Supplementary material

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Article title: Effect of timing of umbilical cord clamping and birth on fetal to neonatal transition: OpenModelica-based virtual simulator-based approach

Gas exchange in the lung

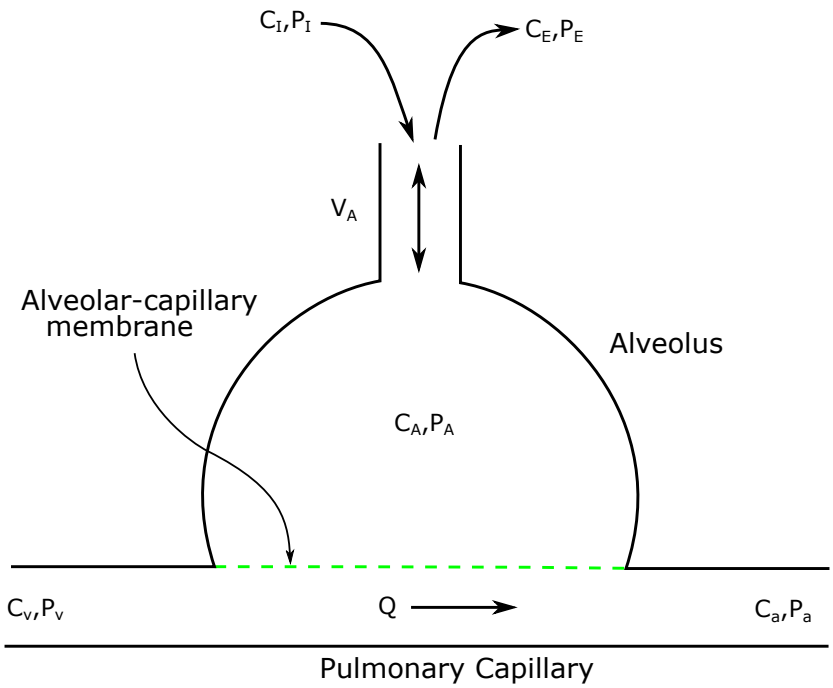

Figure 1: Gas exchange between alveoli and capillaries in the lung

The lungs contain approximately $3x10^8$ alveoli (small sacs) where air (mainly O_2) and blood come together for gas exchange. The main gases exchanged are O_2 picked up by the blood and CO_2 leaving the bloodstream and entering the air spaces of the lung. Gas exchange occurs by diffusion, across the thin alveolar-capillary membrane into the pulmonary capillaries, where there is lower oxygen pressure. Normally this membrane presents such a slight diffusion barrier that the blood in the alveolar capillaries reaches equilibrium with the alveolar air before leaving the capillaries [1].

The blood leaving the right heart is subdivided many times by the pulmonary arterial tree, which branches before it reaches the alveoli. After passing through the alveoli, it is picked up by the pulmonary veins. The alveolar capillaries are connected in parallel in the sense that pulmonary blood flow is the sum of the blood flows of the individual alveoli [1].

Similarly, air entering the trachea is subdivided many times by the bronchial tree before it reaches the alveoli, and the total alveolar ventilation is the sum of the individual alveolar ventilations. However, unlike blood, air leaves the alveoli on expiration through the same bronchial tree through which it entered

on inspiration [1].

Figure 1 is the graphical description of gas exchange in the lungs. P means the partial pressure of oxygen. Q is the blood flow. V_A is the alveolar ventilation[1]. The description of the subscripts is: I : inspired, E : expired, A : alveolar, v : venous, a : arterial. The designations *arterial* and *venous* refer to the character of the blood, not to the anatomy of the vessels involved.

In the lungs, the flow of blood through the lung bed initially has an oxygen concentration of C_v, the flow leaving the lung bed has an oxygen concentration C_a equivalent to the $C_A + C_v$, after gas exchange occurs. The development of the model is based on a series of assumptions that are described below.

- The change in residual alveolar O_2 volume is ignored, so the difference between the O_2 volumes of the inspired and expired airstreams is equal to the O_2 volume entering the pulmonary blood flow.
- The inspired and expired flow rates are equal to each other (V_A) and the ventilation rate is determined by a constant ventilation / perfusion ratio (r);
- The PO_2 in the blood stream leaving the alveoli is determined by the lung diffusion efficiency constant (γ).

Equation (1) is the result of the first assumption, where $\dot{V_A}$ is the alveolar ventilation rate,$[O_2]_I$ is the inspired oxygen, $[O_2]_E$ is expired oxygen, Q is the perfusion rate, and $[O_2]_{in}$ is the pulmonary respiration.

$$\dot{V_A} * ([O_2]_I - [O_2]_E) = Q * [O_2]_{in} \tag{1}$$

However, due to the second assumption, it is known that $r = \frac{\dot{V_A}}{Q}$, so Equation (1) can be expressed as Equation (2).

$$[O_2]_{in} = r([O_2]_I - [O_2]_E) \tag{2}$$

The efficiency of alveolar/blood diffusion is specified by the lung bed constant γ_{PAB} described in Equation (3). This efficiency is the gain of PO_2 through the pulmonary capillaries ($PO_{2,PAB} - PO_{2,PA}$, PA: pulmonary arteries), with respect to the maximum possible gain ($PO_{2,E} - PO_{2,PA}$. This case is possible when the $PO_{2,PAB}$ of the lung bed is balanced with the $PO_{2,E}$ of the alveolar exhaled air. Case in which the maximum gas diffusion would be $\gamma = 1$.

$$[\gamma_{PAB}] = \frac{PO_{2,PAB} - PO_{2,PA}}{PO_{2,E} - PO_{2,PA}} \tag{3}$$

[1]Refers to the volume of fresh air supplied to the alveolus per unit of time.

The oxygen-hemoglobin dissociation curve represents the relationship between the oxygen partial pressure PO_2 in the blood and the oxygen concentration $[O_2]$. The Hill function is used for the representation of the oxygen-hemoglobin dissociation curve [1]. The Hill function is described in Equation (4) where $[Hb]$ represents the concentration of hemoglobin in the blood and P_{50} is the partial pressure of oxygen at 50% of saturation. Each gram of Hb can carry 1.34 ml of oxygen. In Figure 2, the Hill function is illustrated.

$$PO_2 = H([O_2]) = P_{50}\left(\frac{[O_2]}{1.34([Hb]) - [O_2]}\right)^{\frac{1}{2.7}} \tag{4}$$

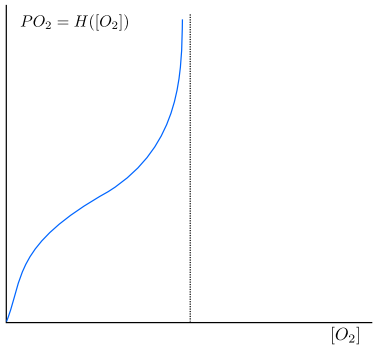

Figure 2: Hill's function

Equation (5) of the ideal gases relates the partial pressure of oxygen PO_2 of the air with the concentration of oxygen in the alveolus $[O_2]$, through the dependent factors K and T which are the ideal gas constant and the absolute temperature respectively.

$$PO_2 = [O_2]KT \tag{5}$$

The oxygen concentration $[O_2]_{in,PAB}$ entering the lung bed is determined by the lung O_2 gas exchange equations. The concentration of incoming $[O_2]_{in}$ is determined by: the ventilation / perfusion ratio (r) (See Equation (2)), the diffusion efficiency (γ) of the gas exchange unit (See Equation (3)), the oxygen-hemoglobin dissociation curve (See Equation (4)), and the partial pressure of oxygen (See Equation (5)). As a result of integrating these equations, the incoming oxygen concentration in the lung bed $[O_2]_{in,PAB}$ defined in the Equation (6) is obtained.

$$[O_2]_{in,PAB} = r[O_2]_I - r\frac{H([O_2]_{in,PAB} + [O_2]_{PA})}{\gamma_{PAB}KT} + r\frac{(1-\gamma_{PAB})H([O_2]_{PA})}{\gamma_{PAB}KT} \tag{6}$$

Gas exchange in the placenta

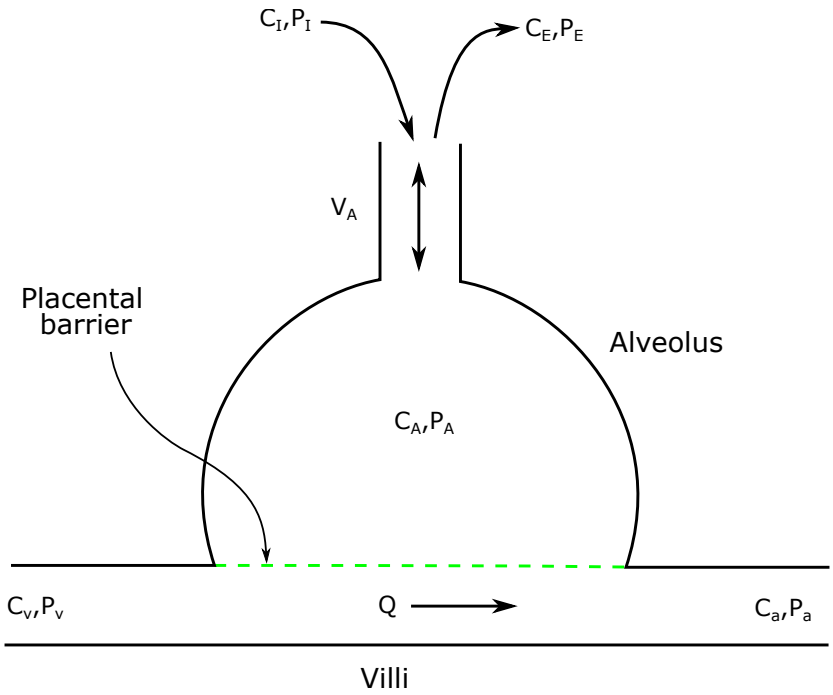

Figure 3: Gas exchange between alveoli and capillaries in the placenta

Gas exchange in the placenta occurs when maternal blood perfuses the intervascular space with oxygen-rich blood, from where oxygen molecules diffuse into the fetal bloodstream across the placental barrier. Therefore, for our model, placental gas exchange will be a modification of the final equation of the pulmonary model exposed in Annex E. As a result of this modification Equation (7) is obtained.

$$[O_2]_{in,PB} = r[O_2]_U - rH_M^{-1}\left(\frac{H([O_2]_{in,PB} + [O_2]_{PLAC})}{\gamma_{PB}} + \frac{(1-\gamma_{PB}) + [O_2]_{PLAC})}{\gamma_{PB}}\right) \tag{7}$$

In Equation (7), HM^{-1} corresponds to the inverse Hill function representing the maternal oxygen-hemoglobin dissociation curve, $[O_2]_U$ is the concentration of oxygen in the uterine arteries, $[O_2]_{PLAC}$ is the concentration of oxygen entering the placenta, $[O_2]_{in,PB}$ is the increase in oxygen concentration across the placental bed and γ_{PB} is the placental respiration efficiency. In Equation (7), r, is calculated as the ratio of the fetal placental flow to the assumed maternal uterine flow of 600 ml/min.

The inverse Hill function is described in Equation (8) where $[Hb]$ represents the concentration of hemoglobin in the blood and P_{50} is the partial pressure of oxygen at 50% of saturation. Each gram of Hb can carry 1.34 ml of oxygen. In Figure 4, the inverse Hill function is illustrated.

$$H_M^{-1} = \frac{(1.34 * [Hb]) \left(\frac{H([O_2])}{P_{50}}\right)^{2.7}}{1 + \left(\frac{H([O_2])}{P_{50}}\right)^{2.7}} \tag{8}$$

The curve in Figure 4 corresponds to the inverse of the Hill function (oxygen-hemoglobin dissociation curve) presented in [1].

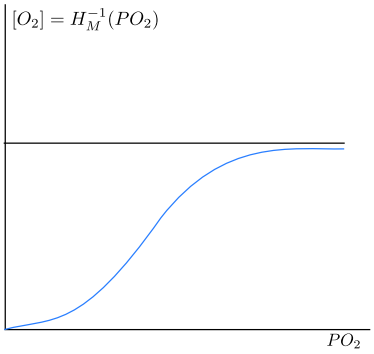

Figure 4: Inverse Hill function

References

[1] F.C. Hoppensteadt and C.S. Peskin. *Modeling and Simulation in Medicine and the Life Sciences (2nd Edition)*. Springer, NewYork, 2002.