Creating Virtual ARDS Patients

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Abstract— **This paper presents the methodology used in patient-specific calibration of a novel highly integrated model of the cardiovascular and pulmonary pathophysiology associated with Acute Respiratory Distress Syndrome (ARDS). We focus on data from previously published clinical trials on the static and dynamic cardio-pulmonary responses of three ARDS patients to changes in ventilator settings. From this data, the parameters of the integrated model were identified using an optimization-based methodology in multiple stages. Computational simulations confirm that the resulting model outputs accurately reproduce the available clinical data. Our results open up the possibility of creating *in silico* a biobank of virtual ARDS patients that could be used to evaluate current, and investigate novel, therapeutic strategies.**

I. Introduction

Computer simulation of critical illness and its treatment can offer an alternative perspective to that of traditional approaches employed in *in vivo* and *in vitro* trials. Complex system dynamics can be modelled and validated against patient-data, leading to the development of computational simulators that can be used as investigational surrogates. Simulation also offers the potential to "look inside" the patient - when models are accurately matched to patients, the non-measurable parameters within the patient can be estimated with confidence.

Several examples exist in the literature detailing the development of models of cardiovascular and pulmonary systems for different applications [1]. With the exception of [2], few have discussed the difficulties that present themselves when integrating organ-level models of these two different systems. For the models used in this study, these difficulties included the different frequencies of the separate models (the cardiac model has a higher frequency), their different characteristics (the pulmonary model is primarily a gas flow model, whereas the cardiovascular model represents the flow of blood through the cardiovascular system), non-linear cardio-pulmonary interactions etc. These issues, along with early work on the development of the integrated model (including innovative equations that were required to reproduce complex cardio-pulmonary interactions) were discussed in [3]. This follow-up paper focuses on the solutions of problems encountered with configuring the model parameters to represent the spectrum of dynamic responses associated with the integrated cardio-pulmonary pathophysiology of mechanically ventilated ARDS patients.

Several previous studies have considered the task of patient specific model calibration (sometimes referred to as model configuration, parameter identification or parameter estimation) in separate cardiovascular and pulmonary models [4-6]. Automated tuning of model parameters has been a common and reliable method [7, 8]. The conventional way to tackle problems involving large numbers of uncertain model parameters is to reduce the number of parameters involved in model calibration to those that are relevant to the available clinical data. This is done through a 'sensitivity analysis' whereby model outputs are assessed for changes in individual model parameters, with respect to the clinical data. The merit of this approach has been shown in previous modeling studies [7] and has been incorporated into the model calibration methodology. The complete model calibration algorithm is shown in Table I.

The paper is organized as follows: Section II introduces the integrated cardio-pulmonary models and describes the model calibration methodology. Section III presents the results of the model calibration against static and dynamic data from individual ARDS patients. Section IV discusses the possible utilization and the limitations of the methodology, and offers some conclusions.

II. Methods

A. Model Description

Our study employs a highly integrated computer simulation model of the pulmonary and cardiovascular systems [3, 9]. The model includes 100 independently configurable alveolar compartments and 19 cardiovascular compartments. Aspects of the model related to pulmonary pathophysiology have been validated in a number of previous studies [10, 11]. The validated pulmonary model was integrated with a multi-compartmental, contractile cardiovascular model with pulsatile blood flow and ventilation-affected, trans-alveolar blood-flow. The cardiac section of the model consists of two contractile ventricles, with atria modeled as non-contractile, low-resistance, high-compliance compartments (the atrial contribution to cardiac performance is lumped with the contractile ventricular model). Ventricular contractility is modeled as a truncated sine-wave that varies ventricular elastance over time. Cardiopulmonary interactions are modeled in a number of ways. Intrapulmonary pressure is transmitted to the intraventricular, intrathoracic and intravascular compartments. Trans-alveolar blood flow is governed by driving (pulmonary artery) pressure, and by independent trans-alveolar vascular resistance; this resistance is affected dynamically in each alveolar compartment by alveolar volume (causing longitudinal stretch) and pressure (causing axial compression). Full details of the mathematical principles underpinning the model are available in [3, 12]. All model outputs presented here are averaged over 1 minute after a simulation time of 30 minutes.

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TABLE I. ALGORITHM FOR FITTING MODEL OUTPUTS TO PATIENT DATA IN THE INTEGRATED MODEL

1) Select model parameters for fitting.
   a) Select model parameters for the pulmonary model
   b) Select model parameters for the cardiovascular model through sensitivity analysis using Eq. (1).
2) Determine model parameters x for pulmonary model
   a) Use the pulmonary model, global optimization, and Eq. (2) to determine parameter values (x)
3) Determine model parameters for cardiovascular model
   a) Use the integrated cardiopulmonary model, global optimization, and Eq. (3), to determine parameter values (u) that minimize E_2 at different values of PEEP

B. Selection of Patient Data

Data regarding three ARDS patients was extracted from three papers from the literature, selected due to their inclusion of data on hemodynamic responses in ARDS patients to changes in mechanical ventilation, specifically changes in cardiac output to variation in positive end expiratory pressure (PEEP). The patients represent a cross section of ARDS patients, with varying severity (using the Berlin definition) and cardiac volemic status. General patient information is listed in Table II.

The first patient dataset was taken from a paper published by Biondi et al [13]. Based on the data at PEEP = 0 cm H_2O, the patient has a PF ratio of 150 mm Hg and cardiac output (CO) of 8 l min^{-1} (moderate ARDS with high CO). The second patient was taken from data published by Pinsky et al [14] and describes a patient with PF ratio of 167 mm Hg and cardiac output of 4.09 l min^{-1} (moderate ARDS with normal CO). The third patient dataset was taken from data published by Jardin et al [15] and describes a patient with PF ratio of 50 mm Hg and cardiac output of 7.3 l min^{-1} (severe ARDS with high CO).

TABLE II. SETTINGS AT PEEP = 0 CM H_2O OF THREE ARDS PATIENTS

	Moderate ARDS with high CO	***Moderate ARDS with normal CO***	***Severe ARDS with high CO***
CO (l min^{-1})	8	4.09	7.3
F_IO_2	0.5	0.45	1
Vt (ml kg^{-1})	12	10	10
PEEP (cm H_2O)	0	0	0

C. Assignment of baseline model parameters

To generate a general hemodynamic profile for a healthy subject, most values of resistances, unstressed volumes and pressures have been taken from standard data where available. The remaining model parameters were manually tuned to obtain model outputs within averaged population ranges as given in [16]. The model equations and healthy subject profile are described in detail in [3] and yield a baseline model with which to initiate the model calibration process.

The pulmonary model has already been used to represent data on ARDS patients in [12]. Prior to the calibration of the cardiovascular model, a sensitivity analysis (SA) was performed. The aim was to determine key model parameters that are predominantly responsible for the model responses corresponding to clinical data, which involved calculating S below for each model parameter.

$$S = \sum \left(y_{max} - y_{min}\right) / y_{baseline} \quad (1)$$

Here, y is model outputs of CO and mean arterial pressure (MAP). y_{max}, y_{min} and $y_{baseline}$ are the maximum, minimum and baseline values of the model outputs calculated during the SA, respectively. A similar sensitivity analysis has earlier shown to be been useful in validating the pulmonary model [11]. The results of the sensitivity analysis indicate key parameters of cardiovascular model (in Table 3) in determining CO and MAP. The parameters are consistent with other cardiovascular modelling studies [7].

D. Model parameter configuration using optimization

The model was configured to fit data from individual ARDS patients in two stages. In the first stage, the model was fitted to static data from separate patients (listed in Table 4). The data consisted of arterial and mixed venous blood gas values and cardiac output estimations for each patient, listing the following measurements at PEEP = 0 cm H_2O: cardiac output in ml min^{-1} (CO), partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), tidal volume (Vt) and fraction of oxygen inhaled air (F_IO_2). The model parameters (x) to be optimized for each of the 100 alveolar compartments were P_{ext}, k_{stiff} and TOP, representing the extrinsic pressure acting on an alveolar compartment, the stiffness of the compartment and the threshold opening pressure, respectively. The values for respiratory quotient (RQ), rate of breathing (VR), total oxygen consumption (VO_2), and the inspiratory duty cycle were additional parameters determined by the optimization algorithm. In this case, the model-fitting problem was formulated to search for a configuration of model parameter values (x) that minimizes objective function E_1 in the equation below:

$$\min_x E_1 = \sqrt[2]{\sum_{i=1}^{4} r_j^2} \quad \text{where } r_i = \frac{y_i - y_i'}{y_i'} \quad (2)$$

where y = [PaO_2, $PaCO_2$, TOP_{mean}, P_{peak}] are the model outputs and y' = [PaO_2', $PvCO_2$', TOP_{mean}', P_{peak}'] are the target values. PaO_2' and $PaCO_2$' are measurements obtained from the patient data. TOP_{mean} is the average TOP of the alveolar units, which is set to 20 cmH_2O [17]. P_{peak} is the peak airway pressure which is minimized to 30 cm H_2O (a target in the 2000 ARDSnet report [18]).

Stage 2 of the fitting process required a search for the optimal values of the parameters of the cardiovascular models (u) effectively allowing the modification of the cardiovascular function. The optimization process was used to fit the data for changes in CO and mean arterial pressure (MAP) to changes in PEEP. For this stage, the optimization problem was formulated to find a configuration of model parameters (u) that minimizes the objective function E_2:

$$\min_u E_2 = \sqrt[2]{\sum_{j=1}^{k} r_j^2} \quad \text{where } r_j = \frac{y_j - y_j'}{y_j'} \quad (3)$$

where $\mathcal{Y}$ y_j = [CO_i, MAP_j] are the model outputs and $\mathcal{Y}'y'$= [CO_i', MAP_i'] are the CO and MAP values reported in

the data for the j[th] PEEP value, with k different settings of PEEP.

The optimization parameters (x) and (u) in stage 1 and stage 2, their sizes, ranges and units are summarized in Table 3. Genetic algorithms (GA's) were employed for the optimization processes of Stage 1 and 2, primarily due to their ease of application in problems with large and small parameter search spaces, and their capability to converge to the global optimum even in highly non-convex parameter spaces. Initial model calibration and analysis were performed on a 64-bit Intel Core i7 3.7 GHz PC, running Matlab (R2014a). Model calibration to data was performed using the 'Minerva' high performance computing cluster provided by the University of Warwick (396 nodes, each with 2×hexa-core 2.66 GHz 24 GB RAM) running Matlab (2015a) with global optimization and parallel computing toolboxes.

TABLE III. PARAMETERS FOR MODEL CALIBRATION

		Parameters	***Dimension***	***Ranges***	***Sensitivity***
x, model parameters used for optimization in Stage 1.		VR (b min^{-1})	1	10 – 20	
		Duty Cycle	1	0.25 - 0.5	
		RQ	1	0.7 - 0.9	
		VO_2 (ml min^{-1})	1	250 – 350	
		TOP (cm H_2O)	100	5 - 70	
		k_{stiff}	100	-1 - 1	
		P_{ext}	100	-30 – 28.8	
		Hb (g dl^{-1})	1	90 – 160	
u, model parameters used for optimization in Stage 2.	Parameter suggested to be most sensitive from SA (S >5%)	$P_{lv,\ dias,c}$ (mm hg)	1	1-5	9%
		$P_{rv,dysc,c}$ (mm hg)	1	1-5	38%
		λ_{lv}	1	1 - 15	25%
		λ_{rv}	1	1 - 15	27%
		λ_{sa}	1	1 - 15	15%
		$\lambda_{sv,}$	1	1 - 15	43%
		R_{sv}	1	0.001 - 0.05	51%
		R_{sa}	1	0.1 - 0.20	63%
		n_{pvr}	1	0.5 - 2	
		q_{pvr}	1	40 - 80	
		γ_{pvr}	1	0.8	

List of Abbreviations SA – sensitivity analysis, VR - Ventilator Rate, Duty Cycle - Inspiratory Time/Time for complete breath, RQ - Respiratory Quotient, VO2 - Oxygen Consumption, TOP - Threshold Opening Pressure, k - alveolar stiffness factor, Pext - Extrinsic pressure, Hb - Haemoglobin in blood, Plv,dias,c – Left Ventricle initial pressure, Prv,dys,c – Right Ventricle Pressure initial pressure, λlv,- left ventricle elastance coefficient, λrv– right ventricular elastance coefficent, λsa – systemic artery elastance coefficent, λsv, systemic vein elastance coefficient, , Rsa - systemic venous resistance, Rsa - systemic arterial resistance, pvr – pulmonary vascular resistance, n_{pvr} – pvr exponential coefficient, q_{pvr} – alveolar volume pvr coefficeint, γ_{pvr} – thoracic pressure splinting coefficient.

III. RESULTS

Table 3 shows the results of the SA. Only parameters with S of > 5% are listed and selected for Stage 2. Table 4 shows the results of Stage 1 of the model calibration process. The minimum value calculated for E_1 was 0.3271 for the moderate ARDS high CO patient, 0.3716 for the moderate ARDS normal CO patient and 0.3823 for the severe ARDS high CO patient.

Figure 1 displays the results of stage 2, where the model outputs were matched to increments in PEEP (given on the horizontal axes of Figure 1. The minimum value calculated for E_2 was 0.1278 for the moderate ARDS high CO patient, 0.0673 for the moderate ARDS normal CO patient and 0.2172 for the severe ARDS high CO patient.

TABLE IV. RESULTS OF STAGE 1 OF MODEL CALIBRATION

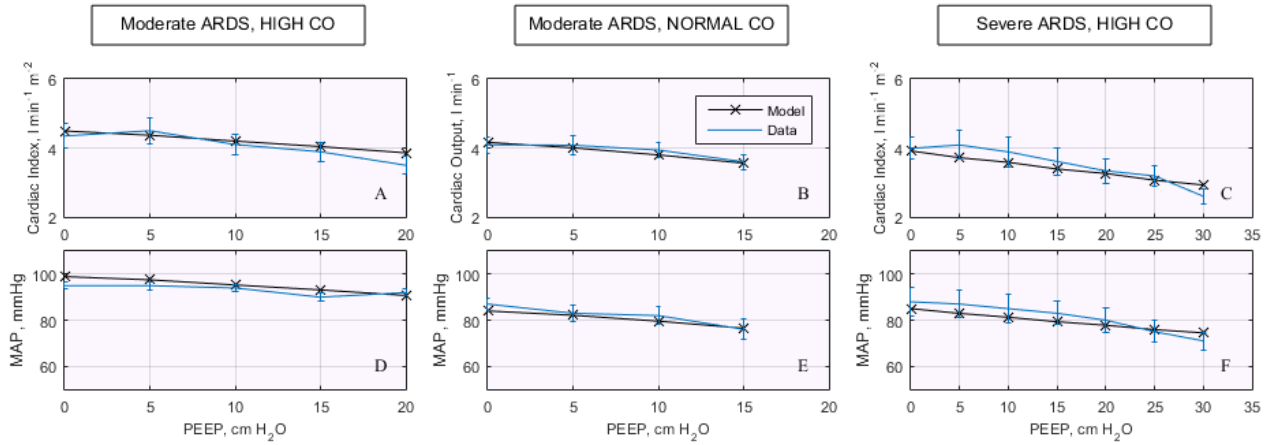
	Moderate ARDS with high CO	***Moderate ARDS with normal CO***	***Severe ARDS with high CO***
PaO_2 (kPa)	11.2 (10.6)	10.8 (10)	7.5 (6.6)
$PaCO_2$ (kPa)	4.4 (5)	5.2 (5.3)	4.3 (3.7)
PvO_2 (kPa)	4.6 (NA)	4.4 (NA)	4.1 (NA)
Shunt (%)	22 (NA)	16 (NA)	44 (NA)
TOP_{mean} (cm H_2O)	28 (NA)	20 (NA)	29 (NA)
P_{peak} (cm H_2O)	32 (NA)	22 (NA)	30 (NA)
The model outputs and (data)			

IV. DISCUSSION AND CONCLUSIONS

The outputs of our calibrated model were consistently very close to the data derived from clinical trials, indicating acceptable validity of the suite of models in reproducing dynamic, in vitro, multi-organ behavior. Further simulations have also indicated that the integrated model is able to simulate and chart blood flow and pressure(s) accurately.

The choice of Genetic Algorithms to perform the optimization was based on their inherent characteristics. Unlike local search algorithms, they are derivative free and less dependent on the initial parameter estimates. There are disadvantages to using GA's, namely that global algorithms like GA's typically require much longer computation times than local gradient-based methods. The algorithms have previously been compared in [11]. To speed up the optimization process, a parallelized computer code implementation of a genetic algorithm was employed in this study. Fortunately, the cost function evaluation process can be accelerated hugely by distributing the tasks to multiprocessors (multiple cores and/or multiple machines). High performance computing facilities available at the University of Warwick were configured and implemented to run the parallel computing processes.

The capability of the integrated model to reproduce the detailed responses of individual ARDS patients opens up the possibility of rationally "designing" new multi-intervention treatment strategies in silico by exploiting the speed, reproducibility, and cost-effectiveness of "virtual" patient trials. In contrast to trials on both animal models and human patients, in silico models of individualized patient and disease pathology are completely configurable and reproducible – different treatments, or combinations of treatments, can be applied to the same spectrum of virtual patients, in order to understand their mode of action, quantitatively compare their effectiveness in multiple different scenarios, and optimize interventions for particular clinical objectives. Seen from an



engineering design perspective, such "virtual" trials using simulations that are rooted in real patient data can offer comparable (or sometimes greater) utility to that of clinical trial data. In particular, modelling studies provide unambiguous outcomes that allow future clinical trials to be honed and directed, massively accelerating the achievement of real changes in clinical practice

The methodology has limitations. The small size of the clinical dataset considered to date does not yet allow for convincing statistical analyses. For simplicity, it is assumed that the parameters determining lung pathology remain unaltered after stage 1. We also assume that stage 2 optimization parameters such as systemic arterial resistance, etc. do not vary with increases in PEEP. This could be improved by the implementation of different autonomic reflexes, which we aim to address in the near future. The sensitivity analysis was performed only locally around the parameter configuration of a baseline healthy subject. Ideally, global sensitivity analysis [7] would provide a better picture of the model parametric space.

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