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Ventilatory oscillations at exercise in hypoxia: A mathematical model

Eric Hermand*, François J. Lhuissier, Nicolas Voituron, Jean-Paul Richalet*

Université Paris 13, Sorbonne Paris Cité, Laboratoire "Hypoxie et poumons", EA2363, 74 rue Marcel Cachin, 93017 Bobigny Cedex, France

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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 (DeltaTp) lengthen the period of oscillations, while high peripheral and central chemoresponses to O_2 and CO_2, low FIO_2 and high DeltaTp 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.

1. Introduction

Recent observations showed the existence of ventilatory oscillations in hypoxia during exercise (Hermand et al., 2015a, 2015b; Latshang et al., 2013). This instability of the ventilatory control system was related, at exercise, to cardiac output, minute ventilation, ventilatory response to hypoxia and to hypercapnia (Hermand et al., 2015a, 2015b). A subtle interplay between CO_2 and O_2 sensing seemed to play a major role in the underlying mechanisms. However, considering the complexity of the system, we thought that developing a model of ventilatory control in these specific conditions of hypoxia and exercise would allow us to unravel the factors involved in this instability.

The first attempt of modeling the ventilatory control system was developed by Grodins, and was based on mass balance equation for O_2 and CO_2 (Grodins et al., 1967). Many of the next developed models followed this approach. Whereas most of them were focused on steady state breathing under hypoxia and/or hypercapnia, only a few covered the complex topic of stability of ventilation control. Longobardo et al. (1982) and Khoo et al. (1982) developed models describing the mechanisms of ventilatory oscillations in sleep apnea syndrome (SAS) and chronic heart failure (CHF). Models became more complex with the addition of numerous cardiorespiratory and neural inputs, and the technological and computing progress (Fan and Khoo, 2002). These simulations have brought valuable clinical insights in our understanding of breathing disorders in SAS and CHF patients, both in their intrinsic mechanisms and in the potential treatments by O_2 or CO_2 inhalation (Cherniack, 2005).

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

2. Methods

2.1. Model description

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

* Corresponding authors.
E-mail addresses: eric.hermand17@gmail.com (E. Hermand), richalet@univ-paris13.fr (J.-P. Richalet).

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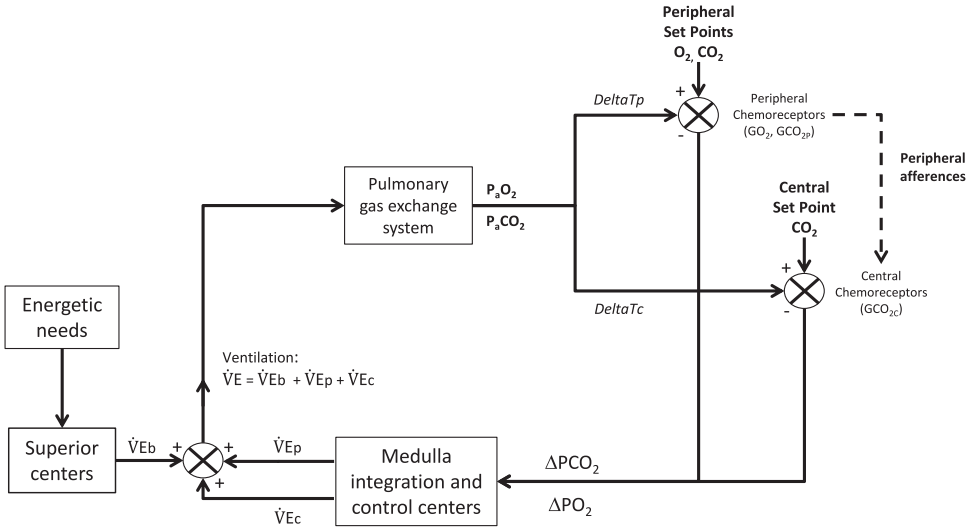

Fig. 1. Respiratory control model. Minute ventilation ($\dot{V}E$) is the sum of a basal value represented by the central command adapted to the metabolic needs (rest/exercise), modulated by peripheral and central components. The P_aO_2 and P_aCO_2 gas information is transported to peripheral and central 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.

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

2.1.1. Protocol design

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

To remain close to physiological behavior, time constants are applied to the basal cardiorespiratory parameters ($\dot{Q}c$, $\dot{V}O_2$, and ventilation $\dot{V}E$) in the transitions from normoxia to hypoxia and from rest to exercise. We obtained realistic values of these time constants by identifying our experimental data with a simple first order system (Fig. 2).

2.1.2. Mass balance equations

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

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

2.1.3. Ventilatory control system

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

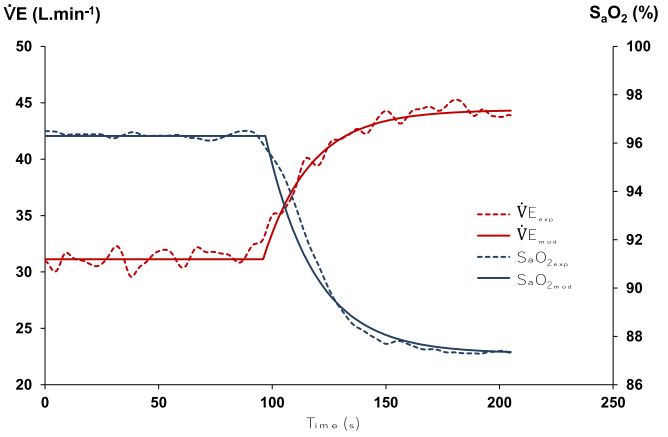

Fig. 2. Example of identification of transition from normoxia to hypoxia at exercise for the determination of time constants, between physiological data ($S_aO_{2\ exp}$ and $\dot{V}E_{\ exp}$, dashed lines) and model ($S_aO_{2\ mod}$ and $\dot{V}E_{\ mod}$, solid lines).

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

In case of disturbances in the ventilatory system, the central and peripheral components will act as negative feedback mechanisms to bring back the system to equilibrium, represented by P_aCO_2 and P_aO_2 set points.

Ventilatory response to hypoxia at rest shows a biphasic response: first, a rise of ventilation due to the activation of peripheral chemoreceptors by the decrease of arterial O_2 pressure; then a progressive decline, called hypoxic ventilatory depression (HVD), after several minutes (Khamnei and Robbins, 1990), mainly due to prolonged neural hypoxia and central CO_2 washout caused by an increase of cerebral blood flow (Ursino et al., 2001). Most models integrate HVD. However, during mild exercise, HVD is largely blunted (Ward and Nguyen, 1991) and our experimental data confirm that ventilation remains steady during the entire exercise phase. Therefore, HVD mechanism was not included in our model.

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

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

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

At the central level, the delay between an instantaneous change of O_2 and CO_2 pressure in the lungs and the corresponding ventilatory response can be split into a circulatory delay and a tissue delay including the diffusion into the tissue (kinetic of H^+ ions crossing the blood-brain barrier) and a neural delay from the chemoreceptors to integration centers and down to ventilatory muscles. Tissue delay is considered negligible at peripheral chemoreceptors, whereas a significant tissue delay (DeltaTct) will be added to the central circulation delay (Ogoh and Ainslie, 2009). Therefore, the delay between changes in O_2 and CO_2 pressures in the lungs and the ventilatory response via central chemoreceptors is the sum

$$DeltaTcc = DeltaTc + DeltaTct$$

2.1.5. Peripheral and central chemoreflex: O_2 and CO_2 gains

The mechanisms of central and peripheral chemoreceptor activation (Grodins et al., 1967; Richalet, 1991) are represented by relations between gas pressure changes and ventilation, with a pure delay, involving O_2 and CO_2 set points and gains.

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

The interaction between O_2 and CO_2 stimuli at the level of the peripheral or central chemoreceptors has been introduced in the model to evaluate its possible implication in the generation of instability (Blain et al., 2010; Duffin, 2010; Smith et al., 2015). Recent works from the Dempsey group (Blain et al., 2010; Smith et al., 2015) confirmed and quantified, in a mammal model, the interaction between peripheral and central chemoreceptors, and between CO_2 and O_2: the nucleus tractus solitarius (NTS) receives afferences from the peripheral chemoreceptors and sends projections into the central respiratory command and, potentially, the central chemoreceptors (Smith et al., 2013).

This led us to design and test three models of combined effects of O_2 and CO_2 (Fig. 3): (1) *Additive model*. additive effects of central response to CO_2 and peripheral responses to O_2 and CO_2. The latter (GCO_{2P}) is defined as a ratio (pcratio) of the peripheral/central gain to CO_2 (GCO_{2C}) (Wolf and Garner, 2007); (2) *Peripheral interactive model*: effect of P_aCO_2 at the peripheral level. The peripheral gain to O_2 is positively modulated by a coefficient ($contribCO_{2p}$) multiplied by the difference between P_aCO_2 and P_aCO_{2C}. (3) *Central interactive model*: interaction between central CO_2 sensing and peripheral input (O_2+CO_2) at the central level. In addition to peripheral action on central respiratory command, central gain to CO_2 is augmented by peripheral afferences (gain to O_2 and CO_2) modulated by the coefficient 'interac' (Blain et al., 2010; Smith et al., 2015).

Central CO_2 gain is obtained from a modified Read's rebreathing test (Read, 1967). This test also gives a value of alveolar CO_2 pressure threshold (P_aCO_{2Cth}) under which CO_2 gain is null. Similarly, peripheral ventilatory response to CO_2, linear above a peripheral P_aCO_2 threshold (P_aCO_{2Pth}), is defined as the product of peripheral CO_2 gain by the difference between P_aCO_2 and P_aCO_2 set point (P_aCO_{2C}) (Casey et al., 1987). Exercise does not modify the ventilatory response to CO_2 (Hulsbosch et al., 1981): therefore, we used the same value for exercise and rest conditions.

Peripheral O_2 gain is obtained at rest and exercise from standard tests previously described (Lhuissier et al., 2012). The O_2 stimulus for peripheral chemoreceptors is tissue PO_2, derived from arterial PO_2, with a hyperbolic response (Weil et al., 1970). However, combining this hyperbolic response and the sigmoid shape of oxyhemoglobin dissociation curve (approximated by the Hill constant NH and P50), an empirical linear relationship appears between ventilatory response to hypoxia and arterial O_2 saturation (Steinacker et al., 1996). $\dot{V}Ec$ is the product of CO_2 gain by the difference between P_aCO_2 and the P_aCO_2 set point (P_aCO_{2C}). Depending on the model used, $\dot{V}Ep$ is the result of the respective contribution of peripheral O_2 and CO_2 gains. See Appendix for equations.

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

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

2.1.7. Alveolar space

Pulmonary alveolar space can be considered as a "mixing box" where O_2 and CO_2 are not instantly homogenous when ventilation changes. Alveolar CO_2 pressure (P_ACO_2) is determined by the equation relating $\dot{V}E$, QR, $\dot{V}O_2$ and rVAVE (see Appendix). When submitted to various environmental or metabolic stresses, the value of P_ACO_2 is not immediately modified by variations of the parameters cited above. A new equilibrium is reached through a first-order equation involving the level of $\dot{V}E$ and the volume of the mixing box (TLC, total lung capacity), from which a time constant $TaupCO_2$ is computed (see Appendix).

2.2. Parameter assignment

All values were obtained from previous research protocols (Hermand et al., 2015a, 2015b) or from the literature (Duffin, 2010; Pianosi and Khoo, 1995; Saunders et al., 1980; Wolf and Garner, 2007; Zapata et al., 2012). The time constants for the main cardiorespiratory parameters ($\dot{V}O_2$, $\dot{Q}c$) were obtained by an identification algorithm from our own data, and in accordance with those found in literature: values are ranged from 10 s for FIO_2 to 15 s for $\dot{V}O_2$ and cardiac output. (MacFarlane and Cunningham, 1992; Pedersen et al., 1999; Thamrin and Murray-Smith, 2009).

2.3. Modeling and sensitivity analysis

The equations describing the various models were translated in a MatLab® script and the ventilatory output was calculated as a function of time, using 1-s time steps. The pattern of ventilatory output was analyzed in various conditions, by incrementing from a basal value the different cardiorespiratory and structure parameters (O_2 and CO_2 gains, FIO_2, delays, P50, TLC, rVAVE, pcratio, $contribCO_{2P}$, interac), one by one, in a maximal range of ± 50% around a nominal value or

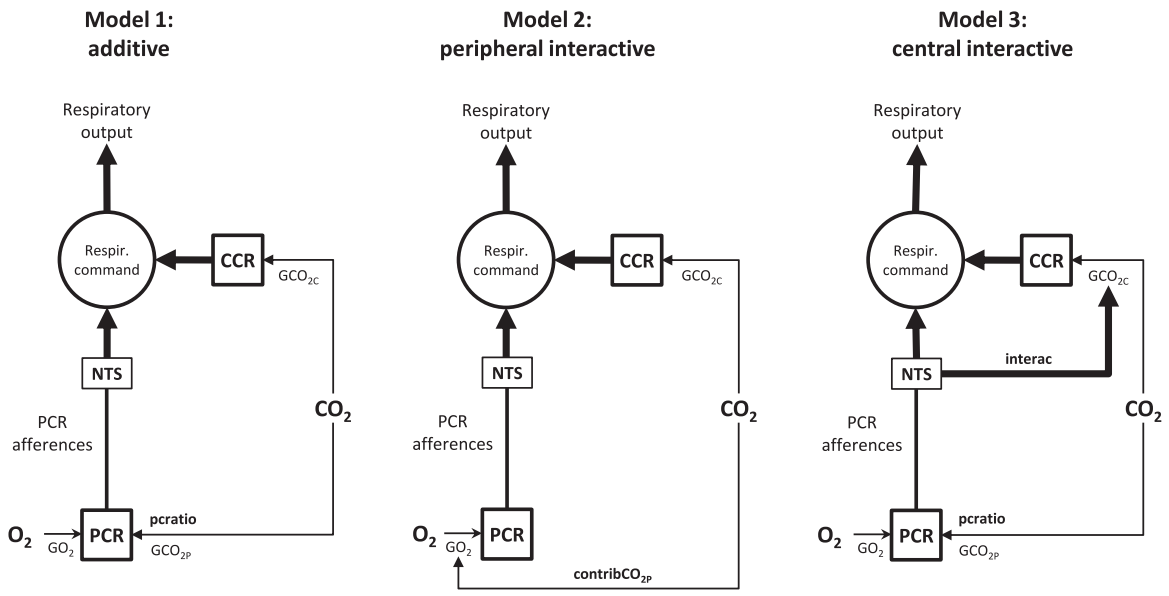

Fig. 3. Diagrams of the three different models: additive, peripheral interactive and central interactive. The central respiratory command receives direct or indirect afferences from peripheral (through nucleus tractus solitaries, NTS) and central chemoreceptors (PCR and CCR, respectively), modulated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

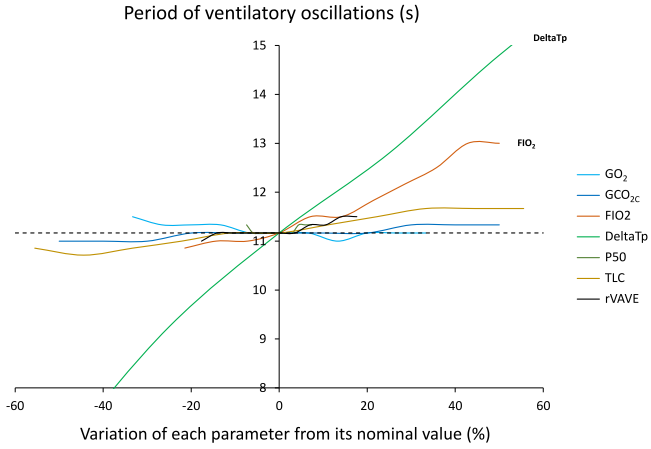

Fig. 4. Period of ventilatory oscillations according to several cardiorespiratory variables from their nominal values: peripheral O_2 gain (GO_2), central CO_2 gain (GCO_{2C}), inhaled fraction of O_2 (FIO_2), delay of blood convection from lung to carotid bodies (DeltaTp), arterial O_2 partial pressure at S_aO_2=50% (P50), total lung capacity (TLC) and alveolar/total ventilation ratio (rVAVE). Period is linearly related to DeltaTp and also depends on FIO_2.

within realistic physiological range. If an oscillatory pattern of ventilation was observed, the period and amplitude of oscillations were computed. Then a sensitivity analysis was performed in order to evaluate the respective influence of each parameter of the model on the period and amplitude of the oscillatory pattern. Although it may not necessarily capture the general behavior in a multidimensional space, a single-parameter analysis allows us assessing the relative contribution of each parameter on the ventilation output.

2.4. Multivariate regression analysis

A multivariate regression was performed to establish potential correlations between period and magnitude of ventilatory oscillations on one hand, and model parameters on the other hand: FIO_2, peripheral chemoresponse to O_2 (GO_2), central chemoresponse to CO_2 (GCO_2), delays from lungs to peripheral and central chemoreceptors (DeltaTp and DeltaTc, respectively), P50, TLC, rVAVE and interaction parameters (pcratio, $contribCO_{2P}$, interac).

2.5. Addition of white noise

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

3. Results

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

3.1. Sensitivity analysis

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

3.1.1. Period of ventilatory oscillations (Fig. 4)

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

3.1.2. Magnitude of ventilatory oscillations (Fig. 5)

Magnitude of ventilatory oscillations was nearly completely blunted, from 0% to −96.5%, when level of hypoxia decreased from FIO_2=0.14 to normoxia (Fig. 7). Peripheral and central gains to O_2 (GO_2) and CO_2 (GCO_{2C}) and increased oscillations from −46% to +35%, and from −32% to +36%, respectively. DeltaTp enhanced

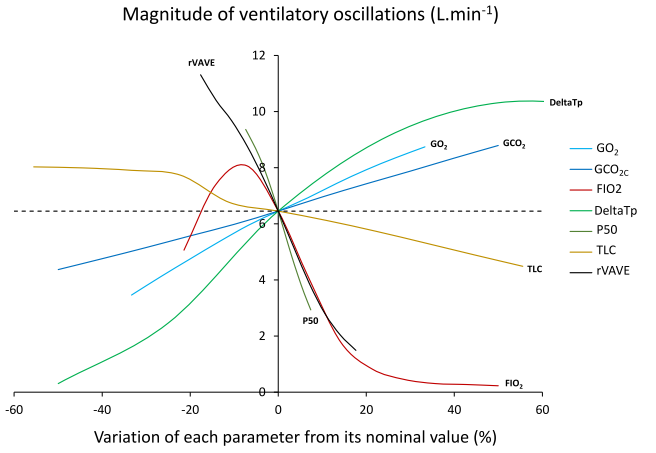

Fig. 5. Magnitude of ventilatory oscillations according to several cardiorespiratory variables from their nominal values: peripheral O_2 gain (GO_2), central CO_2 gain (GCO_{2C}), inhaled fraction of O_2 (FIO_2), delay of blood convection from lung to carotid bodies (DeltaTp), arterial O_2 partial pressure at S_aO_2=50% (P50), total lung capacity (TLC) and alveolar/total ventilation ratio (rVAVE). Magnitude mainly increases with GCO_{2C}, GO_2 (in a nearly linear manner) and DeltaTp, and decreases with P50, rVAVE, TLC and FIO_2.

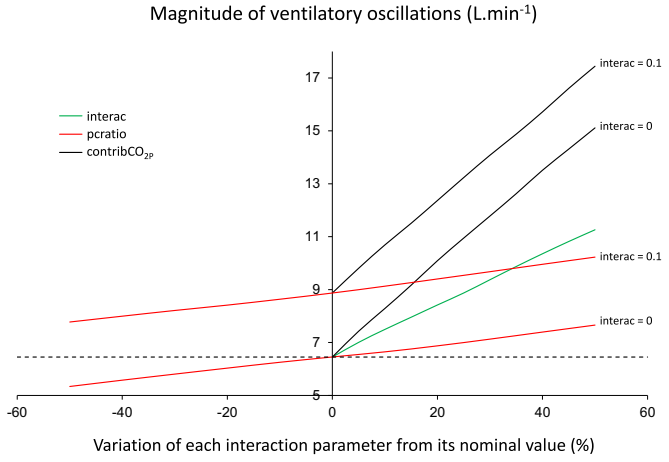

Fig. 6. Magnitude of ventilatory oscillations according to interaction parameters: interac (effect of peripheral O_2/CO_2 gain on central gain to CO_2: *model 3*), pcratio (effect of CO_2 on peripheral gain: *model 1*) and $contribCO_{2P}$ (effect of CO_2 on peripheral gain to O_2: *model 2*). Contributions of pcratio and $contribCO_{2P}$ are computed at 2 values of interac (0 and 0.1) and show an additive effect of the rise from peripheral activity level.

oscillations from −95% to +59%. P50 and TLC had a dampening effect on oscillations, by decreasing them from +45% to −54% and from +24% to −31%, respectively. Finally, a decrease in rVAVE (i.e. an increase in dead space) from 1 to 0.7 increased oscillations from −77% to +75%. The influence of DeltaTcc is mainly due to the tissue component DeltaTct (Fig. 8): magnitude of oscillations shows a phasic pattern that can lead to either enhanced or blunted oscillations, depending on the tissue component.

3.1.3. Effect of interaction between O_2 and CO_2 at the central and peripheral level (Fig. 6)

The effect of $contribCO_{2P}$ (effect of CO_2 on O_2 gain in peripheral chemoreceptors) and interac (effect of peripheral afferences on central gain to CO_2) is very low on period values, in a tight range of 0–4.5% (results not shown). In contrast, a significant positive correlation links magnitude of $\dot{V}E$ oscillations to $contribCO_{2P}$ and interac, from 0% to 134%, and from 0% to 75%, respectively (Fig. 6). The parameter pcratio (ratio of peripheral/central response to CO_2) does not impact period and magnitude of ventilatory oscillations. The effect of interac and $contribCO_{2P}$ are additive.

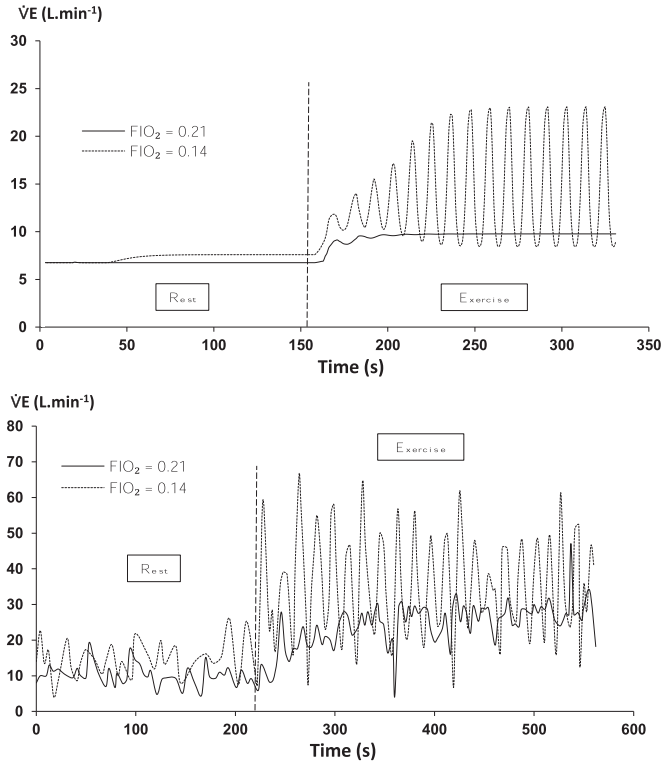

Fig. 7. Variation of $\dot{V}E$ for two levels of FIO_2: ventilatory oscillations in the additive model (upper panel) and physiological data from a subject exercising successively in normoxia and hypoxia (lower panel) (physiological data from Hermand et al. (2015b)).

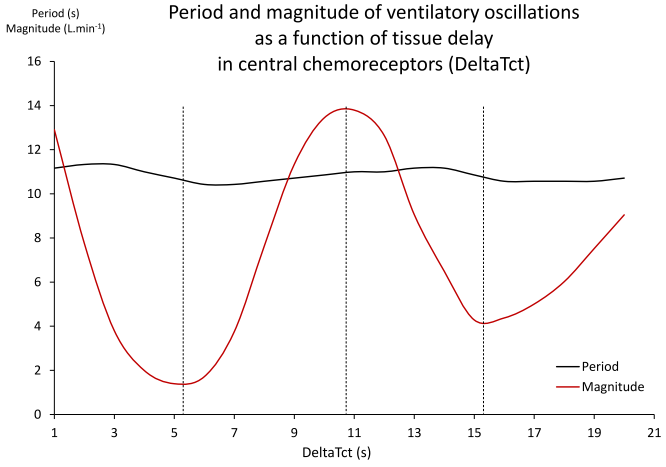

Fig. 8. Variation of period and magnitude of ventilatory oscillations as a function of tissue delay at the central level. The period is not affected by changes in DeltaTct. Magnitude can be almost completely blunted (DeltaTct=5.5 and 15) or enhanced (DeltaTct=10.5).

3.2. Multivariate regression analysis

3.2.1. Period of ventilatory oscillations

The multivariate regression analysis significantly linked $\dot{V}E$ period to FIO_2, GO_{2C}, DeltaTp, DeltaTc and TLC. A trend was observed for GO_2 (p=0.053). $\dot{V}E$ period increased when FIO_2, GCO_{2C}, DeltaTp and TLC increased ($p < 0.001$, $p < 0.05$ for GCO_{2C}) whereas it was shortened when DeltaTc increased ($p < 0.001$, respectively).

3.2.2. Magnitude of ventilatory oscillations

Magnitude of oscillations was enhanced when GO_2, GCO_{2C} and DeltaTp increased ($p < 0.001$) but decreased when FIO_2, DeltaTc, rVAVE, P50 and TLC increased ($p < 0.001$).

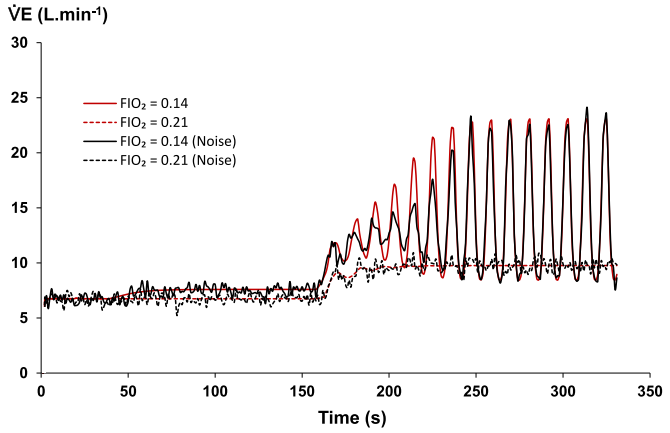

Fig. 9. Effects of added white noise to the central ventilation command, at two levels of FIO_2. There is no significant difference between "noise-enriched" (dashed lines) and "non-noise enriched" (solid lines) models.

3.3. Effect of white-noise addition

The addition of a white noise did not alter magnitude or period of oscillations: there was no significant change between non-noise and noise-enriched models (Fig. 9). Varying the noise coefficient, from 0.001 to 0.5, did not modify the V̇E output behavior either.

4. Discussion

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

The main difference with existing models lies in the inclusion of exercise-oriented components through a higher cardiac output and a consequent decreased circulation time from lungs to central and peripheral chemoreceptors. The existing studies and models were mostly focused on central and obstructive sleep apneas and heart failure during sleep, and described a phenomenon with a much longer period, associated with an enhanced sensitivity to CO_2 (Hall et al., 1996; Javaheri, 1999; Khoo, 2000). The present work confirms previous studies in healthy subjects in which greater ventilatory oscillations were related to a higher cardiac output (mild exercise) and to hypoxia (Garde et al., 2012; Hermand et al., 2015b; Latshang et al., 2013) (Fig. 7). It is remarkable to notice the proximity of the period between theoretical and physiological data, around 11 s (Hermand et al., 2015a). FIO_2 level is also correlated to both period and magnitude of ventilatory oscillations, as observed in our previous studies (from FIO_2=0.165).

The O_2 gain has an important impact on the amplitude of oscillations, as subjects with a higher ventilatory response to hypoxia at exercise show a higher magnitude of oscillations, in coherence with our experimental observations (Hermand et al., 2015b). In addition to this intrinsic sensibility to O_2, the O_2-CO_2 interaction at the peripheral level enhances the instability in a degree depending on model used (Fig. 6). The sensitivity analysis showed that a simple additive CO_2 contribution, via the pcratio coefficient (model 1), brings the least disturbance to ventilatory control system. Then, peripheral afferences to central chemoreceptors (interac contribution, model 3) further augments oscillations. The most unstable situation is created by the peripheral interactive model, in which increased peripheral O_2 gain by a hypercapnic stimulus (contribCO_{2P}, model 2) severely destabilizes the respiratory command. Regardless of the studied model, these simulations highlight the major role played by the peripheral chemoreceptors in the genesis of ventilatory oscillations, with and without CO_2 interaction, and is in accordance with the observations of CHF and SAS patients (Beecroft et al., 2006; Ponikowski et al., 2001; Trombetta et al., 2013). This data provide a new perspective in the current debate about the respective contribution of central and peripheral chemoreceptors in the control of ventilation (Paula-Ribeiro and Rocha, 2016).

The central CO_2 gain is also involved, in a lesser extent, into the genesis of periodic breathing and matches the clinical studies on CHF and SAS patients (Beecroft et al., 2006; Trombetta et al., 2013). This supports our own findings in which ventilatory response to CO_2 is correlated to the magnitude of ventilatory oscillations in healthy subjects (Hermand et al., 2015b).

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

Apart those cited above, one additional parameter comes into play: a greater alveolar/total ventilation ratio decreases the amplitude of oscillatory ventilation, implying that a greater dead space will promote periodic breathing. In heart failure patients, augmented dead space will prevent ventilatory oscillations by an increased $PETCO_2$, which acts on CO_2 apnea threshold and drastically decreased periodic breathing (Patz et al., 2013; Xie et al., 1997). Conversely, in normal subjects, the same increase in $PETCO_2$ will rise V̇E, hence increasing ventilatory oscillations (Hermand et al., 2015a). This adverse effect is particularly noticeable here.

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

4.1. A relation between period of ventilatory oscillations and DeltaTp: a limit value

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

$$\dot{V}E\ period = 1.798 \times DeltaTO_2 + 3.72 \quad (r^2 = 0.9979,\ p < 0.001) \qquad (1)$$

In our previous work (Hermand et al., 2015a), we established a similar equation relating V̇E period to the total respiratory cycle (Ttot):

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

The tight relationship between V̇E period and Ttot points out a theoretical limit of V̇E oscillations period: when Ttot tends toward zero (breathing frequency tending to infinity), V̇E oscillations period tends to approximately 7 s (2). Using the latter value in Eq. (1), we can

deduce a similar theoretical lower limit $DeltaTp_{min}$, when intensity of exercise increases along with $\dot{V}O_2$ and $\dot{Q}c$, below which the ventilatory oscillations disappear: $DeltaTp_{min} \approx 1.8$ s. As DeltaTp is the sum of circulation delay from lungs to carotid bodies and of the time required for the neural system to produce a ventilatory response, we can deduce that this irreducible time $DeltaTp_{min}$ of nearly 2 s is the intrinsic response time of peripheral chemoreceptors, which is in accordance with the existing literature (Black et al., 1971; McClean et al., 1988; Teppema et al., 1982).

5. Conclusions and perspectives

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

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Appendix A

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

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

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

$$\dot{V}Eb(t) = EVO_2(t).\ VO_2(t)$$

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

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

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

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

$$DAaO_2(t) = DAaO_20 + DlimO_2.(\dot{Q}c(t) - \dot{Q}c_{rep})$$

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

Peripheral chemoreceptors

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

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

if $P_aCO_2(t) > P_aCO_{2Pth}$, then the peripheral contribution from a CO_2 stimulus is the linear term $GCO_{2P}.\ [P_aCO_2(t - DeltaTp) - P_aCO_{2C}]$ with P_aCO_{2C} as a P_aCO_2 set point, else it is null.

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

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

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

In the interactive model, the peripheral contribution is:

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

Central chemoreceptors

The central component of ventilation, resulting from a variation of arterial CO_2 content, includes a static central gain to CO_2 (GCO_{2C}) and a delay DeltaTc (see Section 2.1.4), above a central threshold (P_aCO_{2Cth}):

if $P_aCO_2(t) > P_aCO_{2Cth}$, then $\dot{V}Ec(t) = GCO_{2C}.\ [P_aCO_2(t - DeltaTc) - P_aCO_{2C}]$

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).

Variables	Units	Rest	Exercise		
			Min	Nominal	Max
Alveolar CO_2 partial pressure (P_ACO_2)	mm Hg				
Arterial O_2 partial pressure (P_aCO_2)	mm Hg				
Arterial O_2 saturation (S_aO_2)	nu				
Minute ventilation (VE)	L min^{-1}				
Atmospheric pressure (PB)	mm Hg	760		760	
Vapor pressure of water (PH_2O)	mm Hg	47		47	
Arterial O_2 saturation Set point (S_aO_{2C})	%	98		98	
Arterial CO_2 partial pressure Set point (P_aCO_{2C})	mm Hg	40		40	
Alveolo-arterial O_2 difference ($DAaO_2$)	mL/mL	5		5	
Alveolo-arterial CO_2 difference ($DAaCO_2$)	mL/mL	1		1	
Cardiac output ($\dot{Q}c$)	L s^{-1}	6		10	
O_2 metabolic consumption ($\dot{V}O_2$)	mL min^{-1}	0.25		0.8	
Hill constant	nu	2.7		2.7	
Respiratory quotient (QR)	nu	0.7		0.8	
Ventilatory equivalent for oxygen (EVO_2)	nu	30		26	
Arterial CO_2 partial pressure threshold	mm Hg	40	35	45	55
Arterial O_2 partial pressure at S_aO_2=50% (P50)	mm Hg	27	25	28	31
Inhaled fraction of oxygen (FIO_2)	nu	0.14	0.11	0.14	0.21
Central chemoreflex CO_2 gain (GCO_{2C})	L min^{-1} mm Hg^{-1}	0.05	0.025	0.05	0.075
Peripheral chemoreflex O_2 gain (GO_2)	L min^{-1} $\%^{-1}$	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_2 ($DlimO_2$)	mm Hg L^{-1} min	0	0	5	10
Ratio of peripheral/central gain to CO_2 (pcratio)	nu	0.5	0.25	0.5	0.75
Coefficient of CO_2 contribution to peripheral gain ($contribCO_{2P}$)	nu	0	0	0	0.2
Coefficient of peripheral afferences contributing to central gain to CO_2 (interac)	nu	0	0	0	0.2
Central tissue delay (DeltaTct)	s	1	0	1	21

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

In the central interactive model, the central gain to CO_2 (GCO_{2C}) depends on peripheral gains to O_2 and CO_2 (GO_2 and GCO_{2P}, respectively), modulated by a constant interac:

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

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

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

At equilibrium, the alveolar partial pressures in O_2 and CO_2 as a function of time are defined as:

$$P_AO_2(t) = -DAaO_2(t) + (P_B - P_{H_2O}).\ FIO_2(t) - P_ACO_2(t)\ P_ACO_2(t) = \frac{QR(t).\dot{V}O_2(t)}{K.\ \dot{V}E(t).\ rVAVE(t)}$$

where P_B and P_{H20} are atmospheric and water vapor pressures, respectively, FIO_2 is the inhaled fraction of O_2. P_B, P_{H20}, FIO_2, QR, $\dot{V}O_2$ and rVAVE are predetermined as shown in Table 1.

P_ACO_2 is then described through a first-order relation:

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

where $apCO_2$ and $bpCO_2$ are defined as follows: $TaupCO_2 = \frac{TLC}{\dot{V}E(t)}$, $apCO_2 = e^{-\frac{1}{TaupCO_2}}$ and $bpCO_2 = 1 - apCO_2$, P_APCO_2 is the P_ACO_2 variable determined by initial conditions of $\dot{V}O_2(t)$ and $\dot{V}E(t)$.

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