A Model of the Maldistribution of Ventilation and Perfusion, in the Lungs of Heart Failure Patients

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Abstract: The use of mechanical ventilators is widespread within Intensive Care Units, both in patients with normal respiratory function (e.g., post-operative patients) and in subjects with pathologic conditions influencing ventilation mechanics. In particular heart failure, the decreased capacity of the heart to pump blood through the systemic and pulmonary circulation, is clinically known to adversely affect ventilation. Depending on gravity, different areas of the lungs receive different quotas of the pulmonary blood flow, and their alveoli are ventilated to different degrees: the ventilation/perfusion ratio (V/Q) captures this relationship and is normally higher at the apexes and lower at the bases of the lungs (normal distribution of the ratio). Maldistribution of V/Q occurs when these differences are accentuated, and leads to inefficient gas exchange and diminished arterial oxygen saturation. In this work, we introduce a mathematical model of mechanical ventilation and pulmonary blood perfusion, incorporating a representation of the lungs by vertically stacked functional layers. Numerical simulations readily show how progressive degrees of heart pump decompensation are associated with worsening distribution of the ventilation/perfusion ratio, even in the absence of other complicating factors, such as pulmonary edema.

Keywords: heart failure; mathematical modeling; mechanical ventilation; differential equations; pathophysiology

1 Introduction

Cardiac failure and ventilation-perfusion ratio (V/Q) maldistribution are two common and interconnected problems in critical care [1-9]. Cardiac failure is the inability of the heart to pump enough blood to meet the body's needs, while V/Q ratio maldistribution is a severe mismatch between ventilation and perfusion in the lungs. While a certain degree of V/Q distribution is physiologic, since lung apexes

are relatively more ventilated and less perfused than lung bases [10] [11], an exacerbation of the mismatch may lead to dangerous levels of (arterial) hypoxemia (low oxygen levels in blood) and hypercapnia (high carbon dioxide levels in blood). While it is a common perception among Intensive Care professionals that cardiac failure may worsen V/Q distribution, there are no theoretical, quantitative models, so far as we know, supporting our understanding of the mechanisms responsible for this phenomenon and of their relative importance in explaining it.

Cardiac failure can lead to increased V/Q ratio maldistribution in a number of ways. First of all, reduced cardiac output can lead to pulmonary edema [12], with attendant thickening of the air-to-blood barrier (bronchial and alveolar walls), and this can impair the effectiveness of ventilation both by making it more difficult for air to flow through bronchi and by reducing gaseous diffusion from air to blood and vice versa. Reduced cardiac output can also lead to hypoxic pulmonary vasoconstriction (HPV), a narrowing of the blood vessels in the lungs [13]. This is a physiologic response, which to a certain degree usefully redirects blood flow from worse- to better-ventilated areas of the lungs; however, in case of reduced overall cardiac output, this mechanism may actually make some areas of the lungs essentially non-functional, making recovery (e.g., following mechanical ventilation) more problematic. Patients with cardiac failure are also at increased risk for developing ARDS (Acute Respiratory Distress Syndrome), a severe form of respiratory failure characterized lung stiffness, increased work of ventilation, V/Q mismatch and hypoxemia [14] [15]. ARDS patients are also more difficult to ventilate mechanically, due to decreased lung compliance necessitating higher inspiratory pressures, with increased risk of Ventilator-Induced Lung Injury (VILI) [16-18]. The clinical picture is further complicated by the fact that V/Q ratio maldistribution may in turn also lead to cardiac failure, either by increasing pulmonary vascular resistances (via HPV or edema), decreasing oxygen delivery to the myocardium, or increasing systemic resistances to maintain arterial blood pressure in the face of decreasing cardiac output: a multi-factorial vicious circle can thus be established, which may lead to irreversible cardiac failure and death [19] [20].

While the above mechanisms are all recognized, it remains to be seen whether reduced cardiac output, in and by itself, without attendant edema or HPV, may worsen V/Q distribution. A direct investigation in patients is difficult to perform: V/Q ratio may be measured with the Multiple Inert Gas Elimination Technique [21] or by performing a two-phase, radioactive contrast pulmonary ventilation/perfusion scan [22], but these are lengthy and expensive experimental procedures, ill-suited to the investigation of the effects of progressive pump failure on V/Q distribution. The previously mentioned problems frequently occur in any area of medicine, which motivates medical field experts to team up with mathematicians and engineers so as to investigate the problem in-silico exploring different virtual scenarios. In this way, recourse to experimental procedures is minimized, thus decreasing cost, suffering and risk to the patient. Many other Authors have already addressed similar issues with the use of mathematical solutions [28] [29].

The purpose of the present work is thus that of detailing the effect of a simple decrease in cardiac output on ventilation/perfusion ratio distribution in patients undergoing mechanical ventilation, by using a suitable mathematical model of lung ventilation and perfusion. A digital twin of a subject's lungs, developed on the basis of this mathematical model, could be used to carry out in-silico simulations predicting the effects of different therapeutic maneuvers, thus allowing medical doctors to plan and apply personalized treatments [23] [24].

The paper is organized as follows. In Section 2 the mathematical model (subsection 2.1) of pulmonary ventilation of a layered lung is introduced. Subsection 2.2 reports the conditions and parameter values used in the numerical simulations, while Section 3 presents the simulation results. The Discussion section 4 synthesizes and situates the results obtained within a wider reference frame, and in Section 5, conclusions are drawn, as to the utility of the work performed and the possible future directions of investigation.

2 Methods

2.1 Lung Mathematical Model

In this work, a simple mathematical model which describes the mechanics of pulmonary ventilation [25] is adapted for taking into account the description of ventilation/perfusion ratio (V/Q_{blood} [#]; henceforth we will denote with the symbol # a pure number or dimensionless quantity) and evaluate its changes in subjects with cardiac failure. In particular lung Alveoli are considered as a single compartment although composed of H layers, each with its own Compliance (C_{alv}, [*L/mmHg*]) and airway Resistance (R_{alv}, [$mmHg \cdot s/L$]).

Fig. 1 shows a schematic representation of the modeled anatomy. The continuous-time model equations, already described in [25], are adapted to consider the stratified alveolar compartment and are reported below:

$$\frac{dV(t)}{dt} = \frac{d\sum_{h=1}^{H} V_h(t)}{dt} = \sum_{h=1}^{H} Q_h(t) = Q(t) \tag{1}$$

$$Q(t) = \frac{P_{mou}(t) - P_{alv}(t)}{\sum_{h=1}^{H} R_h} \tag{2}$$

$$P_{alv}(t) = \frac{\sum_{h=1}^{H} V_h(t)}{\sum_{h=1}^{H} C_h} + P_{ercw}(t) \tag{3}$$

$$V_{alv}(t) = \sum_{h=1}^{H} V_h(t) - V_{rds} \tag{4}$$

$$P_{ercw}(t) = -\frac{\sum_{h=1}^{H} FRC_h(t)}{\sum_{h=1}^{H} C_h(t)} \tag{5}$$

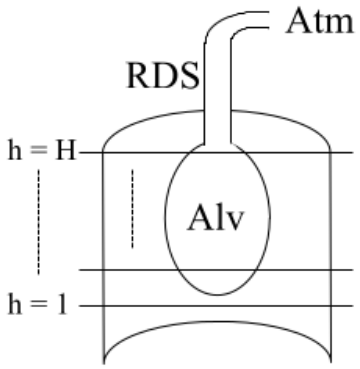

Figure 1

Schematic representation of the modeled anatomy. The lungs are represented as a single compartment (Alv) connected to the environment (ventilator) through the incompressible channel of the Respiratory Dead Space (RDS). In this model formulation the alveolar compartment is divided into H layers, starting from the base towards the apex of the lungs

with V(0) = FRC and h=1,..H where H is the number of layers into which the lungs are divided. In fact, considering H = 1 we recover the equations of the non-stratified model [25].

A brief explanation of the model, with references to physiology, is provided below. In Eq. (1), V(t) ([L]) is the lung volume. Its variation over time is due to the air flow that the subject alternately inhales and exhales and, in this model formulation, is evaluated as the sum of the volumes of the individual lung sections.

Q(t) ([L/s]) in Eq. (2) is the total lung respiratory air flow and grows linearly with the pressure gradient between mouth P_{mou} ([$mmHg$]) and alveoli P_{alv} ([$mmHg$]), while it is inversely proportional to the airway resistance $R_{alv} = \sum_{h=1}^{H} R_h$ ([$mmHg\ s/L$]).

Pmou(t) ([$mmHg$]) is the pressure at the mouth exerted by an external ventilator and represents a forcing function of time t that can in principle be chosen arbitrarily:

$$P_{mou}(t) = \sum_{k=0}^{+\infty} P_{mou}^{max}(k)\ p(t - (k - \varphi_v)t_v), \quad \forall t \geq 0 \tag{6}$$

where k is the index of respiratory cycle, $t_v \geq 2t_{f2}$ is the period of the wave and $\varphi_v \in [0,1)$ is relative phase shift. $P_{mou}^{max}(k)$ is the maximal pressure value and is delivered over an interval of duration ($t_{f2} - t_{f1}$). Each wave is expressed as the product of a maximal pressure at the mouth $P_{mou}^{max}(k)$ and the elementary rectangular waveform:

$$p(t) = \begin{cases} 1 & t_{f1} \leq t < t_{f2} \\ 0 & otherwise \end{cases}$$

For this version of the model, therefore, a very simple pressure waveform (rectangular) with Zero End-Expiratory Pressure (ZEEP) has been considered.

In Eq. (3) $P_{alv}(t)$ ($[mmHg]$) represents the alveolar pressure and it is defined as the sum of two contributions, the ratio between lung air volume V ($[L]$) and lung compliance $C_{alv} = \sum_{h=1}^{H} C_h$ ($[L/mmHg]$) plus the (negative) pressure generated by the elastic recoil of the chest wall P_{ercw} ($[mmHg]$).

In Eq. (4), $V_{alv}(t)$ ($[L]$) is the alveolar volume and represents the volume that is actually involved in the exchange of air. It is evaluated as the difference between the total lung volume V(t) and the respiratory dead space volume V_{rds}.

$P_{ercw}(t)$ ([mmHg]) is the elastic recoil pressure of the chest wall and, in a subject without own respiratory drift it is evaluated as minus the inverse of the ratio between total functional residual capacity $FRC_{tot} = \sum_{h=1}^{H} FRC_h$ ($[L]$) and lung compliance $C_{alv} = \sum_{h=1}^{H} C_h$ (Eq. (5)). In other words, P_{ercw} is calculated to exactly balance the elastic recoil of the lungs themselves, thus maintaining a lung volume of FRC_{tot} at end-expiration, in the absence of external pressure delivery or spontaneous inspiratory effort.

In the present simple version of the model, we do not take into account the variation of P_{ercw} determined by changes of the geometry of the chest wall and keep it constant throughout the respiratory cycle. In the patient with insufficient, but autonomous, breathing additional exogenous ventilation can be possibly added synchronously with existing flow (assisted ventilation modality [26]).

In order to consider pulmonary respiration (the gas exchanges that occur between alveolar air and pulmonary capillaries) it is necessary to consider pulmonary blood perfusion (henceforth simply "perfusion") [27]. If we focus our attention on the pulmonary circulation (but the discussion also extends to the systemic one) we know that cardiac output (Q_{blood}) is equal to the ratio of the pressure variation across (pulmonary) arteries and veins (ΔP_{pulm}) over the resistance that blood encounters (resistance of the pulmonary circulation, R_{circ}). In this way we can evaluate the flows (Q_h) and resistances (R_h) in the individual layers knowing that:

$$G_H = \sum_{h=1}^{H} G_h \tag{7}$$

where G_H is the total conductance of the alveoli, G_h is the conductance in the h^{th} layer and

$$G_h = \overline{G_H}\left[1 + \lambda\left(h - \bar{h}\right)\right] \tag{8}$$

The term $\overline{G_H}$ represent the average conductance evaluated as $\overline{G_H} = \frac{G_H}{H}$, whereas λ is the parameter which indicates the slope of the conductance curve, under the constraint that $\lambda(h - \bar{h}) < 1$. The parameter $\bar{h} = \frac{1}{2}H + \frac{1}{2}$ indicates the middle or central layer.

2.2 Numerical Implementation and Simulations

Numerical simulations were performed in MATLAB and Table 1 contains all the model parameters used, along with their description and units of measurement. We considered a situation of controlled ventilation, with applied pressure $P_{mou}^{max}(k) = 3.777$ ($[cmH_2O]$), $P_{eff}^{max} = 0, t_v = 3$ ($[sec]$) and $\varphi_v = 0$, according to the results shown in [25]. For a healthy subject Q_{blood} = 6 [*L/min*] and ΔP_{pulm} = 15 [*mmHg*] were considered. The resistance of the pulmonary circulation, R_{circ}, is set equal to 2.5 [*mmHg sec/L*].

Table 2 reports the numerical values used in our simulation for $C_{alv}, G_{alv} = \frac{1}{R_{alv}}$ and G_h in each layer. Note that: $\sum_{h=1}^{H} C_{alv,h} = C_{alv}$, $\sum_{h=1}^{H} G_{alv,h} = G_{alv} = \frac{1}{R_{alv}}$ and $\sum_{h=1}^{H} G_h = G_H$.

With the aim of showing model behavior also in pathological conditions, in particular in a heart failure subject, the parameter ΔP_{pulm} has been de creased by 50% and the ventilation/perfusion ratio has been evaluated in each layer, both in physiological and pathological conditions. Simulations results are reported in 3.

Table 1

List of the parameter's values used in the simulation, together with their descriptions and units of measurements

Parameter	**Description**	**Unit**	**Value**
H	number of layers	#	9
FRC_{tot}	functional residual capacity	L	2
C_{alv}	total alveolar compliance	L/mmHg	0.1351
R_{alv}	total alveolar resistance	mmHg s/L	32.038
P_{mou}^{max}	ventilator maximal pressure	mmHg	3.777
t_v	ventilation time	s	3
t_{f1}	time instant of rise	s	0.2
t_{f2}	time instant of downhill	s	0.533
G_H	total conductance of pulmonary circulation	L/(s mmHg)	0.4
V_{rds}	dead space volume	L	0.25
$\bar{h}$	middle layer	#	5
λ	slope parameter	#	0.22

Table 1

List of the parameter's values used in the simulation, together with their descriptions and units of measurements

	$C_{alv,h}$	$G_{alv,h}$	G_h
h_1	0.0229	0.0050	0.0836
h_2	0.0228	0.0048	0.0738

h_3	0.0227	0.0044	0.0640
h_4	0.0226	0.0041	0.0542
h_5	0.0131	0.0036	0.0444
h_6	0.0130	0.0032	0.03467
h_7	0.0090	0.0025	0.0249
h_8	0.0067	0.0020	0.0151
h_9	0.0023	0.0017	0.0053

3 Results

In this section, we report the results of some simulations of the model, as defined in the previous sections. In the first simulation, we consider the case of a healthy subject and evaluate Ventilation, Perfusion and V/Q ratio in the individual layers (Fig. 2 in blue, Fig. 3 and Fig. 4 in red). In the second simulation, we study the case of subject with cardiac failure (cardiac output reduced to 50% of normal) and we show the results in the same graphs (Fig. 2, Fig. 3 and Fig. 4 in blue). In both simulations we consider pressure-controlled ventilation with the same pattern and with the same volumes, therefore the two curves of ventilation (healthy and diseased) shown in Figure 2 are superimposed. The following figures present the model simulation with parameters value reported in Table 1 and Table 2. In red are shown the model simulations for a healthy subject, in blue are reported the model results for a simulated subject with cardiac failure.

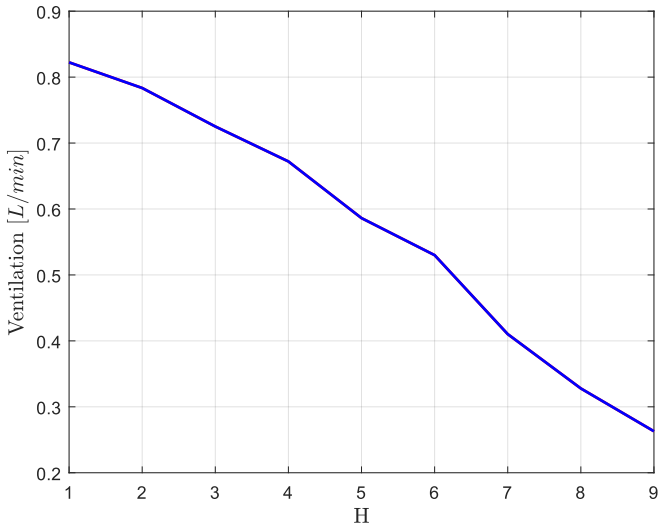

Figure 2

Ventilation in each layer: since ventilation is the same in both healthy and diseased states the two curves overlap

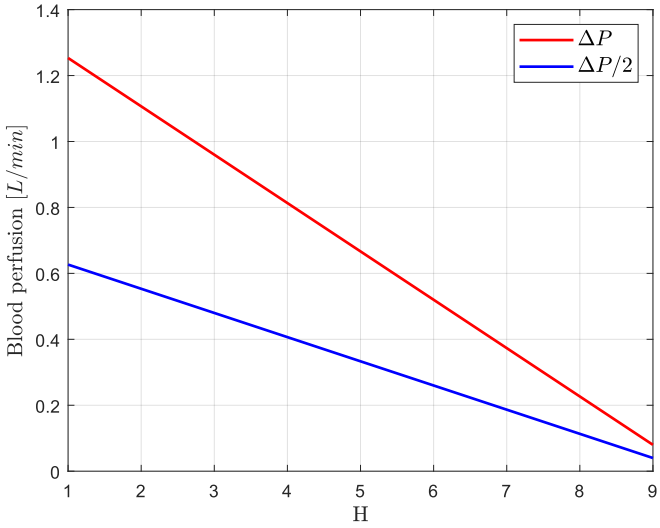

Figure 3
The distribution of perfusion (Q_{blood}) in each layer

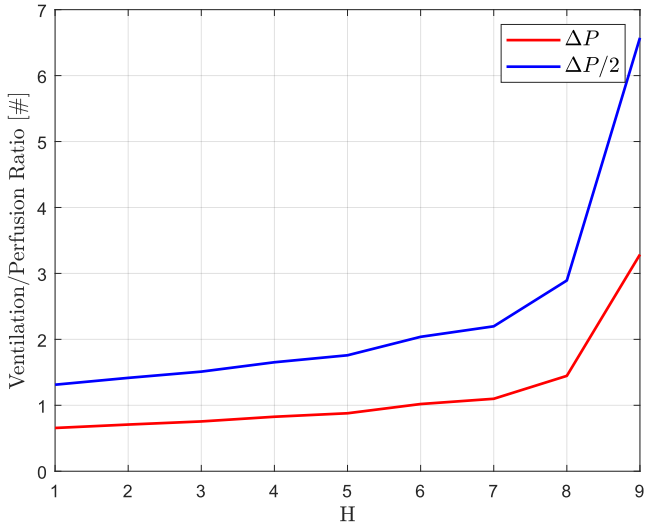

Figure 4
Distribution of the V/Q_{blood} ratio over the different layers

4 Discussion

Caring for cardiac failure patients in a Critical Care Recovery Unit setting (CCRU) is a difficult task, often requiring continuous attention to mechanical ventilation support. In this context, a quantitative, formalized understanding of the factors influencing the effectiveness of gas exchange acquires great importance. The present work is an initial attempt to formalize the impact of the reduction of cardiac output, the hallmark of cardiac failure, on the distribution of the ventilation/perfusion ratio. We extend a previous mathematical model of lung mechanics [25], introducing gravity-induced stratification of ventilation and perfusion. In this new model formulation, the mechanics of pulmonary circulation is also introduced in terms of arteriolar conductance. This allows us to calculate the values of V/Q ratio in different lung layers as depending on cardiac output. The chosen model is essentially the simplest mathematical representation of a lung admitting several layers (basis to apex), where blood and air flows are both independently considered, and where gradients of lung compliance and vascular resistance over the layers are such as to reproduce the pattern of ventilation and blood flow distribution reported in the literature [10], as shown in Figure 3.

The fundamental result obtained can be seen in Figures 2, 3 and 4: everything else remaining the same (compliances, resistances, airflow), when cardiac output is reduced by 50% (from 5 to 2.5 [*L/min*]) ventilation does not change (Fig. 2), but, since perfusion decreases (Fig. 3), ventilation becomes proportionally larger and the ventilation/perfusion ratio increases overall, but more so at the apexes than at the bases (Fig. 4). A larger variation of the V/Q ratio is therefore produced. A single number captures the entity of the phenomenon: the standard deviation SDV/Q of the ventilation/perfusion ratio across the lung layers. In the "normal" (healthy) situation (cardiac output 5 [*L/min*]) this is computed with the model as SDV/Q = 0.824 [*L/min*], while in the reduced cardiac output condition (2.5 [*L/min*]) it becomes SDV/Q = 1.648 [*L/min*]. In other words, to a halving of cardiac output there corresponds (theoretically) a doubling of the standard deviation of the V/Q ratio over the lung.

This result reflects a fundamental mechanical, structural configuration of the lungs and does not necessitate aggravating conditions or pathologic reactions: these, when present, may well further complicate the clinical picture. The current model analysis is in fact just a first step in trying to understand the complex of interacting perturbations and adjustments, which take place in the lungs of the acutely ill cardiac patient.

Future work will extend and improve the mathematical model used: the goal is to make it possible to evaluate operable strategies in setting mechanical ventilator parameters so as to attenuate the severity of the ventilation/perfusion ratio maldistribution in the lungs of these patients and the resulting insufficient oxygen transport to tissues.

Conclusions

An improved model of mechanical ventilation and pulmonary perfusion allows numerical simulations, showing that a decrease in cardiac output, consistent with what is observed in heart failure, can determine on its own, without further complicating factors, a worsening of the distribution of the ventilation/perfusion ratio in the lungs. Future research efforts will formalize an improved version of the model, incorporating gas exchange mechanisms, in order to assess quantitatively, the impact of cardiac failure on arterial saturation.

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