A MATHEMATICAL MODEL FOR GAS EXCHANGE IN THE HUMAN MIDDLE EAR

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Abstract A mathematical model was developed to identify time periods of atelectasis induction in middle ears (ME) ventilated via ventilating tubes (VT). VT’s were deliberately sealed and ME gas content changed in the presence of a preset blood gas pressure. Once sealed, CO₂ rapidly diffuses out of the blood via lining tissues into the ME. This results in initially a total ME pressure rise followed by decrease to sub-atmospheric pressures. Time periods for atelectasis reformation were determined once ME pressure crossed the 760 mmHg value and continued to decline as the atelectasis reached higher grades. Time periods calculated by the model varied from 28 min to 165 min in ME cavities ranging in volume from 0.5 mL to 3 mL respectively. Blood gas pressure in the lining mucosa was altered between arterial gas composition to venal blood composition in a first order fashion. These results are consistent with prior clinical tests that measured an induced return to previous atelectasis state following the closure of the VT’s in 33 tested ears within 25-120 min (43 min on average). The model demonstrates that increase in blood flow rate alter the exchange rate of CO₂ and N₂ 25-120 min (43 min on average). The model may be used as a tool to determine ME physiological cavity volume of ears with VT’s. Keywords - Atelectasis, mathematical model, ventilation tube, diffusion and perfusion limitation.

I. INTRODUCTION

1) Anatomy: The ME (0.4-2.5 mL) is viewed as a gas pocket which is separated from the external ear by the tympanic membrane (TM) and from the inner ear by the promontorium. The ME is connected to the Mastoid (an aerated bone up to 30 mL in volume) and comprise together one gas pocket. The ME is connected to the nasopharynx (NP) via the Eustachian Tube (ET). The anterior part of the ME is covered by respiratory epithelia. Under inflammatory conditions, when new cells appear, they may differentiate mainly into cells producing mucous or cells bearing cilia. The ME lumen is separated from the blood circulation by its epithelium, the lining of the blood vessels and some connective tissue between them.

2) Physiology: Gas particles have the tendency to pass from an environment of high partial pressure to an environment of low partial pressure until equilibrium is reached. This is true for each individual gas independent of the partial pressures of other gases. The passage of gas occurs through any semi-permeable gas environment as well as through liquid, tissue, blood vessel walls or epithelial lining, but at different specific rates. The gas composition in a ME with a VT is different from the gas content of arterial or venal blood. The CO₂ pressure in arterial and venal blood is 34 and 41 mmHg (respectively) higher than that of a ME with VT. The N₂ pressure in arterial and venal blood is 5 mmHg higher than that of a ME with VT. On the other hand, the O₂ pressure in arterial and venal blood is 36 and 45 mmHg (respectively) lower than that of a ME with VT. (Table I). In respect of these partial pressure gradients, the CO₂ in lining blood will diffuse into the ME thus increasing the total pressure whereas O₂ and N₂ will diffuse from the ME into the lining blood. When total gas pressure in the ME decreases to a certain limit, an active action of swallowing or yawning introduces a bolus of gas from the NP into the ME, thus increasing the total pressure within. This action is called: ventilation.

II. METHODOLOGY

The purpose of this study was to attempt to simulate the gas exchange between the ME and surrounding blood following the closure of the VT. The gases in the ME and blood tend to reach a partial pressure equilibrium, thus abolishing the partial gas pressure between the two compartments. This tendency changes the gas composition both in the ME and in the surrounding blood. As a consequence of a specific gas transfer, the gas proportion in the ME is altered (diluted or concentrated).

Model simulations differed in ME volume, initial gas pressures in the surrounding blood vessels and blood flow rate.

1) ME assumptions: The effect of gas exchange in the ME is almost instantaneous. Gases are equally distributed in the ME. The temperature in the ME and surrounding tissue and blood vessels is constant at 37 degrees Celsius. Following the sealing of the VT, gas begins to transfer across the tissue while each gas in the ME reach a pressure equilibrium with corresponding gas in the surrounding blood vessels. As a result, a partial pressure variation in the ME effects the total pressure in the ME and displaces the TM, thus changing the
# A Mathematical Model for Gas Exchange in the Human Middle Ear

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**Supplementary Notes**
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## Abstract

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ME volume. In order to simplify the model, two model embodiments were chosen to describe the above characteristics:

Model A: the ME is held at a constant volume following the VT closure. The partial and total pressure in the ME changes in response to gas transfer.

Model B: the total pressure in the ME is constant at 760 mmHg. The partial pressure in the ME varies as well as the volume of the following ME displacement of the TM.

2) Tissue assumptions: We assume for model simplicity that the tissue is homogenous in thickness and number of blood vessels per unit volume. It is widely accepted that soft tissue consists of 93% water. Therefore, we assume that the tissue separating the ME from surrounding blood vessels consists mostly of water. We used the solubility coefficient of gases in saline to simulate solubility of gases in tissue.

The tissue in its metabolic processes derives O2 from surrounding blood and exports waste CO2 to surrounding blood. In face of a gas cavity such as the ME, it is possible that some of the O2 for metabolic processes originates from the ME and some of the waste CO2 is exported into the ME. For model simplicity, we assume that the gases used in tissue metabolism originate from the blood and that metabolism waste is transferred to the blood.

3) Blood assumptions: The gases in the ME strive to abolish the partial pressure difference between the ME and blood. The gases in the capillary blood change from arterial blood composition to venal blood composition in face of tissue metabolism. We changed the partial gas pressures in the blood in a first order form.

Gas exchange between blood and the ME may be influenced by blood flow rate and by the solubility (pressure dependent) of each gas in blood. The blood flow rate (perfusion rate) was calculated using an algorithm based on the removal of N2 from the ME. Gas solubility in blood was derived from the dissociation curve of each gas. The first derivative of the dissociation curve results in the solubility curve of each gas in blood.

4) Types of gas exchange: If consumption and production of gas (O2, CO2) by the surrounding tissue is neglected, the gas exchange of closed cavities is determined by the blood flow rate of blood in the cavity walls, by diffusion through the tissue layer separating capillary blood from the interior of the cavity, or by both of these occurring. [2]

If perfusion is the sole limiting factor (there being no resistance to diffusion), the flow rate of each gas between the ME and lining blood vessels is determined using:

$$\left(\frac{dn}{dt}\right) = \dot{V} \cdot \beta_i \cdot (P_{ME_i} - P_{Bl_i})$$  \hspace{1cm} (1)

Table II defines symbols used in above and following equations.

If diffusion is the sole limiting factor (perfusion rate must be so high that there is no difference between arterial and venous gas composition), the gas flow rate is determined using:

$$\left(\frac{dn}{dt}\right) = D_i \cdot \alpha_i \cdot \frac{A}{\tau} \cdot (P_{ME_i} - P_{Bl_i})$$  \hspace{1cm} (2)

A combined perfusion-diffusion limitation is more likely to occur which determines the gas flow rate using:

$$\left(\frac{dn}{dt}\right) = \dot{V} \cdot \beta_i \cdot (P_{ME_i} - P_{Bl_i}) \cdot (1 - e^{-m_i})$$  \hspace{1cm} (3)

where

$$m_i = \frac{D_i \cdot \alpha_i \cdot \frac{A}{\tau}}{\dot{V} \cdot \beta_i}$$  \hspace{1cm} (4)

The comparative effectiveness of perfusion and diffusion limitation depends upon the value of m: m>3, practically pure perfusion limitation; 1<m<3, combined perfusion-diffusion limitation with prevailing perfusion limitation; 0.1<m<1, combined perfusion-diffusion limitation with prevailing diffusion limitation; m<0.1, practically pure diffusion limitation. [2]

Gas exchange via the mucosa can be accelerated when submucosal capillaries dilate and blood flow increases due to the ME inflammation, whereas it can be diminished when the mucosa thickens and submucosal connective tissue proliferates due to prolonged inflammation.

The simulations of models A & B consisted of solving eq. (1)-(3) using a computer C++ program.

III. RESULTS

A. m values

The effect of various blood flow rates on the m values is described in Table III. For blood flow rate six times or more than the default rate, the exchange rate of all gases in the ME
is diffusion limited. For slower blood flow rates, the \( m_{N_2} \) and \( m_{CO_2} \) values become larger, thus altering the exchange rate to be combined perfusion-diffusion limitation with prevailing diffusion. For very slow blood flow rates (tenth of the default flow rate), the \( m_{O_2} \) and \( m_{CO_2} \) are larger than 3 thus altering the exchange rate to be perfusion limited. Throughout these simulations, \( m_{O_2} \) was smaller than 0.1, thereby determining the exchange of \( O_2 \) to be diffusion limited.

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### B. Model A – partial pressures

Fig. 1 shows \( CO_2 \) and \( O_2 \) partial pressures in the ME cavity following closure of the VT (using eq. (1)). \( CO_2 \) reaches equilibrium with blood \( CO_2 \) pressure after 20 minutes whereas \( O_2 \) is still far from such equilibrium. The \( O_2 \) pressure line may seem linear but it is actually a declining exponent with a much smaller rate constant relatively to the \( O_2 \) time constant.

An exponent with a different rate constant characterizes each gas. The ratio of the \( CO_2 \) to \( O_2 \) rate constants determined from a curve fitting software (curve expert 3.1): \( m_{CO_2}/m_{O_2} = 71.3 \frac{1}{min}/3.3 \frac{1}{min} = 21.4 \) are slightly larger then the \( D_{i}a_{i} \) ratio of the two gases. The slight difference may be explained by the presence of \( N_2 \) in the ME cavity which dilutes the concentration of \( CO_2 \) and \( O_2 \) in the ME. It may also be explained by blood flow rate that is not a component in the diffusion equation.

### C. Models A&B – Total pressures

Fig. 2 depicts the product of the total pressure and volume of the ME as a function of time following the closure of the VT of an initial 1 mL ME with VT. The two lines represent the two extreme conditions of the ME: 1) Model A - total pressure (dashed line) variation and constant ME volume (TM is not displaced following VT closure) and 2) Model B - ME volume (continuous line) variation and constant total ME pressure (TM is displaced following VT closure). The area between the two lines characterize the pressure-volume product feasibility of a 1 mL ME following the sealing of the VT.

### D. Summary

The blood entering the ME mucosa is assumed to be in arterial gas composition whereas the blood leaving the ME mucosa is assumed to be in venous gas composition. Along the capillary length, the blood partial pressures change gradually from arterial partial pressures to venous partial pressures. The closure of the VT force the gases in the once closed ME to reach a new steady state with the lining mucosa blood.

The time periods for atelectasis reformation for various ME volumes determined by the model simulation are depicted in Fig. 3. The circled and diamond lines depict the time periods for atelectasis reformation for blood composition shifting from arterial to venal composition. A ME with constant total pressure and varying volume (circled line) determines slower time periods for reformation of atelectasis than a ME with constant volume and varying total pressure.
(diamond line). The squared line and the triangulated line describe similar conditions to the described above except for the gas composition in the blood which remained arterial.

The dashed line and the continuous line describe similar conditions to the described above except for the gas composition in the blood which remained venous.

The two horizontal line represent in-vivo experiments in 33 ME’s with VT’s that were sealed [1]. Time periods for atelectasis reformation varied between 25 and 120 minutes (two horizontal lines). Crossing the model simulation results for varying blood gas composition (circled and diamond lines) with the two horizontal dashed lines, results in darker shaded area which we propose determine the likelihood that the 33 ME’s tested varied in volume between 0.5 and 35 mL. Other shaded areas, less likely are the triangles that resulted from simulation of arterial or venal blood composition. These shaded areas determine the volumes of the 33 ME’s tested to be in the volume range of 0.5-1 mL and 0.5-3.5 mL respectively.

IV. DISCUSSION

The initial gas pressure composition in the ME following the closure of the VT affects each of the gases to reach a steady state with the corresponding blood gas. Parameters such as: the pressure difference across the diffusion barrier of each gas, the diffusion conductance, solubilities in tissue and blood, tissue characteristics and volume of the ME have profound effect on each gas flow rate.

An interesting development in the total pressure following VT sealing is the formation of a peak positive pressure of nearly 786 mmHg as shown in Fig. 2.

Since the total gas pressure in the venous blood is 56 mmHg lower than that of a ME with VT (760-704), one would expect the total pressure in the ME (remembering these ears were previously atelectatic) to decrease once the VT is sealed. Clinical trials do show that sealing the VT to entrance of ambient air results in total pressure decrease [2].

The reason for the initial elevation in the total pressure may be explained by the net inflow of gas following the closure of the VT. CO2 has the largest flow rate: 8 times larger than that of O2 and 276 times larger than that of N2. CO2 flows from the blood to the ME whereas O2 and N2 flow from the ME to the blood.

Eight minutes following the closure of the VT, the absolute value of the O2 flow rate is larger than the absolute sum of the CO2 and N2 flow rates. As a result of the net outflow of molecules from the ME to the blood, the total ME pressure begins to decline thus lowering the total pressure in the ME eventually to sub-atmospheric pressures.

V. CONCLUSION

The model simulation for various volumes of ME’s (Fig. 3) suggest that our model can serve as a tool that enables the user to evaluate the volume range (depending on blood flow rate) of the ME by comparing the time measured to induce in-vivo atelectasis to Fig. 3. We suggest that the area between the circled and diamond line represent the feasibility range of the time periods for atelectasis reformation in various volumes of ME’s with sealed ventilating tubes.

REFERENCES
