MODELING OF DIFFUSION BASED CORRELATIONS BETWEEN HEART RATE MODULATIONS AND RESPIRATION PATTERN

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Abstract-**The objective of this work is to lay the foundation for the understanding of oxygen dynamics in the lung during respiration, and this effect on pulmonary hemodynamics. We raised the following questions:**

- **What is the variation of the oxygen flow rate into pulmonary capillaries during the respiratory cycle?**
- **What is the tradeoff between maintaining a constant blood flow rate through the pulmonary system, and, maintaining a constant oxygen saturation level of the blood flowing through the pulmonary system?**

A three-stage model was developed. The first stage describes the distribution of gas volume in the various generations of the bronchial tree. The second stage describes the oxygen diffusion process from the pulmonary gas in the alveoli into the pulmonary capillaries. The third stage uses the results of the two previous stages to estimate: a) the dynamics of oxygen partial pressure (pO_2) in different lung generations as the respiratory cycle progresses, b) the changes in the overall volume of oxygen available to bind with the hemoglobin during different stages of the respiratory cycle, and c) how the changes in a and b can affect the heart rate

The model was tested under various respiration patterns (FRC, TV, rate).

Keywords – Modeling, Diffusion, Heart Rate fluctuations

I. INTRODUCTION

Under a whole-body management perception, the main purpose of respiration is to allow the circulating blood to continuously supply the demand for fresh oxygen in body tissue. Under a typical setting of extra-cellular environment (pH, temperature pCO_2, etc) [1], the oxygen transfer from the blood to body tissue depends on the saturation level of the hemoglobin molecules. Tissue oxygenation is optimal when the hemoglobin molecules are fully saturated, namely *sat*(Hb)~98%. Therefore, a strong coupling between the volume of oxygen penetrating the pulmonary capillaries and the volume of blood flowing through the pulmonary capillaries is required in order to generate optimal conditions for tissue oxygenation.

The lung can be viewed as a binary tree consisting of 25 generations of partially elastic cylinders. A cylindrical element in each generation splits into two smaller cylindrical elements in the next generation. This tree, referred to as the bronchial tree, is open to the external environment only at the top end, (generation-0). This entire complex is placed in a closed environment. The process of inspiration is a result of increasing the negative pressure around the bronchial tree, causing expansion of the tree elements, thus resulting in a pressure gradient inside the bronchial tree: high pressure at generation-0 (1Atm), low pressure at higher generations. This pressure gradient is equalized by suction of outside air into the bronchial tree. During expiration the pressure gradient reverses: low pressure at generation-0 (1Atm), high pressure at higher generations. As a result, the gas in the higher generations is pushed up the bronchial tree, and out through the trachea.

Gas exchange with blood occurs mostly at the alveolar layer. Therefore, oxygen must make its way down to the alveoli prior to participating in the gas exchange process. When considering the dynamics of oxygen flow in the lung we can summarize as follows [1]:

- The outside air is the only source of oxygen.
- During inspiration, oxygen molecules drift towards the alveolar layer. Some reach the alveolar layer directly by airflow. The remaining molecules flow with the gas only part of the way down the bronchial tree, and must diffuse further through the gas for the rest of the pathway. At this stage, diffusion occurs along the direction of flow.
- During expiration, the gas flow causes the oxygen molecules to drift away from the alveolar layer. Therefore, diffusion occurs in the direction opposite to the flow.

When considering all the above, we notice that the flow rate of oxygen into the alveolar layer cannot be constant over time. The amplitude of its fluctuations depends both on the morphology of the lung as well as on the pattern of respiration.

The diffusion rate of oxygen from the alveolar layer into the blood cycle depends both on the oxygen volume available in the alveoli, and, on the instantaneous physical dimensions of the alveoli. Therefore, the volume of oxygen that can penetrate into the pulmonary capillaries changes over time.

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Abstract

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II. METHODS

In order to simulate and quantify the dynamics of oxygen diffusion into the blood cycle, we developed a three-stage model. The first stage allows us to calculate the gas distribution within the different elements of the bronchial tree, for a given total lung volume and lung morphology. The second stage allows us to simulate diffusion within the lung tree and from the alveolar layer into the capillary system, per total lung volume. The third stage allows us to simulate the dynamics of oxygen diffusion into the pulmonary capillaries during the respiratory cycle.

A. First Stage

The first stage assumes a specific structure for the bronchial tree, including typical radius, length and wall-thickness of an average element in each generation, plus the typical elastic property of an average element in each generation [2,3]. This allows us to calculate the expansion of each element when placed in a negative pressure environment. This approach leads to a Volume/Pressure curve for each generation in the bronchial tree.

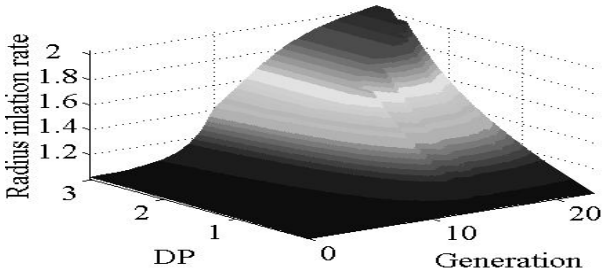

Fig 1: This figure describes the radial stretch of elements in different generations of the bronchial tree, due to a negative pressure environment, at 0-3 mmHg below pressure at the onset of inspirium (-3mmHg).

B. Second Stage

The second stage is dedicated to describing the process of oxygen diffusion from an alveolus into the pulmonary capillaries. When considering this diffusion process, we must consider the probability of an oxygen molecule to diffuse from its initial location towards the alveolar membrane, to cross the membrane, and then to diffuse along the rest of its way into the capillary environment. For a molecule that collides with the alveolar membrane, the probability to dissolve into the membrane depends on its solubility in the membrane [4]. The time dependence of the flux of molecules that collide with the membrane must therefore be taken into account. The equations disclose a dependence of the collision rate on the physical dimensions of the alveolus. Thus, the overall volume of oxygen, which diffuses from the alveoli into the pulmonary capillaries, depends on the total volume of gas in the alveoli.

This model assumes elongated alveoli characterized by the inner radius (R_{alv}). The capillaries are aligned along the longitudinal axis of the alveolus.

The expression for the volume of oxygen that diffuses from a single alveolus into a single capillary during a time interval Δt can be written as:

$$V_{O_2}(R_{alv},\Delta t)=\int_{t=0}^{t=\Delta t}\int_{r=0}^{r=2R_{alv}} V_{O_2}(r)F_1(t,r)F_2(r)F_3(\Delta t-t)\,dr\,dt \quad (1)$$

$V_{O_2}(r)$: is the volume of oxygen that was at distance r from the membrane at t=0.

$F_1(r,t)$: is the probability of a molecule that was at distance r from the membrane at t=0, to collide with the membrane at time t.

$$F_1(t,r)=\frac{\partial}{\partial t}\left[\int_{r'=r}^{\infty}\frac{1}{\sqrt{4\pi\ t\ D_{alv}}}e^{\left(\frac{-|r'|^2}{4t\ D_{alv}}\right)}d\ r'\right] \quad (2)$$

$F_2(r)$: For a molecule that has already diffused the distance r at time t towards the membrane, $F_2(r)$ is the probability to dissolve into the membrane. It is given by multiplying the solid angle for interaction Ω, and the oxygen solubility S_{O_2}.

$$F_2(r)=\Omega\cdot S_{O_2} \quad (3)$$

$F_3(\Delta t-t)$: is the probability of a molecule (that has dissolved into the membrane) to diffuse across the membrane into the capillary blood, during the remaining time interval $\Delta t-t$. R_{mem} is the thickness of the membrane separating the gas in the alveolus from the capillary blood.

$$F_3(t=\Delta t-t)=\int_{r=R_{mem}}^{\infty}\frac{1}{\sqrt{4\pi t\ D_{cap}}}e^{\left(\frac{-|r|^2}{4t\ D_{cap}}\right)}dr \quad (4)$$

D_{alv}, D_{cap}, stand for the O_2 diffusion coefficient in the media (alveoli and capillary respectively).

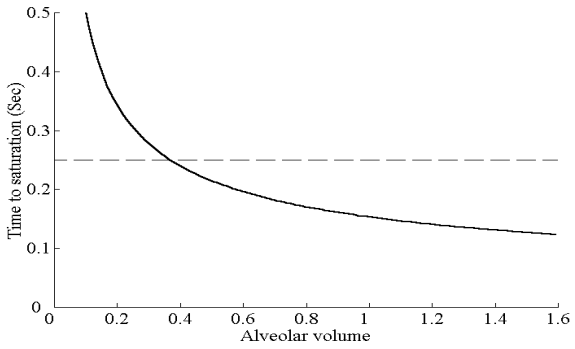

Fig 2: Describes the time required for sufficient oxygen to diffuse into the capillary blood in order to obtain saturation, as a function of the gas volume in the alveolus. The dashed line at 250msec stands for the time required to obtain saturation for Heart-Rate = 60bpm and Stroke Volume = 80cc.

The above approach is vital for this simulation because, during respiration, the total gas volume in the alveolar layer is modulated. Therefore the average volume of an alveolus fluctuates together with the width of alveolar volume distribution around the average volume. As a result, the basic conditions for oxygen diffusion into the blood vary as function of respiration.

C. Third Stage

The third stage simulates the dynamics of oxygen diffusion during the continuous process of respiration. We sample the respiratory signal (recorded with Respitrace). Then, from stage 1, we calculate the distribution of the total lung volume among all the different generations of the bronchial tree. Specifically, we calculate the total alveolar volume and the distribution of alveolar volume.

Here, we use the output from stage-2, to simulate oxygen diffusion both in the bronchial tree and between the alveoli and the capillaries. At this point we obtain a pO_2 distribution map for all elements in each generation of the bronchial tree, in alveoli of different volumes, and in the capillaries attached to each of these alveoli.

By using stage-1, we calculate the distribution of gas volume within the bronchial tree after Δt. We use a conversion matrix formalism in order to keep track of changes in the pO_2 map due to flow associated with the redistribution of the gas. This process is performed iteratively in one of two routes (see below), in order to simulate the effect on heart rate and blood saturation level.

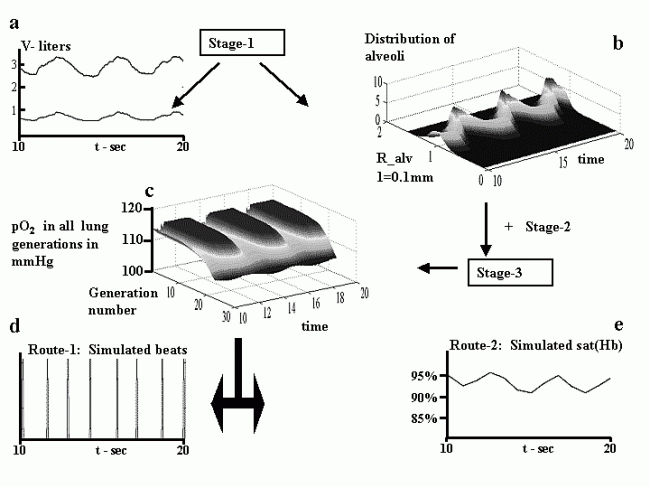

Fig 3: This figure illustrates the flow chart through the various steps of the model. **a)** top line: instantaneously measured respiratory signal and **a)** bottom line: calculated volume of alveolar gas, which stage-1 plots as a function of time. **b)** a plot of the alveolar size distribution as a function of time. Stage-3 uses the output of stages-1,2 to generates **(c)** a map of the pO_2 dynamics in the bronchial tree, and the total volume of oxygen that diffuses into the pulmonary capillaries. Choosing Route-1,(constant *sat*(Hb)) we use **(c)** to calculate the left ventricular filling rate and the estimated times of the heart-beats **(d)**, notice non equal intervals. Choosing Route-2 (constant flow) we use **(c)** to calculate **(e)** the average saturation level of the blood at each beat, note fluctuations in saturation level.

Route one: The first simulation option is to investigate what happens when we require that all the blood, that leaves the pulmonary capillaries, be saturated to a specific level (say 98%). We thus apply the simulation to calculate how the flow rate in the pulmonary capillaries should be adjusted in order to meet this requirement. By integrating the flow rate over all pulmonary capillaries, we calculate the left ventricular filling rate. After integrating over time, we calculate the filling volume. Once a volume of blood equivalent to the stroke volume has entered the left ventricle, we mark the time as an optional time to generate a heart beat. The left ventricle volume is reset to zero and we continue. This allows us to trace the fluctuations that may occur in the heart rate as a result of dynamically changing conditions for oxygen diffusion, and the requirement to maintain a constant *sat*(Hb) level in the left ventricle blood.

Route two: The second simulation option is to investigate what happens when we specify a constant flow rate of the blood in the pulmonary capillaries, or a periodic profile of flow rate during each beat-to-beat interval. Both options result in a constant heart rate and we use the simulation to follow the dynamics of *sat*(Hb) level in the blood as it leaves the pulmonary capillaries, and makes its way to the left ventricle.

III. Results

In simulations of both types, we investigate the model's behavior under different respiration patterns. Each respiration pattern is characterized by three parameters: Functional Residual Capacity (FRC), Tidal volume (TV) and the respiratory rate. Both types of simulations reflect the same behavior: the O_2 diffusion rate into the pulmonary capillaries is not constant over time, rather it modulates in high accordance to respiration. Modulations of beat-to-beat intervals are observed in the route-1 simulations, while modulations in the *sat*(Hb) level appear in route-2 simulations.

In this paper we will focus on results from route-1 simulations. For each simulation, the Stroke-Volume (SV) and the required saturation level are maintained constant. The results are characterized by 2 statistical parameters: mean heart rate (HR_mean) and standard deviation of the heart rate (HR_std), reflecting HR fluctuations.

When studying the model's behavior we notice that for a given respiration rate, as we increase FRC or TV values, HR_mean increases. The behavior of HR_std is more complicated. As FRC increases and TV is maintained, HR_std decreases. This agrees with the mechanism of respiration, since the average alveoli volume increases as the FRC increases. Therefore, more alveoli enjoy a higher diffusion rate for a larger portion of the respiratory cycle, and modulations in the total O_2 diffusion rate are milder.

When FRC is kept constant and TV is increased, the alveoli average volume undergoes stronger modulations during the respiration cycle. The portion of time that the total O_2 diffusion rate is relatively low increases. Therefore, modulations in beat-to-beat interval will increase. As TV continues to increase, the alveoli enjoy better ventilation, which compensates for O_2 losses in the alveoli and increases the total O_2 diffusion rate into the pulmonary capillaries. As a result, the HR_std decreases.

As can be expected, when the SV is increased a larger volume of oxygen is required. Therefore, if the respiratory pattern is maintained, mean heart rate must decrease. As a result, each beat covers a larger portion of the respiration cycle, and the differences in the total O_2 diffusion rate between different beats are milder. As a result, the HR_std decreases.

When studying our model at different respiration frequencies, the following can be noticed. For a low respiratory frequency (0.2Hz), lung ventilation is high. This allows an increase in mean heart rate accompanied by high HR_std (long periods of low mean alveoli volume). As respiration frequency increases, both the HR_mean and HR_std decrease, optimizing at ~0.32Hz. Further increase in respiration rate leads to a significant decrease in alveolar ventilation, causing both a decrease in HR_mean and an increase in HR_std.

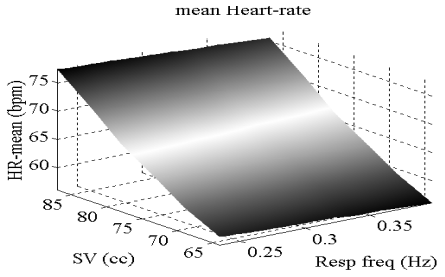

Fig 4: This figure shows the mean Heart Rate, as calculated from simulations with various respiration frequencies and Stroke Volumes. Notic, mean Heart Rate increases with SV and decreases with Respiration frequency.

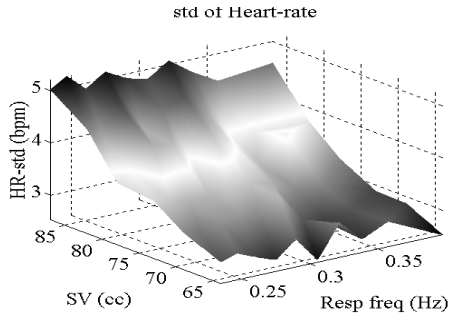

Fig 5: This figure shows the standard deviation of the Heart Rate, as calculated from simulations with various respiration frequencies and Stroke Volumes. Notice, HR fluctuations increase with SV, and are generally higher for low frequency respiration. For most SV values the increase in HR_std occurs at ~0.3 Hz.

When applying different SV values to these simulations of varying respiratory frequency and constant FRC and TV, the model's behavior follows the changes noticed when applying different SV values to the simulations of constant respiratory frequency and varying FRC and TV described above. As SV increases, both HR_mean and HR_std decrease.

IV. Discussion

The results of these simulations indicate that the mechanism of respiration causes significant changes in the diffusion conditions in the alveolus-capillary micro-environment. These changes originate from the changes in diffusion efficiency due to the mechanical stretch of the alveolus and from the changes in the ventilation rate of both the entire lung and the alveolar layer. The stretch allows a higher collision rate of oxygen molecules with the membrane, and also an increase in membrane permeability. To this we must add the cumulative deteriorating affect of the oxygen diffusion to the capillaries on the pO_2 level in the alveoli. This effect can be enhanced when alveolar ventilation is poor, or reduced for high alveolar ventilation.

As TV increases and FRC decreases, the changes in alveolar volume distribution between end-inspirium and end-expirium increase. Therefore, the amplitude of modulations will increase. When respiratory rate is reduced, alveolar ventilation becomes more uniform through the respiration cycle and the amplitude of modulations decreases.

There seems to be a dynamic threshold for the oxygen flux into the blood. If we wish to increase the oxygen flux, compensation must be provided by either adjusting respiration pattern or by increasing heart rate fluctuations. If the heart rate modulations are limited, under some respiratory patterns fluctuations of *sat*(Hb) may be unavoidable.

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