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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 (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

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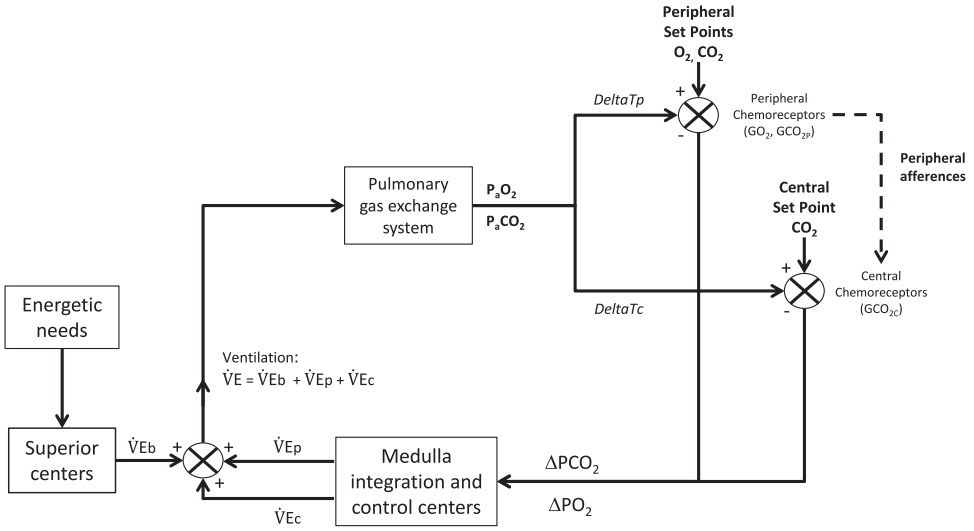

Fig. 1. Respiratory control model. Minute ventilation ($\dot{V}E$) is the sum of a basal value represented by the central command adapted to the metabolic needs (rest/exercise), modulated by peripheral and central components. The P_aO_2 and P_aCO_2 gas information is transported to peripheral and central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

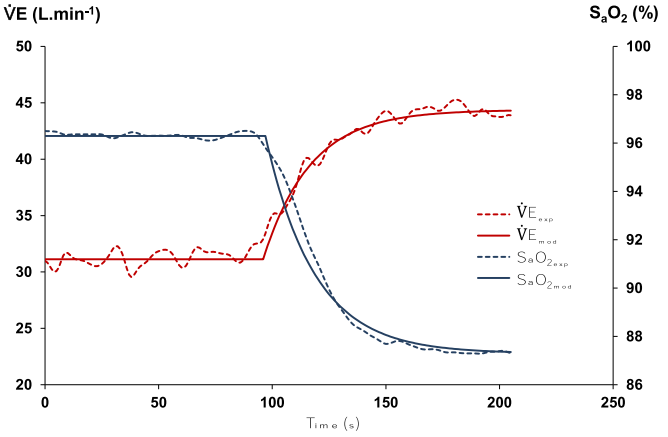

Fig. 2. Example of identification of transition from normoxia to hypoxia at exercise for the determination of time constants, between physiological data ($S_aO_{2\ exp}$ and $\dot{V}E_{\ exp}$, dashed lines) and model ($S_aO_{2\ mod}$ and $\dot{V}E_{\ mod}$, solid lines).

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

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.