Physiological modelling of oxygen-enhanced MRI in the lung

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INTRODUCTION • Qualitative assessment of lung function has been shown to be feasible using oxygen-enhanced MRI (OE-MRI) in which hyperoxia is used to induce signal change in the lung parenchyma as a result of the paramagnetic effect of dissolved oxygen [1]. However, there has been little attempt to date to relate the observed OE-MRI signal directly to physiological parameters indicative of lung function [2]. Here, by consideration of gas exchange processes in the lung we present a two-compartment mathematical model to relate the observed signal change during a dynamic OE-MRI experiment with the ventilation-perfusion ratio V/Q.

TWO COMPARTMENT MODEL • For the purpose of describing oxygen exchange within a unit volume lung parenchyma, we consider two compartments. The first is the gaseous space within the alveolus and the second is the parenchymal water within tissues and blood within alveolar capillaries. In the first compartment oxygen exists in a gaseous state, in the second we must consider both the oxygen dissolved in water and blood plasma and that bound to haemoglobin.

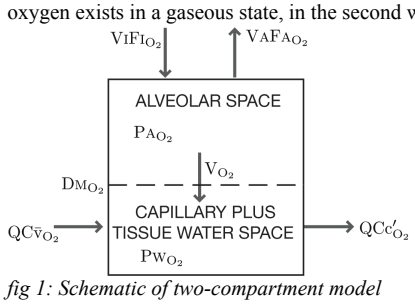

fig 1: Schematic of two-compartment model

Figure 1 presents a schematic diagram of the model. V_I, V_A are the inspired and expired alveolar ventilations (ml gas/min/ml lung), $F_{I_{O2}}$, $F_{A_{O2}}$ are the fractional inspired and alveolar oxygen concentrations, $P_{A_{O2}}$, $P_{W_{O2}}$ are the partial pressures of oxygen in the alveolar and in the capillary blood and parenchymal tissue water space (mm Hg), $D_{M_{O2}}$ is the diffusing capacity of the alveolar membrane to oxygen (ml O_2/min/mm Hg/ml lung), V_{O2} is the oxygen transfer across the membrane (ml O_2/min/ml lung), Q is the capillary blood flow (ml blood/min/ml lung), $C_{v_{O2}}$ is the systemic venous oxygen concentration (ml gas/ml blood), $C_{c'_{O2}}$ is the end-capillary oxygen concentration (ml gas/ml blood). We assume the two compartments are instantaneously well-mixed with respect to oxygen. In the second compartment this assumption neglects diffusion gradients within the tissue water space and across the tissue-capillary membranes. Mixed-venous blood in the capillary is assumed to equilibrate rapidly with the compartment on entering. In the first compartment, in equilibrium, the net input of oxygen into the space due to ventilation is balanced by the net transfer of oxygen across the alveolar membrane into the second compartment.

If the system is not in equilibrium (e.g. as a result of a change in the fractional inspired oxygen concentration) and we make the approximation that $V_I = V_A$ then the rate of change of fractional oxygen concentration in the alveolar space is given by:

$$v_A \frac{dF_{A_{O_2}}}{dt} = V_A(F_{I_{O_2}} - F_{A_{O_2}}) - D_{M_{O_2}}(P_{A_{O_2}} - P_{W_{O_2}}) \quad (1)$$

which may be rewritten,

$$\left(\frac{v_A}{P_{B-H_2O}}\right)\frac{dP_{A_{O_2}}}{dt} = V_A\left(F_{I_{O_2}} - \frac{P_{A_{O_2}}}{P_{B-H_2O}}\right) - D_{M_{O_2}}(P_{A_{O_2}} - P_{W_{O_2}}) \quad (2)$$

by substituting the alveolar fractional oxygen concentration by the alveolar partial pressure of oxygen ($P_{B\text{-}H20}$ is the barometric pressure minus water vapour pressure, v_A is the fractional alveolar volume). The diffusing capacity of the membrane is determined by the diffusion coefficient and solubility of oxygen in the solvent of the membrane (i.e. water), and the surface area per unit volume and thickness of the membrane. In the second compartment, in equilibrium, the transfer of oxygen across the alveolar membrane is balanced by the net removal of oxygen in the blood, determined by the difference in end-capillary and systemic venous oxygen contents and the capillary blood flow. (We neglect metabolism by the lung parenchyma, estimated at 5% of the whole-body metabolism [3], but note that if included, as long as it remained constant, it would not affect the final result.) If the system is not in equilibrium, the rate of change of the oxygen concentration $C_{W_{O2}}$ in compartment 2 (with fractional volume v_W) is given:

$$v_W \frac{dC_{W_{O_2}}}{dt} = D_{M_{O_2}}(P_{A_{O_2}} - P_{W_{O_2}}) - Q(C_{c'_{O_2}} - C_{\bar{v}_{O_2}}) \quad (3)$$

which we rewrite in terms of partial pressure,

$$\alpha'_{O_2} v_W \frac{dP_{W_{O_2}}}{dt} = D_{M_{O_2}}(P_{A_{O_2}} - P_{W_{O_2}}) - Q(C_0 + \beta_{O_2} P_{W_{O_2}} - C_{\bar{v}_{O_2}}) \quad (4)$$

by: 1. representing the oxygen content of blood at a partial pressure P_{O2} as $C(P_{O2}) = C_0 + \beta_{O2} P_{O2}$ where the oxygen solubility in blood β_{O2} is the gradient of the oxygen content curve (according to the haemaglobin dissociation curve) evaluated at the partial pressure P_{O2} and C_0 is the extrapolation to zero pressure as illustrated in fig. 2. (Note that both β_{O2} and C_0 depend on the partial pressure.); 2. similarly representing the oxygen concentration in the capillary plus tissue water compartment, $C_{W_{O2}}$ as $f_w \alpha_{O2} P_{W_{O2}} + f_B(C_0 + \beta_{O2} P_{W_{O2}})$, with f_w and f_B the fractions of water and whole blood respectively in this compartment and α_{O2} the solubility of oxygen in water; 3. making the approximation that for the change in partial pressure that we are modelling (i.e over the course of the OE-MRI study) the time-varying solubility β_{O2} may be approximated by its average value (such that β_{O2} and C_0 are constant over time); 4. defining $\alpha'_{O2} = f_w \alpha_{O2} + f_B \beta_{O2}$. Equations (2) and (4) form coupled equations for the rate of change of partial pressure in the two compartments under the assumptions outlined.

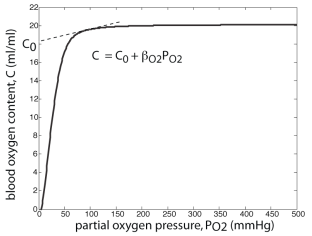

fig 2: blood oxygen solubility β_{O2}

Diffusion across the alveolar membrane is rapid such that equilibration between alveolar and capillary partial pressures occurs in a time that is short compared to the capillary mean transit time (of around 0.75s). This remains true in disease for diffusion impairments down to around ¼ of normal values [4] and for a wide range of V_A/Q ratios. This means that while the end capillary oxygen partial pressure may be low compared to normal values due to pathology (and end-capillary haemagloblin may be significantly below saturation) it is essentially in equilibrium with the alveolar partial pressure. The rate of replacement of mixed alveolar gas by fresh inspired gas occurs over longer timescales determined by the rate of ventilation. We therefore combine equations (2) and (4) and re-arrange to give:

$$\frac{dP_{W_{O_2}}}{dt} + (v + q\lambda_B)P_{W_{O_2}}(t) = (P_{B-H_2O})(vF_{I_{O_2}}(t) + q(C_{\bar{v}_{O_2}}(t) - C_0)) \quad (5)$$

with $v = V_A/[1-(1-\lambda')]v_W$, $q = Q/[1-(1-\lambda')]v_W$, $\lambda_B = \beta_{O2} P_{B\text{-}H20}$ and $\lambda' = \alpha'_{O2} P_{B\text{-}H20}$.

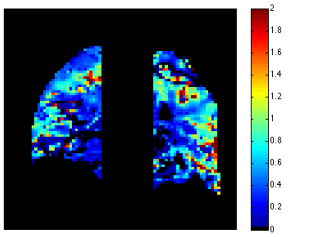
fig 3: Example V_A/Q map

Equation (5) may be solved using an integrating factor, and using the initial condition that for $t<0$ the system is in equilibrium (i.e. $dP_{W_{O2}}/dt = 0$ for $t<0$), we obtain, with $\Delta P_{W_{O2}}(t) = P_{W_{O2}}(t) - P_{W_{O2}}(t<0)$, $\Delta F_{I_{O2}}(t) = F_{I_{O2}}(t) - F_{I_{O2}}(t<0)$, $\Delta C_{v_{O2}}(t) = C_{v_{O2}}(t) - C_{v_{O2}}(t<0)$:

$$\frac{\Delta P_{W_{O_2}}(t)}{P_{B-H_2O}} = v\int_0^t e^{(v+q\lambda_B)(t'-t)}\Delta F_{I_{O_2}}(t')dt' + q\int_0^t e^{(v+q\lambda_B)(t'-t)}\Delta C_{\bar{v}_{O_2}}(t')dt' \quad (6)$$

or:

$$\frac{\Delta P_{W_{O_2}}(t)}{P_{B-H_2O}} = \frac{v}{v+q\lambda_B}\Delta F_{I_{O_2}}(1 - e^{-(v+q\lambda_B)t}) + q\int_0^t e^{(v+q\lambda_B)(t'-t)}\Delta C_{\bar{v}_{O_2}}(t')dt' \quad (7)$$

if the input function $\Delta F_{I_{O2}}(t)$ may be assumed to be a step function induced by switching to breathing elevated levels of O_2, such that $\Delta F_{I_{O2}}(t>0)$ is constant.

DYNAMIC OE-MRI • In an OE-MRI study it is possible to obtain a time series of $R_1 (=1/T_1)$. The change in R_1 in the parenchymal blood and tissue water induced by a change in inspired oxygen fraction may be converted to a change in partial oxygen pressure $\Delta P_{W_{O2}}$ via a knowledge of the relaxivity of O_2 [5]. Equation (6) or (7) may then be fitted voxel-by-voxel varying the fit parameters v, q and λ_B. The change in systemic venous oxygen concentration $\Delta C_{v_{O2}}(t)$ is an input which may be measured or must be assumed. V_A/Q may then be calculated from $V_A/Q = v/q$. An example V_A/Q for a healthy volunteer obtained from OE-MRI data is presented in figure 3.

CONCLUSION • We have presented a model which relates the observed evolution of the OE-MRI signal following a change in inspired oxygen fraction to physiological parameters. This technique has the potential to provide regional quantitative V_A/Q maps to be obtained from OE-MRI alone.

REFERENCES [1] Edelman RR *et al,* Nat Med. 1996, 2:1236. [2] Mai VM *et al,* JMRI 2001, 14:574; Arnold JF *et al,* JMRI 2007, 26:637. [3] Loer SA *et al*, Anesthesiol. 1997, 86: 532. [4] Wagner PD and West JB, JAP 1972, 33:62. [5] Zaharchuk G, Acad Radiol. 2006, 13:1016.