Study of ventricular interaction during pulmonary embolism using clinical identification in a minimum cardiovascular system model

Thomas Desaive[1], Alexandre Ghuysen[2], Bernard Lambermont[2], Philippe Kolh[2], Pierre C. Dauby[1], Christina Starfinger[3], Christopher E. Hann[3], J. Geoffrey Chase[3], Geoffrey M. Shaw[4]

[1] Institute of Physics, University of Liège, Belgium
[2] Hemodynamics Research Laboratory, University of Liège, Belgium
[3] Centre of Bioengineering, University of Canterbury, Christchurch, New Zealand
[4] Department of Intensive Care Medicine, Christchurch Hospital, Christchurch, New Zealand

***Abstract*— Cardiovascular disturbances are difficult to diagnose and treat because of the large range of possible underlying dysfunctions combined with regulatory reflex mechanisms that can result in conflicting clinical data. Thus, medical professionals often rely on experience and intuition to optimize hemodynamics in the critically ill. This paper combines an existing minimal cardiovascular system model with an extended integral based parameter identification method to track the evolution of induced pulmonary embolism in porcine data. The model accounts for ventricular interaction dynamics and is shown to predict an increase in the right ventricle expansion index and a decrease in septum volume consistent with known physiological response to pulmonary embolism. The full range of hemodynamic responses was captured with mean prediction errors of 4.1% in the pressures and 3.1% in the volumes for 6 sets of clinical data. Pulmonary resistance increased significantly with the onset of embolism in all cases, as expected, with the percentage increase ranging from 89.98% to 261.44% of the initial state. These results are an important first step towards model-based cardiac diagnosis in the Intensive Care Unit.**

I. Introduction

There are many cardiovascular (CVS) models in the literature ranging from very complex finite element models [1] to relatively simpler pressure volume approaches [2]. However, the focus is often on only specific areas of CVS dysfunction. Although there are full CVS models, patient specific parameter optimization is either not considered or restricted to small subsets of the overall much larger parameter set, describing specific aspects of the CVS [3]. This approach can dramatically limit the range of CVS disturbances that can be detected, thus prohibiting use as a broader diagnostic tool. For relatively larger, more complex system models computational cost and feasibility can also be a major issue.

This research employs a physiologically validated minimal model [4] capable of capturing patient dynamics commonly seen in an Intensive Care Unit (ICU), while using a relatively small number of physiological variables. A highly efficient solution method [5], [6] provides the necessary simplicity, flexibility and rapid forward simulation that is required in a clinical environment. Finally, a linear, convex and integral-based identification method that allows virtually all the parameter set to be identified is employed to create patient specific models from clinical data [7]. This model is applied to porcine data studying pulmonary embolism (PE) and we emphasize the role of ventricular interaction (VI).

II. Methodology

A. CVS model

Our model is a lumped parameter model similar to [4], where the left and right ventricle chambers are characterized by the flow in and out of the chamber, the pressure up- and downstream and the resistances of the valves, and inertia of the blood. An overview of the model is given in Figure 1.

The equations for the left ventricle are defined:

$$V_{pcd} = V_{lv} + V_{rv} \tag{1}$$

$$P_{pcd} = P_{0pcd} \cdot (e^{\lambda_{pcd}(V_{pcd}-V_{0pcd})} - 1) \tag{2}$$

$$P_{peri} = P_{pcd} + P_{th} \tag{3}$$

$$V_{lvf} = V_{lv} - V_{spt} \tag{4}$$

$$\begin{aligned} P_{lvf} = {} & driL \cdot E_{eslvf} \cdot (V_{lvf} - V_{dlvf}) \\ & + (1 - driL) \cdot P_{0lvf} \cdot (e^{\lambda_{lvf}(V_{lvf}-V_{0lvf})} - 1) \end{aligned} \tag{5}$$

$$P_{lv} = P_{lvf} + P_{peri} \tag{6}$$

$$P_{pu} = E_{pu} \cdot (V_{pu} - V_{dpu}) + P_{th} \tag{7}$$

$$\dot{V}_{ao} = Q_{av} - Q_{sys} \tag{8}$$

$$Q_{sys} = \frac{P_{ao} - P_{vc}}{R_{sys}} \tag{9}$$

$$P_{ao} = E_{ao} \cdot (V_{ao} - V_{dao})^f \tag{10}$$

$$\dot{V}_{lv} = Q_{av} - Q_{mt} \tag{11}$$

$$\begin{aligned} \dot{Q}_{mt} = {} & H(H(P_{pu} - P_{lv}) + H(Q_{mt})) \\ & \cdot \frac{(P_{pu} - P_{lv} - R_{mt} \cdot Q_{mt})}{L_{mt}} \end{aligned} \tag{12}$$

$$\begin{aligned} \dot{Q}_{av} = {} & H(H(P_{lv} - P_{ao}) + H(Q_{av})) \\ & \cdot \frac{(P_{lv} - P_{ao} - R_{av} \cdot Q_{av})}{L_{av}} \end{aligned} \tag{13}$$

where H is the Heaviside function, dri_L is the left ventricle driver function (see below), f is a nonlinear factor ranging from 0.8 to 1.4, and all other variables are as shown in Figure 1. Similar equations are used for the right ventricle and pulmonary/ systemic circulation. For a more detailed description see [4], [5], [8]. The parameter f in Equation (10) provides more flexibility to capture the peak of P_{ao} seen in clinical data.

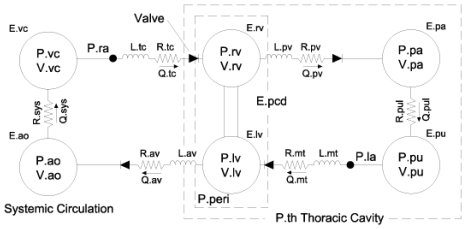


Fig. 1. Minimal CVS model overview

1) Activation Function: The electrical activation of the left and right ventricles are described using a driver function and time varying elastance to model cardiac muscle activation. Separate driver functions are chosen for the left and right ventricles.

$$dri_k = A_k \cdot e^{(-b_k \cdot (t - \frac{period}{c_k})^2)}, \; k = L, R \tag{14}$$

where $\text{period} = \frac{1}{\text{heartrate}}$, $A_L = 1$, $b_L = 2582.177$, $c_L = 2.07$ and $A_R = 1$, $b_R = 91.5975$, $c_R = 2.18$ for the left (L) and right ventricles (R).

2) Ventricular Interaction: VI is an important dynamic [9], [10]. In PE, if the embolus is large and associated with pulmonary artery obstruction, right ventricular dilation may occur and cause a leftward septum shift through ventricular interdependence [11], [12]. Thus, the septum volume V_{sept} may be an important dynamic to capture in this case and it is described by a time-varying P-V relationship [6].

B. Integral Based Parameter Identification

An integral-based parameter identification method has been developed [7] that transforms the typically non-linear and non convex identification problem into a linear, convex problem using limited data and minimal computation. This method was extended in [6] to rapidly identify the porcine specific parameters from experiments. The available measured data for this study includes the pressure waveforms in the aorta (P_{ao}), pulmonary artery (P_{pa}) and both ventricles (P_{lv}, P_{rv}), and the volumes of both ventricles (V_{lv}, V_{rv}).

Given these waveforms the integral identification process leads to a system of linear equations for the full CVS model [6]:

$$A \cdot \overrightarrow{x} = \overrightarrow{b} \tag{15}$$

$$\begin{aligned} \overrightarrow{x} = \Big(& L_{av}, L_{mt}, L_{tc}, L_{pv}, E_{eslvf}, P_{0lvf}, E_{esrvf}, \\ & P_{0rvf}, E_{ao}, E_{pa}, E_{vc}, E_{pu}, R_{av}, R_{mt}, R_{tc}, R_{pv}, \\ & P_{ao0}, P_{pu0}, P_{pa0}, P_{vc0}, R_{sys}, R_{pul} \Big)^T \end{aligned} \tag{16}$$

with $\overrightarrow{x}$ being the solution vector of the parameters to be identified, which can be found by linear least squares. More details about this integral method and parameter definitions can be found in [7]. Note that in an ICU setting, the waveforms P_{ao} and P_{pa} would be available with catheters, but the left ventricle volumes are not typically measured. However stroke volume (SV) and global end-diastolic volume ($GEDV$) are readily available from the PiCCO monitor (Pulsion Medical Systems AG, Munich, Germany). Thus an estimate of the minimum and maximum volumes could be done based on a known blood distribution for the different compartments of the body [13]. An extension to the integral method [6] has shown that only the maximum and minimum pressures in the aorta and pulmonary artery and the volumes are sufficient for parameter identification. Future work will evaluate the importance of these volume estimates in the ICU and possibly consider the use of portable ultrasound probes [14] for more accuracy.

In this paper, the parameters are identified for each period of measured data during the porcine experiment of PE. Thus, time varying changes from the initial healthy state to the fully diseased state are captured as might be desired for a clinical system. As a result, this type of identification provides a potential for monitoring CVS disease state in an evolving patient.

C. Porcine Experiments and Data

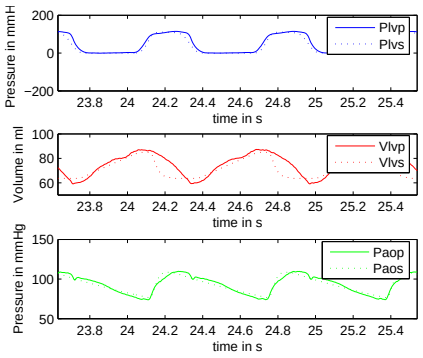
Under the control of the Ethics committee of the Medical Faculty of the University of Liège, pulmonary embolization was induced in pigs with autologous blood clots [15]. The clots were injected every two hours with decreasing concentrations. Aortic pressure and pulmonary artery pressure are measured using micromanometer-tipped catheters (Sentron pressure-measuring catheter; Cordis, Miami, FL) while 7F, 12 electrodes (8-mm interelectrode distance) conductance micromanometer tipped catheters (CD Leycom, Zoetermeer, The Netherlands) are used to measure pressures and volume of both ventricles. The hemodynamics variables are recorded every 30 min. This research uses data from 6 pigs in that study.

III. Results and Discussion

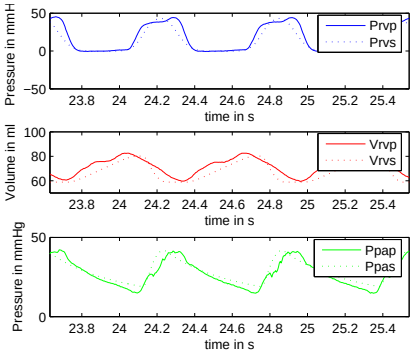
The parameter identification method is applied to the pig data. The identified parameters are used to rerun the CVS model and produce pressure and volume curves, which are then compared to the clinical data.

Figure 2 shows the simulated model output for the pressure in the ventricles (P_{lvs}, P_{rvs}), the volume in the ventricles (V_{lvs}, V_{rvs}) and the pressure in the aorta, pulmonary artery (P_{aos}, P_{pas}) overlaid with the corresponding clinical data ($P_{lvp}/P_{rvp}, V_{lvp}/V_{rvp}, P_{aop}/P_{pap}$) at 30 min into the PE experiment. The simulation data matches the measured porcine data very well with errors within 4.2 mmHg and 4.4 ml for maximum and minimum pressures and volumes respectively. Note that errors are not considered in the waveform shapes since there are dynamics which cannot be captured by the current minimal CVS model. For example, the diacrotic notch cannot be captured as there is no atrium

in the model. Thus, any error metric like the overall root-mean-squared-normalized error is not suitable as it will be corrupted by modelling error. Better waveform shapes could be obtained by adding further complexity to the model, but the philosophy in this research is to only add extra dynamics if a significant clinical benefit can be demonstrated. Future clinical trials will help determine what further dynamics are necessary for adequate diagnosis and therapy prediction.



(a) 30 min, left ventricle



(b) 30 min, right ventricle

Fig. 2. Pig 1, Model output (dashed line) vs clinical data (solid line)

This identification process is repeated in all the measured periods (every 30 min) during the PE experiment using the pig's steady state response data. Hence, Figure 3 shows the time evolution (for one pig) of the identified pig specific parameters systemic and pulmonary vascular resistance, R_{sys} and R_{pul}. These resistances differ significantly between healthy and disease state with R_{pul} increasing by 261.44%.

The model also captures the specific hemodynamic changes resulting from PE. The volume in the right ventricle (V_{rv}) increases due to the increased afterload, which causes right ventricle dilation. Figure **??** shows the time evolution of the left and right end-diastolic volume ratio ($RVEDV/LVEDV$) as an index for the expansion of the right ventricle during the experiment. As expected, this index increases. Also shown in Figure **??** is the RVEDV/LVEDV index where VI is set to zero ($V_{spt} = 0$). With $V_{spt} = 0$, the model significantly overpredicts the right ventricle expansion index at 180 min and in general is significantly different from the model with non-zero V_{spt}. This is also typical for the other pigs. The other hemodynamic pressure variables as well as stroke volume hardly change throughout the

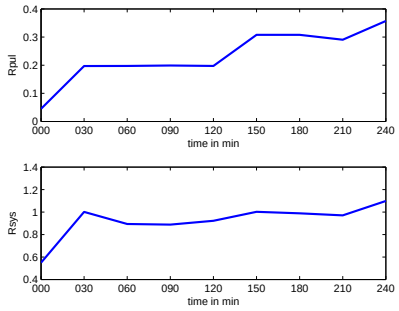


Fig. 3. Pig 1: Pulmonary vascular (R_{pul}) and systemic (R_{sys}) resistance during PE experiment

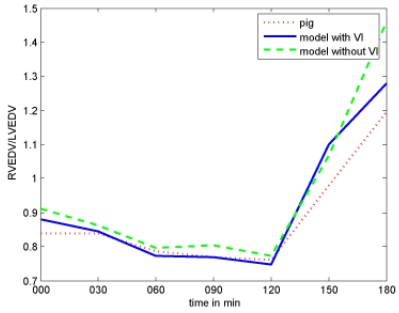


Fig. 4. Pig 2: RVEDV/LVEDV, simulated vs porcine data (Dotted is clinical data, solid is identified model with VI and dashed is identified model without VI)

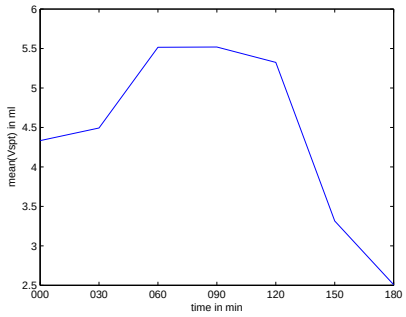


Fig. 5. Pig 2: Mean septum volume V_{spt} during PE experiment

simulation whether or not V_{spt} is zero. Similar results have been observed in dogs [16] and for a significantly more complex VI model [17]. The main problem however, is that it is very difficult to measure VI experimentally and there is very little data available in the literature. The result of Figure **??** does show that the VI in this model is physiologically accurate, but whether or not this dynamic is important for diagnosis in the ICU remains to be shown in future human clinical trials.

VI changes are also captured, where Figure 5 shows the time evolution (for one pig) of the mean value of the septum volume (V_{spt}) over a cardiac cycle, decreasing from the beginning to the end of the experiment. This result agrees with the physiological fact that the overfilled right ventricle compresses the underfilled left ventricle during the

embolization. Hence, V_{spt} decreases because it is defined as being part of the right ventricle volume [2], [8]. Finally, note that as the embolism grows and left ventricle volume decreases, the systemic resistance R_{sys}, increases in Figure 3 as a reflex response to raise blood pressure and divert more blood to the heart.

Pig	%increase R_{pul}	%increase R_{sys}	%increase E_{eslvf}	%increase E_{esrvf}	%decrease V_{spt}
Pig 1	261.44	40.66	29.10	154.60	9.13
Pig 2	89.98	49.34	74.78	20.56	40.15
Pig 3[1]	24.23	27.16	0.81	9.74	8.37
Pig 4	166.85	39.21	19.06	56.44	19.84
Pig 5	103.63	21.16	71.51	80.07	27.64
Pig 6	99.52	53.90	11.00	14.64	14.00

TABLE I

CVS PORCINE SPECIFIC PARAMETERS

Table I summarizes important parameters for the 6 pigs and shows the maximum percentage increase for pulmonary vascular resistance (R_{pul}) and maximum percentage changes in systemic vascular resistance (R_{sys}) and the contractilities (E_{eslvf}, E_{esrvf}) in the ventricles during the PE experiment. As expected, R_{pul} increases [18] while R_{sys} increases as a reflex. The contractilities in the left and right ventricles also increase as a reflex response, but drop at the end of the experiment, where the pig are in a near death state and are no longer able to regulate their circulation [19], [20].

IV. CONCLUSIONS

In this paper, we demonstrate the potential of using a minimal CVS model and integral based parameter identification method for real time patient specific modelling and diagnosis. A wide range of clinically measured porcine hemodynamics in pulmonary embolism were successfully captured over time. The integral method identified all model parameters with less than 5% error in clinical pressure and volume outputs. More importantly, critical measures and expected physiological responses to pulmonary embolism were all successfully captured in the presence of noise and using real clinical data.

The accurate diagnosis and treatment of pulmonary embolism requires an interdisciplinary approach and remains a difficult and expensive task due to non-specific and challenging clinical signs, which sometimes do not coincide with clinical suspicion. A real time patient specific CVS model as demonstrated here could thus potentially assist medical staff in diagnosing pulmonary embolism using data and catheters typically used in the ICU.

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[1]This pig only had limited data and insufficient time for the parameters to change significantly.

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