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Model-Based Decision Support Algorithm to Guide Fluid Resuscitation ⋆

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Abstract: Fluid resuscitation is the first choice therapy for sepctic shock. However, fluid infusion only increases cardiac output in approximately 50 % of cases, while an excess of fluid can have harmful effects. Therefore, clinicians are looking for indices to predict the effect of fluid infusion on cardiac output, before giving fluid.
In this work, a minimal mathematical model of the cardiovascular system is used, representing the heart, an artery and a vein. The nine model parameters, including total stressed blood volume, are identified from experimental data. The experimental data was recorded during three 500 ml fluid infusions on two pigs infected with endotoxin, to simulate septic shock.
The total stressed blood volume parameter is negatively associated with the change in cardiac output after fluid infusion, as observed in previous studies. Subsequently, an algorithm is proposed to guide fluid resuscitation, based on the value of this parameter. The use of the algorithm results in 60 % less fluid being given with virtually no effect on cardiac output.
The decision algorithm has the potential to be used in human clinical trials since the data required for parameter identification can be obtained in an intensive care unit.

Keywords: parameter identification, mathematical models, medical applications.

1. INTRODUCTION

Septic shock is a life-threatening condition caused by an infectious agent. The associated inflammatory response modifies the blood vessels properties and causes a leakage of fluid out of the vessels that reduces perfusion (Gupta et al., 2015). In addition, vaso-motor and pressure control can be reduced. Consequently, the oxygen demand of the organs cannot be met by the cardiovascular system (CVS).

Fluid infusion is the first therapy to restore correct fluid balance in septic shock (Gupta et al., 2015). However, fluid infusion increases cardiac output (CO) in only approximately 50 % of the cases (Maas et al., 2012). In addition, excess fluid can be harmful by increasing capillary hydrostatic pressure and worsening interstitial oedema. Clinicians are thus looking for reliable indices of fluid responsiveness. Such indices must be able, before giving fluid, to predict the change in CO following a fluid infusion.

Pironet et al. (2015) previously introduced a simple three-chamber CVS model whose parameters could be identified from intensive care unit (ICU) data. Total stressed blood volume (SBV), defined as the total pressure-generating blood volume in the CVS is one parameter of that CVS model. Using data from healthy pigs, Pironet et al. (2015) showed that SBV was consistently associated with changes in CO after fluid infusion. This work investigates whether this association still holds in pathologic situations, using experimental data from infected pigs.

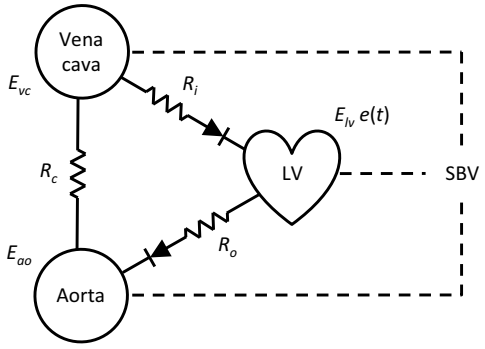

Fig. 1. Schematic representation of the CVS model.

2. METHODS

2.1 Cardiovascular System Model

The CVS model used in this work is presented in Fig. 1. It consists of three elastic chambers representing the left ventricle (lv), the aorta (ao) and one vena cava (vc). The aorta and the vena cava are described by:

$$P_{ao}(t) = E_{ao}\, V_{S,ao}(t) \tag{1}$$

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$$P_{vc}(t) = E_{vc}\ V_{S,vc}(t), \tag{2}$$

where P is pressure, E is elastance and V_S is stressed volume. Stressed volume is the part of actual volume that contributes to pressure.

The left ventricle is modelled using (Suga et al., 1973):

$$P_{lv}(t) = E_{lv}\ e(t)\ V_{S,lv}(t), \tag{3}$$

where E_{lv} is the maximum (end-systolic) elastance and $e(t)$ is the normalised elastance, defined as:

$$e(t) = \exp\left[-W\left((t \bmod T) - \frac{T}{2}\right)^2\right]. \tag{4}$$

In Equation 4, T represents the duration of a heartbeat and W is a parameter dictating the width of the Gaussian curve $e(t)$. Because of the modulo operator, the function $e(t)$ is T-periodic. It ranges from nearly 0, during cardiac filling, to 1, at end-systole.

The three chambers are connected by vessel resistances representing the systemic circulation, R_c, the aortic valve, R_o, and the whole right circulation, from the tricuspid to the mitral valves, R_i. Flow, Q_c, through the systemic circulation is described by:

$$Q_c(t) = \frac{P_{ao}(t) - P_{vc}(t)}{R_c}. \tag{5}$$

The model assumes (i) that there is flow through the valves only if the pressure gradient is positive and (ii) that the flow through an open valve can also be described by Equation 5. Therefore:

$$Q_i(t) = \begin{cases} \dfrac{P_{vc}(t) - P_{lv}(t)}{R_i} & \text{if } P_{vc}(t) > P_{lv}(t) \\ 0 & \text{otherwise,} \end{cases} \tag{6}$$

$$Q_o(t) = \begin{cases} \dfrac{P_{lv}(t) - P_{ao}(t)}{R_o} & \text{if } P_{lv}(t) > P_{ao}(t) \\ 0 & \text{otherwise.} \end{cases} \tag{7}$$

Finally, the continuity equation gives the rate at which the volumes of the chambers change:

$$\dot{V}_{S,lv}(t) = Q_i(t) - Q_o(t), \tag{8}$$

$$\dot{V}_{S,ao}(t) = Q_o(t) - Q_c(t), \tag{9}$$

$$\dot{V}_{S,vc}(t) = Q_c(t) - Q_i(t). \tag{10}$$

Summing the previous equations gives:

$$\dot{V}_{S,lv}(t) + \dot{V}_{S,ao}(t) + \dot{V}_{S,vc}(t) = 0. \tag{11}$$

Consequently, the total stressed blood volume contained in the left ventricle, aorta and vena cava is a constant and a model parameter:

$$V_{S,lv}(t) + V_{S,ao}(t) + V_{S,vc}(t) = \text{SBV}. \tag{12}$$

Overall, the model has nine parameters: three elastances, E_{lv}, E_{ao} and E_{vc}, three resistances, R_i, R_o and R_c, the cardiac period, T, the width, W, and SBV. Parameter identification is used to compute the value of SBV and the other parameters from experimental data.

2.2 Experimental Data

To identify the model parameters, experimental animal data were used. These data were recorded during vascular filling experiments performed on two anaesthetised pigs, weighing 23.5 and 29 kg. The experiments were performed with the approval of the Ethics Commission for the Use of Animals at the University of Liège.

The pigs were first given a muscle relaxant, sedated and anaesthetised. The use of a muscle relaxant implied the need for mechanical ventilation, which was performed with a positive end-expiratory pressure of 5 cmH_2O. The hearts of the animals were then accessed through a median sternotomy. Catheters (Transonic, NY) were positioned to provide continuous recording of:

- Left ventricular pressure, P_{lv}, and volume, V_{lv},
- Aortic pressure, P_{ao},
- Vena cava pressure, P_{vc},
- Flow through the proximal aorta, Q_{ao}.

A PiCCO monitor (Pulsion AG, Germany) was also used for pig 1, providing beat-to-beat recording of:

- Stroke volume, SV,
- Mean vena cava pressure, $\bar{P}_{vc}$,
- Amplitude of the vena cava pressure, PP_{vc}.

The experimental procedure consisted in one first infusion of 500 ml saline solution over 30 minutes. Then, an endotoxin (lipopolysaccharide from *E. Coli*, 0.5 mg/kg) was infused over 30 minutes to induce a septic condition. After induction of septic condition, a second infusion of 500 ml saline solution was performed over 30 minutes. Twenty minutes later, a third infusion of 500 ml saline solution was performed, again over 30 minutes.

Since cardio-pulmonary interaction is not accounted for in the model, only data during temporary interruptions of the mechanical ventilation were used. The mechanical ventilator was paused for 20 s before each saline infusion and every time 100 ml of the 500 ml total saline solution had been infused. This procedure resulted in 15 pairs of data for each animal, 5 for each 500 ml fluid infusion. Only the last heartbeat of the 20 s interruption period was used for parameter identification, so that the haemodynamic signals were stabilised after the load change caused by pausing the ventilator.

2.3 Parameter Identification

The parameter identification procedure aims to reproduce the measured signals with the model. It involved four steps, described in the following four sections.

I. Initial Parameter Values To assign initial values to the model parameters, approximate formulae were used in combination with the available data (Pironet et al., 2015).

1. The cardiac period, T, was computed as the distance between two successive minima of the aortic pressure.
2. The initial value of the circulatory resistance was computed as (Klabunde and Dalley, 2004):

$$R_c \approx \frac{\bar{P}_{ao} - \bar{P}_{vc}}{\text{SV}} T, \tag{13}$$

where $\bar{P}_{ao}$ is the mean aortic pressure.