Synergy-COPD: Abnormal O_2 Transport/O_2 Utilization Leads to High Mitochondrial ROS Generation and Systemic Effects in COPD Patients with Poor Prognosis

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Keywords— modelling integration, mechanistic and probabilistic modelling of physiological processes, systems medicine, oxygen transport and oxygen utilization, systemic effects of COPD

Chronic Obstructive Pulmonary Disease (COPD) is one of the four highest prevalent chronic conditions included into the priorities of the NCD (non-communicable diseases) policy of the World Health Organization. It is a preventable and treatable disorder caused by inhalation of irritants, mainly tobacco smoking. Although COPD is primarily a pulmonary disorder, a significant percentage of patients show systemic effects of the disease that are clearly associated to poor prognosis. Moreover, there is evidence suggesting that underlying abnormal metabolic pathways responsible for systemic effects of COPD can be shared by clusters of co-morbid conditions often seen in NCD patients (1, 2). Synergy-COPD is a VPH project aiming to design, implement and validate a simulation environment and clinical decision support systems (CDSS) for bio-researchers and clinicians to enhance both understanding and management of COPD phenotypes through the use of integrated multi-scale models of the human body. Within this scenario, the current study addresses a numerical analysis of the interplay between mitochondrial respiration and oxygen transport that has been pivotal to complete integration of the modelling describing oxygen transport system, central metabolism, mitochondrial respiration and Reactive Oxygen Species (ROS) generation (3).

By mid-90's, Wagner PD (4, 5) presented an algebraic model, based on well-established principles of mass conservation, that considered the oxygen transport and utilization pathway as an integrated system. Given the transport capacity of the lungs, heart, blood and muscles, the model computes how much O_2 can be supplied to the tissues, and what are the partial pressure of oxygen (P_{O_2}) values at each step. This approach stresses that it is the interaction between diffusion and convection that sets maximum O_2 supply to the cell. Therefore, modelling this system requires knowledge of ventilation, cardiac output/muscle blood flow, O_2-haemoglobin dissociation curve and the two conductances: lung and tissue O_2 diffusing capacities, to yield estimates of alveolar, arterial and venous P_{O_2} and as a result, whole body oxygen uptake ($\dot{V}_{O_2}$). One of the basic assumptions of this modelling is that at maximal $\dot{V}_{O_2}$, mitochondrial P_{O_2} could be neglected (i.e. assumed to be zero) for modelling purposes. It is of note; however, that mitochondrial P_{O_2} cannot physiologically be zero since then oxidative phosphorylation could not occur.

The current study focuses the analysis on the effects of releasing the assumption of zero mitochondrial P_{O_2} on the O_2 transport/O_2 utilization system. The rate of mitochondrial O_2 consumption has been modelled as a hyperbolic function, where the amount of oxygen consumption by the body tissue is a function in the maximal aerobic capacity of the mitochondria ($\dot{V}_{MAX}$), partial pressure of oxygen at the mitochondria (PmO_2) and the mitochondrial P_{50}.

Therefore, now the O_2 transport though the system involves five sequential processes, as displayed in **Figure 1**: 1) ventilation to bring O_2 from air to the alveolar gas, 2) diffusion of O_2 from alveolar gas into capillary blood, 3) circulatory transport of O_2 from lungs to tissue micro-vessels, 4) Diffusion of O_2 from tissue micro-vessels to mitochondria and 5) mitochondrial respiration.

Hence, the current numerical model encodes these five sequential processes in a set of five equations with five dependent variables (i.e. Alveolar oxygen partial pressure (PAO_2), arterial oxygen partial pressure (PaO_2), venous oxygen partial pressure (PvO_2) and mitochondrial oxygen partial pressure (PmO_2) and seven main independent variables: alveolar ventilation ($\dot{V}_A$), cardiac output ($\dot{Q}_T$), oxygen partial pressure in inhaled air (PIO_2), slope of the O_2-hemoglobin dissociation curve (β), lung (DLO_2) and muscle (DMO_2) diffusing capacities and the P_{50} and aerobic mitochondrial capacity ($\dot{V}_{MAX}$).

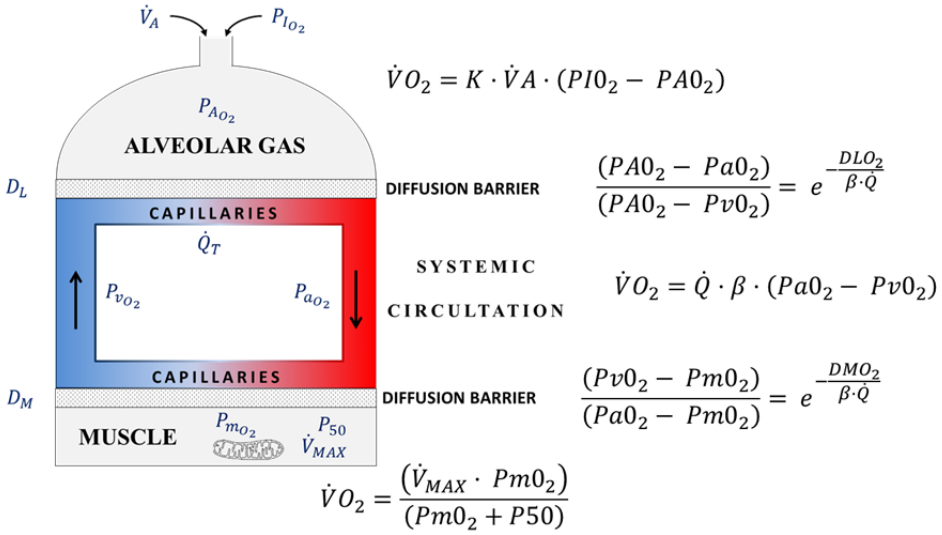

Figure 1: ***Schematic representation showing the different stages of the oxygen transport system considered.*** Air passes through the ventilation process to reach the alveoli. From there, oxygen diffuses into the blood. The amount of oxygen uptake by the blood is the product of the cardiac out and the difference in oxygen concentration between arteries and veins. The oxygen is further diffused from blood to muscle cells where the amount of oxygen consumed by the mitochondria controls the maximum amount of oxygen that could be consumed by the whole body.

The impact of modelling the mitochondrial metabolism in the oxygen transport and utilisation system have been analysed by considering a physiologically wide range of mitochondrial respiration curves, simultaneously varying mitochondrial respiration curve parameters, namely: $\dot{V}_{MAX} \in [1.000, 2.000, 3.000, 4.000, 5.000]\ ml/min$ and $P_{50} \in [0.3, 0.5, 0.7, 1, 2]\ mmHg$.

Figure 2 shows that higher values of $\dot{V}O_2$ correspond to scenarios where the mitochondrial respiration is characterised by high mitochondrial aerobic capacity $\dot{V}_{MAX}$ and low P_{50}. Our results indicate that mitochondrial metabolism has a strong impact (blue empty circles) on VO_2max compared to the previous assumption neglecting mitochondrial PO_2 (red solid circle).

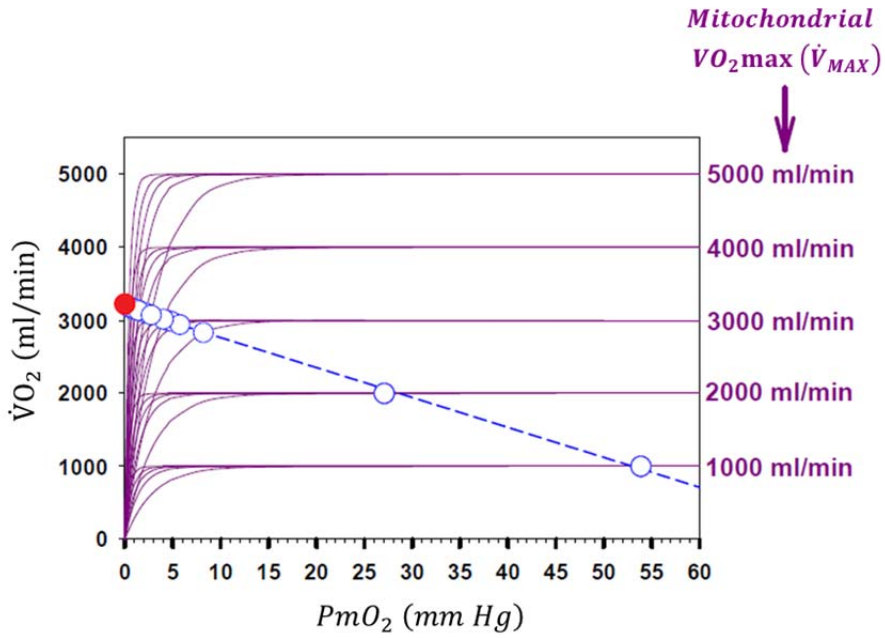

Figure 2: Summary graph showing how body $\dot{V}_{O_2}$VO2 is affected by considering the mitochondrial metabolism step in the oxygen transport and utilisation system. Each mitochondrial respiration curve is depicted in purple and for every mitochondrial respiration curve; body VO_2 values have been computed and represented as blue empty circles. The red solid circle corresponds to body VO_2 when no mitochondrial metabolism is considered (i.e. $\mathbf{PmO_2 = 0}$).

To sum up, the higher mitochondrial $\dot{V}_{MAX}$ and smaller P_{50}, the more O_2 can be metabolized for a given upstream (heart, lungs, blood, muscle) transport system and thus lower mitochondrial P_{O_2} levels are needed. Accordingly, the zero assumption of PmO_2 at $\dot{V}_{O_2}MAX$ can only be considered acceptable at low mitochondrial P_{50} and high $\dot{V}_{MAX}$ values. The current analysis has played a key role in the process of integration of mechanistic modelling ultimately leading to estimation of ROS levels. Moreover, the study has facilitated to properly address the complexities of the interactions between mechanistic and probabilistic modelling in Synergy-COPD that should allow exploring the underlying mechanisms of systemic effects associated to abnormally high mitochondrial ROS generation. We believe that fulfilment of Synergy-COPD aims will pave the way for Systems Medicine of NCD

References

1. Bousquet J, Anto J, Sterk P, Adcock I, Chung K, Roca J, et al. Systems medicine and integrated care to combat chronic noncommunicable diseases. Genome Medicine. 2011;3(7):43.
2. Turan N, Kalko S, Stincone A, Clarke K, Sabah A, Howlett K, et al. A Systems Biology Approach Identifies Molecular Networks Defining Skeletal Muscle Abnormalities in Chronic Obstructive Pulmonary Disease. PLoS computational biology. 2011;7(9):e1002129.
3. Selivanov VA, Votyakova TV, Pivtoraiko VN, Zeak J, Sukhomlin T, Trucco M, et al. Reactive Oxygen Species Production by Forward and Reverse Electron Fluxes in the Mitochondrial Respiratory Chain. PLoS computational biology. 2011;7(3):e1001115.
4. Wagner PD. Algebraic analysis of the determinants of VO2,max. Respir Physiol. 1993;93(2):221-37. Epub 1993/08/01.
5. Wagner PD. A theoretical analysis of factors determining VO2 MAX at sea level and altitude. Respir Physiol. 1996;106(3):329-43. Epub 1996/12/01.