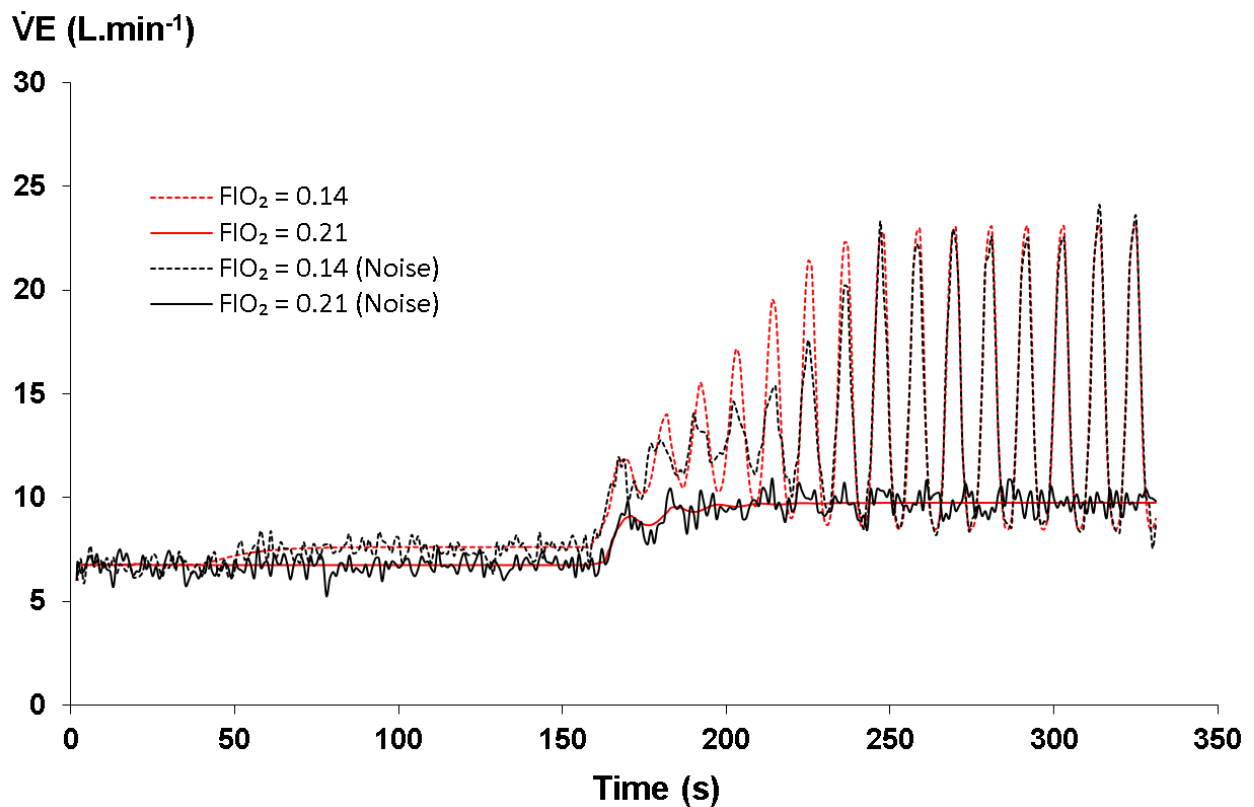


**Figure 7.** Variation of  $\dot{V}E$  for two levels of  $FIO_2$ : ventilatory oscillations in the additive model (upper panel) and physiological data from a subject exercising successively in normoxia and hypoxia (lower panel) (physiological data from Hermand et al., 2015b).

248

### 249 3.3. Effect of white-noise addition

250 The addition of a white noise did not alter magnitude or period of oscillations: there was no significant  
 251 change between non-noise and noise-enriched models (Fig. 9). Varying the noise coefficient, from  
 252 0.001 to 0.5, did not modify the  $\dot{V}E$  output behavior either.



**Figure 9.** Effects of added white noise to the central ventilation command, at two levels of  $FIO_2$ . There is no significant difference between “noise-enriched” (dashed lines) and “non-noise enriched” (solid lines) models.

253

#### 254 **4. Discussion**

255 To our knowledge, this model is the first attempt to describe the phenomenon of ventilatory  
 256 oscillations observed in healthy subjects. Our observations underline the key role of  $\dot{Q}_c$ ,  $FIO_2$ ,  $GO_2$   
 257 and  $GCO_{2C}$  in the genesis of such oscillations, their period and amplitude. First, resting conditions,  
 258 even in hypoxia, did not provoke ventilatory oscillations, whereas a double stimulus hypoxia / exercise  
 259 promoted the emergence of periodic breathing. Subjects with a higher ventilatory response to hypoxia  
 260 ( $GO_2$ ) or with a higher ventilatory response to  $CO_2$  ( $GCO_{2C}$ ) showed greater ventilatory oscillations  
 261 during exercise performed in hypoxia. Moreover, a greater cardiac output  $\dot{Q}_c$  (lower  $\Delta T_p$ ) was  
 262 significantly correlated to a higher magnitude and a shorter period.

263 The main difference with existing models lies in the inclusion of exercise-oriented components  
 264 through a higher cardiac output and a consequent decreased circulation time from lungs to central and  
 265 peripheral chemoreceptors. The existing studies and models were mostly focused on central and  
 266 obstructive sleep apneas and heart failure during sleep, and described a phenomenon with a much  
 267 longer period, associated with an enhanced sensitivity to  $CO_2$  (Hall et al., 1996; Javaheri, 1999; Khoo,  
 268 2000). The present work confirms previous studies in healthy subjects in which greater ventilatory  
 269 oscillations were related to a higher cardiac output (mild exercise) and to hypoxia (Garde et al., 2012;  
 270 Hermand et al., 2015b; Latshang et al., 2013) (Fig. 7). It is remarkable to notice the proximity of the



271 period between theoretical and physiological data, around 11 seconds (Hermand et al., 2015a). FIO<sub>2</sub>  
272 level is also correlated to both period and magnitude of ventilatory oscillations, as observed in our  
273 previous studies (from FIO<sub>2</sub> = 0.165).

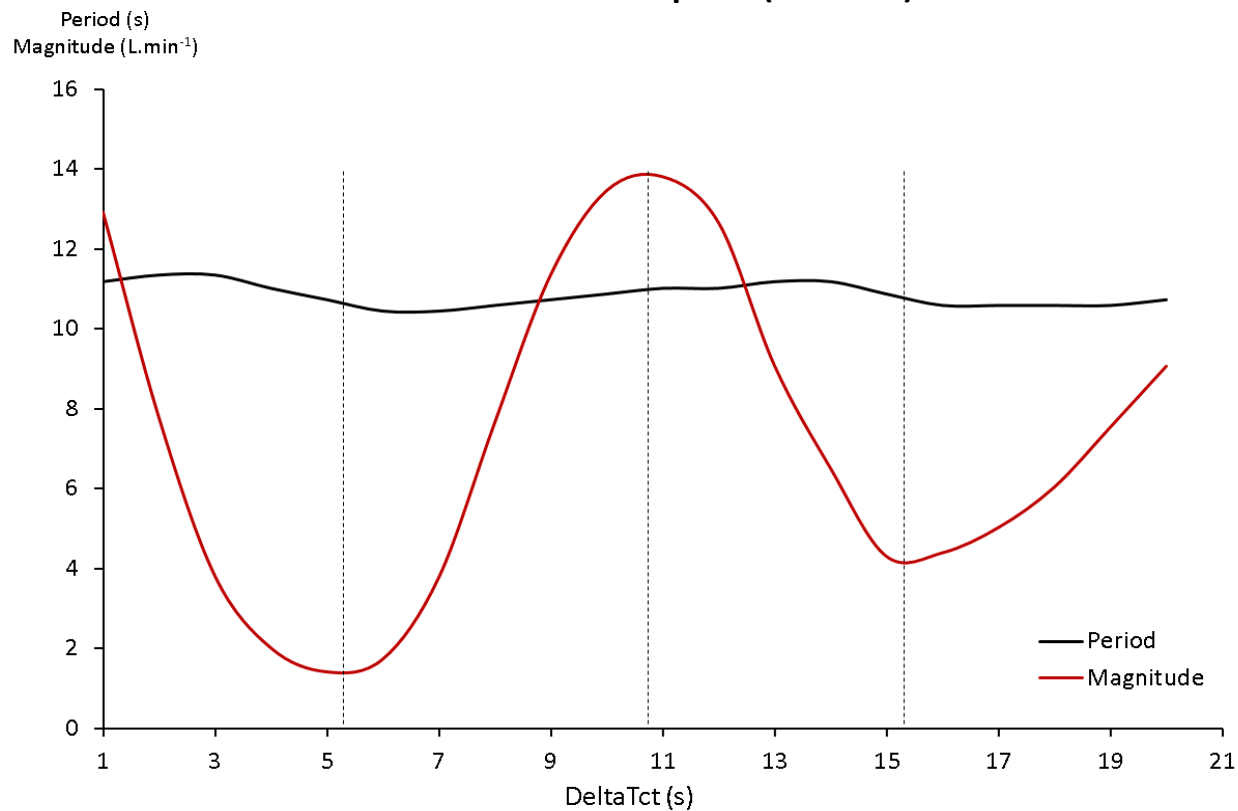
274 The O<sub>2</sub> gain has an important impact on the amplitude of oscillations, as subjects with a higher  
275 ventilatory response to hypoxia at exercise show a higher magnitude of oscillations, in coherence with  
276 our experimental observations (Hermand et al., 2015b). In addition to this intrinsic sensibility to O<sub>2</sub>,  
277 the O<sub>2</sub>-CO<sub>2</sub> interaction at the peripheral level enhances the instability in a degree depending on model  
278 used (fig. 6). The sensitivity analysis showed that a simple additive CO<sub>2</sub> contribution, via the pcratio  
279 coefficient (model 1), brings the least disturbance to ventilatory control system. Then, peripheral  
280 afferences to central chemoreceptors (interac contribution, model 3) further augments oscillations. The  
281 most unstable situation is created by the peripheral interactive model, in which increased peripheral O<sub>2</sub>  
282 gain by a hypercapnic stimulus (contribCO<sub>2P</sub>, model 2) severely destabilizes the respiratory command.  
283 Regardless of the studied model, these simulations highlight the major role played by the peripheral  
284 chemoreceptors in the genesis of ventilatory oscillations, with and without CO<sub>2</sub> interaction, and is in  
285 accordance with the observations of CHF and SAS patients (Beecroft et al., 2006; Ponikowski et al.,  
286 2001; Trombetta et al., 2013). This data provide a new perspective in the current debate about the  
287 respective contribution of central and peripheral chemoreceptors in the control of ventilation (Paula-  
288 Ribeiro and Rocha, 2016).

289

290 The central CO<sub>2</sub> gain is also involved, in a lesser extent, into the genesis of periodic breathing and  
291 matches the clinical studies on CHF and SAS patients (Beecroft et al., 2006; Trombetta et al., 2013).  
292 This supports our own findings in which ventilatory response to CO<sub>2</sub> is correlated to the magnitude of  
293 ventilatory oscillations in healthy subjects (Hermand et al., 2015b).

294 If both central and peripheral gains play a role in their appearance, they do not seem to play a major  
295 role in the period of the phenomenon. The latter is strongly dependent on DeltaTp, illustrating the role  
296 of cardiac output and circulation delay. As evidenced in figure 8, a phase shift between peripheral and  
297 central responses to chemical stimuli can lead to either a reinforcement or a blunting of ventilatory  
298 oscillations. Depending on the value of this phase shift, our model predicts that the effects of hypoxia  
299 and hyperventilation-induced hypocapnia can be either hyperadditive or hypoadditive, which could  
300 account for the variability of experimental observations (Paula-Ribeiro and Rocha, 2016). This original  
301 observation highlights the role of dynamics of central control processes in modulating the determinant  
302 effect of peripheral chemoreceptors on ventilatory instability. For any given value of DeltaTct, the  
303 period of oscillations remains around 11 seconds, reinforcing the essential role of peripheral  
304 chemoreceptors in both magnitude and period (fig.8).

## Period and magnitude of ventilatory oscillations as a function of tissue delay in central chemoreceptors (DeltaTct)



**Figure 8.** Variation of period and magnitude of ventilatory oscillations as a function of tissue delay at the central level. The period is not affected by changes in DeltaTct. Magnitude can be almost completely blunted (DeltaTct = 5.5 and 15) or enhanced (DeltaTct = 10.5).

305

306 Apart those cited above, one additional parameter comes into play: a greater alveolar / total ventilation  
 307 ratio decreases the amplitude of oscillatory ventilation, implying that a greater dead space will promote  
 308 periodic breathing. In heart failure patients, augmented dead space will prevent ventilatory oscillations  
 309 by an increased PETCO<sub>2</sub>, which acts on CO<sub>2</sub> apnea threshold and drastically decreased periodic  
 310 breathing (Patz et al., 2013; Xie et al., 1997). Conversely, in normal subjects, the same increase in  
 311 PETCO<sub>2</sub> will rise  $\dot{V}E$ , hence increasing ventilatory oscillations (Hermand et al., 2015a). This adverse  
 312 effect is particularly noticeable here.

313 Finally, spontaneous variations in central ventilatory command did not influence the stability of the  
 314 ventilation control system (fig. 8). Thus, this added chaotic component, very close to what is observed  
 315 in real life, is not a determinant factor in the genesis of ventilatory oscillations.

316

317 *A relation between period of ventilatory oscillations and DeltaTp: a limit value*

318 The significant correlation between period of oscillatory ventilations and DeltaTp (Fig. 4) is illustrated  
 319 by the equation of linear regression relating those two parameters:

320 
$$\dot{V}E \text{ period} = 1.798 \times \text{Delta}T_{O_2} + 3.72 \quad (1) \quad (r^2 = 0.9979, p < 0.001)$$

321 In our previous work (Hermant et al., 2015a), we established a similar equation relating  $\dot{V}E$  period to  
322 the total respiratory cycle ( $T_{tot}$ ):

323 
$$\dot{V}E \text{ period} = 1.13 \times T_{tot} + 6.99 \quad (2) \quad (r^2 = 0.55, p < 0.001)$$

324 The tight relationship between  $\dot{V}E$  period and  $T_{tot}$  points out a theoretical limit of  $\dot{V}E$  oscillations  
325 period: when  $T_{tot}$  tends toward zero (breathing frequency tending to infinity),  $\dot{V}E$  oscillations period  
326 tends to approximately 7 seconds (2). Using the latter value in equation (1), we can deduce a similar  
327 theoretical lower limit  $\Delta T_{p_{min}}$ , when intensity of exercise increases along with  $\dot{V}O_2$  and  $\dot{Q}_c$ , below  
328 which the ventilatory oscillations disappear:  $\Delta T_{p_{min}} \approx 1.8$  seconds. As  $\Delta T_p$  is the sum of  
329 circulation delay from lungs to carotid bodies and of the time required for the neural system to produce  
330 a ventilatory response, we can deduce that this irreducible time  $\Delta T_{p_{min}}$  of nearly 2 seconds is the  
331 intrinsic response time of peripheral chemoreceptors, which is in accordance with the existing  
332 literature (Black et al., 1971; McClean et al., 1988; Teppema et al., 1982).

333

334

### 335 **5. Conclusions and perspectives.**

336 Our model reproducing the control of ventilation in specific metabolic and environmental conditions  
337 closely matches with the observed experimental data in various protocols and studies. Furthermore, it  
338 demonstrates the crucial role of circulatory delays and gains of chemoreceptors in the homeodynamic  
339 behavior of the respiratory control system when exposed to brisk changes in physiological or  
340 environmental constraints. As pointed out in previous papers, the magnitude of transport delay and  
341 control loop gain plays a major role in many physiological conditions, especially in periodic breathing  
342 (Batzel and Kappel, 2011). The intrinsic neural reactivity of peripheral chemoreceptors to a change in  
343 gas pressures is also confirmed and quantified by a new and original approach through the analysis of  
344 ventilatory oscillations. We also extrapolate from our model the existence of an intrinsic oscillatory  
345 pattern in the control system of ventilation in healthy humans. The interaction between  $O_2$  and  $CO_2$   
346 sensing either at central or peripheral level plays an important but not exclusive role in the genesis of  
347 the ventilatory instability. Slight differences in the dynamics of the central vs. peripheral components  
348 might be determinant for the stability of the whole system. Further improvements may be carried out  
349 both in modeling and experimenting. On the one hand, the effect of an additional input, the inhaled  
350 fraction of carbon dioxide on ventilatory oscillations ( $FICO_2$ ) may be added to the model. Indeed,  
351 contrary to what is observed in patients suffering from sleep apnea, a higher  $FICO_2$  exacerbates  
352 ventilatory oscillations (Hermant et al., 2015a). On the other hand, this model could be tested on other  
353 subjects at exercise, such as heart failure patients, in which cardiac function is impaired whereas  
354 chemosensitivity to  $CO_2$  is increased.

355

356 **Acknowledgement.** We are very grateful to Jacques Richalet for his accurate advice on modeling  
357 physiological processes.

358

Variables	Units	Rest	Exercise		
			Min	Nominal	Max
Alveolar CO <sub>2</sub> partial pressure (P <sub>A</sub> CO <sub>2</sub> )	mmHg				
Arterial O <sub>2</sub> partial pressure (P <sub>a</sub> CO <sub>2</sub> )	mmHg				
Arterial O <sub>2</sub> saturation (S <sub>a</sub> O <sub>2</sub> )	nu				
Minute ventilation (V̇E)	L.min <sup>-1</sup>				
Atmospheric pressure (PB)	mmHg	760		760	
Vapor pressure of water (PH <sub>2</sub> O)	mmHg	47		47	
Arterial O <sub>2</sub> saturation Set point (S <sub>a</sub> O <sub>2C</sub> )	%	98		98	
Arterial CO <sub>2</sub> partial pressure Set point (P <sub>a</sub> CO <sub>2C</sub> )	mmHg	40		40	
Alveolo-arterial O <sub>2</sub> difference (DAaO <sub>2</sub> )	mL/mL	5		5	
Alveolo-arterial CO <sub>2</sub> difference (DAaCO <sub>2</sub> )	mL/mL	1		1	
Cardiac output (Q̇c)	L.s <sup>-1</sup>	6		10	
O <sub>2</sub> metabolic consumption (V̇O <sub>2</sub> )	mL.min <sup>-1</sup>	0.25		0.8	
Hill constant	nu	2.7		2.7	
Respiratory quotient (QR)	nu	0.7		0.8	
Ventilatory equivalent for oxygen (EVO <sub>2</sub> )	nu	30		26	
Arterial CO <sub>2</sub> partial pressure threshold	mmHg	40	35	45	55
Arterial O <sub>2</sub> partial pressure at S <sub>a</sub> O <sub>2</sub> = 50% (P50)	mmHg	27	25	28	31
Inhaled fraction of oxygen (FIO <sub>2</sub> )	nu	0.14	0.11	0.14	0.21
Central chemoreflex CO <sub>2</sub> gain (GCO <sub>2C</sub> )	L.min <sup>-1</sup> .mmHg <sup>-1</sup>	0.05	0.025	0.05	0.075
Peripheral chemoreflex O <sub>2</sub> gain (GO <sub>2</sub> )	L.min <sup>-1</sup> .% <sup>-1</sup>	10	10	15	20
Total lung capacity (TLC)	L	9	4	9	14
Circulatory delay from lung to carotid bodies (DeltaTp)	s	8	2	4	12
Circulatory delay from lung to brain (DeltaTc)	s	10	3	6	13
Alveolar / total ventilation ratio (rVAVE)	nu	0.7	0.7	0.85	1
Coefficient of diffusion limitation of O <sub>2</sub> (DlimO <sub>2</sub> )	mmHg.L <sup>-1</sup> . min	0	0	5	10
Ratio of peripheral/central gain to CO <sub>2</sub> (pcratio)	nu	0.5	0.25	0.5	0.75
Coefficient of CO <sub>2</sub> contribution to peripheral gain (contribCO <sub>2P</sub> )	nu	0	0	0	0.2
Coefficient of peripheral afferences contributing to central gain to CO <sub>2</sub> (interac)	nu	0	0	0	0.2
Central tissue delay (DeltaTct)	s	1	0	1	21

**Table 1.** Nominal values for the variables used in model simulations. In the sensitivity analysis, parameters were assigned values ranging from a minimal (Min) to a maximal (Max).

359

360

361 **Appendix**

362 **Basal cardiorespiratory parameters:**  $\dot{V}E_b$ ,  $\dot{V}O_2$ ,  $EVO_2$ ,  $\dot{Q}c$ ,  $rVAVE$ ,  $QR$ .

363  $O_2$  consumption  $\dot{V}O_2$ , cardiac output  $\dot{Q}c$ , alveolar/total ventilation ratio  $rVAVE$ , respiratory quotient  
364  $QR$  and ventilatory equivalent for oxygen  $EVO_2$  are set at known physiological values for rest/exercise  
365 and normoxia/hypoxia, as indicated in table 1.

366 The basal value of  $\dot{V}E$  for all phases is calculated as follows:

$$\dot{V}E_b(t) = EVO_2(t) \cdot VO_2(t)$$

367

368 The arterial  $O_2$  pressure  $P_aO_2$  and arterial  $O_2$  saturation follow the equation:

$$S_aO_2 = \frac{\left(\frac{P_aO_2}{P50}\right)^{NH}}{1 + \left(\frac{P_aO_2}{P50}\right)^{NH}}$$

369 where  $P50$  is the arterial  $O_2$  partial pressure at  $S_aO_2 = 50\%$ , and  $NH$  is the Hill constant.

370

371 **The alveolar-arterial difference in  $O_2$  ( $DAaO_2$ )** is determined as:

$$DAaO_2(t) = DAaO_{20} + DlimO_2 \cdot (\dot{Q}c(t) - \dot{Q}c_{rep})$$

372 where  $DAaO_{20}$  is the alveolar-arterial difference in  $O_2$  at rest,  $DlimO_2$  a known coefficient of  
373 diffusion, and  $\dot{Q}c_{rep}$  the cardiac output at rest.

374

375 **Peripheral chemoreceptors**

376 This linear expression involves the peripheral gain to  $O_2$  ( $GO_2$ ) and to  $CO_2$  ( $GCO_{2P}$ ) and a pure delay  
377  $\Delta Tp$  from lung to peripheral chemoreceptors (blood convection).

378 The peripheral gain to  $CO_2$ , above a peripheral threshold  $P_aCO_{2Pth}$  is defined as:

379 if  $P_aCO_2(t) > P_aCO_{2Pth}$ , then the peripheral contribution from a  $CO_2$  stimulus is the linear term

380  $GCO_{2P} \cdot [P_aCO_2(t - \Delta Tp) - P_aCO_{2C}]$  with  $P_aCO_{2C}$  as a  $P_aCO_2$  set point,

381 else it is null.

382 In the additive and central interactive models, the peripheral contribution is:

$$\dot{V}Ep(t) = GO_{2P}(t) \cdot [S_aO_{2C} - S_aO_2(t - \Delta Tp)] + GCO_{2P}(t) \cdot [P_aCO_2(t - \Delta Tp) - P_aCO_{2C}]$$

384 with  $S_aCO_{2C}$  as a  $S_aCO_2$  set point.

385 In the interactive model, the peripheral contribution is:

$$\dot{V}Ep(t) = GO_{2P}(t) \cdot [1 + contribCO_{2P} \cdot (P_aCO_2(t - \Delta Tp) - P_aCO_{2C})] \cdot [S_aO_{2C} - S_aO_2(t - \Delta Tp)]$$

386

387

388 **Central chemoreceptors**

389 The central component of ventilation, resulting from a variation of arterial CO<sub>2</sub> content, includes a  
390 static central gain to CO<sub>2</sub> (GCO<sub>2C</sub>) and a delay DeltaTc (see section 2.1.4), above a central threshold  
391 (P<sub>a</sub>CO<sub>2Cth</sub>):

392 if P<sub>a</sub>CO<sub>2</sub>(t) > P<sub>a</sub>CO<sub>2Cth</sub>, then  $\dot{V}Ec(t) = GCO_{2C} \cdot [P_aCO_2(t - DeltaTc) - P_aCO_{2C}]$

393 else  $\dot{V}Ec(t) = 0$ .

394 In the central interactive model, the central gain to CO<sub>2</sub> (GCO<sub>2C</sub>) depends on peripheral gains to O<sub>2</sub>  
395 and CO<sub>2</sub> (GO<sub>2</sub> and GCO<sub>2P</sub>, respectively), modulated by a constant interac:

$$GCO_{2C}(t) = GCO_{2C} \cdot \{1 + interac \cdot [GO_2(t) \cdot [S_aO_{2C} - S_aO_2(t - DeltaTp)]] \\ + GCO_{2P}(t) \cdot [P_aCO_2(t - DeltaTp) - P_aCO_{2C}]\}$$

396 and  $\dot{V}Ec(t) = GCO_{2C}(t) \cdot [P_aCO_2(t - DeltaTc) - P_aCO_{2C}]$

397

398 **Equations of alveolar and arterial gas pressures: steady state and first order**

399 At equilibrium, the alveolar partial pressures in O<sub>2</sub> and CO<sub>2</sub> as a function of time are defined as:

400  $P_AO_2(t) = -DAaO_2(t) + (P_B - P_{H_2O}) \cdot FIO_2(t) - P_ACO_2(t)$

401  $P_ACO_2(t) = \frac{QR(t) \cdot \dot{V}O_2(t)}{K \cdot \dot{V}E(t) \cdot rVAVE(t)}$

402 where P<sub>B</sub> and P<sub>H<sub>2</sub>O</sub> are atmospheric and water vapor pressures, respectively, FIO<sub>2</sub> is the inhaled fraction  
403 of O<sub>2</sub>. P<sub>B</sub>, P<sub>H<sub>2</sub>O</sub>, FIO<sub>2</sub>, QR,  $\dot{V}O_2$  and rVAVE are predetermined as shown in table 1.

404 P<sub>A</sub>CO<sub>2</sub> is then described through a first-order relation:

$$\frac{dP_ACO_2}{dt} + P_ACO_2(t) = P_ACO_2(t) \cdot apCO_2 + bpCO_2 \cdot P_APCO_2(t)$$

405 where apCO<sub>2</sub> and bpCO<sub>2</sub> are defined as follows:  $TaupCO_2 = \frac{TLC}{\dot{V}E(t)}$ ,  $apCO_2 = e^{-\frac{1}{TaupCO_2}}$  and

406  $bpCO_2 = 1 - apCO_2$ , P<sub>A</sub>PCO<sub>2</sub> is the P<sub>A</sub>CO<sub>2</sub> variable determined by initial conditions of  $\dot{V}O_2(t)$  and  
407  $\dot{V}E(t)$ .

408

409

410

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