Noname manuscript No.
(will be inserted by the editor)

Mathematical modeling of extracorporeal CO_2 removal therapy

A validation carried out on 10 pigs

Simon Habran · Thomas Desaive · Philippe Morimont · Bernard Lambermont · Pierre Dauby

the date of receipt and acceptance should be inserted later

Abstract The Extracorporeal CO_2 removal device ($ECCO_2RD$) is used in clinics to treat patients suffering from respiratory failures like acute respiratory distress syndrome (ARDS) or chronic obstructive pulmonary disease (COPD). The aim of this device is to decarboxylate blood externally with low blood flow. A mathematical model is proposed to describe protective ventilation, ARDS and an extracorporeal CO_2 removal therapy ($ECCO_2RT$). The simulations are compared with experimental data carried out on 10 pigs. The results show a good agreement between the mathematical simulations and the experimental data, which provides a nice validation of the model. This model is thus able to predict the decrease of PCO_2 during $ECCO_2RT$ for different blood flows across the extracorporeal lung support.

Keywords Patient-Specific Modeling · Critical care · Hypercapnia · Extracorporeal lung support

S. Habran received his Master of Science Degree in Chemical Engineering and Material Science from the University of Liège, in 2014. He is currently a PhD student at the GIGA - In Silico Medicine research group, Liège (Belgium).

T. Desaive is a Senior Research Fellow at the University of Liege in Bio-Engineering and Director of their GIGA In Silico Medicine research unit. He specialises in cardiovascular, pulmonary and metabolic system modeling and experiments.

P. Morimont is Cardiologist and Critical Care Specialist. He works at the University Hospital of Liège since 2001. He received his Ph.D. in Hemodynamics at the GIGA-Cardiovascular Sciences of the University of Liège in 2012.

B. Lambermont is medical doctor specialized in internal medicine and intensive care. He did his PhD in 1998. Currently he is working as Professor of clinics and head of medical ICU at the University Hospital of Liege, Belgium.

P. C. Dauby is professor of mechanics and bioengineering at the University of Liège. He is a member of the GIGA-In silico medicine research group.

Simon Habran
University of Liege, GIGA - In Silico Medicine, Belgium
E-mail: simon.habran@ulg.ac.be

Thomas Desaive · Philippe Morimont · Pierre Dauby
University of Liege, GIGA - In Silico Medicine, Belgium

Bernard Lambermont
University of Liege, GIGA - Cardiovascular Sciences, Belgium

1 Introduction

Acute Respiratory Distress Syndrome (ARDS) is still life threatening despite new strategies in mechanical ventilations [28,18,8]. Mortality and morbidity of chronic obstructive pulmonary disease (COPD) are also considerable [34,7]. For moderate ARDS ($Pa_{O_2}/F_{I,O2} > 100$ mmHg [10], where Pa_{O_2} is the arterial partial pressure in O_2 and $F_{I,O2}$ is the inspired oxygen fraction) or COPD, a small extracorporeal lung support (ECLS), called the extracorporeal CO_2 removal device ($ECCO_2RD$), can be used [23,4,9,33,1,32] (see Fig. 1). The aim of such a device is to decrease the CO_2 partial pressure without being too invasive, while the effect on oxygenation remains very low with this configuration. The main difference between an $ECCO_2RD$ and a larger ECLS used in veno-venous extracorporeal membrane oxygenation (vv-ECMO) is the volume of the gas

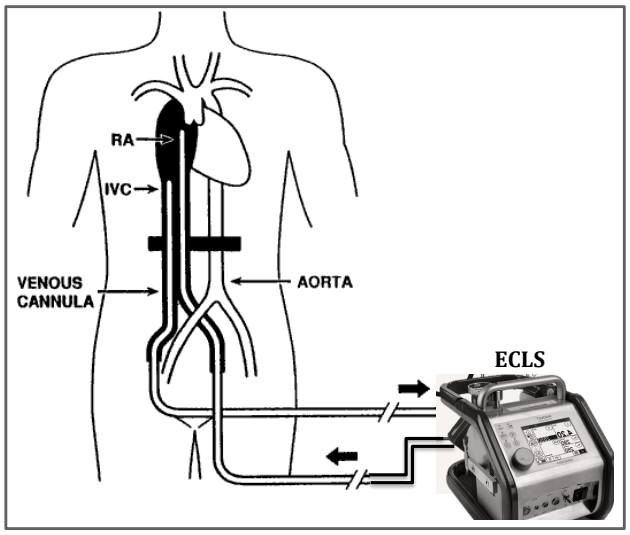

Fig. 1 Extracorporeal lung support (ECLS). RA is the right atrium and IVC is the inferior vena cava. Figure adapted from M.J. Murray and D.J. Cook [21].

exchanger, which is smaller for $ECCO_2RD$. Given the small volume of the gas exchanger in the $ECCO_2RD$, the blood flow entering the device must be smaller than 0.8 l/min (see, as an exemple, the $ECCO_2RD$ of NovaLung® [37]).

The purpose of this paper is to develop and validate a mathematical model of the respiratory system assisted by an $ECCO_2RD$ to improve the use of this device. More precisely, before starting the extracorporeal CO_2 removal therapy ($ECCO_2RT$), it is important to assess the appropriate blood flow that must cross the device for a given patient's status and therapeutic strategy. Indeed, if this blood flow has been determined, clinicians can decide if an $ECCO_2RD$ can be used instead of a larger ECLS and they can also choose the appropriate cannulae size, which must be kept as small as possible in order to reduce complications, like hemorrhage and infections. Developing a mathematical tool to facilitate this preliminary step of care is the main long-term target of this research. In order to propose solutions adapted to the patient's status, the mathematical model is made as patient-specific as possible given the available data in the intensive care unit (ICU). In addition, the model has to be simple enough to allow real-time parameter identification, but also complex enough to be able to simulate pulmonary abnormalities and the respiratory system when protective ventilation is introduced and when an $ECCO_2RD$ is switched on.

Scientists have already developed several mathematical models of the respiratory system (lung gas exchange and tissues gas exchange) for many years [12, 35,3] but these models usually do not take into account pulmonary gas exchange abnormalities like ARDS and COPD. Some authors have proposed modeling these abnormalities by including a perfusion/ventilation mismatch [16] or by decreasing the diffusion across the alveolar capillary membrane [29]. However, very few authors have developed models of the respiratory system connected to an extracorporeal lung support [6,36, 22,20]. The models of Walter et al. [36] and Brendel et al. [6] describe lung, tissues and $ECCO_2RD$ gas exchange but to account for gas exchange abnormalities in the lung, these authors introduce two purely empirical parameters. The appropriate account of gas exchange abnormalities is of paramount importance in this work and parameters with a clear physiological interpretation are introduced to describe these abnormalities. Moreover, the goal of the authors cited above is different from ours since they use their models in a control algorithm designed to maintain appropriate long-term gas contents of the blood, while our approach will help clinicians determining the best settings of an $ECCO_2RD$ before it is used.

In the following sections, the different components of the mathematical model are described and the experimental procedures that were carried out on 10 pigs are presented. Then the model predictions are compared to the data. Finally, these results are analyzed and discussed.

2 Methods

2.1 Mathematical modeling

The model is a lumped parameter model of the respiratory system connected to an $ECCO_2RD$. Besides the $ECCO_2RD$, 2 other compartments are considered: one lung compartment and one tissues compartment (the 3 compartments are sketched in Fig. 2). The equations of the model will not be presented here since the different components were already introduced separately elsewhere. However, for the interested reader, the mathematical model is recalled in Appendix A.

The impairments of pulmonary gas exchange is described by two parameters: f_s which describes the importance of the pulmonary shunt (this parameter is also used in the works of D. S. Kabring et al. [16] and of S. E. Rees et al. [29]) and $\dot{V}_L$ which is the mean effective ventilation (the ventilation that actually participates in gas exchange). In addition, the production of CO_2 (MR_{CO_2}) and the consumption of O_2 (MR_{O_2}) by metabolism are two important parameters for the appropriate description of the respiratory system. The

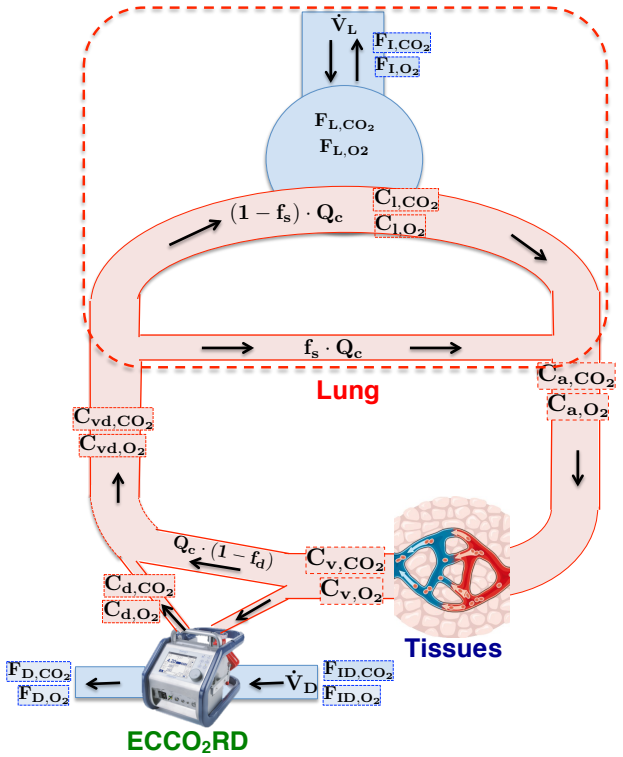

Fig. 2 Model of pulmonary gas exchange connected to an $ECCO_2RD$. $F_{I,i}$, $C_{a,i}$ and $C_{v,i}$ are respectively the inspired fraction, the concentration in arteries and the concentration in veins of component i ($i = O_2$ or CO_2). Q_c is the mean cardiac blood flow. f_s and f_d are the fraction of pulmonary blood crossing the shunt and the fraction of blood passing through by the $ECCO_2RD$. $\dot{V}_D$ is the ventilation of the $ECCO_2RD$ and $\dot{V}_L$ is the mean effective ventilation of the lungs. The other symbols are defined in Appendix A.

values of these four parameters are estimated for each subject as explained in section 2.3.2.

An appropriate blood chemistry model is also needed. In the present work, the relation between O_2 concentration and O_2 partial pressure P_{O_2} follows the equations of Grodins et al. [12] and the relation between total CO_2 concentration C_{CO_2}, pH in blood plasma and CO_2 partial pressure P_{CO_2} follows the equations of Trueb et al. [35]. Note however that in the C_{CO_2}-P_{CO_2} relation, a correction term k_{HCO_3} must be introduced to account for variations in standard HCO_3 concentration between individuals (more details are provided in section 2.3.1).

2.2 Experimental data

Two sets of retrospective experiments (approved by the Ethics Committee of the Medical Faculty of the University of Liège) including an $ECCO_2RD$ are used to validate the mathematical model. The first set of experiments, that are referred to as *experiments H* in the text below, are carried out on 4 healthy pigs, named H1 to H4, subject to protective ventilation. For the 6 animals A1 to A6 of *experiments A*, ARDS is induced in addition to protective ventilation (for the detailed protocol of the induction of ARDS, see Morimont et al. [24]). Pigs have been chosen for the animal trials because their cardiovascular and respiratory physiology are similar to human.

At the beginning of both sets of experiments, the pigs are anesthetized and intubated. After a 30 min stabilization period, whose end defines the baseline situation, several experimental data (blood flow, CO_2 and O_2 concentrations in venous and arterial blood samples) are measured and the settings of the ventilator are also recorded. Then protective ventilation is introduced for about 45 min. In *experiments A*, ARDS is induced during this phase of the protocol by the normal saline lavage method [24]. After that, the $ECCO_2RD$ (PALP®, Maquet, Germany) is switched on to remove the excess CO_2. In all experiments, the gas flow through the device is set to 10 liters of atmospheric air per minute. The blood flow in the $ECCO_2RD$ is fixed to several values, which are specified in the results section.

The body blood flow is measured with thermodilution technique (PiCCO®, Pulsion, Germany) and also with an admittance pressure-volume catheter (Transonic®, USA) in the right ventricle. Tidal volume, F_{I,O_2}, respiratory frequency and driving pressure are fixed by the ventilator (Engström Carestation®, General Electric, Germany) and note that F_{I,CO_2} is always equal to 0. Arterial and venous blood samples are analyzed during the experimentation with a RapidPoint500® device (Siemens, Germany). In *experiments H*, additional blood samples are analyzed at the inlet and outlet cannulae and the gas exiting the $ECCO_2RD$ is also analyzed with a CARBOCAP® device (Vaisala, Finland).

Note that the two sets of experiments are important for the purpose of this work since they complement one another. *Experiments H* are needed because more data is available and the estimation of all the parameters of the model is feasible. However, the model must also be validated in case of gas exchange abnormalities. Therefore, *experiments A* are also needed since an ARDS is induced.

2.3 Estimation of the parameters

As already mentioned in section 2.1, several parameters describe the patient's status (in this case the animal's status) and must be estimated with several

measurements. These parameters are thus subject-specific and their estimation is of course crucial. The parameters related to the blood chemistry are considered in the first subsection below while those related to the lungs and tissues compartments are discussed in the second subsection. These parameters are estimated for each pig and their values will be given in section 4. Other parameters, which are not subject specific, must also be considered in the mathematical model and are described in the Appendix A.5. Some of these parameters are taken from the literature and are derived from human study. These parameter values are also discussed in the Appendix A.5

In addition, the value of the diffusion coefficient characterizing the membrane of the $ECCO_2RD$ is not provided by the manufacturer and this quantity must also be considered as a parameter. Its value is determined by a procedure which is explained in the last subsection below.

2.3.1 Blood chemistry

Quantity $k_{\mathrm{HCO_3}}$ is a subject-specific parameter in the equations of Trueb et al. [35] and it must be evaluated for each pig. Its values is assumed constant in time and can be estimated by using values of pH, $P_{\mathrm{CO_2}}$ and the haemoglobin saturation with O_2 in arteries during baseline situation.

2.3.2 Gas exchange in the lungs and in the tissues

$MR_{\mathrm{CO_2}}$ and $MR_{\mathrm{O_2}}$ describe the CO_2 production and O_2 consumption by the tissue. These parameters are assumed to not be affected by the ventilator settings or by the induction of ARDS. These quantities are thus estimated only at baseline for each animal. Using the values of cardiac output and O_2 concentrations in arterial and venous blood samples in a time independent situation, parameter $MR_{\mathrm{O_2}}$ can be determined. For the CO_2 production in the tissues, the equality $MR_{\mathrm{CO_2}} = MR_{\mathrm{O_2}}$ is assumed. Note also that the body temperature of the animals is not controlled in our experiments and a significant decrease of the temperature is observed as soon as the $ECCO_2RT$ is started (blood loses heat in the pipes and in the device). This temperature decrease induces a change in the metabolism and the values of $MR_{\mathrm{CO_2}}$ and $MR_{\mathrm{O_2}}$ have to be modified accordingly (see Appendix B for the details). However, since the temperature of the body is controlled in the ICU, it will not be necessary to take this effect into account in a future application of the mathematical model in clinics.

Parameters f_s and $\dot{V}_L$ describe the global efficiency of gas exchange in the lungs and their estimation is very important. To our knowledge, this present approach is unique in the literature since it is the first time that the pulmonary gas exchange abnormalities are described with these two parameters when an ECLS is connected to the respiratory system. The settings of the ventilator (tidal volume and respiratory frequency) and ARDS notably influence the gas exchange. The parameters f_s and $\dot{V}_L$ must be thus re-evaluated each time these settings are modified and after the induction of ARDS. For this reason, these quantities must be identified twice in both experiments: once during baseline situation and once during protective ventilation (combined with ARDS induction in *experiments A*). The identification of these parameters is obtained by fitting the measurements of arterial PCO_2 and PO_2 (the venous counterparts being linked to the arterial values by the previously determined $MR_{\mathrm{CO_2}}$ and $MR_{\mathrm{O_2}}$) with the corresponding simulated values. During baseline, the system is completely stabilized and the variables are thus time independent. The identification of these parameters is more delicate after introducing the protective ventilation and inducing ARDS. Indeed this phase of the experiment is usually too short (45 min) to reach a steady state in the respiratory system. In that situation, the fitting of f_s and $\dot{V}_L$ is based on the comparison of the measurements and the time evolution obtained from the solution of the differential equations.

2.3.3 Diffusion in the $ECCO_2RD$

The CO_2 exchanges in the $ECCO_2RD$ is characterized by the CO_2 diffusion coefficient across the synthetic membrane $D_{\mathrm{CO_2}}$. Its value is independent of the patient's status and of the ventilator settings. It can be obtained by fitting the predictions of the $ECCO_2RD$ mathematical model with measures of PCO_2 in the inlet and outlet canulae and in the gas flowing out of the device.

For the O_2 diffusion coefficient across the synthetic membrane $D_{\mathrm{O_2}}$, the measurements of the O_2 fraction in the gas flowing out of the $ECCO_2RD$ was not available. In addition, the accuracy of measurements in blood is not high enough to estimate $D_{\mathrm{O_2}}$ in our pig experiments. For these reasons, $D_{\mathrm{O_2}}$ is assumed to be 40 times smaller than $D_{\mathrm{CO_2}}$ as is the case for the heart-lung machine described in [22]. This estimation of $D_{\mathrm{O_2}}$ is a bit rough but it is still sufficient for the main purpose of this work. Indeed this quantity has only a minute influence on the time evolution of PCO_2, which is the main quantity of interest in this work.

2.4 Statistics

The goal of the mathematical model is to predict the decrease of PCO_2 for different blood flows entering the $ECCO_2RD$. All parameters are thus estimated before the $ECCO_2RT$ and the model must be able to describe this therapy without changing any parameter. To test the predictions of the model, the mean difference ($|\overline{\Delta P}|$) between the simulations and the experimental data is estimated with the following formula:

$$|\overline{\Delta P}| = \frac{1}{n}\sum_{i=1}^{n}|Psim_i - Pexp_i| \quad (1)$$

where n is the number of measurements, $Pexp_i$ is the PCO_2 measurement i and $Psim_i$ is the corresponding PCO_2 simulated with the model. The mean relative difference ($|\overline{\Delta P/P}|$) provides another way to estimate the error :

$$|\overline{\Delta P/P}| = \frac{1}{n}\sum_{i=1}^{n}\frac{|Psim_i - Pexp_i|}{Pexp_i}. \quad (2)$$

In addition, in order to estimate if the model tends to overestimate or to underestimate the partial pressure, the mean difference and the mean relative difference are also computed without the absolute value (and the corresponding symbols are written as $\overline{\Delta P}$ and $\overline{\Delta P/P}$).

3 Results

In this section, the mathematical model is tested by simulating an $ECCO_2RT$ and the numerical results of the model are compared to the experimental data obtained in *experiments H* and *experiments A*. In the first subsection, the values of the specific parameters corresponding to each animal are given. Then, the results of the simulations are presented.

3.1 Values of the parameters

To determine the diffusion coefficients across the membrane of the $ECCO_2RD$, we use the data of *experiments H*. Using the method presented in section 2.3, one finds $D_{CO_2} = 6.33 \times 10^{-5}\ l_{CO_2}/s/mmHg$ and $D_{O_2} = 1.58 \times 10^{-6}\ l_{O_2}/s/mmHg$. As already mentioned, the settings of the $ECCO_2RD$ are such that the atmospheric air flow is always equal to 10 liters per minute, while parameter Q_d is changed several times (Q_d = 200 ml/min, Q_d = 400 ml/min and Q_d = 600 ml/min) for *experiments H* and set to one value (around 700 ml/min) for *experiments A*.

The other parameters of the model are given in Table 1 for all animals. Parameter F_{I,O_2} is one of the ventilator settings. On the other hand, the values of MR_{CO_2}, MR_{O_2}, k_{HCO_3}, f_s and $\dot{V}_L$ are determined by the procedures described in section 2.3. Note that in Table 1, parameter f_s increases when protective ventilation is induced and it increases even more when protective ventilation is coupled with ARDS. On the other hand, the effective ventilation $\dot{V}_L$ decreases when protective ventilation is induced.

Cardiac blood flow values for the different animals during the experiments are also parameters of the model and Fig. 3 provides these values for pigs H2 and A6 for which detailed results are presented below.

The other parameters, which are not subject specific, are given in Table 3 in Appendix A.5.

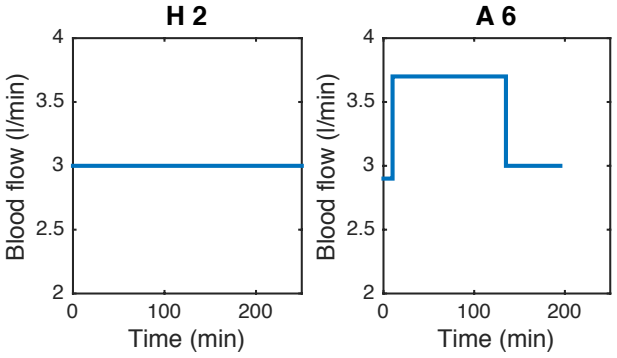

Fig. 3 Time evolution of the cardiac blood flows for pigs H2 and A6.

3.2 Comparison between experimental and numerical results

Using the values of the parameters given above, the mathematical model is able to describe the gas exchange for *experiments H* and *experiments A* during the $ECCO_2RT$. The main results consist of the time evolution of PCO_2 at several places in the body. Fig. 4 illustrates the time evolution of PCO_2 in veins, in the right ventricle and in arteries for pig H2 and Fig. 5 illustrates the time evolution of PCO_2 in veins and in arteries for pig A6. The results for the other pigs are not presented since they present similar features. Note that the error on the measurements is equal to $0.03 \times \{value\ of\ the\ measurement\} + 0.17$ mmHg, according to the manufacturer of the RapidPoint500® device. In the figures, the vertical lines indicate the

Table 1 Measurements, settings of the ventilator and identified parameters for *experiments H* (H1 – H4) and *A* (A1 – A6)

	Experiments H ("healthy" pigs)				*Experiments A* (pigs with ARDS)					
Data	H1	H2	H3	H4	A1	A2	A3	A4	A5	A6
Baseline situation										
Measurements										
Weight (kg)	22	29	28	31	28	35	22	22.7	30	30
Ventilator settings										
F_{I,O_2}	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5
Identified parameters										
MR_{CO_2} (l_{CO_2}/min) $= MR_{O_2}$ (l_{O_2}/min)	0.147	0.202	0.183	0.226	0.173	0.182	0.142	0.108	0.133	0.195
k_{HCO_3} (l_{CO_2}/l)	0.06	0.028	0.068	-0.001	0.042	0.05	-0.053	0.018	0.055	0.06
f_s	0.044	0.066	0.047	0.029	0.037	0.08	0.133	0.08	0.059	0.050
$\dot{V}_L$ (l/min)	3	5.85	4.325	6.875	3.24	3.9	2.76	2.2	3.92	4.58
	Protective ventilation				**Protective ventilation and ARDS**					
Ventilator settings										
F_{I,O_2}	1	1	1	1	0.5	0.5	1	1	1	1
Identified parameters										
f_s	0.105	0.092	0.081	0.128	0.304	0.436	0.49	0.57	0.409	0.532
$\dot{V}_L$ (l/min)	0.93	1.8	1.695	2.1	1.58	1.92	1.44	1.2	2	2.66

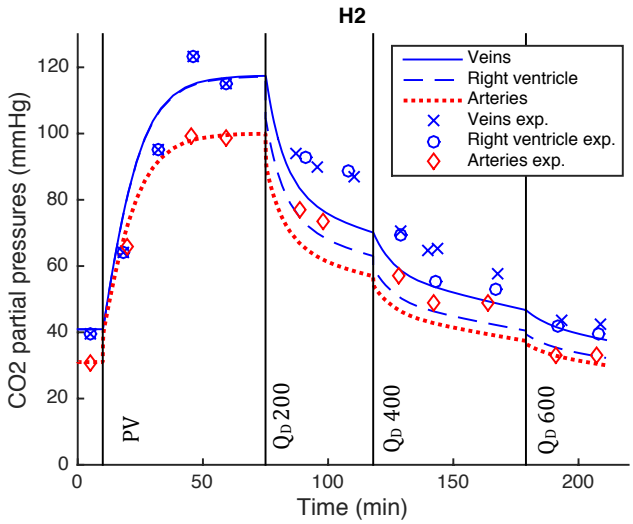

Fig. 4 Time evolution of calculated (curves) and measured (crosses, circles and diamonds) CO_2 partial pressures in veins, in the right ventricle and in arteries for pig H2. The labels PV and Q_D 200 (Q_D 400 and Q_D 600) mean respectively the start of protective ventilation and blood flow through the $ECCO_2RD$ set to 200 (400 and 600) ml/min.

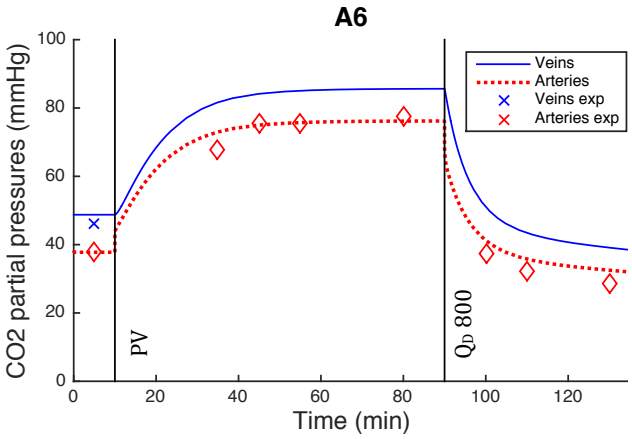

Fig. 5 Time evolution of calculated (curves) and measured (crosses and diamonds) CO_2 partial pressures in veins and in arteries for pig A6. The labels PV and Q_D 800 mean respectively the start of protective ventilation and blood flow through the $ECCO_2RD$ set to 800 ml/min.

beginning of the different phases of the experiments. As expected, the PCO_2 in the body increases when protective ventilation and ARDS are induced and decreases when the $ECCO_2RD$ is initialized.

Figs. 4 and 5 show a good agreement between the numerical simulations and the corresponding experimental data. During baseline situation (the first 10 minutes in Fig 4 and Fig 5), the agreement is perfect for the PCO_2 in arteries since parameters f_s and $\dot{V}_L$ are identified to fit the PCO_2 in arteries. On the other hand, the agreement is not perfect for the PCO_2 in veins because MR_{CO_2} is not estimated with the measurements but with the approximation $MR_{CO_2} = MR_{O_2}$. After baseline situation, protective ventilation is induced (combined with ARDS in *experiments A*) and the agreement is still good since parameters f_s and $\dot{V}_L$ are re-evaluated. Now the comparison between experimental and numerical results during $ECCO_2RT$ will be analysed in detail. During this period, all parameters are kept constant and the agreement between simulations and experimental data remains quite good, for a relatively long period of

time. Table 2 provides the mean errors $\overline{\Delta P}$ and the mean relative errors $\overline{\Delta P/P}$ with and without absolute value for each pig of the two sets of experiments. The number of experimental data (# data) is also given. Note that the standard deviation of the errors is not given for *experiments A* since the number of measurements is small (less than 5 measurements). One can observe that the errors for *experiments H* are larger than for *experiments A*. However, *experiments H* have more experimental data in different parts of the body (*experiments A* have only arteries measurements during $ECCO_2RT$). For *experiments H*, the model always underestimates PCO_2 (the value of $\overline{\Delta P}$ and $\overline{\Delta P/P}$ is always negative) whereas underestimations and overestimations are almost as likely for *experiments A*. In addition, the mean errors are also computed for all pigs (last column) and one can observe that the global relative error $|\overline{\Delta P/P}|$ is equal to 11%.

4 Discussion

This section discusses the physiological meaning of important parameters and discusses the ability of our model to predict the decrease of the PCO_2 during $ECCO_2RT$. The possible application of the mathematical model in the ICU is also discussed and, finally, the limitations of the model are described.

4.1 Modeling of lung gas exchange

Walter et al. [36] and Brendel et al. [6] have already developed a 3 compartments mathematical model (lung, tissues and $ECCO_2RD$ compartments) similar to that used in our approach. However, the above authors use two empirical parameters to describe pulmonary gas exchange abnormalities. Since the aim of our work is to find parameters specific to a given subject before the $ECCO_2RT$ is initiated, the description of the possible abnormalities is quite crucial. For this reason, our model uses two parameters with clear physiological meaning to describe the impairments of gas exchange: f_s which describes the importance of the pulmonary shunt and $\dot{V}_L$ which is the mean effective ventilation. In the literature, the mean effective ventilation $\dot{V}_L$ is often not identified as in our approach, but directly estimated [29,17]. $\dot{V}_L$ depends on the tidal volume and the respiratory frequency, which are easily known since they are settings of the ventilator. But $\dot{V}_L$ also depends on the dead space V_{Dead}, which is much more difficult to obtain. Some authors assume that this space is equal to 150 ml for an adult patient [29], while others measure the dead space with a stand-alone respiratory monitor [17]. In our experiments on pigs, the assumption of a human value equal to 150 ml can not be made. It is not either possible to estimate V_{Dead} with a gas analyser at the outlet of the ventilator. Indeed, the experimental data related to the CO_2 expired out of the ventilator are not enough precise to estimate the dead space with the small ventilation used in our experiments. Consequently, $\dot{V}_L$ is identified at the same time as the pulmonary shunt f_s and these two parameters describe the efficiency of gas exchange in the lungs. Whereas parameter f_s describes the fraction of blood that does not participate in gas exchange, parameter $\dot{V}_L$ describes the actual air flux in the lungs. In physiology, the quality of gas exchange in the lungs depends on many factors, such as for example, ventilation-perfusion mismatch or the quality of diffusion across the alveolar-capillary membrane. In the present work, these effects are not explicitly modeled and parameters f_s and $\dot{V}_L$ must thus be considered as lumped parameters that allow global description in the mathematical model all the possible anomalies of gas exchange.

During the animal experiments, the tidal volume is decreased drastically when the protective ventilation starts. Of course, the effective ventilation changes with the tidal volume but the pulmonary shunt can also change since the dynamics of the lung is modified. The induction of ARDS has also an impact on the pulmonary shunt. Therefore, it is necessary that the two parameters are estimated twice: first during the baseline situation and then during protective ventilation (combined with ARDS induction in *experiments A*). The changes of these two parameters between the two phases are discussed in the next subsection.

4.2 Values of the parameters

Table 1 shows that the two lumped parameters f_s and $\dot{V}_L$ behave as physiologically expected. Indeed, during ARDS, many alveoli do not work properly and the increase of the pulmonary shunt with ARDS is observed in physiology [2,31]. The value of f_s during ARDS ($45.7\pm3.6\%$) is larger than in previous studies of human ARDS ($31\pm10\%$ [16]) but note that the experiments are carried out on pigs and that ARDS is not "real" since it is only simulated by injecting water into the lungs. The value of f_s at baseline ($6.3\pm0.9\%$) is also larger than expected for a healthy human (2% [13]) but the pigs are intubated and anesthetized and thus not in a truly physiologically healthy state. The small increase of f_s during protective ventilation for *experiments H* can be interpreted by the collapse of some alveoli when the pressure in the lungs is lower. With regards to

Table 2 Errors between the simulations and the measurements during the $ECCO_2RT$ for *experiments H* and *A*. The line # data indicates the number of experimental measurements available during $ECCO_2RT$.

	Experiments H				*Experiments A*						
Data	H1	H2	H3	H4	A1	A2	A3	A4	A5	A6	**All pigs**
$\lvert\overline{\Delta P}\rvert$ (mmHg)	13.15 ± 8.00	10.03 ± 6.60	6.88 ± 5.48	7.97 ± 5.66	5.96	6.03	0.07	5.57	0.79	3.88	**6.03 ± 7.72**
$\lvert\overline{\Delta P/P}\rvert$	0.19 ± 0.11	0.15 ± 0.06	0.12 ± 0.05	0.12 ± 0.05	0.12	0.14	0.002	0.14	0.02	0.12	**0.11 ± 0.002**
$\overline{\Delta P}$ (mmHg)	-13.13 ± 10.68	-10.03 ± 5.52	-4.71 ± 6.29	-6.62 ± 5.94	-5.96	6.03	-0.07	-5.57	-0.79	3.88	**-3.7 ± 17.83**
$\overline{\Delta P/P}$	-0.19 ± 0.11	-0.15 ± 0.06	-0.09 ± 0.09	-0.11 ± 0.08	-0.12	0.14	-0.002	-0.14	-0.02	0.12	**-0.06 ± 0.01**
# data	23	23	24	16	4	2	1	2	1	3	**10**

parameter $\dot{V}_L$, its decrease during protective ventilation is clearly related to the drastic decrease of the tidal volume.

MR_{CO_2} and MR_{O_2} values are in the same range as in previous studies. All pigs of *experiment H* and pigs A1, A2 and A4 have MR_{O_2} (and MR_{CO_2}) values very close to the standard empirical relation used by Karagiannidis et al. [15]: MR_{O_2} $(= MR_{CO_2})$ $= 7 \times 10^{-3} l_{O_2}/min/kg$.

4.3 Quality of the PCO_2 prediction

Even if the CO_2 removal therapies considered are rather complex for *experiments H*, since the settings of the device are changed several times during the period of interest, the model is able to describe the general behavior of the system throughout the whole experiment. The global relative error $\lvert\overline{\Delta P/P}\rvert$ for all pigs of *experiments H* and *experiments A* is larger than the accuracy of the blood analyser RapidPoint500 (11% compared to 3%) but the simulation of the PCO_2 prediction depends on several other measurements like the cardiac output, the inspired fraction of O_2 and the PO_2. In addition, for the simulations, the extracorporeal blood flow is assumed to be perfectly controlled whereas in reality, it is difficult to achieve that goal. Recall also that the parameters f_s and $\dot{V}_L$ are kept constant throughout the $ECCO_2RT$ and are estimated before $ECCO_2RT$. Therefore, we can consider that our mathematical model of the respiratory system connected to an $ECCO_2RD$ can predict rather nicely the decrease of the PCO_2 during $ECCO_2RT$. For this reason, our model can be considered as validated by the pig experiments.

The purpose of the mathematical model is to find an appropriate extracorporeal blood flow for a specific patient. Therefore, it is interesting to know how the 11% relative error on the PCO_2 impacts the prediction of the blood flow. To test the sensitivity of the extracorporeal blood flow with respect to the PCO_2 error, we have considered the "mean pig" of all the experiments. This "mean pig" is obtained by considering the mean of all the parameters given in Table 1 ($MR_{CO_2} = MR_{O_2} = 0.17$ l/min, $\dot{V}_L = 1.7$ l/min, $f_s = 0.25\%$ and $k_{HCO_3} = 0.03$ l_{CO_2}/l, $F_{I,O_2} = 0.9$ and a weight of 28 kg) and we have used our mathematical model to determine the blood flow that allows to achieve a PCO_2 equal to 50 mmHg in arteries after 1 hour of $ECCO_2RT$. Then, the blood flows corresponding to 50+11% mmHg and 50-11% mmHg is also determined. The situation is illustrated in Fig 6 and the values of the three blood flows are respectively 268 ml/min, 199 ml/min and 377 ml/min. The positive and negative errors in PCO_2 thus give rise to 26% and 40% of imprecision in the calculated blood flows respectively, which is not negligible but nevertheless acceptable in comparison with the global error of all our experiments. In addition, in a clinical environment, the patients' status is often quite unstable like our pig experiments and it is reasonable to have an uncertainty over the appropriated blood flow.

4.4 Application of the model in the ICU

The results show that the mathematical model is able to predict the decrease of PCO_2 during $ECCO_2RT$ carried out on pigs. This is a very encouraging step for trying to extend the use of this model to the ICU. It could improve care for patients under $ECCO_2RT$. In the context of this possible extension of the use of the model, two additional points need to be made.

First, recall that in the simulations described in section 3.2, the cardiac blood flow, which is continuously measured in experiments, is introduced as a given function of time in the calculations. However, if the model is to be used in the ICU before starting the ECCO2RT in order to determine the best settings of the device, the change of cardiac output is of

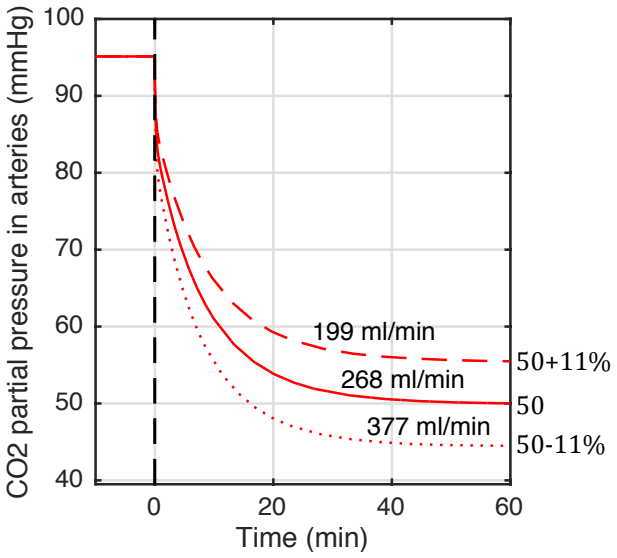

Fig. 6 Decrease of the PCO_2 in arteries during $ECCO_2RT$ for different extracorporeal blood flow.

course unknown when the calculations are carried out. To check if this would affect the predictions of the mathematical model, a constant cardiac blood flow is introduced in our calculations and the corresponding mean relative errors between the simulations and the experimental data become 10.7%. This error is the same than the previous one obtained with the time-varying blood flow, which indicates that the predictions are not affected if the blood flow is considered constant . This is of course a very important result for the use of the mathematical model in the ICU.

Second, it is interesting to mention that the time needed for a numerical simulation of PCO_2 decrease during a one hour $ECCO_2RT$ is around 3 min (on a standard laptop computer and using $MATLAB^{®}$). This computation time is thus sufficiently small to allow the model to participate in the rapid decision making that is required by clinicians at the patients bedside in the ICU.

4.5 Limitations

CO_2 production MR_{CO_2} and O_2 consumption MR_{O_2} are two important quantities in the functioning of the respiratory system. These two quantities are equal for carbohydrate metabolism but if the patient's metabolism uses different sources like fats or proteins, MR_{CO_2} is smaller than MR_{O_2} [25,11]. Unfortunately, because the total concentration of CO_2 in the blood depends on 3 chemical species (CO_2 dissolved in blood, HCO_3^- and CO_2 complexed with hemoglobin), the identification of the value of MR_{CO_2} from blood sample analyses has proved to be quite delicate and even impossible in our experiments. For this reason, we have introduced the rough approximation of equal MR_{CO_2} and MR_{O_2}.

If the long-term purpose of this work is to provide an additional therapeutic tool to clinicians, other limitations must also be emphasized. First, the status of the pigs used in experiments do not exactly correspond to that of humans in the ICU. In the experiments, hypercapnia was induced by protective ventilation and injection of water in the lungs, but no real ARDS or chronic obstructive pulmonary disease was considered. In addition, even if the pig cardiopulmonary system is close to that of human, ICU patients could have different responses to $ECCO_2RT$.

Finally, this mathematical model is validated only for a specific ECLS, which is the Maquet $ECCO_2RD$ (PALP®, Germany). Other, and larger ECLS like vv-ECMO, should also be considered. In particular, it is worth mentioning that larger ECLS are also used to oxygenate blood and this work do not consider this possibility.

5 Conclusions and future works

In this work, a lumped parameter model of the respiratory system connected to an extracorporeal CO_2 removal device ($ECCO_2RD$) is built. This device is used to decrease the PCO_2 when a patient suffers from acute respiratory distress syndrome (ARDS) or from chronic obstructive pulmonary disease (COPD). Two parameters are introduced in the model to characterize the possible impairments of gas exchange in the lung. Parameter f_s charaterises the pulmonary shunt and is defined as the fraction of blood flow that does not participate in gas exchange in the lungs. The effective ventilation $\dot{V}_L$ is the ventilation that actually participates in gas exchange. The values of f_s and $\dot{V}_L$ are identified from measurements available in the ICU and are patient-specific. In the tissues, production of CO_2 and consumption of O_2 by the metabolism are considered as parameters of the model and are also identified in a patient-specific way. Cardiac output is another important parameter of the model. If all these parameters are identified before the extracorporeal CO_2 removal therapy ($ECCO_2RT$), the mathematical model can correctly simulate the decrease of PCO_2 during $ECCO_2RT$.

To validate the mathematical model, PCO_2 predictions are compared with experimental results obtained in pigs. The results show that the model is able to reproduce experimental data for quite long periods of time (up to about 150 minutes for *experiments H*

and up to about 60 minutes for *experiments A*) and until a total decarboxylation of blood is reached. The quite good agreement between the theoretical approach and animal data can thus be considered as a strong argument proving the validity of our model.

A next interesting step would be a detailed validation of the model in an ICU environment, using retrospective data corresponding to real human pathologies. After this validation, the model could become a useful tool for determining the most appropriate blood flow that must be sent to the $ECCO_2RD$ for a given therapeutic strategy and a final PCO_2-target. Then the most appropriate and smallest canulae would be determined in order to obtain the expected decarboxylation.

Acknowledgments Financial support by F.R.S-FNRS (PDR T.1058.14) is cordially acknowledged.

References

1. Abrams, D., Roncon-Albuquerque Jr, R., Brodie, D.: What's new in extracorporeal carbon dioxide removal for COPD? Intensive care medicine **41**(5), 906 (2015)
2. Anzueto, A., Gattinoni, L.: Prone position in ARDS. Acute Respiratory Distress Syndrome **233**, 313 (2016)
3. Batzel, J.J., Kappel, F., Scneditz, D., Tran, H.T.: Cardiovascular and respiratory systems: modeling, analysis, and control, vol. 34. SIAM (2007)
4. Bein, T., Weber-Carstens, S., Goldmann, A., Müller, T., Staudinger, T., Brederlau, J., Muellenbach, R., Dembinski, R., Graf, B.M., Wewalka, M., et al.: Lower tidal volume strategy (3 ml/kg) combined with extracorporeal CO2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS. Intensive care medicine **39**(5), 847–856 (2013)
5. Ben-Tal, A.: Simplified models for gas exchange in the human lungs. Journal of Theoretical Biology **238**(2), 474 – 495 (2006). DOI http://dx.doi.org/10.1016/j.jtbi.2005.06.005. URL http://www.sciencedirect.com/science/article/pii/S0022519305002390
6. Brendle, C., Hackmack, K.F., Kühn, J., Wardeh, M., Janisch, T., Kopp, R., Rossaint, R., Stollenwerk, A., Kowalewski, S., Misgeld, B., et al.: Continuous gas transfer monitoring during extracorporeal membrane oxygenation. Biomedical Signal Processing and Control **31**, 321–330 (2017)
7. Burney, P.G., Patel, J., Newson, R., Minelli, C., Naghavi, M.: Global and regional trends in COPD mortality, 1990–2010. European Respiratory Journal **45**(5), 1239–1247 (2015)
8. Enger, T.B., Philipp, A., Videm, V., Lubnow, M., Wahba, A., Fischer, M., Schmid, C., Bein, T., Müller, T.: Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: a prospective observational study. Critical Care **18**(2), R67 (2014)
9. Fanelli, V., Ranieri, M.V., Mancebo, J., Moerer, O., Quintel, M., Morley, S., Moran, I., Parrilla, F., Costamagna, A., Gaudiosi, M., et al.: Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. Critical Care **20**(1), 36 (2016)
10. Ferguson, N., Fan, E., Camporota, L., Antonelli, M., Anzueto, A., Beale, R., Brochard, L., Brower, R., Esteban, A., Gattinoni, L., Rhodes, A., Slutsky, A., Vincent, J.L., Rubenfeld, G., Thompson, B.T., Ranieri, V.M.: The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med **38**(10), 1573–1582 (2012). DOI 10.1007/s00134-012-2682-1. URL http://dx.doi.org/10.1007/s00134-012-2682-1
11. Gnaiger, E.: Calculation of energetic and biochemical equivalents of respiratory oxygen consumption. In: Polarographic oxygen sensors, pp. 337–345. Springer (1983)
12. Grodins, F.S., Buell, J., Bart, A.J.: Mathematical analysis and digital simulation of the respiratory control system. Tech. rep., DTIC Document (1967)
13. Guyton, C.A., Hall, E.J.: Textbook of Medical Physiology. Elsevier (Eleventh Edition) (2006)
14. Hinski, S.T.: Respiratory Care Clinical Competency Lab Manual (chapter 23). Elsevier Health Sciences (2014)
15. Karagiannidis, C., Kampe, K.A., Sipmann, F.S., Larsson, A., Hedenstierna, G., Windisch, W., Mueller, T.: Veno-venous extracorporeal CO2 removal for the treatment of severe respiratory acidosis: pathophysiological and technical considerations. Crit Care **18**(3), R124 (2014)
16. Karbing, D.S., Kjaergaard, S., Andreassen, S., Espersen, K., Rees, S.E.: Minimal model quantification of pulmonary gas exchange in intensive care patients. Med Eng Phys **33**(2), 240–8 (2011). DOI 10.1016/j.medengphy.2010.10.007. URL http://www.ncbi.nlm.nih.gov/pubmed/21050794
17. Karbing, D.S., Kjærgaard, S., Smith, B.W., Allerød, C., Espersen, K., Andreassen, S., Rees, S.E.: Decision support of inspired oxygen fraction using a model of oxygen transport. IFAC Proceedings Volumes **41**(2), 8080–8084 (2008)
18. Klinzing, S., Wenger, U., Steiger, P., Starck, C.T., Wilhelm, M., Schuepbach, R.A., Maggiorini, M.: External validation of scores proposed for estimation of survival probability of patients with severe adult respiratory distress syndrome undergoing extracorporeal membrane oxygenation therapy: a retrospective study. Critical Care **19**(1), 142 (2015)
19. Linares, O.A., Schiesser, W.E., Fudin, J., Pham, T.C., Bettinger, J.J., Mathew, R.O., Daly, A.L.: In silico ordinary differential equation/partial differential equation hemodialysis model estimates methadone removal during dialysis. Journal of pain research **8**, 417 (2015)
20. Messai, E., Bouguerra, A., Harmelin, G., Di Lascio, G., Bonizzoli, M., Bonacchi, M.: A numerical model of blood oxygenation during veno-venous ECMO: analysis of the interplay between blood oxygenation and its delivery parameters. Journal of clinical monitoring and computing **30**(3), 327–332 (2016)
21. Michael J. Murray, D.C.: Cardiopulmonary Bypass: Principles and Practice (chapter 33). Lippincott Williams & Wilkins (2008)
22. Misgeld, B.J.E.: Automatic control of the heart-lung machine. Ruhr-Universität Bochum, Diss (2006)
23. Morimont, P., Batchinsky, A., Lambermont, B.: Update on the role of extracorporeal CO2 removal as an adjunct to mechanical ventilation in ards. Critical Care **19**(1), 1 (2015)

24. Morimont, P., Guiot, J., Desaive, T., Tchana-Sato, V., Janssen, N., Hella, D., Blaffart, F., Defraigne, J., Lambermont, B.: Veno-venous extracorporeal CO2 removal improves pulmonary hemodynamics in a porcine ARDS model. Acta Anaesthesiologica Scandinavica **59**(4), 448–456 (2015)
25. Péronnet, F., Massicotte, D., et al.: Table of nonprotein respiratory quotient: an update. Can J Sport Sci **16**(1), 23–29 (1991)
26. Pironet, A., Dauby, P.C., Morimont, P., Janssen, N., Chase, J.G., Davidson, S., Desaive, T.: Model-based decision support algorithm to guide fluid resuscitation. IFAC-PapersOnLine **49**(5), 224–229 (2016)
27. Potkay, J.A.: The promise of microfluidic artificial lungs. Lab Chip **14**, 4122–4138 (2014). DOI 10.1039/C4LC00828F. URL http://dx.doi.org/10.1039/C4LC00828F
28. Ragaller, M., Richter, T.: Acute lung injury and acute respiratory distress syndrome. Journal of Emergencies, Trauma and Shock **3**(1), 43–51 (2010). DOI 10.4103/0974-2700.58663. URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823143/
29. Rees, S.E., Kjærgaard, S., Thorgaard, P., Malczynski, J., Toft, E., Andreassen, S.: The automatic lung parameter estimator (ALPE) system: Non-invasive estimation of pulmonary gas exchange parameters in 10-15 minutes. Journal of clinical monitoring and computing **17**(1), 43–52 (2002)
30. Rees, S.E., Klæstrup, E., Handy, J., Andreassen, S., Kristensen, S.R.: Mathematical modelling of the acid–base chemistry and oxygenation of blood: a mass balance, mass action approach including plasma and red blood cells. European journal of applied physiology **108**(3), 483–494 (2010)
31. Sawheny, E., Ellis, A.L., Kinasewitz, G.T.: Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. Chest **144**(1), 55 – 62 (2013). DOI http://dx.doi.org/10.1378/chest.12-2296. URL http://www.sciencedirect.com/science/article/pii/S001236921360450X
32. Sklar, M.C., Beloncle, F., Katsios, C.M., Brochard, L., Friedrich, J.O.: Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review. Intensive care medicine **41**(10), 1752–1762 (2015)
33. Terragni, P., Maiolo, G., Ranieri, V.M.: Role and potentials of low-flow CO2 removal system in mechanical ventilation. Current opinion in critical care **18**(1), 93–98 (2012)
34. Thom, T.J.: International comparisons in COPD mortality. Am Rev Respir Dis **140**(3 Pt 2), S27–34 (1989)
35. Trueb, T., Cherniack, N., D'souza, A., Fishman, A.: A mathematical model of the controlled plant of the respiratory system. Biophysical journal **11**(10), 810–834 (1971)
36. Walter, M., Weyer, S., Stollenwerk, A., Kopp, R., Arens, J., Leonhardt, S.: A physiological model for extracorporeal oxygenation controller design. Conf Proc IEEE Eng Med Biol Soc **1**, 434–437 (2010)
37. XENIOS: ila activve minilung petite kit. http://www.xenios-ag.com/novalung-products/minilung-petite-kit/ (2016)

Appendix

A Mathematical modeling

The 3 compartments of the mathematical model are sketched in Fig. 2 (see section 2.1) and the corresponding equations are described below.

Our model, which is sketched in Fig. 2 (see section 2.1), is a lumped parameter model of the respiratory system connected to an $ECCO_2RD$. Besides the $ECCO_2RD$, two other compartments are considered in our model: one lung compartment and one tissues compartment (in which the metabolism of the patient is taken into account). The lung compartment allows the description of pulmonary abnormalities thanks to a pulmonary shunt f_s and an effective ventilation $\dot{V}_L$. In addition, a blood chemistry model is also needed. All the corresponding equations are described below and the estimation of all the parameters are explained in the last subsection.

A.1 Pulmonary gas exchange

Our model of pulmonary gas exchanges is based on the work of Batzel et al. [3]. In their work, the authors consider that diffusion of O_2 and CO_2 is fast so that equilibrium can be assumed between the alveoli and the pulmonary capillaries. The concentrations of O_2 and CO_2 in the alveoli are thus equal to the concentrations in the arteries. This assumption does not hold for gas exchanges abnormalities and this model need to be completed with additional parameters and additional equations. Our model considers two physiological parameters: f_s which describes the importance of the pulmonary shunt (like in the work of D. S. Kabring et al. [16] and S. E. Rees et al. [29]) and $\dot{V}_L$ which is the mean effective ventilation. In this context, the material balance of CO_2 in the lungs can be written as :

$$V_{L,CO_2} \cdot \dot{P}_{L,CO_2} = 863 \cdot (1 - f_s) \cdot Q_c \cdot (C_{vd,CO_2} - C_{l,CO_2}) + \dot{V}_L \cdot (P_{I,CO_2} - P_{L,CO_2}) \quad (3)$$

where:

- V_{L,CO_2} (l) is the effective volume of CO_2 in the lungs,
- $P_{L,CO_2} = F_{L,\mathrm{CO}_2} \cdot (P_{atm} - 47)$ is the CO_2 partial pressure in the air contained in the lungs (in mmHg). F_{L,CO_2} is the corresponding molar fraction of CO_2 in the lungs, P_{atm} (mmHg) is the atmospheric pressure and 47 mmHg is the saturated water vapor pressure at 37°C,

- Q_c (l/min) is the cardiac output,
- C_{vd,CO_2}(l_{CO_2}/l) is the CO_2 concentration in blood entering the right atrium (mixture of venous blood and treated blood from the $ECCO_2RD$, see Fig. 2),
- C_{l,CO_2} (l_{CO_2}/l) is the CO_2 concentration in the lung (in the pulmonary capillaries),
- $P_{I,CO_2} = F_{I,CO_2} \cdot (P_{atm} - 47)$ is the inspired CO_2 partial pressure (in mmHg). F_{I,CO_2} is the inspired fraction of CO_2 (always 0 in our approach),
- $\dot{V}_L = fr \cdot (V_T - V_{Dead})$ is the mean effective ventilation of the lung (in l/min). fr (min^{-1}) is the respiratory frequency, V_T (l) is the tidal volume and V_{Dead} (l) is the dead space.

After decarboxylation of blood in the lungs, pulmonary blood is mixed with venous blood from the shunt and the concentration of CO_2 in arteries C_{a,CO_2} (in l_{O_2}/l) is given by:

$$C_{a,CO_2} = f_s \cdot C_{vd,CO_2} + (1 - f_s) \cdot C_{l,CO_2} \tag{4}$$

The pulmonary gas exchange equations for O_2 are similar to equations 3 and 4 with corresponding notation for the different quantities (V_{L,O_2}, P_{L,O_2}, F_{I,O_2}, P_{I,O_2} and F_{I,O_2}).

A.2 Tissues gas exchange

In the tissues, the material balance equations for O_2 and CO_2 are given by [3,36]:

$$V_{T,O_2} \cdot \dot{C}_{v,O_2} = Q_c \cdot (C_{a,O_2} - C_{v,O_2}) - MR_{O_2} \tag{5a}$$

$$V_{T,CO_2} \cdot \dot{C}_{v,CO_2} = Q_c \cdot (C_{a,CO_2} - C_{v,CO_2}) + MR_{CO_2} \tag{5b}$$

where V_{T,O_2} and V_{T,CO_2} are the effective volume of CO_2 and O_2 in the tissues. C_{v,O_2} and C_{v,CO_2} are the O_2 and CO_2 concentrations in veins (in l_{O_2}/l and l_{CO_2}/l)). MR_{O_2} and MR_{CO_2} (in l_{O_2}/min and l_{CO_2}/min)) are the quantities of O_2 used and CO_2 produced by metabolism.

A.3 $ECCO_2RD$

$ECCO_2RD$ is considered as a second lung compartment taking a fraction f_d of the systemic blood flow Q_c in the inferior vena cava and rejecting the corresponding decarboxylated blood in the right atrium (see Figs. 1 and 2). However, the diffusion of O_2 and CO_2 across the synthetic membrane is less fast than across the lung membrane and the exchange surface is smaller than the alveolar-capillary membrane. As a consequence, the hypothesis of equilibrium between the gas and blood compartments in the device does not hold and the diffusion of O_2 and CO_2 across the synthetic membrane must be taken into account. A sketch of the gas exchanger is shown in Fig. 7 [27]. The geometry is quite complex (it is similar to a cross-flow plate heat exchanger) and several assumptions have to be considered to model this device. The geometry of the device is reduced to one dimension and the gas and blood flows are considered in opposite directions (see for instance [6,19]. The material balance equations for CO_2 in the gas and in the blood are thus given by :

$$V_D \frac{\partial F_{M,CO_2}}{\partial t} - \dot{V}_D \frac{\partial F_{M,CO_2}}{\partial X} = S \cdot D_{s,CO_2}(P_{m,CO_2} - P_{M,CO_2}) \tag{6a}$$

$$V_d \frac{\partial C_{m,CO_2}}{\partial t} + Q_d \frac{\partial C_{m,CO_2}}{\partial X} = S \cdot D_{s,CO_2}(P_{M,CO_2} - P_{m,CO_2}) \tag{6b}$$

where,

- F_{M,CO_2} and C_{m,CO_2}(l_{CO_2}/l) are respectively the CO_2 fraction in the gas and the CO_2 concentration in the blood along the synthetic membrane,
- P_{M,CO_2} and P_{m,CO_2} (mmHg) are the CO_2 partial pressures in the gas and in the blood along the synthetic membrane,
- $\dot{V}_D$ and Q_d (l/s) are the gas and blood flows,
- V_D and V_d (l) are respectively the volumes in the gas side and in the blood side of the $ECCO_2RD$,
- S (m^2) is the exchange surface between the blood side and the gas side,
- D_{s,CO_2} (l_{CO_2}/s/mmHg/m^2) is the CO_2 diffusion coefficient across the synthetic membrane and
- $X = x/L$ is the nondimensional 1-D coordinate where x is the distance along the $ECCO_2RD$ and L is the length of the $ECCO_2RD$.

The true exchange surface area of the device is given by the manufacturer but is not directly related to the exchange area of the 1-D model. Therefore, a global equivalent diffusion coefficient D_{CO_2} (l_{CO_2}/s/mmHg) is considered instead of the product $S \times D_{s,CO_2}$ (as has been done in previous studies [5,22]).

The first terms of the left hand sides of equations 6 describe the time accumulation of CO_2 in the volumes V_D and V_d. The two boundary conditions for equations 6 give the values of the concentrations at the gas and blood inlets. Since these two inlets correspond to X=0 and X=1 respectively, the system of differential equations and boundary conditions must be solved iteratively (note that $F_{M,i}(0,t) = F_{D,i}$, $C_{m,i}(0,t) = C_{v,i}$, $F_{M,i}(1,t) = F_{ID,i}$ and $C_{m,i}(1,t) = C_{d,i}$ where i =

O_2 or CO_2). The equations for the O_2 material balance, with the corresponding symbols (F_{M,O_2}, C_{m,O_2}, D_{O_2}, P_{M,O_2}, P_{m,O_2}, P_{D,O_2} and P_{d,O_2}), are similar. Since the time accumulation terms in the volumes V_D and V_d are small compared to the CO_2 and O_2 gas transfer, these terms are considered as negligible in our simulations.

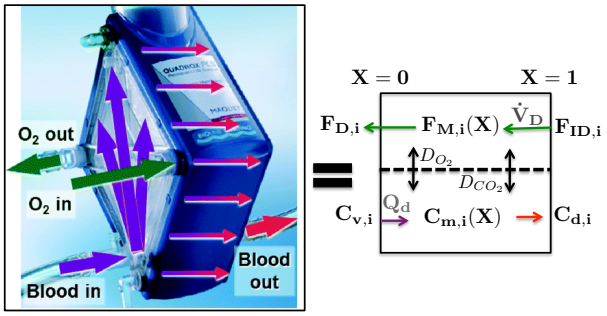

Fig. 7 The Maquet®'s gas exchanger on the left and the model of the ECCO$_2$RD on the right. All symbols are defined in the text (i = O_2 or CO_2)

After crossing the device, the treated blood is mixed with venous blood and the concentration of CO_2 entering the right atrium C_{vd,CO_2} is given by:

$$C_{vd,CO_2} = f_d \cdot C_{d,CO_2} + (1 - f_d) \cdot C_{v,CO_2} \tag{7}$$

The concentration C_{vd,O_2} is calculated in the same way.

A.4 Blood chemistry

The relations between partial pressures and total concentrations of gases are really complex in blood. Indeed, O_2 and CO_2 are not only dissolved in blood plasma since they can also be complexed with hemoglobin. In addition, CO_2 is also subject to the hydratation/dehydratation reaction:

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+ \tag{8}$$

which influences the pH.

In the model, the relation between O_2 concentration C_{O_2} and O_2 partial pressure P_{O_2} follows the equations of Grodins et al. [12]:

$$C_{O_2} = 4 \cdot C_{Hb} \cdot Sat_{O_2}(P_{O_2}) + \alpha_{O_2} \cdot P_{O_2} \tag{9a}$$

$$Sat_{O_2} = (1 - \exp(-S \cdot P_{O_2}))^2 \tag{9b}$$

$$S = 0.44921 \cdot pH - 0.10098 \cdot pH^2 + 0.0066815 \cdot pH^3 - 0.454 \tag{9c}$$

where C_{Hb} (l_{Hb}/l) is the hemoglobin concentration, Sat_{O_2} is the saturation of hemoglobin with O_2, S is an empiric parameter which accounts for the Bohr effect and α_{O_2} (l_{O_2}/l/mmHg) is the solubility coefficient of O_2 in blood plasma. The relations between total CO_2 concentration C_{CO_2}, pH in blood plasma and CO_2 partial pressure P_{CO_2} follow the equations of Trueb et al. [35]:

$$C_{CO_2} = (0.149 - 0.014 \cdot Sat_{O_2}(P_{O_2})) \cdot {P_{CO_2}}^{0.35} + k_{HCO_3} \ , \tag{10a}$$

$$C_{Pl,CO_2} = (1.19 + (4 \cdot C_{Hb} - 0.2)) \cdot C_{CO_2} \ , \tag{10b}$$

$$pH = -\log_{10}\left(K_{HCO_3} \cdot \frac{\alpha_{CO_2} \cdot P_{CO_2}}{C_{Pl,CO_2} - \alpha_{CO_2} \cdot P_{CO_2}}\right) \ , \tag{10c}$$

where k_{HCO_3} (l_{CO_2}/l) is a correction term which is introduced to compensate for variations between individuals in standard HCO_3 concentration [35], C_{Pl,CO_2} (l_{CO_2}/l) is the total CO_2 concentration in blood plasma, K_{HCO_3} is the equilibrium constant of chemical equation 8 and α_{CO_2} (l_{CO_2}/l/mmHg) is the solubility coefficient of CO_2 in blood plasma.

A.5 Parameters of the mathematical model

Many parameters appear in the mathematical model. They are either estimated with experimental measurements or taken from the literature. Table 3 provides a list of all parameters and explain how their values are determined.

For identified parameters, the identification procedure is explained in the section 2.3. Other parameters are directly estimated with a measuring device: the cardiac blood flow is measured with thermodilution technique (PiCCO®, Pulsion, Germany) and also with an admittance pressure-volume catheter (Transonic®); the haemoglobin concentration is measured with a blood analyser (RapidPoint500®, Siemens, Germany). Note that the cardiac output is a varying parameter whose changes over time are measured continuously and introduced in the model as an input function of time. The haemoglobin concentration is estimated in arterial and venous blood samples for every pig and the mean of all these values is used.

The parameters taken from the literature are derived from human study. α_{CO_2}, α_{O_2} and K_{HCO_3} are taken from Rees et al. [30] and the effective volumes V_{T,CO_2}, V_{T,O_2}, V_{L,CO_2} and V_{T,O_2} are assumed proportional to the body weight and their values are adapted from [3] (where these parameters are given for a man weighing 75 kg). For the chemical parameters

(α_{CO_2}, α_{O_2} and K_{HCO_3}), taking values from human studies is reasonable since the human blood is very similar to the pig blood. On the other hand, for the effective volumes, the morphology of humans is quite different than pigs and taking the values adapted from Batzel et al. is a rough approximation. However, the effective volumes influence just the unstable terms of the system. Therefore, this approximation impacts only the transitory terms which is not very important for the goal of this paper.

Finally, some parameters are controlled during the experiments since they are the settings of the ventilator and of the ECCO$_2$RD .

B Decrease of MR_{O_2} and MR_{CO_2} with temperature

The detailed analysis of the temperature dependence of metabolism is not the purpose of the present paper since the final goal of our approach is to develop a model to be used in the ICU, where temperature is controlled and kept constant. However, in the experiments to which the model was compared, the temperature of the animals was decreasing. It was thus necessary to take this effect into account to obtain a good validation of the model, but given our final purpose, a rather rough description of the temperature changes is of course sufficient.

The decrease of temperature in the experiments during ECCO$_2$RT is illustrated in Fig. 8 for 3 pigs (for the other pigs, the temperature had not been recorded). Unfortunately it was not possible to estimate the corresponding decrease of parameters MR_{O_2} and MR_{CO_2}. Indeed, the estimation of these parameters requires stabilized (i.e. time independent) data (see section 2.3), which were not available in the experiments during the ECCO$_2$RT.

To study the metabolism changes with temperature, we made a retrospective analysis of other experiments carried out in our lab (see [26]), for which appropriate data were available. The composition of the gas expired out the ventilator has been recorded continuously for two pigs (pig 1 and pig 2). In a stabilized situation, the CO_2 production by the metabolism is equal to the CO_2 extraction by the ventilator and we can write the following equation:

$$MR_{CO_2} = \dot{V}_L \cdot F_{E,CO_2}, \tag{11}$$

where F_{E,CO_2} is the end tidal CO_2 volume fraction and $\dot{V}_L$ is estimated from the tidal volume and the respiratory frequency given by the ventilator and an assumed dead space fixed equal to 30% of the tidal volume [14]. The O_2 consumption (MR_{O_2}) can be estimated similarly. Fig. 9 and Fig. 10 show the time evolutions of MR_{CO_2} and MR_{O_2} and the time evolution of temperature for the two pigs. We observe on these figures that the temperature, MR_{O_2} and MR_{CO_2} decrease linearly. The decrease of MR_{O_2} and MR_{CO_2} are similar (a little bit larger for MR_{O_2}) . Therefore, we use the slope of the linear interpolation of MR_{CO_2}, MR_{O_2} and that of the linear interpolation of the temperature to estimate the decrease of the metabolism production rates with temperature. For pigs 1 and 2, the rates found are respectively 0.0138 l/min/°C and of 0.0125 l/min/°C for MR_{CO_2} and 0.0213 l/min/°C and of 0.0275 l/min/°C for MR_{O_2} and we have taken the mean value 0.0188 l/min/°C. Then from Fig. 8, we can calculate a mean time rate of change for the temperature of the animals used in the experiments, and we found the value 0.0255°C/min. Finally, from this value and from the value of the metabolism rate of change with temperature, we deduce the following estimation of the time rate of change of metabolism production rates in the experiments: 4.78×10^{-4} l/min^2. This value was used in our simulations for all animals.

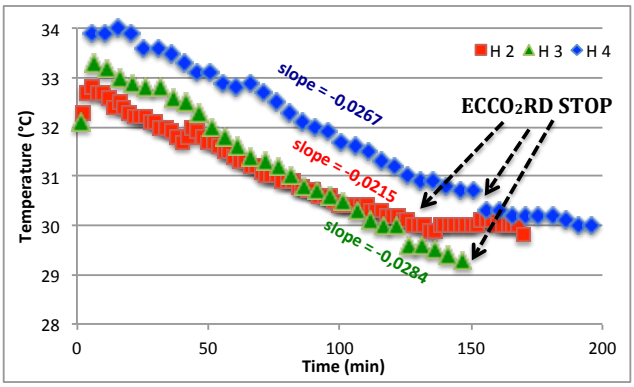

Fig. 8 Decrease of temperature for 3 pigs (H2, H3 and H4) when the ECCO$_2$RD is switched on.

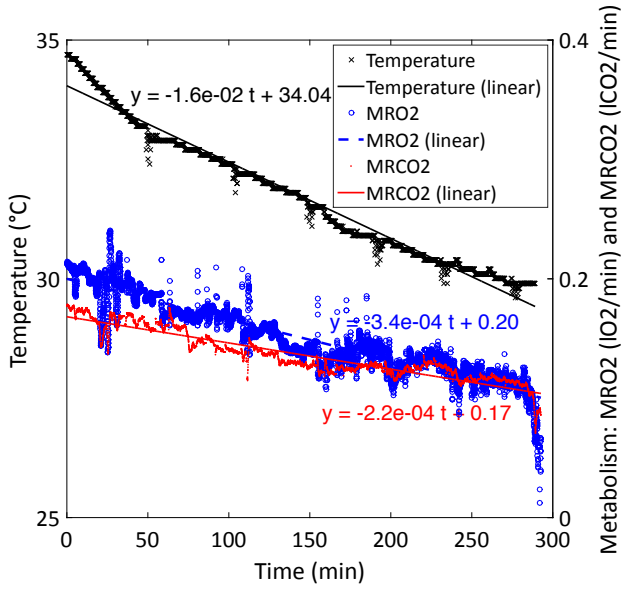

Fig. 9 Time evolution of MR_{CO_2} and MR_{O_2} and time evolution of temperature for pig 1.

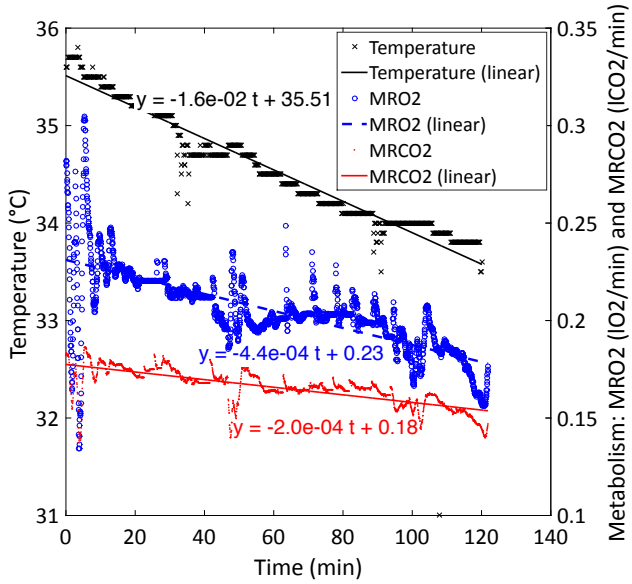

Fig. 10 Time evolution of MR_{CO_2} and MR_{O_2} and time evolution of temperature for pig 2.

Table 3 Parameters of the mathematical model

Parameters	Descriptions	Values
	Identified parameters	
D_{CO_2}	CO_2 diffusion coefficient across the synthetic membrane	6.33 $\times 10^{-5}$ l_{CO_2}/s/mmHg
D_{O_2}	O_2 diffusion coefficient across the synthetic membrane	1.58 $\times 10^{-6}$ l_{O_2}/s/mmHg
f_s	Pulmonary shunt	Subject-specific
k_{HCO_3}	Correction term for variations between individuals in standard HCO_3 concentration	Subject-specific
MR_{CO_2}	Quantities of CO_2 produced by metabolism	Subject-specific
MR_{O_2}	Quantities of O_2 used by metabolism	Subject-specific
$\dot{V}_L$	Effective ventilation	Subject-specific
	Measured parameters	
C_{Hb}	Hemoglobin concentration	0.15 l_{Hb}/l
Q_c	Cardiac output	Not constant
	Parameters taken from the literature	
α_{CO_2}	Solubility coefficient of CO_2 in blood plasma	$6.9 \cdot 10^{-4} l_{CO_2}$/l/mmHg [30]
α_{O_2}	Solubility coefficient of O_2 in blood plasma	$2.837 \cdot 10^{-5} l_{O_2}$/l/mmHg [30]
K_{HCO_3}	Equilibrium constant of chemical equation 8	$10^{-6.1}$ [30]
V_{L,CO_2}	Effective volume of CO_2 in the lungs	43 ml/kg [3]
V_{L,O_2}	Effective volume of O_2 in the lungs	33 ml/kg [3]
V_{T,CO_2}	Effective volume of CO_2 in the tissues	200 ml/kg [3]
V_{T,O_2}	Effective volume of O_2 in the tissues	80 ml/kg [3]
	Ventilator settings	
F_{I,CO_2}	Inspired fraction of CO_2	0
F_{I,O_2}	inspired fraction of O_2	Not constant
	$ECCO_2RD$ settings	
F_{ID,CO_2}	Fraction of CO_2 at the gas inlet for the $ECCO_2RD$	0
F_{ID,O_2}	Fraction of CO_2 at the gas inlet for the $ECCO_2RD$	0.21
Q_d	Extracorporeal blood flow	Not constant
$\dot{V}_D$	Ventilation of the $ECCO_2RD$	10 l/min