Cardiovascular Model for Development and Test of Automated Hemodynamic Regulation with Medication

N Sprunk[1,2], A Mendoza Garcia[1], U Schreiber[2], R Bauernschmitt[3], A Knoll[1]

[1]Technical University of Munich, Munich, Germany
[2]German Heart Centre, Munich, Germany
[3]Isar Herzzentrum, Munich, Germany

Abstract

After cardiac surgery patients are transferred to the intensive care unit for recovery. Physicians assess the patient's hemodynamic state every now and then and apply medication, if needed. This time consuming task may be done by an automated hemodynamic regulation, allowing a more continuous regulation reducing the time of recovery and enabling physicians to attend more critical tasks. To develop such a controller, extensive tests and evaluation of its performance in different situations is needed. In this paper we describe a simulation model that allows extensive evaluation of the automated regulation. This model is able to simulate the human cardiovascular system with different common disorders. Also adequate reactions to four types of drugs were implemented. The simulation of both the disorders and the reactions to drug infusions were configured to fit physiological data collected from previous animal experiments.

1. Introduction

Patients commonly develop different hemodynamic instabilities after cardiac surgery during their recovery in the intensive care unit. To monitor and treat these hemodynamic instabilities with drugs, an automated controller is under development in our group. To develop such an automated hemodynamic regulation, extensive testing and reevaluation is needed before it can be used on patients. Usually animal experiments provide the most appropriate testing environment. After each experiment the algorithms of the automated regulation might be improved. This however is a time consuming and expensive task. Furthermore if the automated regulation fails in one experiment, it is desirable to test exactly the same situation again with its improved algorithm. Unfortunately with animal experiments this cannot be achieved, as each animal is slightly unique in its physiology and reactions. Thus the benefits of a simulation environment with adequate reactions to medications are comprehensible. Automated regulation can be tested extensively, even without numerous animal experiments. Furthermore the behaviour of different algorithms can be re-tested and compared easily.

2. Previous research

Cardiovascular models have been subject of previous research. Among those with focus on medication reactions, one was done by Yu C. et al[1]. They also developed a hemodynamic regulation system and used dopamine and sodiumnitroprusside as drugs. In the search for an adequate simulation for the evaluation of our hemodynamic regulation, different models and environments have been tested. The Physiome project offers a simulation environment called JSim and various models for free download. A circulatory model based on Olansen et al.[2] was tested. It turned out to be very accurate, but also quite performance intensive. The enhancement with disorders and medication reactions was quite difficult, because of error messages, that were hard to analyze. These adjustments were easier in the model of [3]. They developed a Matlab model, also for the purpose of hemodynamic regulation. Still the final decision was made on another model in the end, as it does not depend on Matlab, which is not available for free.

3. Methods

The cardiovascular model used is a circulatory model with six compartments developed by a research group at MIT [4][5], called CVSim. This basic model was enhanced to simulate different disorders and the reactions tocertain drugs. The pathologies are introduced to the model by changing some of the parameters in the original cardiovascular model into a state of disorder. To react upon drug dosages the base model is amended with a medication model, which defines the pharmacodynamics and -kinetics for each drug.

3.1. Cardiovascular model

The base cardiovascular model consists of six compartments. It defines one compartment for each heart ventricle (left, right) and two for each the systemic and pulmonary circulation (arteries, veins). Each compartment is represented by its electrical equivalents. A ventricle compartment is represented by a capacitance, a resistance and two diodes, which model the opening and closing of the heart's valves. The compartments for the arteries and veins are represented by a capacitance and a resistance. The contractions of the heart are simulated by reducing and increasing the compliance of the heart ventricles at a frequency defined by a baroreceptor model. The circulatory system is shown in fig.1.

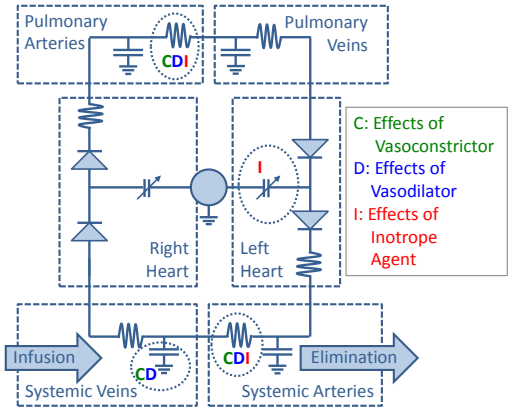

Figure 1. Cardiovascular System defined in CVSim consisting of six compartments; enhanced with infusion of drugs and their effects on resistances and compliances in different compartments

3.2. Pathologies

After cardiac surgery patients commonly develop different pathologies, which compromise their process of recovery. As the automated regulation should be able to handle the prevalent situations that can occur after cardiac surgery, it has to be tested for exactly these. Three common pathologies were implemented in the proposed model: hypertension, hypotension and congestive heart failure.

3.2.1. Hypertension

Hypertension occurs, when arterial pressure rises. It has to be treated with vasodilators, to ward of the risk of rupturing the surgical suture lines. Also continuously high blood pressure bears the risk of a heart attack or failure. Postoperative hypertension is commonly caused by stress or pain, which causes the release of catecholamins, which actually lead to the rise in blood pressure. This complex process can be approximated by an increased set point of the baroreflex [6]. In the proposed model hypertension is introduced by raising the set point for arterial pressure of the baroreflex complex. This leads the baroreflex algorithms to actively engage to meet this target. Via the graphical user interface the set point can be set to a higher value. The user can choose a value up to 170 mmHg.

3.2.2. Hypotension

In contrast to hypertension, hypotension indicates a low arterial pressure. This state has to be treated with vasoconstrictors. Hypotension can be a risk factor for the patient, as very low blood pressure does not ensure perfusion of vital organs with blood, which might lead to organ failure. There are three common causes for post-operative hypotension. One is the widening of blood vessels, which is simulated similar to the hypertension by changing the set point of the baroreflex complex. For this, the set point can to be decreased down to a value of 50 mmHg, if needed. The second very common cause of post-operative hypotension is hypovolemia, a decreased total volume of blood. This can be easily modelled in changing the total blood volume of the simulated process. The third common cause of hypotension is a reduced contractivity of the heart, which can be understood as a mild case of congestive heart failure.

3.2.3. Congestive heart failure

In congestive heart failure (CHF) the heart is unable to pump sufficient blood to perfuse all the organs. It might occur in conjunction with increasing hypotension. Inotrope agents are used as treatment to regain the heart's contractility. CHF is modelled as a decrement of both the systolic and diastolic compliance in the left ventricle. In severe CHF the values can be set down to values of 0.1 and 0.68 respectively.

3.3. Medication model

To make the model react upon infusions of different drugs, a medication model is introduced. It is divided into two sub models. The pharmacokinetic model defines how the drug is spread in-between the different compartments, where it is infused and eliminated. The pharmacodynamic model computes the effects based on the concentrations calculated in the pharmacokinetic model.

Four different drug types were implemented: vasoconstrictor, vasodilator, inotrope agent and volume. In the described model, Isosorbide dinitrate (ISDN) was used as vasodilator, Norepinephrine (NEP) as vasoconstrictor and Dopamine (DPM) as inotrope agent.

3.3.1. Pharmacokinetic model

The pharmacokinetic model defines the paths of the drug inside and through the body. The infusion of the drugs is modelled in the systemic veins compartment, before entering the right heart. From there, the concentrations are spread from one compartment to the next with the flow (Q) generated by the heart. To simplify matters, the concentration (C) is equally distributed instantly within the volume (V) of a single compartment. Formula 1 shows, how the change in concentration is calculated for each compartment.

$$\frac{dC_i}{dt} = \frac{C_{i-1} * Q_{i-1} - C_i * Q_i}{V_i} \quad (1)$$

$$elimination = C_{i-1} - C_{i-1} * e^{-\frac{ln(2.0)*\Delta t}{halflifeConstant}} \quad (2)$$

The degradation of a drug is implemented in the systemic blood circulation using a first-order elimination. A constant percentage of the current concentration in the site of elimination is degraded each time interval. This elimination was modelled as a logarithmic process, dependent on the current concentration (formula 2).

3.3.2. Pharmacodynamic model

The pharmacodynamic model defines the actual effect a drug has on the body. For each drug the effect was calculated with the formula 3 [7]. The formula was enhanced by adding a sensitivity factor, to be able to change a patient's sensitivity for a certain drug. The default value of the sesitivity factor is 1. It can be used to simulate a patient with increased or decrease sensitivities to certain drugs. By adapting the remaining parameters of the formula, the reactions to each drug were approximated to data observed in animal experiments.

$$E = sensitivity * \frac{E_{max} * (k_1 * \frac{C_i}{k_2})^n}{(EC_{50})^n + (k_1 * \frac{C_i}{k_2})^n} \quad (3)$$

The current concentration in the corresponding compartment is used to calculate the extent of the effect. The concentration, which results in 50% of the maximum effect is defined by EC_{50}. The parameter E is the current effect whereas E_{max}, is the maximum factor this effect can produce.

3.3.2.a Vasoconstrictor

The main effect of a vasoconstrictor is to narrow the blood vessels. This was implemented as an increment of resistance in the systemic and pulmonary arteries. Furthermore the compliance is decreased to model the vessel change in the systemic veins compartment. As vasoconstrictor NEP was implemented.

3.3.2.b Vasodilator

A vasodilator has essentially the contrary effect to a vasoconstrictor. Thus it is implemented to decrease both systemic and pulmonary arterial resistance and increase systemic venous compliance. As an example, table 1 shows the parameters used for the vasodilator ISDN.

3.3.2.c Inotrope Agent

Inotrope agents increase the muscular activity of the heart muscle and thus are able to increase cardiac output. In the simulation the effect was modelled as an increment of the compliance in the left ventricle. Furthermore inotrope agents also can have a vasoconstricting effect, as the implemented DPM has. For this reason an effect to decrease the systemic and pulmonary arteries resistance is also calculated.

Table 1. Parameters for the Pharmacodynamic Model of the Vasodilator ISDN

	Systemic Resistance	Pulmonary Resistance	Systemic Venous Compliance
E_{max}	0.45	0.023	145.8
k_1	0.01	0.01	0.01
k_2	0.0025	0.000242	0.00267
EC_{50}	0.04	0.09	0.06
n	2.5	2.46	2.8

For these three types of drugs vasoconstrictor, vasodilator and inotrope agent, different drugs can be implemented, by changing the according parameters.

3.3.2.d Volume

Volume is not implemented as a medication with effects on vascular or myocardial cells, but as an simple increment of volume in the system veins compartment.

4. Implementation

The simulation model and all its sub models are implemented in C, with an additional graphical user interface developed in Java. They are connected using the Java Native Interface. Both the Java and the C code were extended to simulate the disorders and the reactions to different drugs.

5. Results

To test the implemented models for the disorders and the medication reactions, the simulation runs were compared with both data from literature and data collected in previous animal experiments.

The simulation of disorders were compared to values from literature to fit values for hypertension, hypotension and CHF. In a hypertensive crisis mean arterial pressure (MAP) can rise up to 160 mmHg [8]. By adjusting the set point in the arterial baroreflex, the model is also able to

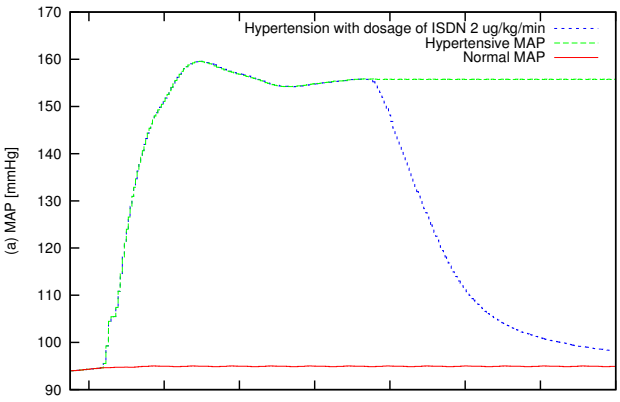

Figure 2. Comparision of simulation runs: Mean Arterial Pressure (MAP) in normal situation, in hypertensive case and treated hypertension; the treatment with Isosorbide dinitrate at 2 ug/kg/min was started in the simulation, when the hypertension reached its stable state at about 160 mmHg; MAP lowered from 155 mmHg to 100 mmHg

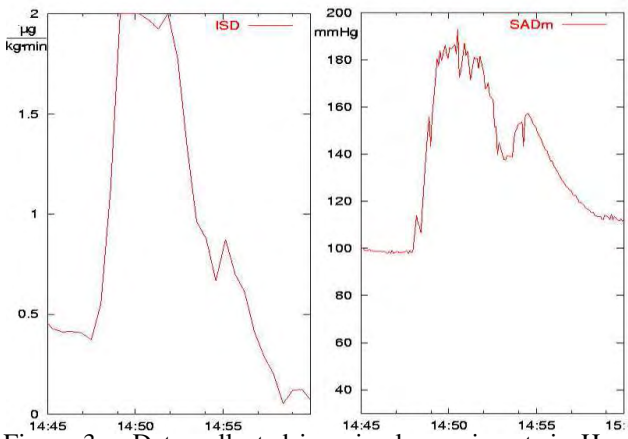

Figure 3. Data collected in animal experiment, in Hypertensive state a dosage of ISDN was given and MAP (SADm) lowered from 180 to 110 mmHg

reach this value (fig. 2). Furthermore a MAP of as low as 60 mmHg can be reached by decreasing the set point to model hypotension. For CHF the model can reach a value of below 4 l/min for cardiac output, which is characteristical for this disorder [9].

The reactions of the simulated model to infusion of different drugs was adapted to data from animal experiments [10]. Figure 2 and 3 show the effect of ISDN infusion in the experimental and the simulated data. In both cases MAP is on a hypertensive level, 180 mmHg in experiment and 160 mmHg in simulation. After a dosage of 2 ug/kg/min of ISDN, the MAP is significantly falling in both cases, to 110 mmHg in experimental data and 100 mmHg in simulation. Likewise the reactions to NEP and DPM were modelled and compared with data from the same experiments.

6. Conclusion

The results of the simulation and their comparison to both literature and data from animal experiments show that the proposed simulation can be used for development and test of hemodynamic regulation. The three pathologies hypertension, hypotension and CHF can all be simulated. The according treatment is also modelled with reactions to four commonly used drugs. When different drugs need to be tested, the pharmacokinetic and -dynamic models can be adapted. As the model has shown to be an adequate approximation, it is now used for evaluating and improving the automated hemodynamic regulation.

Acknowledgements

This research was funded by the Graduate School of Information Science in Health (GSISH) and the Technical University of Munich (TUM) Graduate School

References

[1] Yu C, Roy RJ, Kaufman H. A circulatory model for combined nitroprusside-dopamine therapy in acute heart failure. Med Prog Technol May 1990;16(1-2):77–88.

[2] Olansen JB, Clark JW, Khoury D, Ghorbel F, Bidani A. A closed-loop model of the canine cardiovascular system that includes ventricular interaction. Comput Biomed Res Aug 2000;33(4):260–295.

[3] El-Brawany MA. A functional cardiovascular model with iv cardiac drugs action. The Online Journal on Electronics and Electrical Engineering OJEEE 2009;1(1).

[4] Heldt T, Mukkamala R, Moody GB, Mark RG. Cvsim: An open-source cardiovascular simulator for teaching and research. The Open Pacing Electrophysiology Therapy Journal 2010;3:45–54.

[5] Mukkamala R, Moody GB, Mark RG. Introduction of computational models to physionet. Comput Cardiol 2001; 28:77–80.

[6] Middeke M. Arterielle Hypertonie. Georg Thieme Verlag, 2005.

[7] Gabrielsson J, Weiner D. Pharmacokinetic/pharmacodynamic data analysis: concepts and applications. Taylor & Francis, 2001.

[8] Martina B. Medikamentse behandlung hypertensiver krisen. Swiss Medical Forum 2005;5:317–321.

[9] Klabunde RE. Cardiovascular physiology concepts. Lippincott Williams & Wilkins, 2005.

[10] Bauernschmitt R, Hoerer J, Schirmbeck E, Keil H, Schrott G, Knoll A, Lange R. Fuzzy-logic based automatic control of hemodynamics. Computers in Cardiology 2003;30:773–776.

Address for correspondence:

Nicole Sprunk, Experimentelle Chirurgie, Herzzentrum München
N.Sprunk@tum.de