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Periodic ventilation: Consequences for the bodily CO_2 stores and gas exchange efficiency

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ABSTRACT

Using a mathematical model of CO_2 transport, we investigated the underlying cause of why and to what extent periodic ventilation is less efficient for CO_2 excretion/elimination compared to continuous/tidal ventilation leading to elevated CO_2 stores unless mean alveolar minute ventilation ($\dot{\bar{V}}_A$) is elevated. The model predicts that the reduced efficiency of periodic ventilation is intrinsic to the sequential arrangement and differences in the relative storage capacities (product of size and CO_2 capacitance coefficient) of the lungs, blood and tissues that leads to predominant blood and tissue storage during apnoeic periods. Consequently, overall CO_2 transport becomes more prone to perfusion and diffusion limitation during periodic ventilation. At constant cardiac output ($\dot{Q}$) inefficiency will increase with the apnoeic duration (t_{ap}) concomitant with increasing blood and tissues CO_2 storage and with the relative time spent apnoeic (t_{ap}/t_{cyc}) due to increasing $\dot{V}_A/\dot{Q}$ mismatch. Conversely, temporal variation of $\dot{Q}$ to better match $\dot{V}_A$ can reduce inefficiency radically. Thus such adjustment in blood flow is necessary for efficient CO_2 elimination in periodic ventilation.

1. Introduction

Periodic/episodic lung ventilation, *i.e.* a ventilation pattern characterised by ventilatory bouts of several breaths interspersed among apnoeas of variable duration, is widespread amongst ectothermic vertebrates, but also characteristic for diving birds and mammals as well as humans with respiratory disturbances (Boutilier et al., 2001; Burggren and Shelton, 1979; Dempsey et al., 2010; Hicks and White, 1992; Milsom, 1991; Shelton and Boutilier, 1982). Integrative mathematical models have provided a useful avenue to gain insight to the underlying control mechanisms in both humans and diving mammals (Cherniack and Longobardo, 2006; Khoo et al., 1991; Khoo et al., 1982; Longobardo et al., 1966; Mackey and Glass, 1977; Milhorn et al., 1965; Stephenson, 2005; Vielle and Chauvet, 1993). However, the overall effects of periodic *versus* continuous tidal ventilation on bodily CO_2 stores and the associated efficiency of CO_2 transport, have received much less attention. Theoretical considerations demonstrate that periodic ventilation, characteristic of sleep apnoea, elevates blood and tissue CO_2 levels, unless mean alveolar minute ventilation ($\dot{\bar{V}}_A$) is elevated (Rapoport et al., 1993). This clearly indicates that periodic ventilation is less efficient for CO_2 excretion, which has been confirmed by direct measurements of gas exchange in humans with sleep apnoea (Berger et al., 2000) and mechanically ventilated turtles under anaesthesia (Malte et al., 2013), a reptile that spontaneously exhibits periodic ventilation. The cause of inefficiency of periodic ventilation has been attributed to temporal mismatch between ventilation and blood flow ($\dot{V}_A/\dot{Q}$ mismatch) (Rapoport et al., 1993) and periodic breathers are known to vary heart rate in accordance to $\dot{V}_A$ (Bradley and Floras, 2003; Burggren, 1975; Butler, 1982; Butler and Jones, 1971; Guilleminault et al., 1984; Kooyman et al., 1992; Meir et al., 2008; Ponganis et al., 1997; Thompson and Fedak, 1993; Wang and Hicks, 1996). However, it is not clear to what extent temporal $\dot{V}_A/\dot{Q}$ matching could compensate the inefficiency and how inefficiency of periodic ventilation is related to the apnoeic duration (t_{ap}) and the relative time spent apnoeic (t_{ap}/t_{cyc}).

Here we present an analysis of CO_2 transport that incorporates tissues and lung diffusion to identify the factors that determine the intrinsic cause of the inefficiency of periodic ventilation. We hypothesize that increasing apnoeic duration (t_{ap}) and increasing fraction of time spent apnoeic (t_{ap}/t_{cyc}) increases inefficiency of CO_2 excretion. Furthermore, the model predicts that lower efficiency of CO_2 excretion during periodic ventilation is an inherent consequence of the sequential arrangement and differences of the

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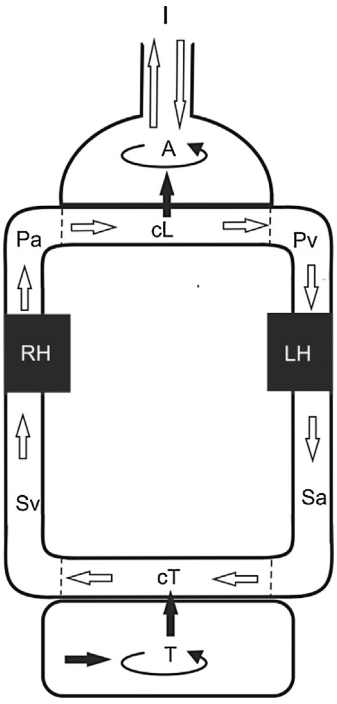

Fig. 1. Overview of model.
Panel A is a schematic illustration of the cardio-respiratory system as it was modelled consisting of 10 compartments/stores for CO_2 with the used abbreviations as follows: A: alveolar lung, cL: lung capillary, Pv: pulmonary venous, LH: left heart, Sa: systemic arterial, T: tissues, cT: tissue capillary, Sv: systemic venous, RH: right heart, Pa: pulmonary arterial.

relative storage capacities (product of compartmental size and specific CO_2 capacitance coefficient) of lungs, blood and tissues that inevitably render periodic ventilation patterns more prone to perfusion or diffusion limitations compared to continuous/tidal ventilation.

2. Materials and methods

2.1. Outline of the model and its assumption

The model of the cardio-respiratory system with its 10 compartments/stores for CO_2 is shown in Fig. 1 (see also Table 1). CO_2 is produced within the tissue compartment and transported to the surroundings in a series of diffusive and convective steps. For each compartment, a time dependent mass balance was derived (see Appendix A). The model assumes constant capacitance coefficient of tissues and blood for CO_2 (*i.e.* linear CO_2 binding curve), absence of Bohr/Haldane effect and lungs and tissues are treated as single uniform compartments, *i.e.* no spatial heterogeneity.

For the present simulations, the cardio-respiratory system is considered as a passive system without regulation and all CO_2 stores are modelled as simple well-stirred compartments. Alveolar ventilation is described as a sinusoidal flow and the volume of the lung alveolar compartment is time dependent (see Appendix A). Diffusion was incorporated by deriving an expression for the mean capillary tension using the model of Piiper and Scheid (Piiper and Scheid, 1981), which is possible by assuming a linear CO_2 binding curve (constant capacitance coefficient) along with a diffusional pseudo/quasi steady-state as argued by Adaro et al. (Adaro et al., 1973) and Malte (Malte, 1992) (see Appendix A). The product of the capacitance coefficient (β_x) and size of a compartment (V_x) gives the storage capacity for CO_2 (*i.e.* mLSTPD $mmHg^{-1}$) and the normal/default arrangement of the storage capacities of tissues, blood and lungs are represented as the relative areas of the boxes in Fig. 3A.

2.2. Input values and solutions to differential equations

The 11 mutually dependent differential equations (Appendix A) were solved simultaneously by numerical integration in Mathematica 7.0 (Wolfram Research, Champagne Il., USA). The input parameters to the equations, along with the abbreviations, are given in Table 1. The input values used are typical for a 70 kg human, but the model does not aim to accurately simulate human respiratory disturbances, but rather to provide general theoretical predictions.

2.3. Evaluating overall efficiency of gas exchange

The total bodily CO_2 store at any time ($V_{totCO_2}(t)$, mL STPD), *i.e.* the sum of the CO_2 contents (V_{xCO_2}) in the tissues, blood and lungs, equals the product of the partial pressure in the compartment (P_{xCO_2}, mmHg) and its storage capacity (product of capacitance coefficient (β_x, mL STPD mL^{-1} $mmHg^{-1}$) and size (V_x, mL)):

$$V_{totCO_2}(t) = \sum_x \left(P_{xCO_2}(t)\,\beta_x V_x\right) \quad (1)$$

A measure of the efficiency of a ventilation pattern in facilitating overall CO_2 transport/excretion in an ideal homogenous system with a single tissue compartment is the steady-state value of the mean P_{CO_2} (denoted by an overbar $\bar{P}_{CO_2}$) for a given set of cardio-respiratory parameters, including mean alveolar minute ventilation ($\dot{\bar{V}}_A$) and cardiac output ($\dot{Q}$). Thus, elevated $\bar{P}_{CO_2}$ indicates that a larger steady state mean driving partial pressure gradient is required to transport CO_2 from tissues to the environment, *i.e.* a manifestation of an overall reduced efficiency of CO_2 transport. For constant CO_2 capacities $\bar{P}_{CO_2}$ is proportional to the mean CO_2 content/store (mLSTPD, $\bar{V}_{totCO_2}$) which is given by the integral of the instantaneous $V_{totCO_2}(t)$ during the ventilation pattern divided by the duration of the total cycle (sum of apnoea and ventilatory bout, *i.e.* the repeatable unit, t_{cyc}). This can be evaluated as the sum of the baseline minimum CO_2 content at the start of apnoea ($V_{totCO_2}(t_0)$) and the mean amplitude of fluctuations during the cycle (*i.e.* the integral term seen below):

$$\bar{V}_{totCO_2} = V_{totCO_2}(t_0) + \frac{\int_{t_0}^{t_0+t_{cyc}} \left(V_{totCO_2}(t_0+t) - V_{totCO_2}(t_0)\right)\cdot dt}{t_{cyc}} \quad (2)$$

The mean driving partial pressure ($\bar{P}_{CO_2}$) is then given by the mean bodily CO_2 content ($\bar{V}_{totCO_2}$) divided by the total storage capacity (sum of the individual capacities):

$$\bar{P}_{CO_2} = \frac{\bar{V}_{totCO_2}}{\sum_x (\beta_x \cdot V_x)} \quad (3)$$

2.4. Stimulations

2.4.1. Distribution of accumulated CO_2 during apnoea

The fractional distribution of accumulated CO_2 in the different compartments was evaluated as the CO_2 content accumulated in the specific compartment relative to the total accumulated CO_2 in the body.

A sensitivity analysis was conducted to investigate effects of varying O_2 uptake from the lung (hence varying changes in lung volume during apnoea). Thus, an empirical relation for O_2 uptake