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Infant Circulation Model based on the Electrophysiological Cell Model

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***Abstract*— It is important to use a myocardial cell model to evaluate the effects of the drugs to the hemodynamic parameters. We developed an infant circulation model which incorporates an accurate myocardial cell model including a beta adrenergic system. The beta adrenergic system is essential mechanism for reproducing the response of baroreflex control system. The parameters of the published adult human circulation model were modified to fit the infant hemodynamic values. The guinea pig myocardial cell model was introduced to the circulation 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.**

I. 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 potential in the analysis of biological functions. Biosimulation models are also expected to provide 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 integrates an autonomic nervous system. However, the heart chamber model is based on 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, their incorporation into cardiovascular models is unquestionably desirable.

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

II. Cardiovascular model

The model is constructed from fundamental models decribed in this section (Table I). Since the species and the age of the subjects of each model is different from that of the human infant, we modified the parameters and the structure of each model.

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TABLE I
List of the fundamental models.

Element	Model	Species	Reference
cardiac cell	Kyoto model	guinea pig	[2]
left ventricle	Laplace law		
circulation	Heldt model	adult human	[3]
control system	Heldt model	adult human	[3]

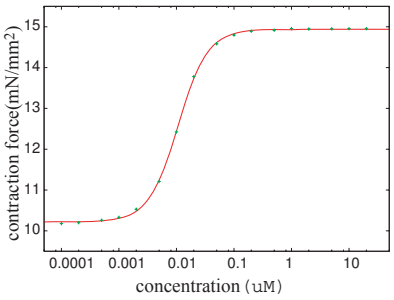


Fig. 1. Relation between ISP concentration and maximum contraction force.

A. Myocardial cell and left ventricle model

The Kyoto model[2] is an accurate cell model which incorporates most of the known ion channels and transporters, a mitochondrion as well as a contraction model. In addition, it is the only model which incorporates a beta adrenergic system. Since our model considers an autonomous nervous system, we need to use a myocardial cell model which includes a beta adrenergic stimulus system. The contractility of the model is modified by the isoproterenol (ISP) concentration (Fig.1).

Since 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 crossbridge 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.

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 $2F_{ext}/R = P_{lv}/h$ [4]. Through this equation, LV pressure and volume are connected to the cell contraction force.

B. 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. Our study also used HUT 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. [3] is mathematically formulated in terms of an electric analogous model with 12 compartments that can represent the posture change (Fig.2). 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,

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

ΔV represents the compartment volume change due to change in transmural pressure ΔP_{trans}. ΔV_{max} represents the maximum change in compartment volume and C_0 the compartment compliance at baseline transmural pressure.

We modified the hemodynamic parameters of the Heldt model to fit the infant circulation parameters. For this purpose, a scaling method proposed by Goodwin et al. [1] was employed. In their study, the adult human circulation model proposed by Beneken et al. [5] 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.

As initial compartment volumes, those used in the Heldt model were applied. From these pressure values, the initial compartment volumes can be calculated, resulting in the initial total blood volume of 783.9ml which is slightly larger then the physiological value of 640ml.

To simulate the tilt effect, we applied following bias pressure to the lower three compartments in accordance with [3].

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

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 [6]. This fact is modeled in the Heldt model as follows:

$$V_{total} = (5700ml - \Delta V) + \Delta V \cdot 0.9^{\frac{t-t_0}{60s}} \quad (3)$$
$$\Delta V = 600ml \cdot \sin(\alpha_{max}) \quad (4)$$

In our model, we modified the above equation to fit the total volume of 783.9ml.

$$V_{total} = (783.9ml - \Delta V) + \Delta V \cdot 0.9^{\frac{t-t_0}{60s}} \quad (5)$$
$$\Delta V = 78ml \cdot \sin(\alpha_{max}) \quad (6)$$

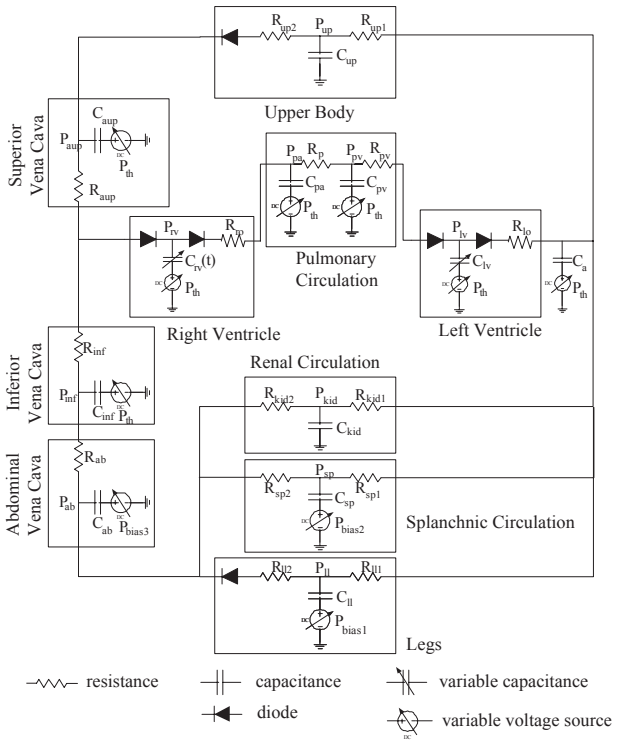
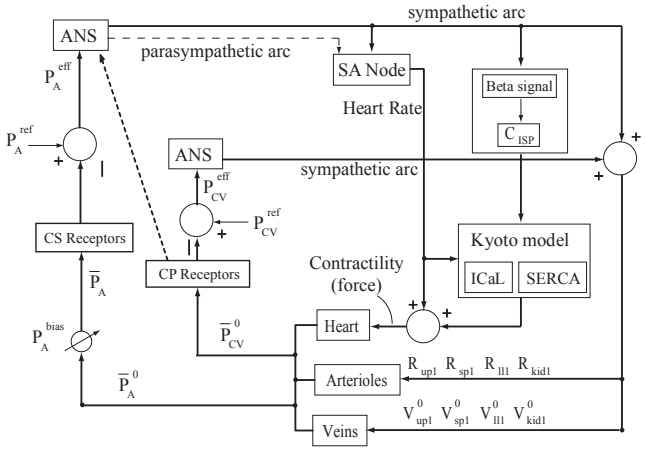


Fig. 2. Heldt circulation model. [3]



CS, carotid sinus; CP, cardiopulmonary: ANS, autonomic nervous system; SA, sinoatrial

Fig. 3. Block diagram of our control system.

C. Control model

In the Heldt model, 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 cardiac contractility (C_{sys}) [3]. We took over the same control system without any parameter modifications. While cardiac contractility is controlled by the maximum elastance parameter of the time varying elastance model in the Heldt model, however, the contractility in our heart model is controlled by the ISP concentration. Thus, the control system was modified to represent the ISP concentration.

First, we derived a transform function between the original

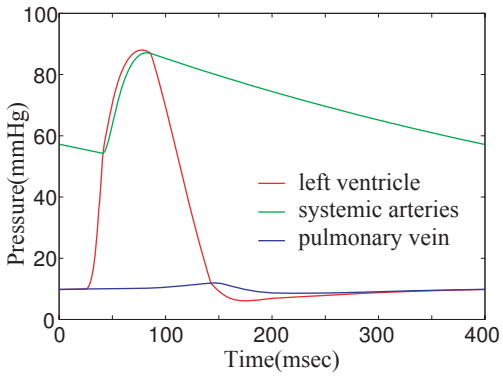


Fig. 4. Pressure at left ventricle, artery and pulmonary vein in the resting situation in supine position.

contractility control signal and the ISP concentration under baseline heart rate of 150(bpm). An open loop control system was created from the original Heldt model. By providing a constant cardiac contractility control signal to this system, we obtain a mean blood pressure. By providing several control signal values, we obtain a relational function between the cardiac contractility control signal and the mean blood pressure. Subsequently another open loop control system was created from the proposed model which incorporates our Laplace heart and the cell model. By providing a constant ISP concentration to the cell model, we obtain a mean blood pressure. By providing several ISP concentrations, we obtain a relational function between the ISP concentration and the mean blood pressure. By deleting the mean blood pressure parameter from these two functions, we obtained the desired transform function from the cardiac contractility control signal to the ISP concentration.

While cardiac contractility of the time varying elastance model in the Heldt model is independent of heart rate, however, cardiac contractility is affected by heart rate in the real myocardial cell as well as in the myocardial cell model applied in our study. Therefore, a cell force compensation function for heart rate change was derived by measuring the cell force under various heart rate. This compensation function is applied to the contraction force of the cell model and the resulting force is used as the contraction force of the Laplace heart model.

The block diagram of our control system is shown in Fig.3.

III. Experimental Results

A. Resting hemodynamics

Figure 4 shows the resulting pressure at the left ventricle, systemic arteries and pulmonary vein in resting situation in supine position. Table II demonstrates that the hemodynamic parameters of the simulation results match the physiological values from [7][8][9]. It took 50 seconds to simulate one second of real hemodynamics with Pentium IV 3GHz PC.

B. HUT test

Using the constructed model a simulation experiment of the HUT test was conducted. In the simulation, the tilt angle was increased from 0 to 70 degree in 2 seconds.

TABLE II

Hemodynamic parameters of the supine position at rest and with Nifekalant.

Variable	Target	Simulation results	Nifekalant
Heart			
HR(bpm)	115-145	150.6	150.7
LVEDV(ml)	17	27.1	27.2
LVEDP(mmHg)	5	6.08	6.58
LVESV(ml)	5	13.4	13.6
LVESP(mmHg)	82	88.0	87.8
CO(L/min)	1.2-2.0	2.07	2.06
Circulation			
maxAP(mmHg)	70-110	87.1	86.9
minAP(mmHg)	50-65	54.3	54.2
CVP(mmHg)	3-12	1.8-3.2	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.

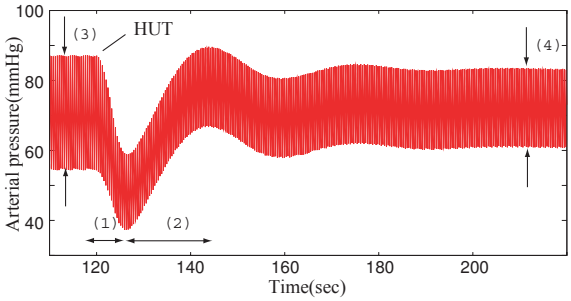


Fig. 5. Arterial pressure at HUT test.

The simulation results of arterial pressure and heart rate are shown in Fig.5 and Fig.6, respectively. The tilt started at 120 sec in Fig.5 and Fig.6. The typical parameters of hemodynamic change during HUT are summarized in Table III with the results reported in physiological experiments. The results are in good agreement with the experimental data.

C. Effect of an IKr blocker to the hemodynamics

One of the important aim of incorporating the cell model to the circulation model is to accomplish the evaluation of the effect of drug to the hemodynamics. We used nifekalant which is known as a pure IKr blocker, and the permeability of the IKr channel was reduced to 50%. Resulting hemodynamic parameters are shown in Table.II. The results show that there are very small differences in hemodynamic

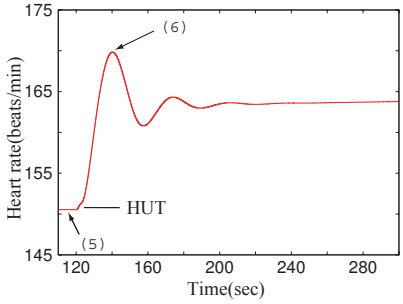


Fig. 6. Heart rate at HUT test.

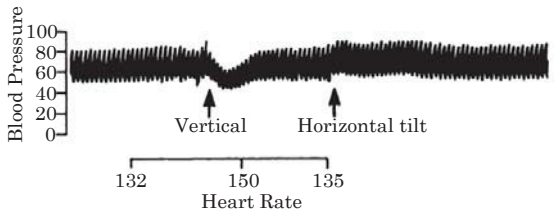


Fig. 7. Blood pressure of HUT test by Moss et al. [11]

parameters by applying nifekalant which is consistent with the published experimental data [10].

IV. Discussion

By means of the experimental results presented in section III-A, we have verified that our simulation model reproduces the physiological values of infant hemodynamics.

Due to the limitation of the experiments, infant cardiac cell models are still under development. In spite of this situation, the simulation experiments explained in section III-B showed good agreement with experimental data published by Moss et al. [11](Fig.7). They reported that the pressure decreases within 2 to 9 seconds after the start of HUT, and recovers within 4 to 30 seconds. The pressure pulse width changes from 22 mmHg to 17 mmHg which is a 23% reduction. Further, they reported that 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. Both results are close to the experimental data stated above.

Edner et al. reported heart rate changes of a 45 degree HUT test [12]. Their experimental results showed that heart rate initially increases, but then decreases again and finally recovers. Our simulation results again showed good agreement with the experimental results.

From the results, 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.

From the experimental results in section III-C, nifekalant has very small effect to the hemodynamic parameters. However, there are small differences in the LV volume and the pressure between our results and experimental results.. Though the action potential prolonged after administration of nifekalant, the Ca^{2+} transient remained almost constant. Since the contraction force is predominantly determined by Ca^{2+} concentration, the hemodynamic parameters determined by the LV contraction force were not affected by nifekalant. This kind of analysis is only available with the circulation model which incorporates an accurate myocardial cell model.

V. Conclusions

We developed an infant circulation model which incorporates an accurate myocardial cell model including a beta adrenergic system. Our model showed good agreement with the physiological experiments of resting hemodynamics, HUT test and drug administration. This model may be used to demonstrate the essential functions of the infant cardiovascular dynamics. This kind of model could be a valuable tool particularly in clinical and medical training. Since the accuracy of the human adult cardiac cell models are increasing, constructing a human adult hemodynamics model will be our next work.

TABLE III

Comparison of transient response of HUT test to experimental data.

Variables	Unit	Simulation	experiments
(1)	s	6.3	2-9[11]
(2)	s	17.6	4-30[11]
(3)	mmHg	32.7	22[11]
(4)	mmHg	23.2	17[11]
(5)	beats/min	150	132[12]
(6)	beats/min	169	150[12]

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