A mathematical model of respiration under protective ventilation and extracorporeal CO2 removal therapy

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1. Introduction

Nowadays, acute respiratory distress syndrome (ARDS) remains life threatening despite new strategies in mechanical ventilations [1,2,3] and, to limit ventilation induced lung injury (VILI) [4], protective ventilation is recommended for patients with ARDS. Protective ventilation is characterized by low tidal volumes (6ml/kg) and a plateau pressure below 30 cmH_2O. However, such a ventilation can induce hypercapnic acidosis and be deleterious for the right ventricle by increasing pulmonary hypertension [5,6]. Therefore, hypercapnic acidosis must be strictly controlled by eliminating the excess CO_2. This control can be done in intensive care units (ICU) using an extracorporeal CO_2 removal device ($ECCO_2RD$, see Figure 1).

The aim of the present study is to build a mathematical model of the respiratory system connected to an $ECCO_2RD$ to optimize the gas exchanges efficiency. The model must be simple enough to provide rapid solutions and to estimate specific parameters from available clinical data. But it also must be complex enough to be able to simulate the respiratory system when protective ventilation is used and when this system is assisted by an $ECCO_2RD$.

We will first describe the mathematical model. Then experiments carried out on pigs will be used to validate the approach and the agreement between the model and experimental data will be discussed.

2. Materials and Methods

In this study, the respiratory system linked to an $ECCO_2RD$ is reduced to a small number of "compartments" (*lumped parameter model*). We consider two compartments for the respiratory system: the lung and the tissues. In addition, a third compartment is added to model the $ECCO_2RD$ (see Figure 1).

Our mathematical model of pulmonary gas exchanges and tissues gas exchanges is based on the work of Batzel et al. [7]. Transport delays in the blood circulation are taken into account and the hypothesis of equilibrium between alveoli and pulmonary capillaries concentrations is taken for granted. To include pulmonary insufficiencies in our model, additional parameters and additional equations must be considered. Some authors describe pulmonary gas exchanges abnormalities by dividing the lung into 2 compartments to model ventilation/perfusion mismatch [8,9]. Since the identification of the parameters of these two compartments is not easy (and even impossible in our case with the available experimental data), we will use a simpler approach. To describe the global quality of gas exchanges and to allow the modeling of lung injuries in a simple way, we will consider a pulmonary shunt, characterized by the fraction f_S of blood flow which does not participate in the gas exchange, and the dead volume V_D.

The $ECCO_2RD$ can be considered as a second lung compartment which removes the CO_2 from the blood and which also oxygenates the blood. The device takes a fraction of the systemic blood flow in the inferior vena cava and rejects the decarboxylated blood in the right atrium (see Figure 1). The dynamics of gas exchanges along the synthetic membrane is different from that in the lung. The exchange surface in the $ECCO_2RD$ is indeed much smaller than in the lungs and the hypothesis of equilibrium between the gas and the blood is not valid. Therefore, the diffusion of O_2 and CO_2

between the gas and the blood across the synthetic membrane has to be modeled [10]. In this study, we consider a 1-D model, with air and gas flows in opposite directions (see for instance [11]).

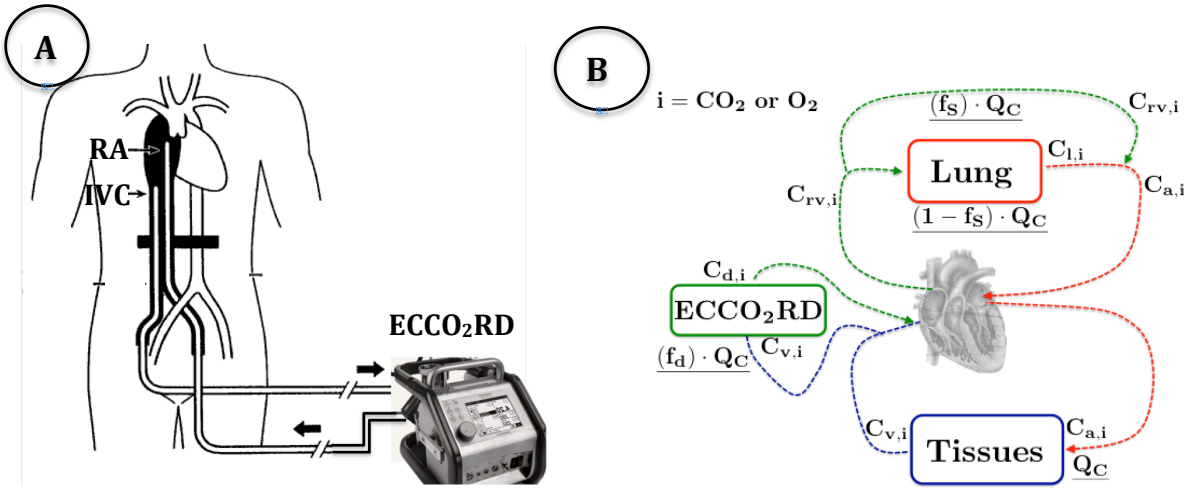

Figure 1. (A) Patient assisted by an $ECCO_2RD$ (Figure adapted from M.J. Murray and D.J. Cook [12]). The abbreviations RA and IVC mean respectively the right atrium and the inferior vena cava. (B) The three compartments of our model. The symbols f_S and f_d are respectively the pulmonary shunt fraction and the fraction of cardiac blood flow (Q_C) which crosses the $ECCO_2RD$. The symbols $C_{a,i}$, $C_{v,i}$, $C_{d,i}$, $C_{rv,i}$ and $C_{l,i}$ denote respectively the blood concentrations for component i in arteries, in veins, after the $ECCO_2RD$, in the right ventricule and in the lung.

The blood chemistry model proposed by Batzel et al. [7] is not valid in our case since the CO_2 partial pressure can vary very significantly, especially when protective ventilation is used and when the $ECCO_2RD$ is switched on. These variations can influence the pH in blood plasma, which then modifies the O_2 haemoglobin saturation curve. To take this into account, we use the relation between O_2 concentration and O_2 partial pressure following the work of Grodins et al. [13]. The relations between CO_2 concentration, pH in plasma and CO_2 partial pressure are based on the work of Trueb et al. [14].

To validate our model, experiments were carried out on 6 pigs, with the approval of the Ethics Committee of the Medical Faculty of the University of Liège. At the beginning of the experiment, after the anesthesia and the intubation of the pig, and a 30 min stabilization period, all the parameters were measured (cardiac blood flow, venous and arterial blood concentrations like O_2, CO_2 and H^+ and parameters fixed by the ventilator) defining our baseline situation. From this baseline situation, severe hypercapnic acidosis was induced thanks to about 40 min of protective ventilation with very low tidal volumes. Then the extracorporeal CO_2 removal device (a PALP Maquet® device is used) was switched on to decarboxylate the blood. The gas flow through the device was set to 10 l/min, while the blood flow was progressively increased from 200 ml/min, to 400 ml/min and finally to 600 ml/min. Each flow was kept constant for about 45 min. Then the decarboxylation process was stopped by fixing the gas flow to 0 ml/min (note that in order to avoid clots formation, the blood flow was kept at 200 ml/min). The cardiac blood flow was measured with thermodilution technique (PiCCO®, Pulsion, Germany) and also with an admittance pressure-volume catheter (Transonic, USA). Tidal volume, PEEP, $F_{I,O2}$, respiratory frequency and driving pressure were fixed by the ventilator (Engström Carestation®). Arterial and venous blood samples were analyzed with a RapidPoint500® (Siemens, Germany) during baseline situation, after protective ventilation and during the CO_2 removal procedure. Additional blood samples extracted from the inlet and outlet cannulas were also analyzed after switching on the $ECCO_2RD$.

The two parameters f_S and V_D, which allow characterizing the quality of gas exchanges, are fitted with experimental data. More details on this fitting will be discussed later on. Finally the CO_2 production (MR_{CO2}) by metabolism can be estimated by:

$$MR_{CO2} = Q_c\,(C_{v,CO2} - C_{a,CO2}), \tag{6}$$

where Q_C is the cardiac output, while $C_{v,CO2}$ and $C_{a,CO2}$ are the total venous and arterial CO_2 concentrations respectively. The O_2 consumption (MR_{O2}) can be determined similarly. These estimated values are kept constant during the baseline situation and during protective ventilation. However, when the $ECCO_2RD$ is switched on, the temperature decreases significantly (for all pigs, the temperature falls by about 4°C between the beginning and the end of the extracorporeal CO_2 removal therapy) and MR_{O2} and MR_{CO2} vary with the temperature. Therefore, MR_{CO2} and MR_{O2} decrease with the temperature in our simulations according to a rate of 6 $\bullet 10^{-3}$ l/min/°C, which was experimentally evaluated. The other parameters of the mathematical model are mainly direct experimental measurements (cardiac blood flow, venous and arterial blood concentrations like O_2, CO_2 and H^+ and parameters fixed by the ventilator).

3. Results

Our results are similar for the 6 pigs. The numerical simulation of the model allows determining the O_2 and CO_2 partial pressures (PO_2 and PCO_2) evolutions at different locations of the respiratory system and for the different stages of the experimental procedure presented before. Our results are similar for the 6 pigs and the corresponding results for pig 5 are presented in Figure 2.

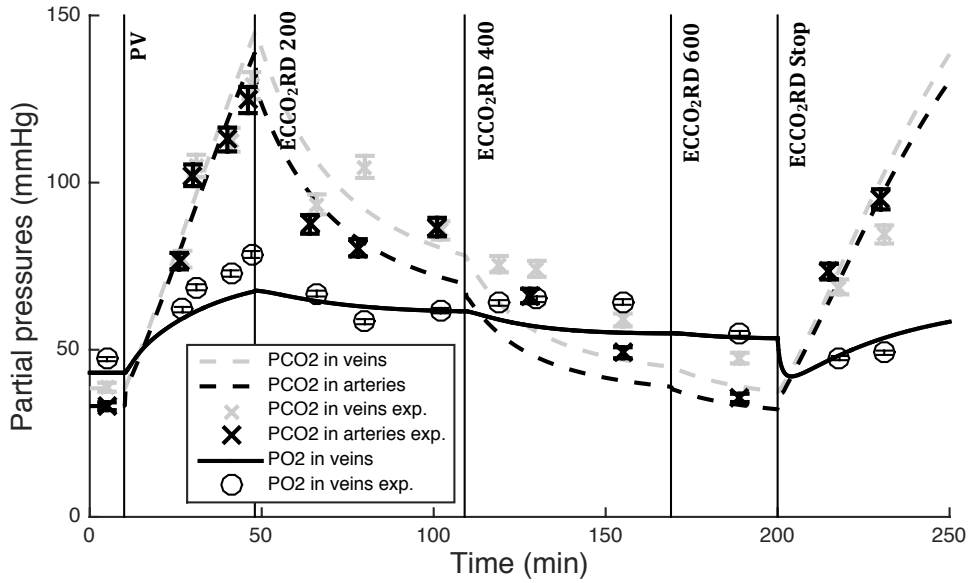

Figure 2: Time evolutions of O_2 and CO_2 partial pressures. The vertical lines indicate the beginning of the different phases of the experiment (PV: start of protective ventilation; $ECCO_2RD$ 200: flow of 200 ml/min in the CO2 removal device; $ECCO_2RD$ 400: flow of 400 ml/min in the CO2 removal device; $ECCO_2RD$ 600: flow of 600 ml/min in the CO2 removal device and $ECCO_2RD$ Stop: the $ECCO_2RD$ is switched off). The solid line shows the O2 partial pressure evolution in veins and the circles show the corresponding experimental data. The dashed lines show the CO2 partial pressures evolutions in arteries and in veins. The crosses show the corresponding experimental data.

4. Discussion and Conclusions

Figure 2 shows good agreement between the model predictions and the experimental data. It is worth stressing that several different experimental situations such as a protective ventilation and an extracorporeal CO_2 removal therapy with different blood flows across the device are considered with a unique model and that the time window of the simulations is also rather large. This thus provides a

strong validation of our approach. Several additional remarks can be done about these results. First, one can observe in Figure 2 the large increase of CO_2 partial pressure in veins and in arteries when the protective ventilation is introduced. The figure also shows clearly that the system hasn't reached a stabilized state after 40 min of protective ventilation. For this reason, it is a delicate process to determine the values of the two parameters f_S and V_D during this state because of the unsteady behaviour. The parameter f_S is assumed to be constant for the whole simulation, but the same hypothesis cannot be introduced for the dead volume V_D. Indeed, when the protective ventilation is introduced, the tidal volume is reduced, which is directly related to the dead volume V_D. Consequently, as a first step, the two parameters f_S and V_D are estimated during steady baseline situation. Then, parameter V_D must be reassessed to fit experimental data during the protective ventilation and the obtained value is kept for the rest of the simulation. It is interesting to stress that very large values of V_D are found: 70% of the tidal volume during baseline situation and 85% of the tidal volume during protective ventilation. The origin of these large values is the dead volume of the ventilator which is quite large due to additional pipes and sensors for gas analysis.

In this work, we have built a mathematical model of the respiratory system assisted by an extracorporeal CO_2 removal device ($ECCO_2RD$) and the predictions of the model are in good agreement with experimental data corresponding to a rather complex situation (time evolution during protective ventilation and for different settings of the $ECCO_2RD$). The model requires a detailed description of blood chemistry, a precise model of gas exchanges in the $ECCO_2RD$ and a careful evaluation of the dead volume. It was also necessary to take into account the temperature dependence of metabolism and a detailed non-stationary modeling was also needed (e.g. transport delays in the blood circulation are taken into account).

In future works, the model will also be used to predict the behavior of patients with pulmonary insufficiencies for which protective ventilation and an $ECCO_2RD$ are used. We hope that our model will help understanding the mechanisms of assisted ventilation and provide clinicians with a new tool allowing the optimization of care in ICU.

5. References

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