

Development of an Integrated Model of Cardiovascular and Pulmonary Physiology for the Evaluation of Mechanical Ventilation Strategies

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Abstract— We describe the development of an integrated cardiovascular and pulmonary model for use in the investigation of novel mechanical ventilation strategies in the intensive care unit. The cardiac model includes the cardiac chambers, the pulmonary circulation and the systemic circulation. The modeling of complex mechanisms for vascular segments, time varying elastance functions of cardiovascular components and the effect of vascular resistances, in health and disease under the influence of mechanical ventilation is investigated. The resulting biomedical simulator can aid in understanding the underlying pathophysiology of critically-ill patients and facilitate the development of more effective therapeutic strategies for evaluation in clinical trials.

I. INTRODUCTION

One of the primary tasks in the Intensive Care Unit (ICU) is to maintain the cardiopulmonary function of patients through, among other means, respiratory support using mechanical ventilation (MV). Such interventions can result in further risks to the patient, for example, large tidal volumes and ventilator pressures are detrimental to patients' lungs [1] while changes in lung inflation and thoracic pressure as a result of MV can have deleterious effects on the functioning of the cardiovascular system [2].

Consequently, selection of appropriate MV settings for providing adequate respiratory support requires due consideration of hemodynamic effects while maintaining oxygenation and reducing the risk of lung injury. This is clearly a complex problem, which can require the management of trade-offs between objectives that could be conflicting. Decisions in an ICU can often be based on poorly understood physiological mechanisms and are dependent on surrogate measurements [3]. Computational modeling can be a potentially powerful aid in understanding and disseminating complex physiology, enabling accurate and early diagnosis, and developing more effective patient specific MV therapy.

Numerous efforts have been made to simulate cardiac and pulmonary pathophysiology, yet few have attempted to incorporate the necessary level of complexity in both systems. In most cases [4-9], focus has been primarily on the cardiovascular system, with the pulmonary system often reduced to a single representative parameter. This level of simplification can provide some information on the effect of changes in intra-thoracic pressure on the cardiovascular

system, but risks associated with particular mechanical ventilation strategies, such as barotrauma, are rarely considered. The lung, with its heterogeneous distribution of ventilation and blood flow, merits more detailed consideration, especially when considering MV strategies.

The Nottingham Physiology Simulator (NPS) has been a useful and powerful tool in developing credible insight into pulmonary pathophysiology [10-11]. Previous studies have incorporated large numbers of alveolar compartments, enabling the simulation of variable gas and blood flows and allowing for simulation of severe ventilation perfusion mismatch for investigation of disease states such as Acute Respiratory Distress Syndrome (ARDS) and Chronic Obstructive Pulmonary Disease (COPD) [10-11]. The current version of the NPS consists of dynamic models of mechanical ventilation, airways, ventilated alveolar compartments, physiological shunt and deadspace. Furthermore, the model reproduces the behavior of the soft tissues of the lung, including viscoelastance and gravitational effects. The individual components of the NPS have undergone extensive validation in previous studies [10-15].

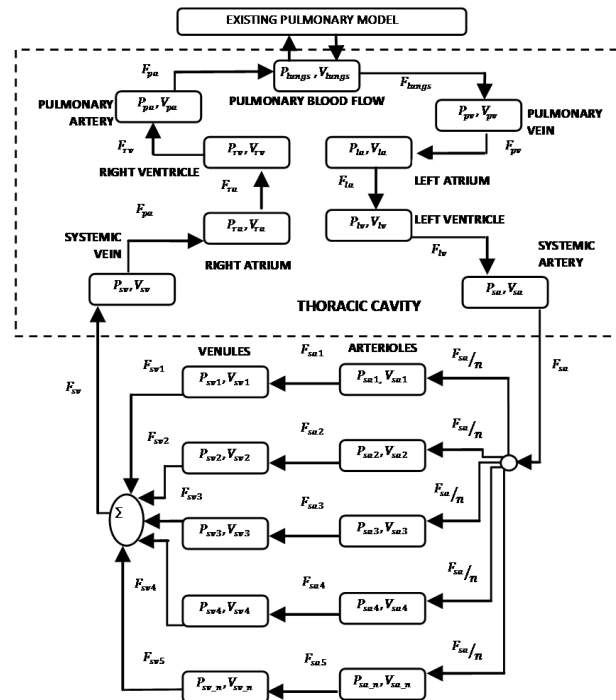


Figure 1. Schematic of cardiovascular extensions to existing pulmonary model

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However, thus far the NPS has only included a relatively simple representation of the cardio-vascular system, using a constant value of cardiac output and no systemic circulation. This paper presents recent work on expanding the NPS to include a comprehensive and fully integrated model of cardiopulmonary pathophysiology. An improved model of the cardiovascular components is presented that simulates the blood flow through the cardiac chambers, the systemic circulation and the pulmonary circulation (Fig. 1). The relevant cardiac pathophysiology has been modeled as a multiscalar, multicompartamental set of systems that is suitable to interface with the existing pulmonary model. The heart is described as a pulsatile pump by simulating the activity of ventricles using an elastance function. The model has separate components for large and small systemic vasculature.

The paper is organized as follows: Section II describes the relevant components of the cardiovascular model in detail. Section III provides simulation results when the model is configured to represent a healthy patient, and a patient with ARDS, and discusses the clinical importance of the key interactions between the cardiac and pulmonary models. Finally, some conclusions are made in Section IV.

II. METHODS

A. Description of the Cardiac model

The cardiac model consists of 19 compartments. Each compartment x , is described with a pressure P_x , a volume V_x and a flow leaving the compartment F_x , which are iteratively updated in a sampling interval. Furthermore, each compartment has the following fixed parameters: a linear resistance R_x to the flow out of the compartment, a coefficient λ_x governing the elastance of each compartment, a $V_{x,u}$, depicting the unstressed volume of the compartment and coefficient $P_{x,c}$, the pressure in the compartment when $V_x = V_{x,u}$. The ventricles are modeled as having time varying elastances over the duration of a cardiac cycle using different exponential functions to describe the filling and emptying of the ventricles [16]. The shift from the systolic to diastolic relationship is governed by a pulsating activation function with period T . For all the compartments, vascular elastance is assumed to be nonlinear and to have an exponential relationship governed by the following equation,

$$P_x = P_{x,c} e^{\frac{\lambda_x(V_x - V_{x,u})}{(V_x + V_{x,u})}}, \quad (1)$$

where the subscript x represents the compartment number and the $\lambda_x, P_{x,c}, V_{x,u}$ are constants that give flexibility in matching specific shapes and peaks of pressure waveforms that could be observed from clinical data. The model employs separate pressure volume relationships for the systolic and diastolic behavior of ventricles as suggested in [16]. The left ventricular pressure calculation is given by:

$$P_{lv} = \varphi P_{lv,syst} e^{\frac{\lambda_{lv,syst}(V_{lv} - V_{lv,syst,u})}{(V_{lv} + V_{lv,syst,u})}} + (1 - \varphi) P_{lv,diast} e^{\frac{\lambda_{lv,diast}(V_{lv} - V_{lv,diast,u})}{(V_{lv} + V_{lv,diast,u})}} \quad (2)$$

The right ventricular pressure calculation is given by:

$$P_{rv} = \varphi P_{rv,syst} e^{\frac{\lambda_{rv,syst}(V_{rv} - V_{rv,syst,u})}{(V_{rv} + V_{rv,syst,u})}} + (1 - \varphi) P_{rv,diast} e^{\frac{\lambda_{rv,diast}(V_{rv} - V_{rv,diast,u})}{(V_{rv} + V_{rv,diast,u})}} \quad (3)$$

The function φ is a ventricle activation function which is assumed to attain the maximum value of $\varphi = 1$ at the peak of systolic contraction. The function φ attains its minimum value 0 at maximal diastole relaxation. A squared half-sine wave function is adopted for φ [16-17] given by:

$$\varphi = \begin{cases} \left(\sin\left(\pi T \frac{u}{T_{syst}}\right) \right)^2 & \text{if } u \geq 0 \text{ and } u \leq \frac{T_{syst}}{2} \\ 0, & \text{if } u > \frac{T_{syst}}{2} \text{ and } u \leq 1 \end{cases} \quad (4)$$

$$T = 1/HR, \quad T_{syst} = \frac{(\tau_{syst} - k_{syst})}{T}, \quad \text{where } T_{syst} = 0.5 \text{ and } k_{syst} = 0.075 \quad (5)$$

u is a real number ranging between 0 and 1 and it models the fraction of the cardiac cycle. $u = 0$ at the end of systole and $u = 1$ at the end of diastole. T_{syst} indicates the systolic period which is proportional to the heart rate HR (in seconds).

The blood flow between compartments is determined by the pressure gradient between compartments across a linear time invariant resistance R_x .

$$F_x = \frac{\eta_x(P_x - P_y)}{R_x}, \quad (6)$$

$$\eta_x = \begin{cases} 0, & \text{if } P_x < P_y \\ 1, & \text{if } P_x \geq P_y \end{cases} \quad (7)$$

The parameter η_x allows the blood to flow in one direction but can be altered to investigate flow backwards into a compartment, such as during aortic regurgitation. The volume of the blood in each compartment is computed by applying conservation of mass as follows

$$V_x = (V_{x0} + (F_x - F_x)\Delta t), \quad (8)$$

where F_x is the flow entering the x th compartment (i.e. the flow leaving the upstream compartment) and F_x is the flow leaving the compartment x . V_{x0} is the volume of compartment x before the iteration, and Δt is the size of the time period in this iteration (set to 1 ms). The total amount of blood in the whole body is obtained by $V_T = \sum V_x$.

B. Cardio pulmonary interactions

The model includes the effect of radial compressive and axial stretching forces exerted onto pulmonary capillaries as a result of increase in lung volume and pressure. The overall effect on resistance to flow through each capillary is difficult to quantify, but we assume the following: (i) at alveolar volumes above the functional residual capacity (FRC), the vessels become compressed and raise the pulmonary vascular resistance (PVR), (ii) at alveolar volumes below FRC, the vessels can collapse and thus result in an increase in PVR, while closer to FRC the PVR remains unaffected. A separate mechanism called hypoxic vasoconstriction, of the vessels contracting in response to hypoxia as a result of alveolar collapse, is already present in the existing pulmonary model. The resultant 'U' shape change in PVR at around the FRC has been suggested previously [3] and has

been implemented in this model as follows. The pulmonary vascular resistance PVR is determined by,

$$\frac{1}{PVR} = \frac{1}{R_{V,1}} + \frac{1}{R_{V,2}} + \dots + \frac{1}{R_{V,N_A}}, \quad = 1, \dots, N_A \quad (10)$$

where the vascular resistance for each alveolar compartment, $R_{V,i}$, is defined as

$$R_{V,i} = pvr_{mult,i} \delta_{Vi} R_{V0}, \quad \text{for } i = 1, 2, \dots, N_A, \quad (11)$$

N_A is the number of alveolar compartments (set to 100), R_{V0} is the default vascular resistance for the compartment with a value set to $160 \cdot N_A$ dynes s $\text{cm}^{-5} \text{min}^{-1}$, and δ_{Vi} is the vascular resistance coefficient, used to implement the effect of Hypoxic Pulmonary Vasoconstriction. $pvr_{mult,i}$ is calculated as follows:

$$pvr_{mult,i} = \left(1 + 0.5 \left(\frac{v_i - v_{FRC}}{v_{FRC}}\right)^2\right) \left(1 + p_i/q\right), \quad (12)$$

where, p_i is the pressure generated within the i^{th} alveolar compartment, v_i is the volume of the i^{th} alveolar compartment, v_{FRC} is a constant representing the volume of the alveolar compartment at rest (fixed to 30 ml) and q is used to adjust the pvr equation. q has been set to 30.

Increase in lung pressures, such as those observed during the addition of incremental PEEP (Positive End Expiratory Pressure) during ventilation, serves to increase mean intrathoracic pressure to bring about the recruitment and maintenance of collapsed alveolar lung units as mentioned above. In addition to the affect on PVR, the average alveolar compartment pressure within the lung exerts an extrinsic pressure which is applied to the intra-thoracic vascular compartments. This phenomenon is known as splinting. The pressure calculation of the compartments within the thoracic cavity therefore has an additional term, P_{tp} , added to them, representing the intrathoracic pressure

$$P_{tp} = \gamma_x (P_{lung} - P_{atm}). \quad (13)$$

$\gamma_x = 0$ for extra-thoracic compartments (see Fig. 1). For the purposes of this study, $\gamma_x = 0.5$, based on the suggestion in [18].

Model parameters have been identified from the published literature where available – parameters whose values were not available from the literature were adjusted within their physiological ranges based on the resulting pressure and flow waveforms.

III. RESULTS

A. Healthy individual results

Table 1 shows the results from a simulation of a healthy male compared to published normal values [19] with baseline MV settings, which show the outputs of the model simulation to be within plausible clinical ranges. Increasing PEEP in the combined cardiopulmonary model results in increased PVR and splinting. The effects of these additional forces are more pronounced in the right heart system which functions at lower blood pressures than the left heart. The increased PVR

(Fig.2) results in increased right ventricular afterload (Fig. 3) and opposes ejection of blood during systole.

TABLE 1. SIMULATED RESULTS VERSUS DATA FROM A HEALTHY MAN [19]

Parameter	Unit	Normal Values	Simulated case
Total blood volume	ml	4490	4490*
Cardiac Output	ml min^{-1}	6.3±2.4	5.584
LV EDV	ml	183±23	171.05
LV ESV	ml	67±11	69.95
RV EDV	ml	260±49	210
RV ESV	ml	144±37	111
Aortic Pressure	mmHg	90-140/70-90	103.1/57.2
LV pressure	mmHg	90-140/6-12	106.6/5.7
RV Pressure	mmHg	20-30/4-13	47.7/5.3

LV: left ventricle, RV: right ventricle, EDV: end diastolic volume, ESV: end systolic volume, * This value was set in the simulator.

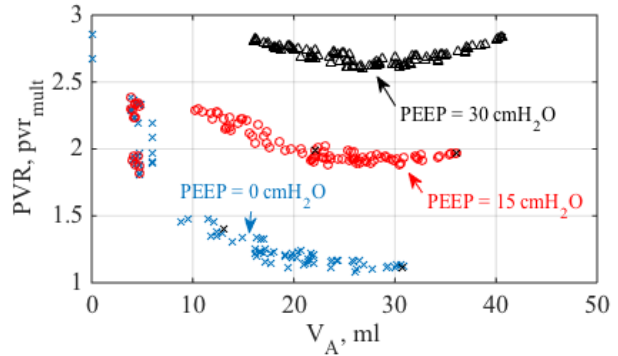


Figure 2. Simulated PVR distribution in a diseased lung (disease configuration from a previous study [10]). PVR – Pulmonary Vascular Resistance, V_A – Alveolar compartmental volume

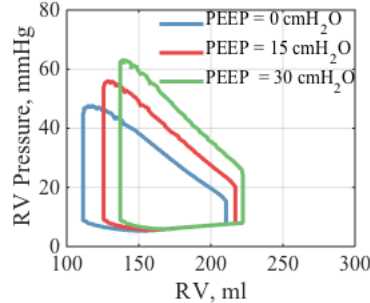


Figure 3. Simulated Right Ventricle pressure volume loop with splinting off.

The increased splinting effect serves to reduce preload and thus reduce ventricular filling during diastole. The combined effect of increased PEEP, PVR and splinting effect is a reduced right ventricular end-diastolic volume, reduced right ventricular end-systolic volume and a marked reduction in right ventricular stroke volume (Fig. 4a). The upstream effect of this is an increase in central venous pressure. The downstream effects on the left ventricle are also reduced end-diastolic volume, reduced end-systolic volume and reduced stroke volume (Fig. 4b). All these effects are demonstrated by the model and are consistent with both expected human physiological behaviour and previous multi-modal measurements of cardiac performance in response to PEEP [20].

If PEEP is increased without the splinting effect, preload is maintained despite the increased intrathoracic pressure, with raised PVR and afterload. The effect is an increased right ventricular end-diastolic volume, an increased end-systolic volume and a reduced right ventricular stroke

volume. This is consistent with plausible physiological reasoning, and early animal experiments [21].

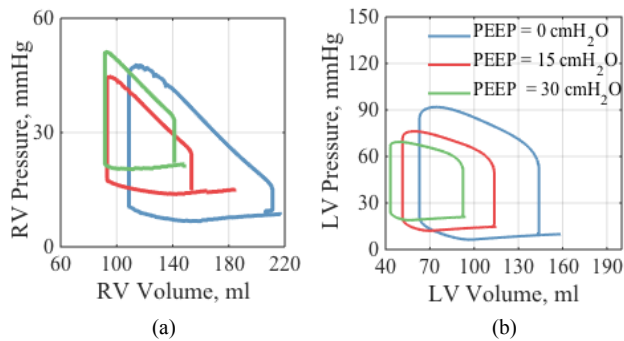


Figure 4. (a) Simulated right ventricle (RV) and (b) left ventricle (LV) pressure volume loop with splinting.

B. ARDS patient results

A patient is simulated with severe ARDS (ratio of arterial oxygen partial pressure to fractional inspired oxygen, PFratio <100mmHg) (for details see ‘patient B’ in [10]). The CVS model is set up to generate a cardiac output of 7.5 l min⁻¹, and heart rate is set to 100 beats per minute. Fig. 5 presents the results of the simulated model, which correspond well with clinical data on the effects of increasing levels of PEEP [22]. Increasing PEEP led to improvement in oxygenation (rise in arterial oxygen tension), which can be attributed to an increase in recruitment of derecruited lung units. Higher levels of PEEP also led to decreases in shunt and decreases in cardiac output.

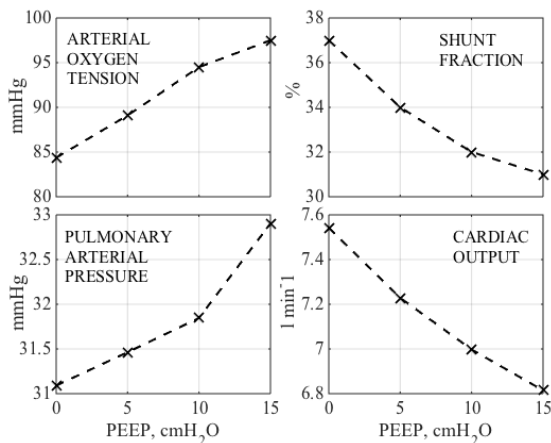


Figure 5: Simulated ARDS patient results. PEEP- Pulmonary End Expiratory Pressure. The patient has an inhaled oxygen fraction of 0.9.

IV. CONCLUSIONS

Integration of a detailed cardiovascular model with the NPS has produced a powerful simulator with the capability to represent the response of multiple clinical indicators to MV interventions. Early results confirm the potential role that the simulator can play in taking into account the hemodynamic changes associated with novel MV therapies. The model has several limitations, such as lack of autonomic reflexes and flow to specialized vascular beds such as the cardiac, renal and cerebral circulations. However, there is potential to extend the blood flow distribution system, which is currently representing the systemic circulation around the body. Future

work will investigate in detail specific disease scenarios, with particular consideration of tissue oxygenation, hypercapnia, and ventilator associated lung injury.

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