

PHYSIOLOGICAL MODELLING OF HEMODYNAMIC EFFECTS OF SIMULTANEOUS ADMINISTRATION OF NORADRENALINE AND DOBUTAMINE TO SEPTIC PATIENTS IN CICU

M. Mahfouf¹ M.A. Denai¹ J.J. Ross²

¹ Dept of Automatic Control & Systems Eng
University of Sheffield
Mappin Street, Sheffield S1 3JD
UK

² Dept of Anaesthetics
Northern General Hospital
Herries Road, Sheffield S5 7AV
UK

M.Mahfouf@sheffield.ac.uk M.Denai@sheffield.ac.uk J.J.Ross@sheffield.ac.uk

ABSTRACT

Septic shock is a medical emergency which requires a supportive treatment with vasoactive agents to restore adequate blood pressure and tissue perfusion. Due to the complex medical conditions of septic patients, the identification of the best therapeutic approach remains one of the major challenges for the clinicians. Thus, an improved understanding of the pathophysiological mechanisms of septic shock is needed. A computer model provides a means of quantifying the key phenomena involved and identifying the potential therapeutic targets. This paper presents a comprehensive physiological and pharmacological model of the cardiovascular system that can simulate the hemodynamic response to vasoactive drugs with differing pharmacologic profiles. The model is used to study the interaction of combined noradrenaline and dobutamine therapy in patients with septic shock who typically remain hypotensive despite fluid administration.

KEY WORDS

Sepsis, septic shock, cardiovascular modeling, pharmacological model, noradrenaline, dobutamine.

1. Introduction

Septic shock is characterized by an overwhelming systemic response to bacterial infection and remains the leading cause of death in the intensive care units. This medical emergency (sepsis) occurs in three different forms which are the (1) *uncomplicated sepsis* that results from a known or suspected infection (2) *severe sepsis* which arises when sepsis occurs in combination with one vital organ dysfunction (3) *septic shock* occurs when sepsis is complicated with persistent hypotension that does not respond to fluid resuscitation.

Patients with septic shock syndrome are characterized by severe physiologic abnormalities such as (1) peripheral arteriolar vasodilation which results in low systemic vascular resistance causing hypotension (2) increased vascular leakage and fluid loss from the intravascular

space causing hypovolaemia and (3) myocardial depression with impaired systolic and diastolic function, noncompliant, dilated and poorly contractile ventricles [1]. After fluid resuscitation, parallel to reversing the underlying cause of infection, supportive treatment of septic patients with vaso-active medication is very often required to restore normal blood pressure and improve the circulatory performance. The most useful inotrope/vasopressor drugs in septic shock are dopamine, dobutamine, norepinephrine and epinephrine. Dobutamine has predominantly β_1 effects. It increases the contractility and heart rate and hence the cardiac output. It also has β_2 effects which cause a mild vasodilatation and thus decreases the afterload. Noradrenaline, on the other hand, is very effective in rising arterial blood pressure through its potent vasoconstriction. Many clinical studies have reported that dobutamine used in conjunction with noradrenaline appears to be the optimal regimen in the therapeutic management of septic shock patients.

The aim of this study is to model the interactions of these two drugs with the cardiovascular system in septic shock conditions. The model developed gives a good understanding of the hemodynamic abnormalities observed in septic patients and successfully predicts the response to different infusion rates of noradrenaline and dobutamine.

The paper is organised as follows. First, the basic features of the model are presented. The model is subsequently used to simulate three classes of septic patients based on quantitative description of sepsis related hemodynamic abnormalities. Finally, the interaction of the model with noradrenaline and dobutamine is described.

2. Model Description

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

throughout the various parts of the body. Drug effects on the cardiovascular system are simulated as changes in the physiological model parameters based on published quantitative data [2]. The overall model structure is shown in Fig. 1.

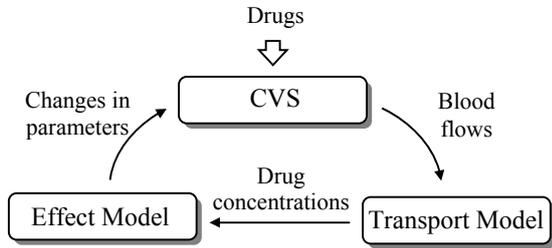


Fig. 1. Structure of the Physiological Model.

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

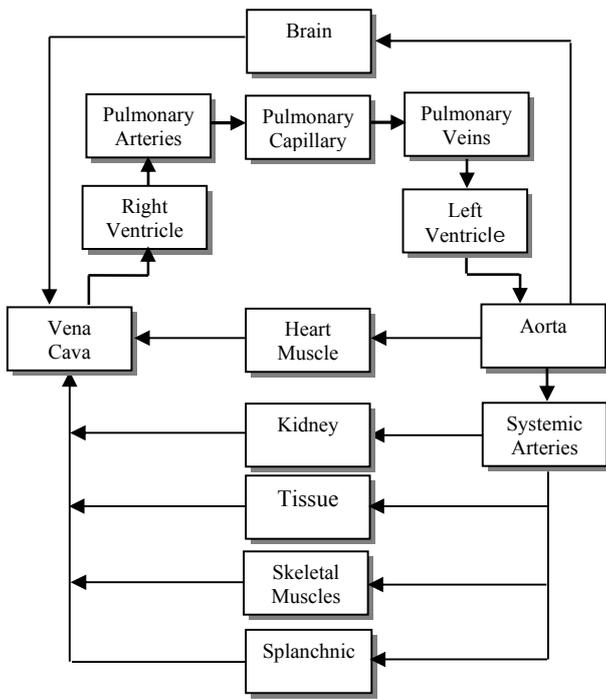


Fig. 2. Cardiovascular System Model Structure.

Each compartment consists of a compliant element (C) and a resistance (R) as shown in Fig. 3.

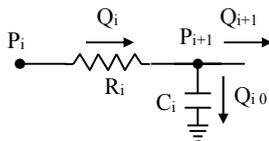


Fig. 3. Electric Analog Model of a Compartment.

The relationships between pressure (P), flow (Q) and volume (V) in a compartment are given as follows:

$$\begin{aligned} P_i &= (V_i - V_{i0}) / C_i \\ Q_i &= (P_i - P_{i+1}) / R_i \\ dV_i / dt &= Q_i - Q_{i+1} \end{aligned} \quad (1)$$

Where 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 a time-varying elastance $E(t)$ modeled with two Hill equations. The first bracket describes the ascending part of $E(t)$ and the second the descending part of $E(t)$.

$$E(t) = E_{\min} + E_{\max} \left[\frac{\left(\frac{t_n}{\alpha_1 T} \right)^{n_1}}{1 + \left(\frac{t_n}{\alpha_1 T} \right)^{n_1}} \right] \left[\frac{1}{1 + \left(\frac{t_n}{\alpha_2 T} \right)^{n_2}} \right] \quad (2)$$

The parameters n_1 , n_2 , $\alpha_1 T$ and $\alpha_2 T$ are obtained from experimentally observed elastance.

The mathematical model of the baroreflex has been adapted from [3]. The model includes the afferent carotid baroreflex pathway, the sympathetic and 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. Fig. 4 depicts the structure of the baroreflex model.

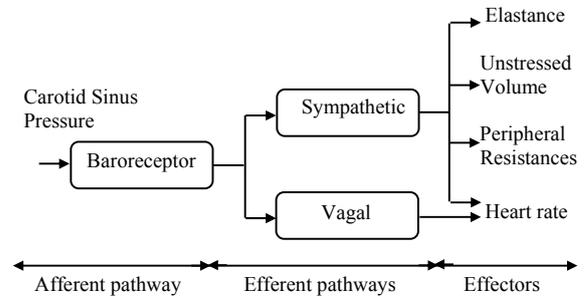


Fig. 4. Baroreceptor Firing Pathways.

The drug transport model consists of the same number of compartments as the CVS and is used to calculate drug concentrations in the relevant body compartments. A single compartment representation is shown in Fig. 5.

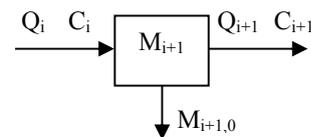


Fig. 5. Drug Transport Model Compartment.

Drug mass in each compartment is governed by the following equation:

$$\frac{dM_{i+1}}{dt} = Q_i \cdot C_i - Q_{i+1} \cdot C_{i+1} - M_{i+1,0} \quad (3)$$

where M_{i+1} is the mass of drug in compartment (i+1), C_i and C_{i+1} represent the inflow and outflow concentrations, Q_i and Q_{i+1} are the inward (leaving the previous compartment) and outward blood flows respectively. $M_{i+1,0}$ denotes the mass of drug removed from that compartment. Drug elimination from the body is assumed to occur within each compartment. The instantaneous drug concentration is calculated as follows:

$$C = M / V \quad (4)$$

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

The drug effect model relating the concentration of drug in the different compartments to the changes in the corresponding parameters values (resistances, compliances, elastances and heart rate) has been described by an exponential function. The parameters of the exponential function are optimised using the Levenberg-Marquardt algorithm based on the available effect data given for noradrenaline and dobutamine respectively [2].

3. Pathophysiological Mechanisms of Sepsis

Sepsis stimulates the release of potent inflammatory mediators into the circulation which induce vasodilatation of vascular smooth muscles and compromise the cardiac function by causing myocardial depression [4].

The theoretical pressure-volume loops corresponding to normal and septic patients are plotted in Fig. 6.

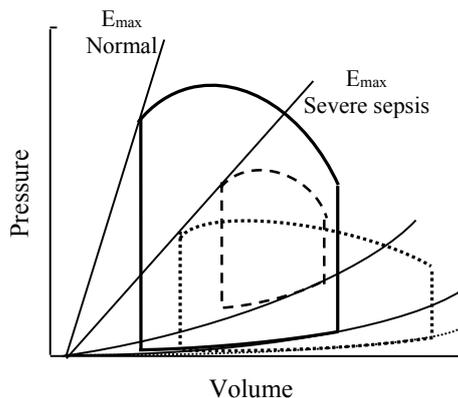


Fig. 6. Pressure-volume loops for normal patient (bold), survivors (dotted) and non-survivors (dashed) [5].

E_{max} 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 transient and return to normal in survivors usually after 7 to 10 days.

4. Simulation Results

The baseline parameters of the CVS model correspond to a human subject of 75 Kg with a total blood volume of 5.6 liters and a heart rate of 75 beats/min [6]. For integration the Euler method was used with a step size initially set to 0.005 sec. and subsequently adjusted with changing heart rates. 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).

Fig. 7 shows the simulated left and right ventricle pressures and the aortic and pulmonary pressures related to a normal subject.

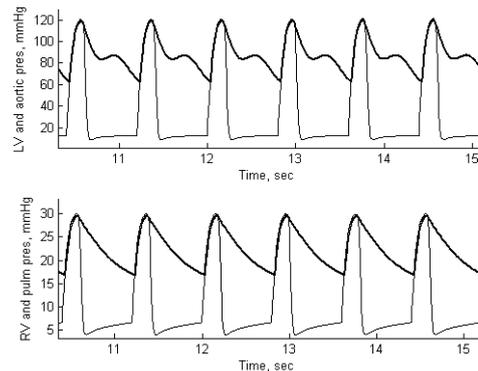


Fig. 7. Simulated left and right ventricle, aortic and pulmonary pressures of a normal subject.

Under normal conditions, the compensatory response to hypotension is mediated by a sympathetic activation of the heart and peripheral vessels which restores the arterial blood pressure to its normal value. The onset of severe sepsis is accompanied by an impairment of the autonomous nervous system leading to a compromised baroreflex function with a deregulation in the sympathetic and parasympathetic activities. Therefore, to better illustrate the interaction between drugs and the physiological model, the baroreflex has been excluded in this simulation study.

For simulation purposes, the model has been parameterized to describe three categories of septic patients: mild, moderate and severe. The simulated pressure-volume curves under mild, moderate and severe sepsis conditions are plotted in Fig. 8. The pressure-volume loops are lowered as a result of a decreasing afterload (vasodilatation) and shifted to the right as a

result of a decreased contractility (myocardial depression).

The three hypothetical models of septic patients are considered separately to evaluate the interaction of combined infusions of noradrenaline and dobutamine.

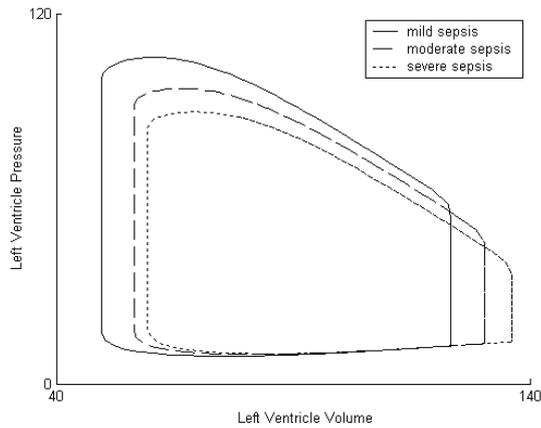


Fig. 8. Left ventricle pressure-volume loops related to the three classes of simulated septic patients.

In the subsequent simulations noradrenaline and dobutamine half-lives have been taken equal to 90 sec and 120 sec respectively. Noradrenaline infusion is started at time 200 sec while dobutamine infusion begins at 1000 sec. A time delay of 30 sec has been assumed between the commencement of infusion and the onset of action, this being deemed to be reasonable.

4.1 Mild Sepsis

Noradrenaline and dobutamine infusions rates were set to $0.15\mu\text{g}/\text{kg}/\text{min}$ and $5\mu\text{g}/\text{kg}/\text{min}$ respectively. The results are shown in Fig. 9.

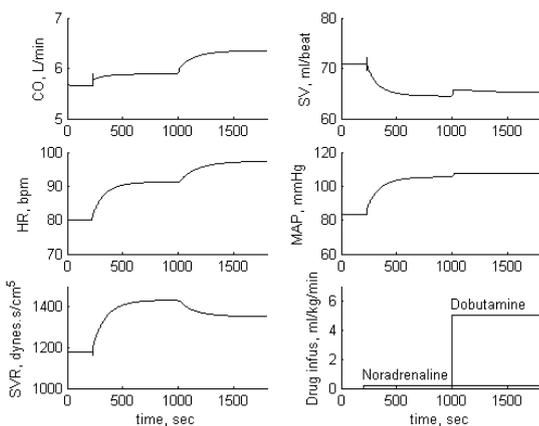


Fig. 9. Hemodynamic response of a subject under mild sepsis.

Noradrenaline produces a marked increase in the SVR due to its vasoconstricting potency which results in an improved MAP. The heart rate is increased and

consequently this result is a fall in stroke volume. At this stage, all hemodynamic variables have reached reasonable steady-state values. The inotropic effect of dobutamine is expected to increase the cardiac output through its direct effect on the ventricle contractility. It also causes an increase in the heart rate and a mild vasodilatation.

Fig. 10 shows the left ventricle pressure and aortic blood pressure during simultaneous infusion of the two drugs.

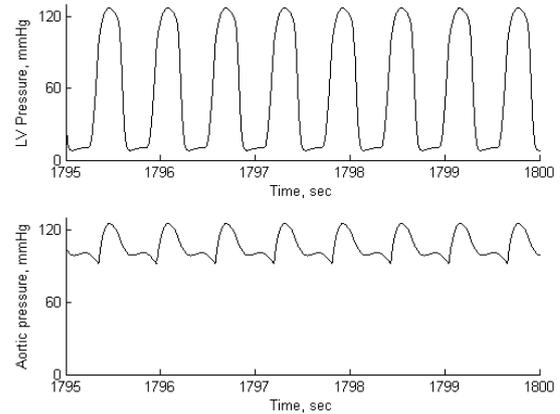


Fig. 10. Left ventricle pressure and aortic pressure related a subject with a mild sepsis.

4.2 Moderate Sepsis

Vasodilatation and hypotension are more pronounced for this category of simulated septic patient hence requiring a higher dose of noradrenaline. The infusion rates were set to $0.25\mu\text{g}/\text{kg}/\text{min}$ for noradrenaline and $2.5\mu\text{g}/\text{kg}/\text{min}$ for dobutamine. The results obtained are shown in Fig. 11. All the hemodynamic parameters were normalized accordingly.

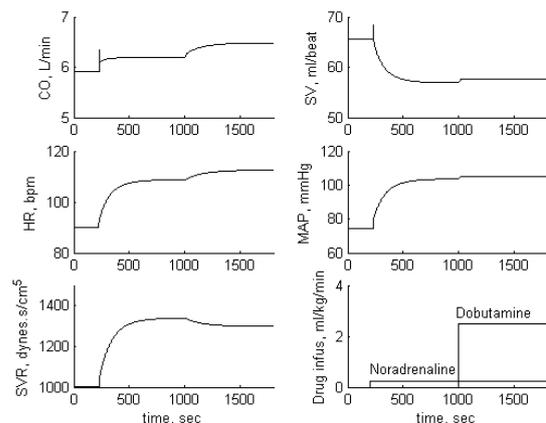


Fig. 11. Hemodynamic response of a subject with moderate sepsis.

The left ventricle and aortic pressures are shown in Fig. 12.

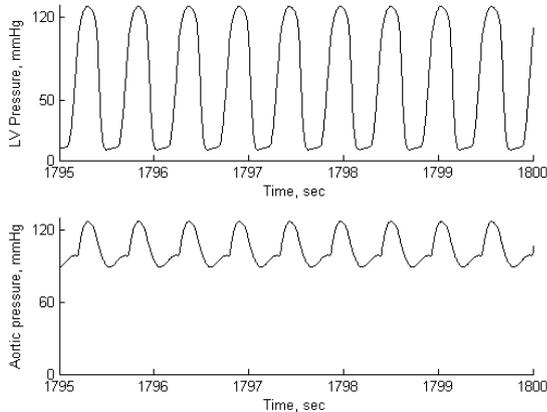


Fig. 12. Left ventricle pressure and aortic pressure related a subject with a moderate sepsis.

4.3 Severe Sepsis

The same protocol is applied to this category of simulated septic patient. The infusion rates used for noradrenaline and dobutamine are $0.8\mu\text{g}/\text{kg}/\text{min}$ and $2\mu\text{g}/\text{kg}/\text{min}$ respectively. The results of Fig. 13, show an improved MAP trace following noradrenaline infusion. There is a marked increase in the cardiac output and high tachycardia due to the chronotropic effects of these two drugs.

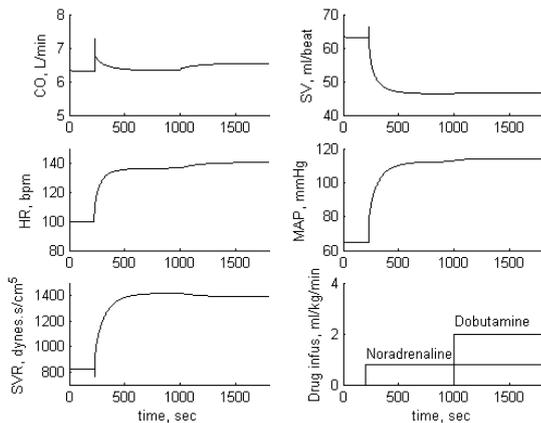


Fig. 13. Hemodynamic response of a subject with severe sepsis.

Fig. 14 shows the left ventricle and aortic pressures in the case of a severe sepsis.

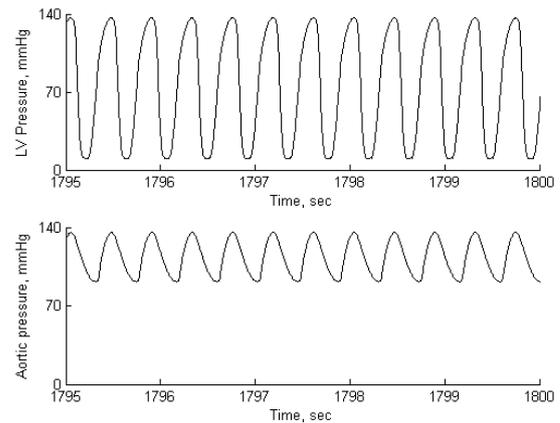


Fig. 14. Left ventricle pressure and aortic pressure related a subject with a severe sepsis.

Table 1 Steady-state hemodynamics after noradrenaline and dobutamine infusions

Patient	CO	HR	SV	MAP	SVR
1	6.3	97	65	107	1352
2	6.4	112	57.6	105	1298
3	6.5	140	46.5	113	1391

Where CO=cardiac output (l/min), HR=heart rate (beats/min), SV= stroke volume (ml/beat), MAP=mean arterial pressure (mmHg) and SVR=systemic vascular resistance (dynes/min/l).

The pressure-volume curves related to the three septic patient models considered in this study are plotted in Fig. 15 (see Fig. 8). The results of Fig. 15 reflect a successful reversal of the hemodynamic abnormalities characterising septic shock. A further improvement of the hemodynamic status requires returning the heart rate to normal using additional medication.

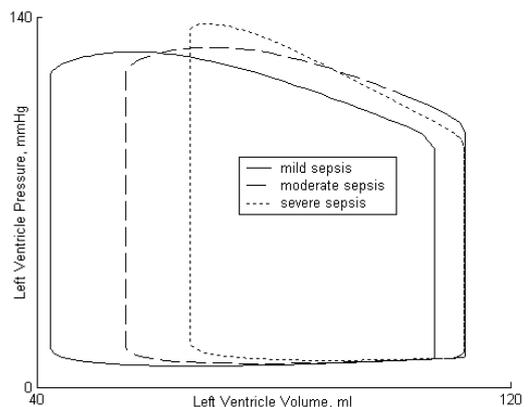


Fig. 15. Left ventricle pressure-volume curves related to the three classes of septic patients after drug infusions.

5. Conclusion

The physiological model described in this research study succeeded in simulating the hemodynamic response of a wide range of patients with sepsis and assess the pharmacological effects of various vasoactive drugs. The classes of patient models considered here have been parameterized based on the (the 3rd author) clinician's quantitative description of the key features of septic shock. The models successfully reproduced the therapeutic effects of noradrenaline and dobutamine observed in clinical practice. It is envisaged to validate the model using real-time clinical data in the near future.

Acknowledgements

The authors gratefully acknowledge the financial support for this project from the UK Engineering and Physical Sciences Research Council (EPSRC) under Grant GR/S94636/1.

References

- [1] J.E. Parillo, The cardiovascular pathology of sepsis, *Ann. Rev. Med.*, 40, 1989, 469-485.
- [2] C.V. Greenway, Mechanisms and quantitative assessment of drug effects on cardiac output with a new model of the Circulation. *Pharm. Reviews*, 33, 1982, 213-251.
- [3] M. Ursino, Interaction between carotid baroregulation and the pulsating heart: A Mathematical Model. *Am J. Physiol Heart Circ Physiol*, 275, 1998, H1733-H1747.
- [4] J.F. Dhainaut, A. Cariou and I. Laurent, Myocardial dysfunction in sepsis, *Sepsis*, 4, 2000, 89-97.
- [5] A. Kumar, C. Haery and J.E. Parillo, Myocardial dysfunction in septic shock, Part I. Clinical manifestation of cardiovascular dysfunction. *J Cardioth and Vascul Anesth*, 15(3), 2001, 364-376.
- [6] T. Masuzawa, Y. Fukui Y. and Smith N.T., 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*, 8, 1992, 50-58.
- [7] C. Martin, X. Viviand, S. Arnaud, R. Vialet and T. Rougnon, Effects of norepinephrine plus dobutamine or norepinephrine alone on left ventricular performance of septic shock patients, *Crit. Care Med.*, 27(9), 1999, 1708-1713.
- [8] C.Martin , X. Viviand , M. Leone, X. Thirion, Effect of norepinephrine on the outcome of septic shock, *Crit Care Med*, 28, 2000, 2758-2765.
- [9] E.J. Bridges, M.S. Dukes, Cardiovascular aspects of septic shock: Pathophysiology, monitoring and treatment, *Critical Care Nurse (25)*, 2005, 14-40.
- [10] P. Seguin, E. Bellissant, Y.Le Tulzo, B. Laviolle, Y. Lessard, R. Thomas, and Y. Malledant, Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock, *Clinical Pharmacology and Therapeutics (71)*, 2002, 381-388.