A PHYSIOLOGICAL MODEL DESCRIBING DOBUTAMINE INTERACTION WITH SEPTIC PATIENTS: A SIMULATION STUDY

M.A. Denaï[*], M. Mahfouf [*] and J.J. Ross[**]

* Dept of Automatic Control & Systems Eng., Univ of Sheffield, Sheffield, UK
** Dept of Anaesthetics, Univ of Sheffield, Sheffield, UK

M.Denai@sheffield.ac.uk

Abstract: The complex and dynamic pathophysiology of sepsis make the design of the best approach to therapy one of the most challenging tasks in ICU. This is due to the large amount of clinical information which need to be effectively and safely put into practice in the management of critically ill patients in general and septic shock patients in particular. The provision of a computer guided treatment strategy based on a comprehensive physiological model is an attractive approach in the management of septic patients. This paper presents preliminary studies on the non-linear modelling of the cardiovascular system interaction with the most routinely used vaso-active drug in ICU. A case study with dobutamine is explored to illustrate the interaction between the cardiovascular and pharmacological models.

Introduction

Sepsis is the systemic response to bacterial infections and is the most common cause of mortality in the intensive care units. Septic shock is associated with three major pathophysiological effects on the cardiovascular system : vasodilation, hypoperfusion and myocardial depression [1]. The first principles of hemodynamic support of patient with septic shock is to provide adequate fluid resuscitation, vasopressor therapy and inotropic therapy. After adequate fluid resuscitation, most septic patients become hyperdynamic. Despite this, myocardial contractility may still be decreased especially in patients with pre-existing cardiac dysfunction. Inotropic agents are useful if the patient demonstrates a low cardiac output state.

One such inotropic agent which is frequently used in intensive care units is dobutamine. Dobutamine's primary effect is to increase myocardial contractility by directly stimulating β_1-receptors in the heart. This is accompanied by a minimal chronotropic and vascular effecs. If used in the presence of low blood pressure, the addition of a vasopressor such as noradrenaline is necessary to restore an adequate systemic vascular resistance.

The physiological model used in this study combines a pulsatile model of the cardiovascular mechanics with pharmacological model which describes drug transport throughout the various parts of the body.

Description of the Physiological Model

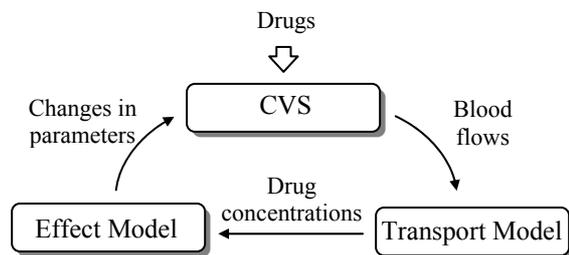The overall model structure is shown in Figure 1.

Figure 1: Structure of the physiological model

The cardiovascular system (CVS) model consists of fourteen compartments describing the systemic, pulmonary, coronary and cerebral circulations. Figure 2 shows the model layout.
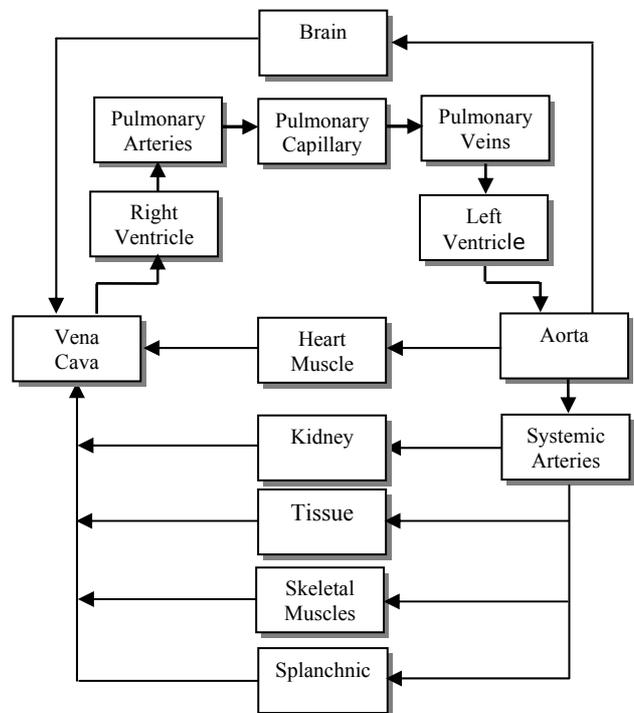

Figure 2: The cardiovascular system model structure

Each compartment consists of a compliant element (C) and a resistance (R) as shown in Figure 3.
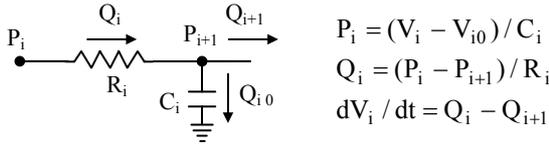
$$P_i = (V_i - V_{i0}) / C_i$$
$$Q_i = (P_i - P_{i+1}) / R_i$$
$$dV_i / dt = Q_i - Q_{i+1}$$

Figure 3: Electric analog model of a compartment

Where P=pressure, Q=flow and V=volume. V_0 denotes the unstressed volume of the relevant compartment.

Flow into the circulation is maintained by a pulsatile cardiac pump where the right and left hearts are described by the following time-varying elastance model [3].

$$E(t) = \begin{cases} E_{diast} + \dfrac{E_{syst} \quad E_{diast}}{2}\left[1 \quad cos(\pi \dfrac{t}{T_{sys}})\right] & 0 \leqslant t \leqslant T_{sys} \\[2mm] E_{diast} + \dfrac{E_{syst} \quad E_{diast}}{2}\left[1 + cos(2\pi \dfrac{t \quad T_{sys}}{T_{sys}})\right] & T_{sys} \leqslant t \leqslant \dfrac{3}{2}T_{sys} \\[2mm] E_{diast} & \dfrac{3}{2}T_{sys} \leqslant t \leqslant T \end{cases}$$

(1)

Where E_{diast} and E_{syst} represent the end-diastolic and end-systolic elastance values respectively, T is the cardiac cycle and T_{syst} defines the systolic interval and is given by $T_{syst}(t) \approx 0.3\sqrt{T(t\text{-}1)}$.

The mathematical model of the baroreflex has been adapted from [4]. The model includes the afferent carotid baroreflex pathway, the sympathetic and the vagal efferent activities. The effector sites of these nerve stimulations are the left and right ventricular maximum elastances, the heart period and the different peripheral arterial resistances. Figure 4 is depicts the structure of the baroreflex model.
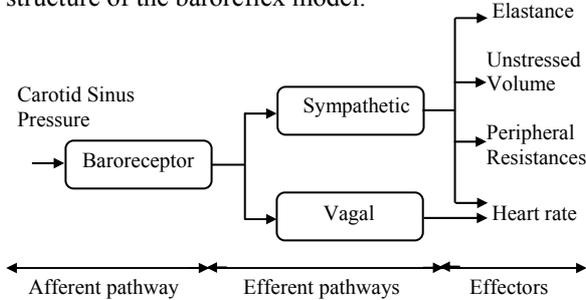

Figure 4: Baroreceptor firing pathways

The drug transport model consists of the same number of compartments as the CVS and is used to calculate the drug concentrations in the relevant body compartments. Drug concentration in each compartment is calculated by applying the following mass balance equation :

$$dM / dt = Q_{in}.C_{in} - Q_{out}.C_{out} - M.ln2/\tau$$

(2)

Where M is the mass of drug in the compartment, C_{in} and C_{out} represent the inflow and outflow concentrations, Q_{in} and Q_{out} are the inward (leaving the previous compartment) and outward blood flows respectively and τ is the drug half-life. The instantaneous drug concentration is calculated as follows

$$C = M / V$$

(3)

Where V denotes the total blood volume available in the relevant compartment (stressed and unstressed).

The drug effect model relates the concentration of drug in the different compartments to the changes in the corresponding parameters values. An exponential function has been employed to describe this relationship. The parameters of the exponential function are optimised using the Levenberg-Marquardt algorithm based on the available effect data given for dobutamine.

Cardiac Dysfunction in Sepsis

Sepsis stimulates the release of multiple inflammatory mediators which induce important effects on vascular smooth muscles and compromise the cardiac function by causing myocardial depression. This results in a rise in the left ventricle compliance and a severely depressed ejection fraction [5]. However this is most commonly masked by an elevated cardiac output. Similar patterns have been observed in the right ventricle.

The theoretical pressure-volume loops corresponding to normal and septic patients are plotted in Figure 5. E_{syst} represents the slope of the end systolic pressure volume relationship and is assimilated to the ventricle contractility. In survivors of severe sepsis, an adequate stroke volume is maintained in the early stage by an increase in the end diastolic volume. In nonsurvivors, failure to increase the end diastolic compliance results in inability to maintain the same stroke volume [5]. These alterations in ventricular function and size are transients and return to normal in survivors after 7 to 10 days in general.
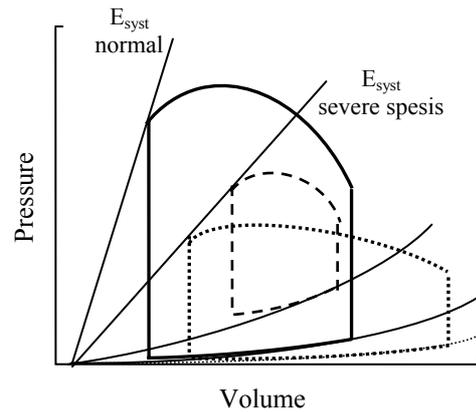

Figure 5: Pressure-volume loops for a normal patient (solid line), survivors (dotted line) and non-survivors (dashed line) of severe sepsis

Simulation Results

The parameters of the CVS model correspond to a human subject of 75 Kg with a total blood volume of 5.6 litres and a heart rate of 75 bpm [2]. For integration the Euler method was used with a step size of 0.005 sec.

Initial compartment volumes have been calculated for each compartment as the sum of the unstressed volume and the volume given by the integration procedure (i.e. the stressed volume).

Initial simulations results are presented for a healthy patient under normal conditions. The steady-states hemodynamic variables are shown in Figures 6-8.
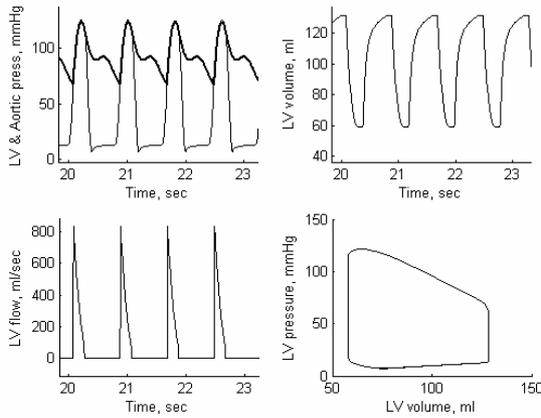

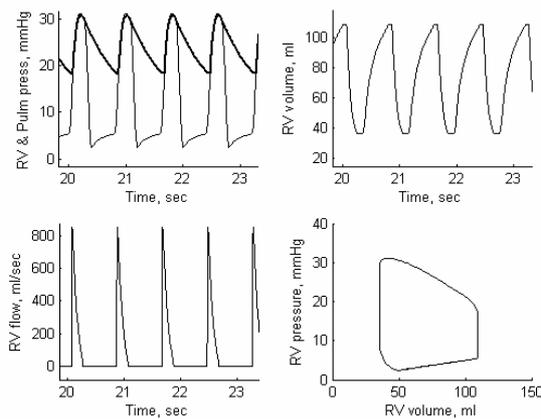Figure 6: Left ventricle pressure, volume and flow
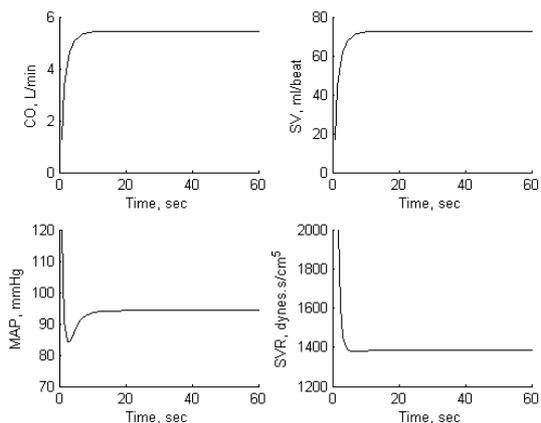

Figure 7: Right ventricle pressure, volume and flow

Figure 8: Hemodynamic parameters

Vascular dilation has been simulated as a 40% decrease in all systemic resistances. Myocardial depression in the early stage of sepsis was simulated as 30% decrease in left and right ventricular systolic elastance. The results are shown in Figure 9-11. A decrease in the systemic vascular resistance (SVR)

reduces the afterload which is relfected by a lower mean arterial pressure (MAP) as shown in Figure 10. The result is an elevated cardiac output despite a reduction in the ventricle contractilities.
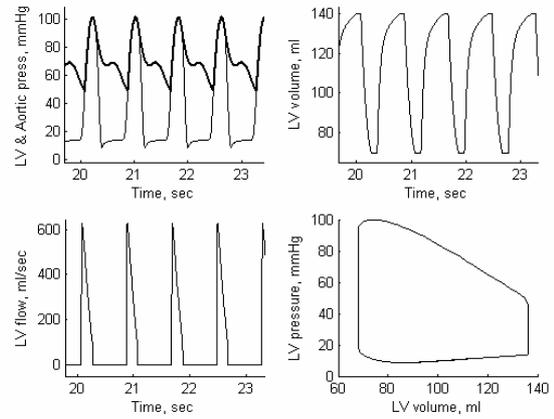

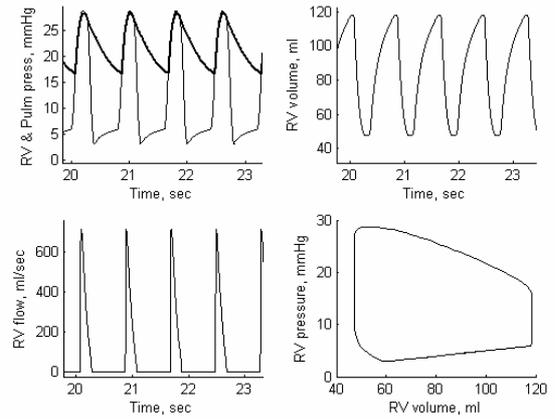Figure 9: Left ventricle pressure, volume and flow in sepsis

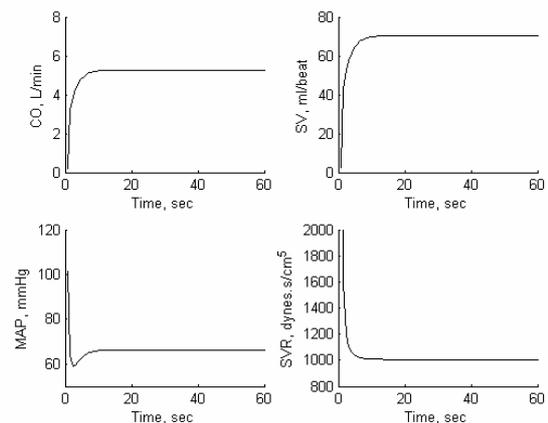Figure 10: Right ventricle pressure, volume and flow in sepsis

Figure 11: Hemodynamic parameters in sepsis

Both PV loops are plotted in Figure 12 for comparison. The PV loops for the left and right ventricles have moved to the right in the septic case owing to a decrease in the slope of the end systolic pressure volume relationship characteristic. The slight increase in the end diastolic volume is the result of

biventricular dilation which accompanies the myocardial depression.
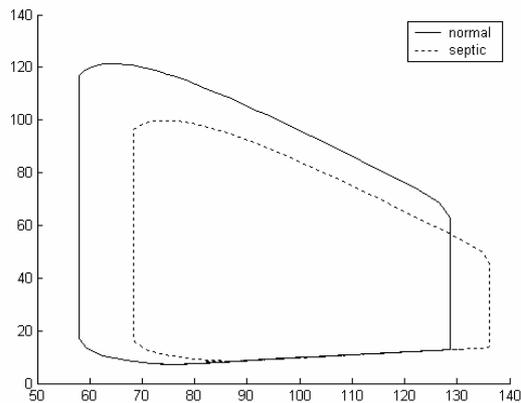

Figure 12: Left ventricle PV loops for normal and septic patients

Dobutamine is a potent inotrope. It works at a number of different receptor sites in the body, however it mostly acts on beta-receptors in the heart to increase the force of myocardial contraction with relatively minor chronotropic and vascular side effects.

Baroreflex control has been removed in the subsequent simulations in order to emphasize the dose related effects of dobutamine on the contractility.

Dobutamine infusion is started at time 200 sec. and the onset of effect is delayed by 30 sec. The results of Figure 13 show a marked increase in the cardiac output as a results of the inotropic effects of dobutamine. There is a small decrease in SVR. For larger doses, there is a significant increase in heart rate and consequently a slight fall in stroke volume.
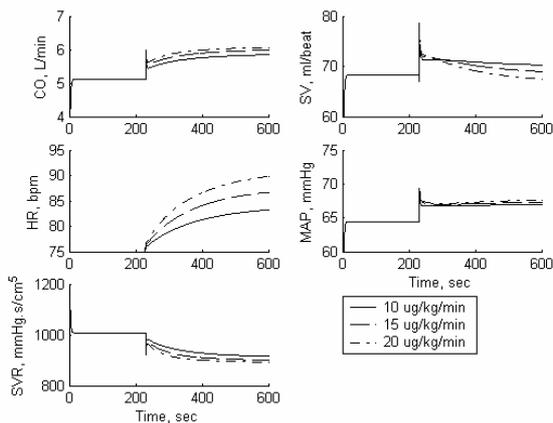

Figure 13: Hemodynamic responses to different dobutamine doses

Figure 14 shows the left ventricle PV loops related to different dosage of dobutamine. The curves are shifted to the left as a result of an improved myocardial contractility. Usually, dobutamine is accompanied with a vasoconstrictor to improve the SVR and hence the afterload. One such vasoactive agent which is frequently used with dobutamine is noradrenaline.
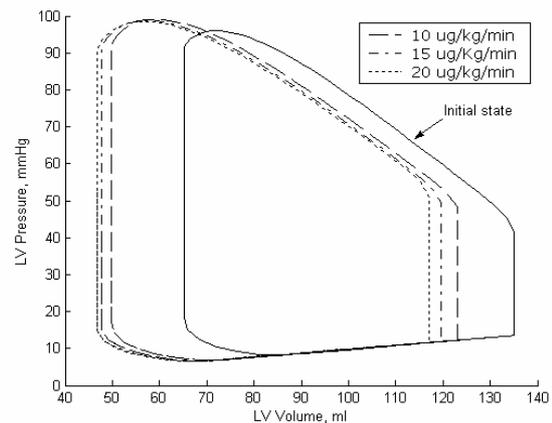

Figure 14: Left ventricle PV loops for different doses of dobutamine

The baroreflex compensates for a decrease in the MAP by adjusting the parameters of the CVS model (Figure 4). On the other hand and according to the data used in this simulation study, dobutamine's controlled parameters are the ventricle contractilities, the heart rate and the muscle arteriolar resistance.

The next simulation results are intended to illustrate the interaction of dobutamine with overall CVS model including baroreflex control. Dobutamine infusion rate has been set to 10 μg/kg/min with baroreflex control included. Figure 15 shows the response of the different hemodynamic variables. Baroreflex control first compensates for the changes induced in SVR and contractility in order to restore an adequate MAP as seen in the initial stage of the simulation. After drug infusion has been initiated, a second counteraction is exerted by the baroreflex in response to dobutamine effects on the circulatory parameters.
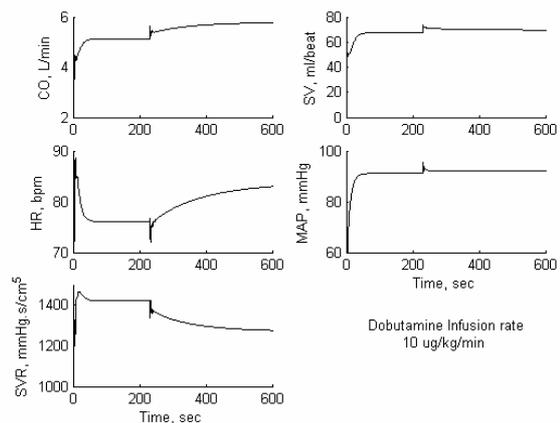

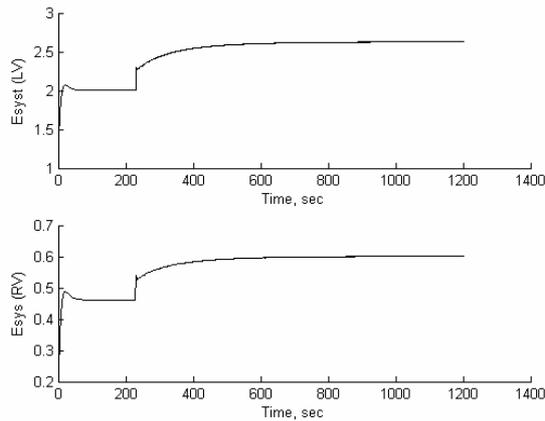Figure 15: Hemodynamic responses with baroreceptor
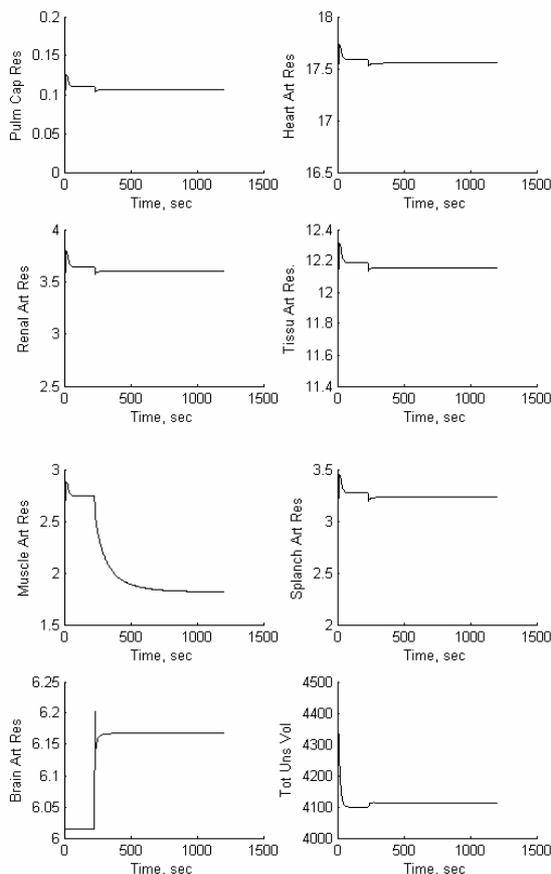
Figure 16: Changes in the ventricles elastances

Figure 17: Changes in the controlled CVS model resistances and unstressed volume

Conclusions

In this paper the interaction of vasoactive drugs, such as dobutamine, with the cardiovascular system in patients with sepsis induced myocardial dysfunction has been modelled and analysed. The physiological model has successfully predicted how the cardiovascular hemodynamics are affected by different drug doses of dobutamine. The model can also be extended to simulate multiple drug therapy given the quantitative information about the direct actions of these drugs on the relevant cardiovascular parameters. It is hoped to conduct such a comprehensive study in the future.

References

[1] KUMAR A., HAERY C. and PARILLO J.E. (2001): 'Myocardial Dysfunction in Septic Shock: Part I. Clinical Manifestation of Cardiovascular Dysfunction', *J Cardioth and Vascul Anesth,* Vol 15, 3, pp. 364-376

[2] MASUZAWA T., FUKUI Y. and SMITH N.T. (1992): 'Cardiovascular Simulation Using a Multiple Modeling Method on a Digital Computer – Simulation of Interaction Between the Cardiovascular System and Angiotensin II', *J. of Clin. Monitoring*, Vol 8, pp. 50-58

[3] HELDT T., SHIM E.B., KAMM R.D. and MARK R.G. (1992): 'Computational Modeling of the Cardiovascular Response to Orthostatic Stress', *J Appl. Physiol*, pp. 1239-1254

[4] URSINO M. (1998): 'Interaction between Carotid Baroregulation and the Pulsating Heart: A Mathematical Model', *Am J Physiol Heart Circ Physiol*, 275, pp. H1733-H1747

[5] DHAINAUT J.F., CARIOU A. and LAURENT I. (2000): 'Myocardial Dysfunction in Sepsis', *Sepsis*, 4, pp. 89-97

Acknowledgement