A Model for Simulation of Infant Cardiovascular Response to Orthostatic Stress

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Abstract. We developed an infant circulation model which incorporates an accurate myocardial cell model including a beta adrenergic system. The beta adrenergic system is essential for the response reproduction of the baroreflex control system. The proposed model was constructed by modifying the parameters of a human adult circulation model with the aid of a guinea pig myocardial cell model, whose baseline heart rate is close to that of an infant. The presented model is in good agreement with results obtained in physiological experiments.

1 Introduction

To improve our knowledge on biological mechanisms, quantitative and integrative studies of each biological element are necessary. Despite the rapid advancement in the accumulation of quantitative data from biological elements, the integrated systems are still not well analyzed. The simulation of complex biological models is of great importance, due to its potency in the analysis of biological functions. Biosimulation models are also expected to develop into powerful tools for medical education.

As a consequence of their complex physiology obstetric patients, neonates, and children often require rapid therapeutic intervention in the acute phase. We believe that simulation models for these patients will be of significant use in medical training. Since the cardiovascular system is one of the most essential physiological systems, we focused on constructing a baseline cardiovascular simulation model for infants.

Goodwin et al. [1] presented an infant cardiovascular simulation model which consists of four heart chambers and 6 compartments. The model also integrates an autonomous nervous system, however, the heart chamber model is based on

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a time varying elastance model, for which the evaluation of the effects on electrophysiological aspects of the myocardial cells is difficult. Since the myocardial cell models are becoming increasingly accurate[2], incorporation of the same into cardiovascular models is unquestionably desirable.

In this paper, we propose an infant cardiovascular model which incorporates such an accurate myocardial cell model.

2 Cardiovascular Model

Since our model considers an autonomous nervous system, we used a myocardial cell model which includes a beta adrenergic stimulus system. The model is constructed from elementary models decribed in this section(Table1).

Table 1. Elementary models of proposed infant cardiovascular model

Element	Model	Species	Reference
cardiac cell	Kyoto model	guinea pig	[3]
left ventricle	Laplace law		
circulation	Heldt model	adult human	[4]
control system	Heldt model	adult human	[4]

2.1 Myocardial Cell and Left Ventricle Model

The Kyoto model proposed by Noma et al was used for the myocardial cell model. The Kyoto model is an accurate cell model which incorporates most of the known ion channels and transporters, a mitochondria as well as a contraction model. In addition, it is the only model which incorporates a beta adrenergic system. The contractility of the model is modified by the isoproterenol (ISP) concentration (Fig.1). Note that the Kyoto model shows a decrease in maximum force and increase of minimum force when the heart rate increase (Fig.2).

For the left ventricle model the Laplace law was applied. Denoting the wall thickness with h, the radius with R, the LV pressure with P_{lv} and the myocardial cell force by F_{ext}, the Laplace law is represented as $2F_{ext}/R = P_{lv}/h$ [5]. Through this equation, LV pressure and volume are related to the cell contraction force.

2.2 Circulation Model

In clinical tests, the head up tilt (HUT) is commonly used for both, adults and infants, to verify the response of the baroreflex system. Likewise, in our study, HUT was used to test the baroreflex. Accordingly, the circulation model was considered to have several compartments, which account for posture change. The human adult circulation model proposed by Heldt et al. [4] is

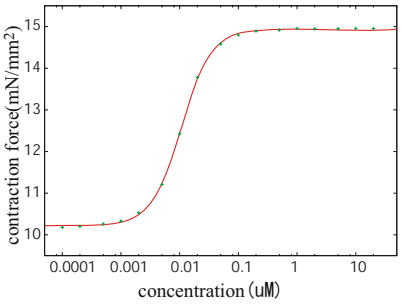
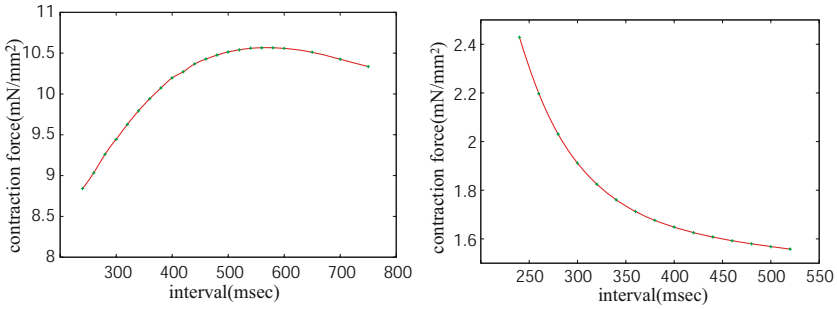


Fig. 1. Relation between ISP concentration and maximum contraction force



(a) Maximum force (b) Minimum force

Fig. 2. Relation between RR interval and force

mathematically formulated in terms of an electric analogous model with 12 compartments that can represent the posture change (Fig.3). 10 compartments representing the peripheral circulation show linear resistance (R) and capacitance (C). The legs, splanchnic and abdominal venous compartments exhibit nonlinear pressure-volume relations according to the following equation,

$$\Delta V = \frac{2 \cdot \Delta V_{max}}{\pi} \cdot \arctan\left(\frac{\pi \cdot C_0}{2 \cdot \Delta V_{max}} \cdot \Delta P_{trans}\right). \tag{1}$$

ΔV represents the compartment volume change due to change in transmural pressure ΔP_{trans}. ΔV_{max} represents the maximal change in compartment volume and C_0 the compartment compliance at baseline transmural pressure. An additional control system built into the model maintains the blood pressure which controls heart rate (HR), peripheral resistance (R), venous zero-pressure filling volume (V^0) and heart contractility (C_{sys}) [4].

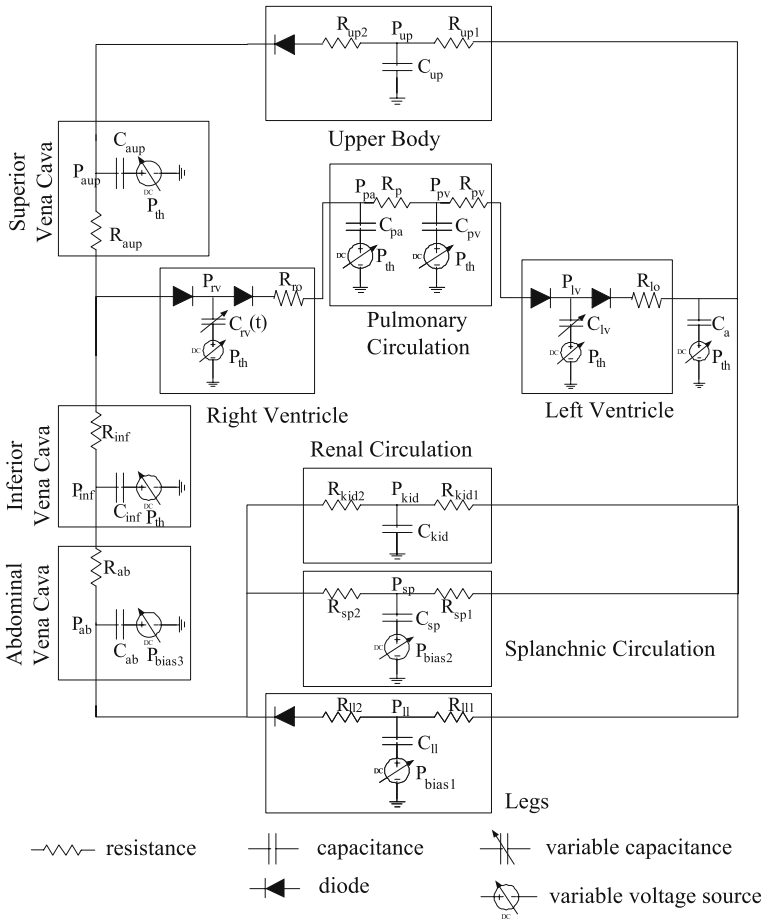


Fig. 3. Heldt circulation model. [4]

3 Construction of Infant Circulation Model

Since the species and the age of the subjects each model is based on is different from that of the human infant, we modified the parameters and the structure of each model.

3.1 Circulation Model Scaling

Since the baseline heart rate of infants is around 130–150(bpm), the myocardial model was constructed by means of the Kyoto model at a baseline heart rate of 150(bpm). The only modification to the model was multiplication of the cross-bridge sliding rate by 7.0, since the original value was determined for 25 degrees room temperature, while the temperature of an infant is around 37 degrees.

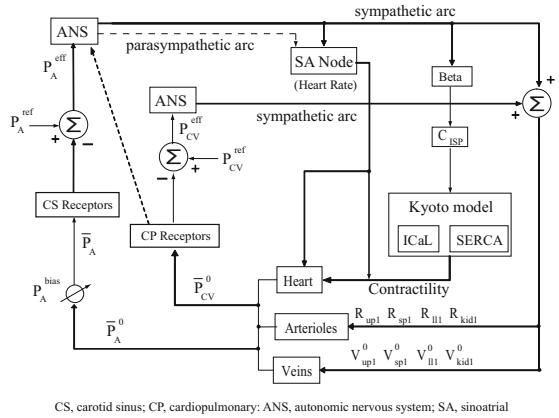


Fig. 4. Block diagram of control system

For the circulation model, we modified the hemodynamic parameters of the Heldt model to fit the infant circulation parameters. Thereby, a scaling method proposed by Goodwin et al. [1] was employed. In their study, the adult human circulation model proposed by Beneken et al. [6] was adjusted to the circulation of a 6 month old infant. Each resistance parameter is multiplied by 2.0, the compliance parameter by 1/5.43 and zero-pressure filling volume by 0.13. The same scaling factors were adopted for our model.

We used the Heldt model initial compartment pressures as initial compartment pressures. From these pressure values, the initial compartment volumes can be calculated, leading to the initial total blood volume of 783.5ml which is slightly large compared to the physiological value of 640ml.

3.2 Control Model Modification

In the Heldt model, the heart function is controlled by its contractility and the given heart rate. We took over the same control system without any parameter modifications. However, in the Heldt model, heart contractility is controlled by the maximum elastance parameter of their time varying elastance model, while the contractility in our heart model is controlled by the ISP concentration. Thus, the control system was modified to influence the ISP concentration. Additionally, in the Heldt model, heart contractility is controlled independently from the heart rate, which is in opposition to the real myocardial cell as well as the myocardial cell model applied in our study. Consequently, deriving a transform function between original heart contractility control signal and ISP concentration was the first task.

An open loop control system was created using the original Heldt model and the pressure input to the baroreceptor varied.In this way, the relation between the heart contractility control signal and the mean blood pressure was determined. Subsequently an open loop control system using the Heldt model was

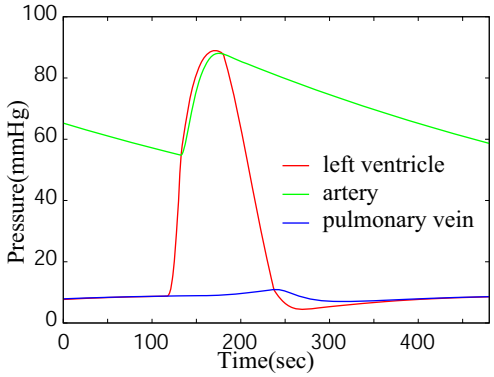


Fig. 5. Pressure at left ventricle, artery and pulmonary vein in resting situation in supine position

designed incorporating our Laplace heart model and the cell model. By changing the ISP concentration, the relation between the ISP concentration and mean blood pressure was deduced. By deleting the mean blood pressure parameter from these two functions, we obtained the desired transform function from heart contractility control signal to ISP concentration.

Subsequently, a compensation function for the heart contractility which is modified with the heart rate was derived. In the real cell, the relation between the cell force and heart rate changes nonlinearly according to the ISP concentration. However, in our model this relation is assumed to be independent of the ISP concentration. The block diagram of our control system is shown in Fig.4.

4 Experimental Results

4.1 Resting Hemodynamics

Figure 5 shows the resulting pressure at the left ventricle, artery and pulmonary vein in resting situation in supine position. Table 2 demonstrates that the hemodynamic parameters of the simulation results match the physiological values from [7][8][9].

4.2 HUT Test

Using the completed model a simulation experiment of the HUT test was conducted. To simulate the tilt effect, we applied following bias pressure to the lower three compartments in accordance with [4].

$$P_{bias} = \begin{cases} P_{max} \cdot \sin(\alpha(t)) & t_0 \leq t \leq t_0 + t_{tilt} \\ P_{max} \cdot \sin(\alpha_{max}) & t > t_0 + t_{tilt} \end{cases} \tag{2}$$

Table 2. Hemodynamic parameters in the supine position at rest

Variable	Target	Simulation results
Heart		
HR(bpm)	115-145	150
LVEDV(ml)	17	27.1
LVEDP(mmHg)	5	6.08
LVESV(ml)	5	13.4
LVESP(mmHg)	82	88.0
CO(L/min)	1.2-2.0	2.0
Circulation		
maxAP(mmHg)	70-110	87.1
minAP(mmHg)	50-65	54.3
CVP(mmHg)	3-12	1.8-3.2

HR: Heart rate, LVEDV: left ventricular end-diastolic volume, LVEDP: left ventricular end-diastolic pressure, LVESV: left ventricular end-systolic volume, LVESP: left ventricular end-systolic pressure, CO: cardiac output, maxAP: maximum arterial pressure, minAP: minimum arterial pressure, CVP: central venous pressure.

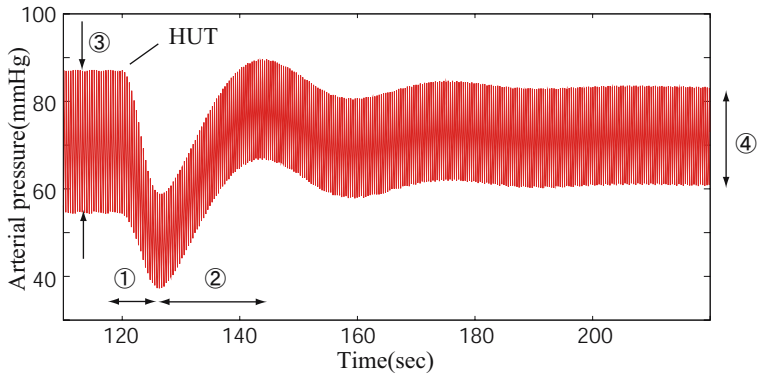


Fig. 6. Arterial pressure at HUT test

Here, t_0 and t_{tilt} denote starting and ending time of the tilt, α_{max} denotes the final angle of the tilt and P_{max} the maximum bias. We used 40.0, 7.0, 5.0 for the P_{max} of the renal, splanchnic and legs compartment, respectively.

In the physiological experiment with a human adult, the blood volume decreases by 600ml within 35 minutes [10]. This fact is modeled in the Heldt model as follows:

$$V_{total} = (5700ml - \Delta V) + \Delta V \cdot 0.9^{\frac{t-t_0}{60s}} \tag{3}$$

$$\Delta V = 600ml \cdot \sin(\alpha_{max}) \tag{4}$$

Table 3. Comparison of transient response to HUT test with experimental data

Variables	Unit	Simulation	experiments
(1)	s	6.3	2—9
(2)	s	17.6	4—30
(3)	mmHg	32.7	22
(4)	mmHg	23.2	17
(5)	beats/min	150	132
(6)	beats/min	169	150

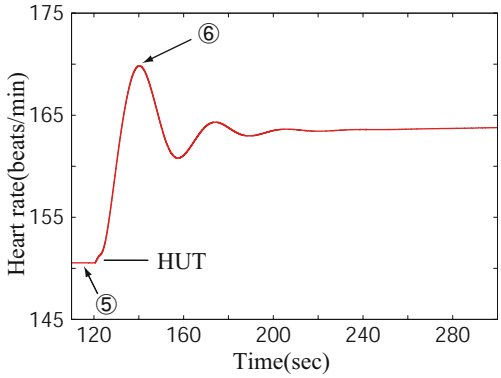


Fig. 7. Heart rate at HUT test

In our model, we modified the above equation to fit the total volume.

$$V_{total} = (783.9ml - \Delta V) + \Delta V \cdot 0.9^{\frac{t-t_0}{60s}} \tag{5}$$

$$\Delta V = 78ml \cdot \sin(\alpha_{max}) \tag{6}$$

In the simulation, the tilt angle was increased from 0 to 70 degree in 2 seconds. The tilt starting time was at 120 seconds. The resulting arterial pressure, heart rate are shown in Fig.6, Fig.7. The resulting features of the hemodynamics are shown in Table 3 in comparison with results gained in physiological experiments. The results are in good agreement with the experimental data.

5 Discussion

By means of the experimental results presented in section 4.1, we have verified that our simulation model is suitable to reproduce the physiological values of infant hemodynamics.

The simulation experiments explained in section 4.2, showed good agreement with experimental data published by Moss et al. [11](Fig.8). They reported that the pressure decreases within 2 to 9 seconds after the start of HUT, and recovers

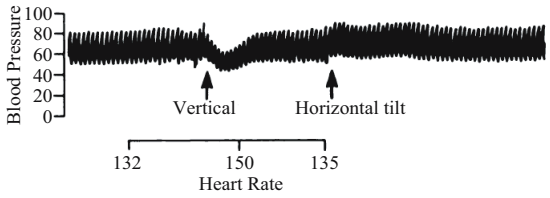


Fig. 8. Blood pressure of HUT test by Moss et al. [11]

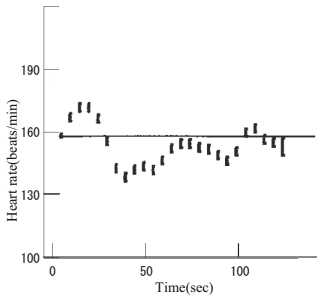


Fig. 9. Heart rate of HUT test by Edner et al. [12]

within 4 to 30 seconds. The pressure pulse width changes from 22 mmHg to 17 mmHg, which equals a 23% decrease. Further, they reported that the heart rate increases from 8 to 38 bpm which equals an 14% increase. Our simulation result showed 29% decrease of the pressure pulse width and 14% increase of heart rate, which is significantly close to the experimental data stated above.

Edner et al. reported the heart rate change when using a 45 degree HUT test [12](Fig.9). Their experimental results showed that the heart rate initially increases, but then decreases again and finally recovers. Also in this case, our simulation results were in good agreement with the experimental results.

From the above, we conclude that our circulation model and control model is capable to simulate the infant hemodynamics not only at resting position but also its response in a HUT test.

6 Conclusions

We developed an infant circulation model which incorporates an accurate myocardial cell model including a beta adrenergic system. The beta adrenergic system is essential in order to reproduce the response of the baroreflex control system. Our model showed good agreement with the physiological experiments. This model may be used to demonstrate the essential functions of the infant cardiovascular dynamics. Especially in clinical and medical training this could be a valuable tool.

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