Modeling Approach for Oxygen Exchange in the Human Lung under Hypobaric Conditions

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1. Introduction.

Physical effort at high altitude can result in serious complications in the human respiratory system even for healthy and well-trained persons. For people with a pulmonary disorder, already a stay at moderate altitude, or transportation by air (e.g. in case of medical evacuation) can lead to significant problems caused by hypoxemia.

In both circumstances the oxygen tension of the inspired air (PI,O_2) and therefore of the arterial blood (Pa,O_2) drops substantially. For healthy people - if at rest - this causes no considerable problems because their arterial oxygen saturation at such altitudes still will be at the horizontal part of the oxyhaemoglobin dissociation curve.

Problem area

Patients with COPD and interstitial lung diseases have mild to severe obstructive and/or restrictive impairment of the lung function. So they may deal with unequal ventilation, ventilation-perfusion mismatch, diffusion disorders, ventilatory restriction, and changes in arterial blood gas tensions. In this kind of lung diseases there is a diminished reserve of gas exchanging surface because of degeneration of alveoli and/or fibrosis of the lungs.

For the individual patient with COPD or interstitial lung diseases the Pa,O_2 at altitude can not be predicted from the sea level value (Ref. 1). Even with normal blood gas tensions at sea level severe drop in oxygen saturation may occur at altitude. Predicting factors seem to be a FEV1 (forced expiratory volume 1st second) < 30 % VC (vital capacity) and/or a significant decrease of the Pa,O_2 with comparatively low exercise. Other empirical formulas to predict Pa,O_2 at altitude from sea level conditions have been derived by Gong (Ref. 2) and Dillard (Ref. 3). These statistical formulas indicate more or less average responses but are not suitable for the predictions for the individual patient.

HAST (high altitude simulation test) may provide more clearness in the individual for the extent of the gas exchanging surface. An important difference of this test with regard to reality is the constant barometric pressure and the comparatively limited duration (30 min). Besides, this test is not without any risk for the patient (hypoxemia induced arrhythmias).

Approach

In this paper we explore the modeling of the human lung gas-exchange under hypobaric conditions. At first the concept of the ventilation-perfusion mismatch is applied to model the pulmonary performance of a healthy person at rest at increasing altitudes. Model results are compared with experimental data from literature at varying altitude. The model is also used for a patient with COPD at moderate altitude. The results illustrate the limited applicability of the mismatch model. Inclusion of diffusion effects improves the results. Only a preliminary validation of the model has been attempted yet. The focus is predominantly on understanding and modeling of possible underlying physics.

2. The ventilation-perfusion mismatch model.

Compartments

The algorithm for the exchange of O_2 and CO_2 is based on the subdivision of the human lung into a number of compartments. Several units, consisting of alveoli and the network of capillaries, are lumped together in each compartment. One assumes that the conditions for all units in one compartment are the same. The ventilation-perfusion ratio v'/q' for a compartment dictates the transfer of O_2 and CO_2 as a function of their mixed venous values PV,O_2, PV,CO_2 and the oxygen inspired presure PI,O_2. Two examples for a range of values of v'/q' are shown in figure 1. Curve A shows the variation of end-capillary values of partial oxygen pressure Pec,O_2 versus Pec,CO_2 for sea level atmospheric conditions, curve B for hypobaric conditions. Each point on a curve represents a compartment with a certain ventilation-perfusion ratio.

The basis for the construction of these curves is that complete equilibration of O_2 and CO_2 has taken place between the capillary blood flow and the alveoli. For CO_2 this is not an issue because its transfer through the alveolar membrane takes place very rapidly. However for O_2 this is only true if: a) the blood barrier resistance of the membrane

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is not too high, b) the contact time of the capillary flow with the alveolar tissue, is not too small, and c) the initial PO_2 difference over the membrane is not small as might occur in hypobaric conditions. We will discuss items b) and c) later on.

The method of Rahn and Riley & Cournand described by Farhi (Ref. 4) is used to find the points of figure 1. The equations are given for completeness:

$$v'_n O_2 = v'_n * (PI, O_2 - PA, O_2) * \frac{1}{k} \equiv q'_n O_2 = q'_n * (cec, O_2 - cV, O_2) \qquad n = 1 \ldots N \qquad (1)$$

It states that for each compartment n the amount of loss of O_2 in the gaseous state, v'_nO_2, equals the transfer of O_2 to the capillaries, q'_nO_2. The concentration in the blood at the end of the capillary is indicated by cec,O_2, at the venous point cV,O_2 ; k is a conversion factor, v'_n and q'_n are the ventilation and perfusion of compartment n.
The uptake of CO_2 into the alveolar gas from the blood is expressed as:

$$v'_n CO_2 = v'_n * PA, CO_2 * \frac{1}{k} \equiv q'_n CO_2 = q'_n * (cec, CO_2 - cV, CO_2) \qquad (2)$$

The equations for the concentrations cO_2 and cCO_2 are taken from West and Wagner (Ref. 5). They are both non-linear functions of Hb, hematocrit, PO_2, PCO_2 and body temperature. By the assumption of fully equilibration the end-capillary values for PO_2 and PCO_2 are equal to their corresponding alveolar values:

$$\begin{aligned} P_n A, O_2 &= P_n ec, O_2 \\ P_n A, CO_2 &= P_n ec, CO_2 \end{aligned} \qquad (3)$$

Ventilation-perfusion distributions

In analogy to the model of West and Wagner we assume a discrete lognormal distribution of ventilation and perfusion over the compartments:

$$v'_n = \frac{V'A \cdot \Delta\xi}{\sigma\sqrt{2\pi}} * \exp\left[-\tfrac{1}{2} \cdot \left(\frac{\xi_n - \mu_v}{\sigma}\right)^2\right] \qquad (4)$$

$$q'_n = \frac{Q' \cdot \Delta\xi}{\sigma\sqrt{2\pi}} * \exp\left[-\tfrac{1}{2} \cdot \left(\frac{\xi_n - \mu_q}{\sigma}\right)^2\right] \qquad (5)$$

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V'A and Q' are the total alveolar ventilation and pulmonary perfusion. In figure 2 an example is shown. The v'_n and the q'_n are plotted versus their logarithmic ratio $\xi_n = \log(v'_n / q'_n)$. The discrete compartments are centered at ξ_n. All compartments are equidistant in ξ and have equal widths $\Delta\xi$. The parameter σ functions in these formulae in two ways. In both the single distributions for v'_n and q'_n it is a measure of the deviation from the means μ_v and μ_q. Its square σ^2 also separates both peaks. From (4) and (5) it follows:

$$\begin{aligned} \mu_v &= \log\left(\frac{V'A}{Q'}\right) + \tfrac{1}{2} \cdot \sigma^2 \\ \mu_q &= \log\left(\frac{V'A}{Q'}\right) - \tfrac{1}{2} \cdot \sigma^2 \end{aligned} \qquad (6)$$

We will use σ as the parameter representing the ventilation-perfusion mismatch. For a healthy young person the mismatch σ is small Then both peaks for ventilation and perfusion lie close together and the width σ of their bell shaped distributions is also small. We assume in case of COPD that the lung degradation can be expressed in an increase of σ. An example of a pure variation in mismatch is shown in figure 3. The growth of σ will lead to a steady decrease of Pa,O_2 and, to a lesser degree, to a steady increase of Pa,CO_2. The responses of the pulmonary ventilation to an increase of Pa,CO_2 or a decrease of Pa,O_2 are not taken into account yet. The metabolic indices $V'O_2$ and $V'CO_2$ are kept constant. Therefore the values of alveolar partial pressures of O_2 and CO_2, averaged over all compartments, are constant as well. By the assumption of fully equilibration one can refrain from the inclusion of alveolar membrane properties and from the effect of reaction speed of the O_2 molecules with Hb.

Circulation

We use two extra equations due to Fick's principle. They describe the consumption of O_2 and the production of CO_2 at the systemic side of the circulation:

$$\begin{aligned} V'O_2 &= CO \cdot (ca, O_2 - cV, O_2) \\ V'CO_2 &= CO \cdot (cV, CO_2 - ca, CO_2) \end{aligned} \qquad (7)$$

The first equation states that the total O_2 consumption equals the arterial and mixed venous concentration difference times the cardiac output CO. The second equation expresses the equivalent for CO_2 production. By the summation of equations (1) and (2) over all compartments including the right-to-left shunt, the same quantities have to found for the O_2 and CO_2 transfer in the total lung.

Baseline conditions

To estimate the mismatch parameter σ for a person, our point of departure is the knowledge of (measured) arterial partial gas pressures Pa,O_2 and Pa,CO_2. The cardiac output CO under resting conditions is estimated from the body surface area BSA. Also the pulmonary shunt fraction psh has to be measured or estimated. The metabolic rates $V'O_2$ and $V'CO_2$ are usually measured as a part of exercise testing. For the perfusion distribution to be fully known only σ has to be determined. The ventilation distribution requires also σ but in addition the total alveolar ventilation V'A. V'A will be determined simultaneously with σ. The non-linear system of equations (1) to (7) is solved by Broydn's procedure (Ref. 6) for chosen values of the interval $\Delta\xi$ and the total number of compartments N. The Broydn procedure is a fast and robust method that finds the roots in analogy with the secant method working in two dimensions. Hence it does not require the elaborate evaluation of a Jacobian matrix. The matching procedure delivers the four quantities: mismatch parameter σ, alveolar ventilation V'A and the mixed venous partial pressures PV,O_2 and PV,CO_2.

To display the interactions of the solution process consider figure 4. It shows Pa,O_2 and Pa,CO_2 as functions of σ and alveolar ventilation V'A. The mixed venous partial pressures are not visualised. According to physical feeling Pa,CO_2 is a decreasing dominant function of V'A and it is a weakly increasing function of σ. Pa,O_2 depends equally on both variables. In general it increases with V'A and it decreases with σ. For a measured pair of arterial partial pressures of O_2 and CO_2 the corresponding values of V'A and σ can be found by the Broydn procedure. From a first guess of V'A and σ with probably incorrect corresponding values of Pa,O_2 and Pa,CO_2 a trajectory in the V'A-σ plane is traversed that tends to approach the measured values of Pa,O_2 and Pa,CO_2.

Hypobaric conditions

In our model no explicit reference is made to the atmospheric pressure, hence we study the consequences of hypobaric conditions by changing the O_2 fraction FI,O_2 of the inspiratory gas. As a starting point we assume that the mismatch parameter σ and cardiac output and the right-left shunt are kept the same and hence the perfusion distribution is kept the same. However the ventilation is allowed to increase as a response to hypoxia:

$$V'E = V'^{b}\,E - G_{Sa} * (S^{b}a,O_2 - Sa,O_2)^{p} \tag{8}$$

Where V'E is the pulmonary minute ventilation, superscript b indicates quantities measured or calculated under basic (i.e. sea level atmospheric and resting) conditions. G_{Sa} is the sensitivity (a negative number) of the minute ventilation to arterial oxygen saturation. For an exponent p = 1 G_{sa} is in the range of -1.55 ±0.98 (Ref. 7). A hypocapnic effect on G_{Sa} is not taken explicitly into account. The real response to hypoxic conditions depends also on the speed by which hypoxic conditions are imposed and on the additional control of alveolar PA,CO_2. (Ref. 8).
From the minute ventilation the alveolar ventilation can be found by:

$$V'A = V'E - f(V'E) * VD \tag{9}$$

The breathing frequency f is a weak function of V'E itself; VD is the physiological dead space. The system of equations (1) to (9) can be solved for the venous and arterial blood gasses using Broydn's procedure. The mismatch σ is kept fixed now, but the ventilation V'A is allowed to adapt itself to hypoxic conditions according to (8) and (9).

3. Application of the model.

Healthy person

At first the mismatch model is applied to a healthy subject starting at sea level and decreasing its FI,O_2 to an equivalent altitude of 9 km (Figure 5). From the barometric pressure for standard atmosphere the PI,O_2 is found and used as an input of the model. A low value of mismatch σ is assumed that is kept fixed. The pulmonary ventilation was allowed to respond to hypoxia according to (8) with an exponent ½. This weak response is a result of hypoxia, damped by the decreased PA,CO_2. The results for arterial pressures are quite comparable with actual measurements of a simulated ascent of the Everest (Ref. 9). In the measured realistic conditions the alveolar-arterial PO_2 difference increases with altitude. At 9 km this amounts to a $P(A\text{-}a),O_2$ = 6 mmHg. This might be attributed to the lack of complete equilibration. The results of the present model show a steady decrease of the alveolar-arterial difference, practically approaching zero for the higher altitudes. This is due to the pattern of the O_2 dissociation curve. At low O_2 saturation the same shunt gives a smaller effect on Pa,O_2 versus PA,O_2.

Patient with COPD

So far things seem to compare reasonably well. However application of the present method to the data of a COPD patient, put forward by the St. Antonius Hospital, showed results deviating from the measured data (Fig. 6). It seems that the ventilation-perfusion mismatch is not the only source attributing to the failure of this subject to cope with the lowered PI,O_2. One of the possibilities is discussed below.

Diffusion limitations

Many patients suffering severe COPD have lost a great deal of their oxygen transfer capabilities. Under normal resting conditions this does not necessarily lead to hypoxemia. But in exercise and under hypobaric conditions this can be a cause of hypoxemia. The transfer properties of the lung are evaluated clinically by measuring a.o. TL,CO that is defined as:

$$TL,CO = \frac{V'CO}{PA,CO} \tag{10}$$

Which measures the uptake of carbon monoxide, CO. See e.g reference 10 for a careful analysis of TL,CO measurements. CO has such a large affinity for Hb that its capillary pressure can be assumed zero and PA,CO can be considered as the driving pressure. Therefore TL,CO characterizes the properties of the blood gas barrier. It is proportional to the membrane surface area and the solubility of CO and is inversely proportional to membrane thickness and the square root of the molecular weight of CO. A reduction of membrane area by COPD will lead to a proportional reduction in transit time of the blood in the capillary bed if the same cardiac output has to be maintained. All other membrane properties are assumed the same. A decrease of transit time *tc* is no problem if the oxygen equilibration time *te* remains sufficient small. However for lower values of PA,O2 this is not possible. In figure 7 three examples are shown of alveolar capillary PO_2 differences during the passage of blood along alveolar tissue. The curves are obtained from approximations of the diffusing equation for oxygen:

$$\frac{dcO_2}{dt} = g * D_{O2} * (PA,O_2 - Pc,O_2) \tag{11}$$

In which t is the time coordinate for a blood parcel moving along a capillary. g is a geometrical shape parameter and DO_2 is the O_2 membrane permeability factor. The O_2 concentration cO_2 in the capillary vascular system depends on the local gas pressures Pc,CO_2 and Pc,O_2. All parameters are taken for healthy non-degraded tissue. Normal value for the contact time is *tc* = 0.76 sec (Ref. 11). Equilibration time *te* is small for a large alveolar-venous oxygen pressure difference and a PA,O_2 on the horizontal part of the O_2 dissociation function (upper curve). *te* increases strongly with decreasing alveolar oxygen pressures (curves PA,O_2=90, 60). For a fixed *tc* < *te*, the alveolar-end-capillary difference $P(A\text{-}ec),O_2$ is small for high PA,O_2 because *te* is small. $P(A\text{-}ec),O_2$ increases for intermediate values (e.g. PA,O_2 = 90) because *te* is increasing. However $P(A\text{-}ec),O_2$ decreases again for smaller PA,O_2, because the alveolar-venous difference is decreasing. But it will not vanish. For lower PA,O_2 there is always a condition where no equilibration can occur because *te* will be much larger than any *tc*.

In our system of equations the first of equation (3) is replaced by:

$$P_n ec,O_2(tc) = P_n A,O_2 - P_n(A-ec),O_2[g, D_{O2}; tc] \qquad n = 1 \ldots N \tag{12}$$

Where the last term follows from an approximate solution of (11) for each compartment and for the yet unknown initial condition PV,O_2 and the compartment dependent PA,O_2. Broydn's procedure again is applied but now with N additional non-linear equations (12).

Patient with COPD and diffusion limitations

Baseline results for FI,O_2 =0.21 of our COPD patient are shown in figure 8A. It displays alveolar and end-capillary values of PO_2 versus the ventilation-perfusion ratio. From TL,CO data it is inferred that the average contact time was reduced to about *tc*=0.38 sec. For alveolar PA,O_2 = 120 mmHg and higher the equilibration takes place before the end of the capillary is reached. For lower alveolar values this is not the case and alveolar-end-capillary differences are shown. This has however not a strong detrimental influence because the ventilation as well as the perfusion are smaller in that region. Figure 8B shows the distributions for FI,O_2 = 0.15. Over the whole range of ventilation-perfusion ratios a substantial alveolar-end-capillary difference occurs in PO_2. The smaller differences now appear at the lower side of the PA,O_2 because here the smaller alveolar-venous difference starts to reduce the alveolar-end-capillary differences. Figure 9 depicts the course of the blood gas values starting from normal FI,O_2 = 0.21 to gradual lower FI,O_2. A reasonable match with HAST measurements is obtained.

4. Concluding remarks.

At hand of a healthy person and one with COPD the application of the ventilation-perfusion mismatch model of the human lung has been investigated. The model can not predict the pulmonary performance at moderate altitude for a COPD patient. It is likely from diffusion data that the reduced contact time of the blood flow in the alveolar bed

may cause the remaining discrepancies. To include such possible effects, the model has been extended with a capillary O_2 equation that accounts for alveolar-end-capillary PO_2 differences. A better match with the Pa,O_2 drop observed in HAST data appears to justify these model extensions. The validation of the improved model requires however the application to a greater number of subjects. This will be pursued in future work. A satisfactory prediction of oxygen saturation at altitude has to take into account more person specific characteristics. Hence the extension of the model might not be limited to ventilation-perfusion mismatch and diffusion effects alone.

5. References.

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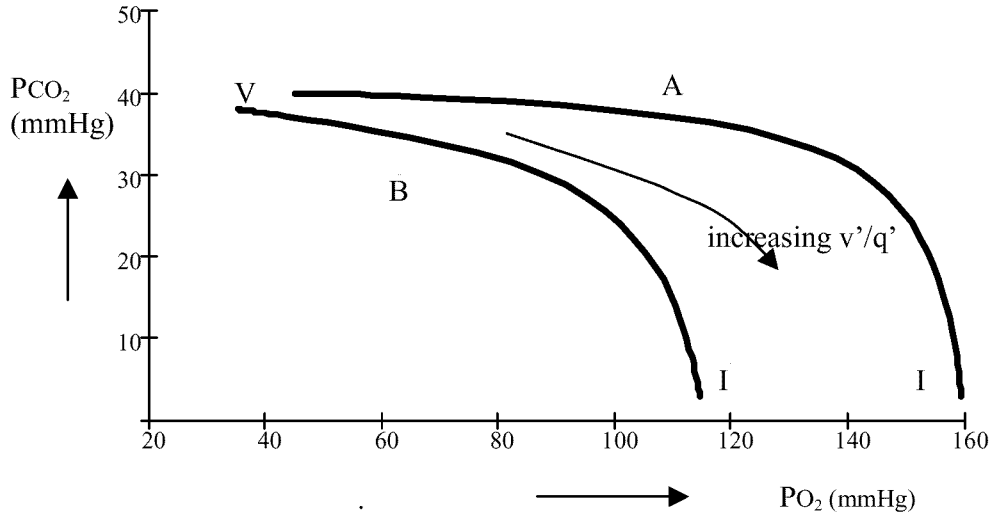

Figure 1. Alveolar PCO_2 versus PO_2 for a subject at sea level (curve A) and at h = 2500 m (curve B). Each point on a curve represents a compartment with a certain v'/q' combination. At the venous points (V) v'/q'=0 and at the inspired points (I) v'/q' approaches infinite.

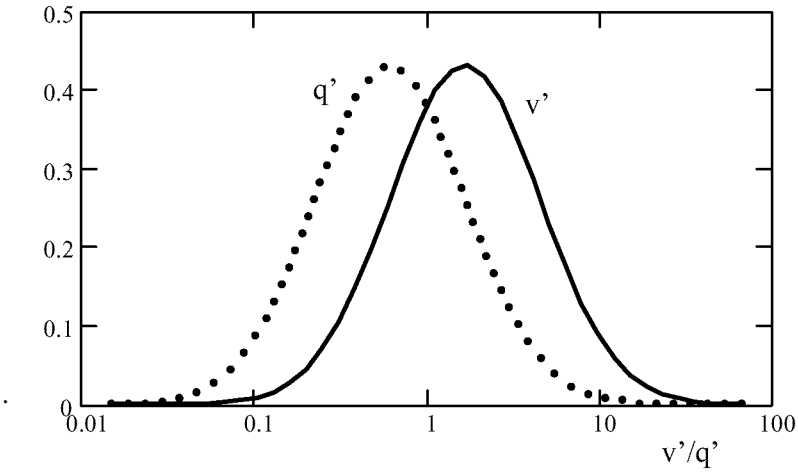

Figure 2. Ventilation v' (L/min) and perfusion q' (L/min) lognormal distributions as function of their ratio v'/q'.

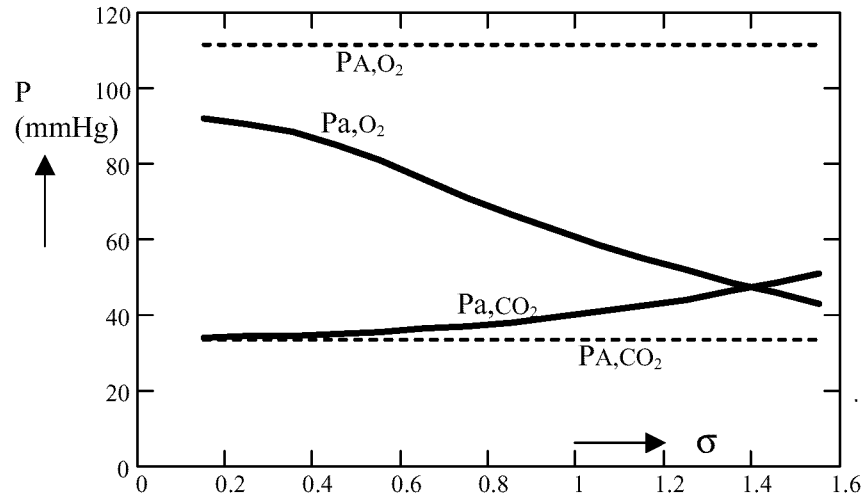

Figure 3. Effect of mismatch parameter σ on alveolar (PA,O_2, PA,CO_2) and arterial partial pressures (Pa,O_2, Pa,CO_2).

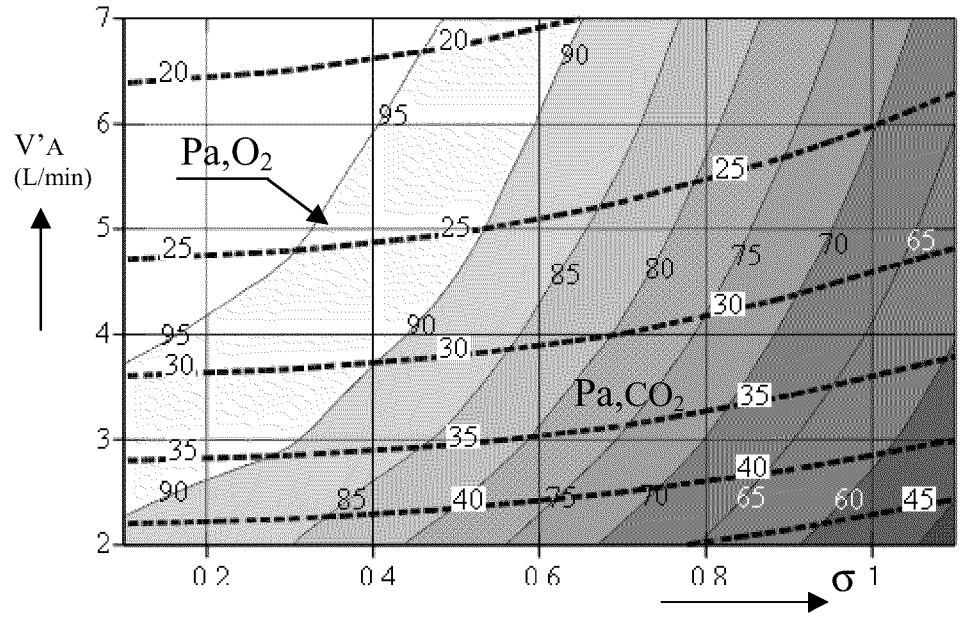

Figure 4. Lines of constant Pa,O_2 (thin lines with grey fill) and of constant Pa,CO_2 (dotted heavy lines) in mmHg as function of mismatch parameter σ and alveolar ventilation V'A. For a pair of measured values of Pa,O_2 and Pa,CO_2 the characteristics V'A and σ can be found.

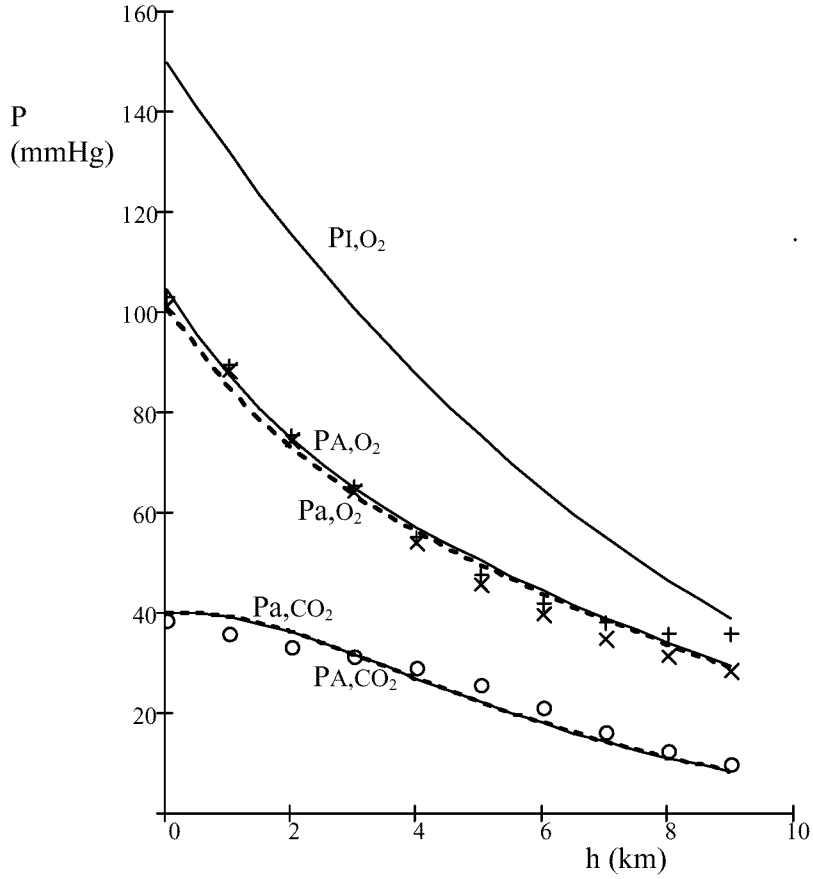

Figure 5. Calculated model and experimental results for a healthy subject.
Calculations: Alveolar (P_{A,O_2}, P_{A,CO_2}): solid lines. Arterial (P_{a,O_2}, P_{a,CO_2}): dashed lines.
Experimental data (Ref. 9): P_{a,CO_2}: o's; P_{a,O_2}: x's; P_{A,O_2}: +'s.
Standard atmosphere P_{I,O_2}: solid line.

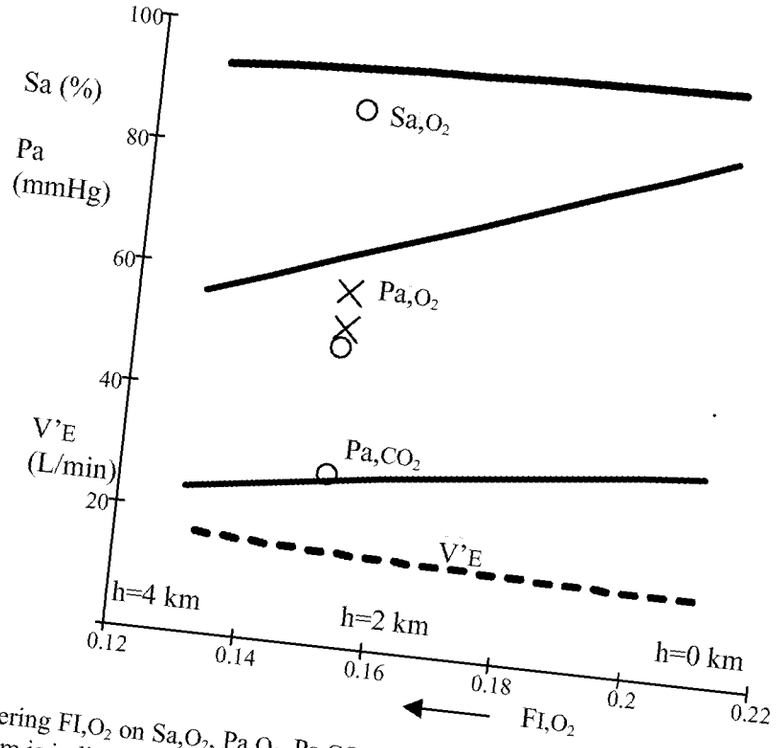

Figure 6. Effect of lowering FI,O_2 on Sa,O_2, Pa,O_2, Pa,CO_2 and V'E of a COPD patient. Equivalent altitude in km is indicated at the bottom of figure. Crosses indicate Pa,O_2 from statistical formulae of Gong (upper) and Dillard (lower) (Ref. 2, 3). Open symbols represent HAST measurements for Sa,O_2, Pa,O_2, Pa,CO_2. Lines are computed by the present ventilation-perfusion mismatch method. Initial baseline conditions at $FI,O_2 = 0.21$ are derived from measurements.

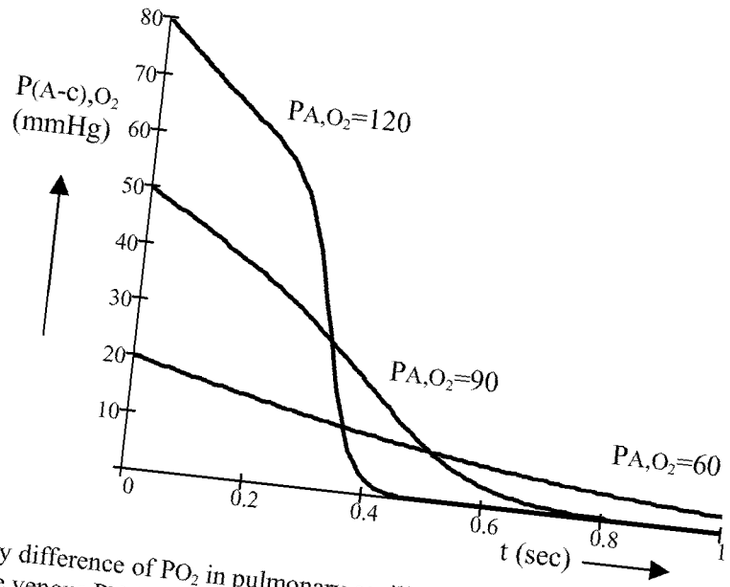

Figure 7. Alveolar-capillary difference of PO_2 in pulmonary capillary as function of time for three values of alveolar PA,O_2 for the same venous PV,O_2=40 mmHg at t=0 sec.

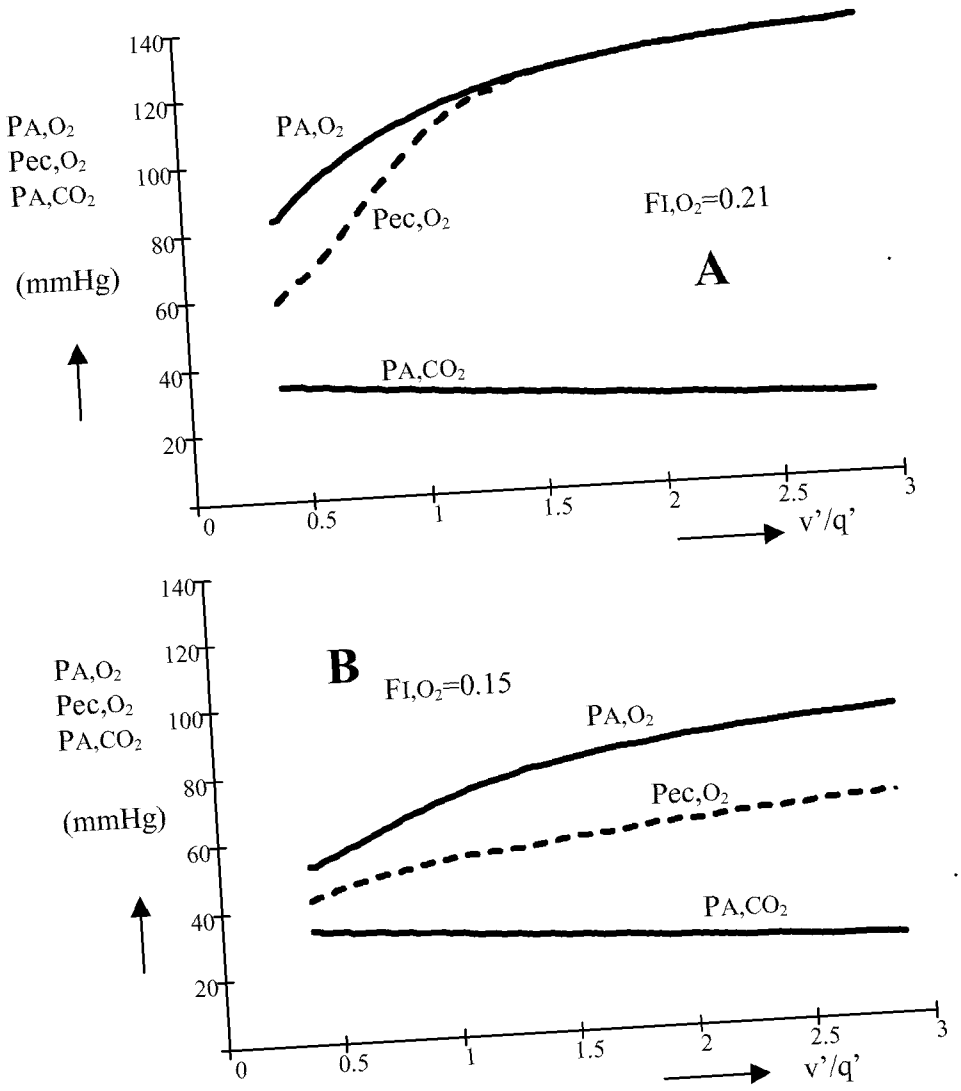

Figure 8. Partial pressures of O_2 and CO_2 versus ventilation-perfusion ratios including the effect of alveolar-end-capillary PO_2 difference.
Top figure A: normal FI,O_2=0.21, bottom figure B: FI,O_2=0.15.

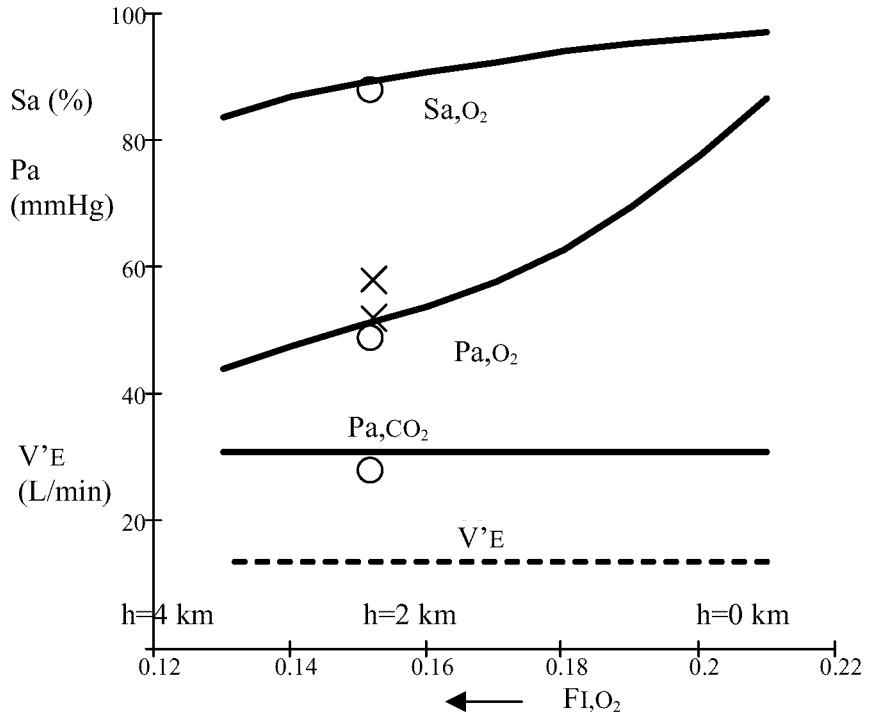

Figure 9. Effect of lowering FI,O_2 on Sa,O_2, Pa,O_2, Pa,CO_2 and V'E. At the bottom altitude is given in km.
Open symbols represent HAST measurements of Sa,O_2, Pa,O_2, Pa,CO_2 of COPD patient.
Crosses are Pa,O_2 from statistical formulae of Gong and Dillard (Refs. 2,3).
Lines are computed by ventilation-perfusion mismatch method including non-equilibration of capillary PO_2.
Initial conditions at FI,O_2=0.21 are derived from measurements.

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