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A Cycle-Averaged Model of Hypoplastic Left Heart Syndrome (HLHS)

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***Abstract*—This paper is concerned with computational modeling of a severe congenital defect called Hypoplastic left heart syndrome (HLHS) that is the most common cardiac malformation with the highest likelihood of deaths in newborns. A lumped parameter model of the HLHS circulation has been developed to study the hemodynamic variables in the various sections of the cardio-pulmonary circulation system. We applied a short-term, cycle-averaging operation to the differential equations of the HLHS model to obtain the cycle-averaged model. Study has been carried out to analyze the variation of blood flow rate in different parts due to parameter changes. Results show that the developed model, could bring a good insight into understanding of the HLHS disease.**

I. Introduction

Hypoplastic left heart syndrome (HLHS) is a congenital heart defect (CHD) in which the left side of the heart is severely underdeveloped. The HLHS causes 23% of cardiac death during the first week of life and 15% of cardiac death within the first month of the newborn's life [1]. HLHS is presently the most common cardiac malformation that results in death in newborns. Without treatment, 95% of these infants die during the first month of life, and none survive beyond 4 months. In babies with HLHS, the aorta and the left ventricle are very small, and the aortic and mitral valves are either too small to allow sufficient blood flow or are closed altogether. A typical HLHS heart is compared with a normal heart in Fig. 1.

Underdevelopment of the left ventricle-aorta complex resulting in critical aortic valve stenosis or aortic valve atresia with an intact ventricular septum is the most recognized form of the HLHS. There are corresponding changes in the right side of the heart in the case of HLHS. All right sided cardiac structures are larger than normal including the right atrium, pulmonary artery and pulmonary valve.

As blood returns from the lungs to the left atrium, it must pass through an atrial septal defect (ASD) to the right side of the heart. In cases of HLHS, the right side of the heart must pump blood to the body through a patent ductus arteriosus (PDA). This maintains fetal parallel circulation where the right ventricle is the only active pump. But since the ductus arteriosus (DA) usually closes within eleven days after birth, for an HLHS baby, blood flow is severely leading to very low circulation and possible death. Hence, the management of neonates with HLHS is very complex. Treatment generally commences with vigorous infusion of prostaglandin to prevent the DA from closing. However, reduction in pulmonary resistance after birth results in an unbalanced circulation where most of the blood goes into the pulmonary circulation thereby compromising systemic oxygen supply.

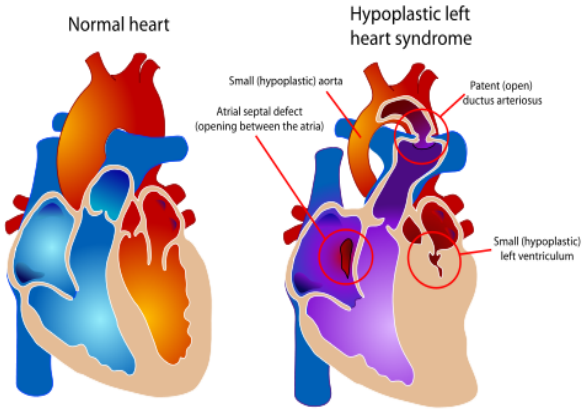

Fig. 1. Comparison between normal heart on the left and HLHS heart on the right. The left ventricle is diminutive. The acsending aorta and arch are extremely hypoplastic, and flow is retrograde. Systemic output is ductal dependent

The need to study the problem of HLHS in detail stems from our recent studies [2, 3] to predict occurrence and extent of Periventricular Leukomalacia (PVL). It has been proved that PVL is common after neonatal cardiac surgery and was found in more than 50% of the neonates after cardiac surgery. However; it is rarely found in older infants [4]. In our work in the field of PVL prediction, we applied computational intelligence techniques to the data obtained from the children suffering from the problem of PVL. The developed decision trees suggest some ranges for critical hemodynamic parameters, such as oxygen concentration and blood pressure, which give a high probability for the occurrence of PVL. But since these numbers have been obtained from a limited set of subjects, it cannot be used as a general applicable criterion for all neonates. Hence, it is important to carry out physiological modeling of the cardiovascular system to understand the underlying causes for a particular range of parameter values to lead to high frequency of PVL occurrence.

Lumped parameter time-varying electrical circuit analogous for the cardiovascular system are frequently used in medical research and teaching for simulating and

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analyzing medical data. Considering the ICU applications, it may be more useful to dynamically track the beat to beat or inter-cycle dynamics instead of instantaneous changes in hemodynamic variables [5]. There, only few studies have been done on the cycle-averaging of cardiovascular models [5, 6] and these works are only limited to the normal heart models.

In this paper a lumped parameter model of the HLHS circulation has been developed to study the blood pressures and flow in the different parts of cardio-pulmonary circulation system. Then, we applied a short-term, cycle-averaging operation to the differential equations of the HLHS model to obtain the cycle-averaged model.

II. Materials and Methods

A. Mathematical Model

Several lumped parameter models of cardiovascular system have been developed in past researches, for instance, [7, 8].The lumped-parameter approach used in this paper to model the HLHS circulation is shown in Fig. 2. Each box represents a lumped parameter model for a complex system of blood vessels and the heart components. This model is built based on methodologies previously published for the fetal [9, 10] and neonatal cerebral circulation [11] and the Norwood procedure [12]. The complete model is composed of three main parts - a hypoplastic heart, systemic circulation and pulmonary circulation. Each compartment is made of resistances, capacitances and inductances. Resistances are used to model the resistance to flow in the arteries and veins, and capacitors for the elasticity of the vessels. Inductors are not typically used for modeling veins.

B. Hypoplastic Heart

The heart has been assumed to be composed of three parts – Right Atrium (RA), Left Atrium (LA) and Right Ventricle (RV). Here, as mentioned earlier, we considered the most severe case of hypoplastic heart in which the left ventricle is completely blocked; however, modeling other types of HLHS is a minor extension from the present study. In the most severe type of this syndrome, the flow to or from the left ventricle is blocked due to stenosis in mitral valve or aortic valve or due to the small size of the left ventricle. Hence the left ventricle for the heart is not taken into consideration in the model.

The activity of the heart is modeled as has been done in [8]. For both the atria and ventricle, the total pressure is expressed as a non-linear function of its volume and cycle-time

$$P(t) = P_s(t) + P_d(t) \quad (1)$$

where,

$$P_s = \alpha(t) E_{max} \, (V(t) - V_u) \quad (2)$$

and

$$P_{d=}(1 - \alpha(t)) P_0 (e^{Ke.V(t)} - 1) \quad (3)$$

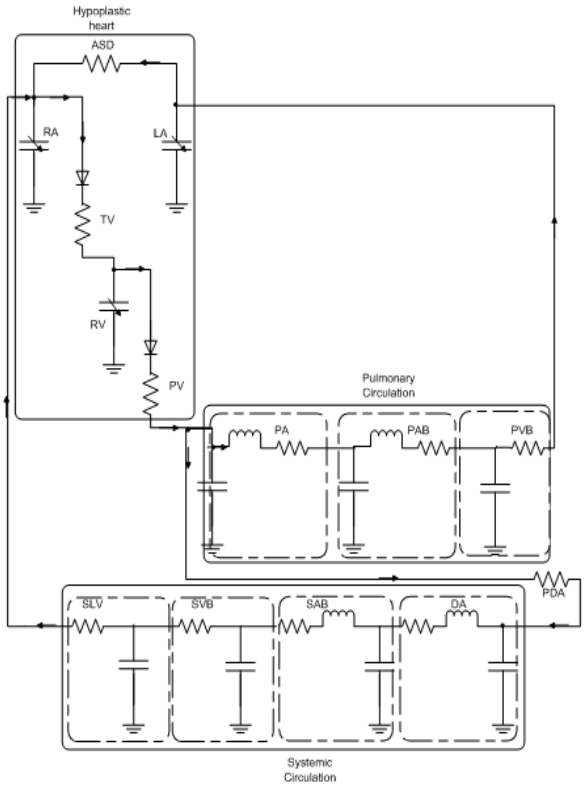

Fig. 2. Lumped parameter model of HLHS. Model is made up of three parts: a-hypoplastic heart, b- pulmonary circulation and c-systemic circulation. Direction of blood flow is shown by arrows. ASD, atrial septal defect; RA right atrium; LA, left atrium; TV, tricuspid valve; RV, right ventricle; PV, pulmonary valve; PA, pulmonary artery; PAB pulmonary arterial bed; PVB, pulmonary venous bed; PDA, patent ductus arteriosus; DA, descending aorta; SAB, systemic arterial bed; SVB, systemic venous bed; SLV, systemic large veins.

where, P is pressure, V is volume, V_u is unstressed volume, E_{max} is the maximum elasticity of the heart wall during the heart cycle. The activation function α is the driving force of the heart model and it models the release of Ca^{2+} which initiates the contraction of heart muscle.

Since the heart muscle's contraction is different for systole and diastole cycles, the activity function is defined by different differential equations in the systole and diastole. During diastole, the activation function is defined by (4):

$$\frac{d\alpha}{dt} = -K_r \alpha \quad (4)$$

where K_r is the relaxation rate. For the systole period the above equation is as (5):

$$\frac{d^2\alpha}{d^2t} + 2K_e \frac{d\alpha}{dt} + K_e^2 \alpha = K_e^2 \alpha_{max} \quad (5)$$

where, K_e is the excitation rate and α_{max} is the limiting value of the activation function.

The solutions to (4) and (5) are as following forms of (6):

$$\alpha(t) = \alpha(t_d) e^{-K_r(t-t_d)}$$
$$\alpha(t) = \alpha_{max} - (\alpha_{max} - \alpha(t_s))(1 + K_e(t - t_s)) e^{-K_e(t-t_s)} \quad (6)$$

where, t_d is the onset of diastole (which we set equal to zero), and t_s is the systole time. E_{max} is a function of volume of the ventricle to account for the decreasing elastance with increasing volume.

$$E_{max} = E_1 + E_2(V(t) - V_u) \quad (7)$$

where E_1 is constant and E_2 is negative-valued constant to account for decreasing elastance of the ventricle. E_2 is zero for the atriaresulting in the constant E_{max}, consistent with the literature.

Again, V_u is the unstressed volume of the chamber which is the volume at zero pressure. This is the x-intercept of the tangent at the end-systolic point for the pressure-volume (P-V) curve.

The atria and ventricles are modeled with variable capacitors to account for the time dependent relationship of pressure with volume. A flow resistance has been introduced between the right and left atria to account for the defect in the walls of the heart permitting a leakage of flow between the atria. In the present work, this leakage has been modeled as an orifice unlike [12] where it was modeled as a simple resistor. The reason for modeling ASD as an orifice instead a resistor is because of its very small diameter in comparison with other compartments which are modeled as resistances. Hence, a non-linear pressure-flow relationship (Darcy-Weisbach equation) is used as mentioned in (8).

$$\Delta P(t) = K_{ASD} \cdot Q(t)^2 \tag{8}$$

The tricuspid and the pulmonary valves are also modeled as orifices and a similar pressure-flow relationships has been used for them.

C. Pulmonary and Systemic Circulation

The pulmonary circulation is divided into three compartments - proximal pulmonary arteries (PA), pulmonary arterial bed (PAB) and pulmonary venous bed (PVB). The PA and PAB are modeled using R-L-C and PVB by R-C circuits. Flow enters in PA from the pulmonary valve and the blood flows out to the left atrium (LA). It should be noted that the PDA is present in the newborn which normally closes after 5-10 days. To model it, a simple resistance is added between the pulmonary artery and the aorta. The addition of PDA to the model is another major difference between this model and other previously developed models; this is especially important in the current study because it is focused on HLHS which is present in neonates. The systemic circulation is divided into four compartments – descending aorta (DA), systemic arterial bed (SAB), systemic venous bed (SVB), systemic large veins (SLV). The DA and SAB are modeled by R-L-C and SVB and SLV are modeled by R-C circuits. Blood comes in from the PDA and flows to the right atrium.

The ASD is assumed as a nozzle, therefore, we can write the relationship between Q and pressure change through a Darcy-Weisbach equation:

$$Q_{ASD} = \begin{cases} \sqrt{\dfrac{P_{RA} - P_{LA}}{K_{ASD}}} & P_{RA} > P_{LA} \\ \sqrt{\dfrac{P_{LA} - P_{RA}}{K_{ASD}}} & P_{LA} > P_{RA} \end{cases} \tag{9}$$

where, P_{RA} and P_{LA} are right and left atria pressures respectively.

By assuming realistic initial values, the numerical integration is carried out for a sufficient number of heart cycles to achieve steady-periodic state values for every parameter. The PDA flow rate is estimated from the (10).

$$Q_{PDA} = \frac{P_{PA} - P_{DA}}{R_{PDA}} \tag{10}$$

where, P_{PA} and P_{DA} are pulmonary artery and descending aorta pressures respectively.

D. Cycle Averaging

The method used for cycle-averaging of the model is based on the algorithm described in [5]. A signal x has a complex Fourier series representation on the interval $[t-T, t]$ that can be written as:

$$x(\omega) = \sum_{n=-\infty}^{\infty} X_n(t) e^{jn\frac{2\pi}{T}\omega} \tag{11}$$

Where ω is frequency, for $\omega \in [0\ 2\pi]$. The $X_n(t)$ are the complex Fourier series coefficients, also referred to as *index-n* averages and denoted by $\langle x \rangle_n(t)$. These complex coefficients are given by:

$$X_n(t) = \langle x \rangle_n(t) = \frac{1}{T}\int_{t-T}^{t} x(\omega) e^{-jn\frac{2\pi}{T}\omega} d\omega. \tag{12}$$

If x were actually periodic with period T, then the X_n (t) would be constants, independent of t. From (12), with n=0, we obtain the standard formula for the cycle-average of the variable x(t), namely:

$$X_0(t) = \langle x \rangle_0(t) = \frac{1}{T}\int_{t-T}^{t} x(\omega) d\omega. \tag{13}$$

Where is *index-0* cycle average of function *x*. This *index-0* cycle-average is simply the dc term in the Fourier series. It is also the short-term average of the variable $x(t)$ that we wish to track in our cycle-averaged models. In the cardiovascular circuit models where we apply these expressions, T is simply the length of the cardiac cycle. By differentiating (12), we easily obtain an expression for the derivative of the index-n cycle-average:

$$\frac{d}{dt}X_n(t) = \frac{dx}{dt} - jn\frac{2\pi}{T}X_n(t). \tag{13}$$

In building our cycle averaged model, we neglected higher order terms in Fourier coefficients and just considered *index-0* cycle average terms. First, we simulated our model for 14 heart cycles and to avoid unsteady state in the model, we just considered last two cycles. Finally, we calculated *index-0* cycle average term for each hemodynamic variable. This procedure is shown in Fig. 3.

E. Parameter Values

The parameter values for the case of a newborn HLHS patient were taken from a child with Norwood Circulation [12] since the first step Norwood procedure is applied for a child in his early few weeks and hence, the parameter values for these infants would be comparable. These values are listed in Table 1.

The value of the resistance for the pulmonary arteries is almost a hundred times of what is used in [12] because, for a newborn baby, it is well known that pulmonary resistance

for a newborn is very high, and it start decreasing with the age of the baby.

The average body surface area for an adult male is around 1.5 m^2 and the average surface area for a child is 0.30 m^2. Hence a scaling factor of five can be assumed while estimating some of the parameters for a child from the parameters of an adult.

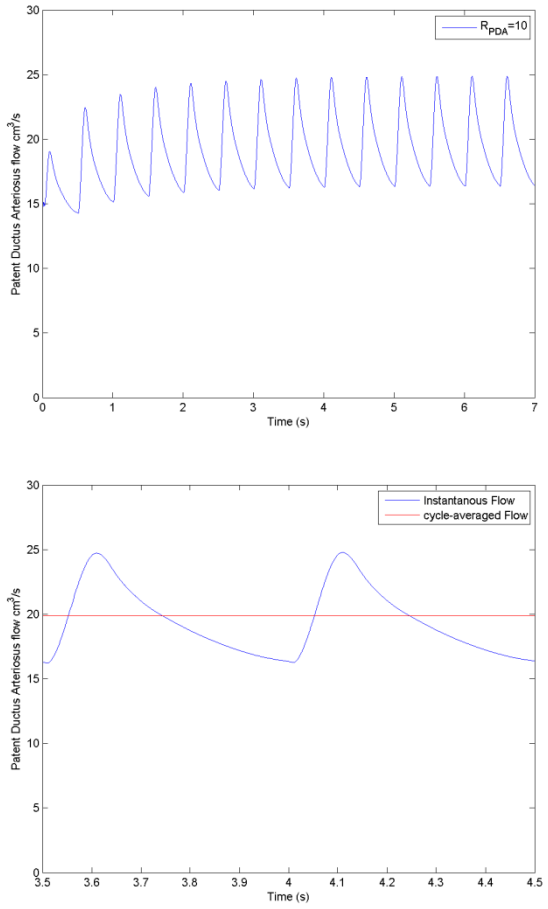

Fig. 3. Top: PDA flow for 14 heart cycles. Bottom: PDA flow for two steady state cycles and cycle averaged flow.

III. Results and Conclusion

Numerical results were obtained by using the parameter values shown in Table 1. Typical important pressure curves for various points of the body are shown in Fig. 4. The pressures depicted by the model in Fig. 4 are consistent with the atrial and ventricular pulmonary pressures of the HLHS heart. The pressure values of the different sections of the heart through the two contraction cycles are consistent with a heart that has a blockage/defect of the left ventricle as in patients with Hypoplastic left heart syndrome - where the right ventricle is responsible for circulating blood to the lungs as well as throughout the body.

IV. Parametric Variation

We performed parametric analysis to investigate the effect of some clinically important parameters on the model performance. Three parameters were chosen which were varied over a certain range and the resulting changes in the hemodynamic parameters were analyzed. The first parameter is the ASD resistance (R_{ASD}).

TABLE I
PARAMETER VALUES

Parameter	Value
Pulmonary Circulation	
PA	
R	2
L	0.00412
C	0.27410
PAB	
R	0.04168
C	0.04078
PVB	
R	0.01097
C	0.88750
Systemic Circulation	
DA	
R	0.19883
L	0.00287
C	0.06118
SAB	
R	3.51120
L	0.00535
C	0.44296
SVB	
R	0.32255
C	0.31030
SLV	
R	0.08265
C	4.07890
Patent Ductus Arteriosus	
R	1

Units of R, L and C are mmHg.s.ml^{-1}, mmHg.s^2.ml^{-1} and ml/mmHg respectively.

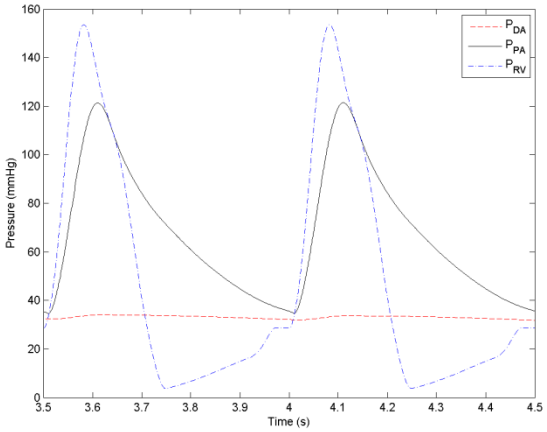

Fig.4. Plot show pressures in right ventricle, descending aorta and pulmonary artery. The heart rate is assumed to be160 bpm based on the average HLHS patient data.

Different values of R_{ASD} would correspond to different cases of patients with varying magnitudes of septal defect. The second parameter varied is the pulmonary artery resistance (R_{PA}); its variation signifies the age of the baby. When a newborn takes his first breath, the resistance of his pulmonary circuit falls significantly and then keeps on reducing for a few days. Finally, the last parameter varied is the resistance of PDA (R_{PDA}). When a baby is born, in both

the cases (normal baby or HLHS baby), the DA is open but then it keeps on constricting within few days and will be closed completely after approximately 2 weeks. (This parameter could be controlled by injection of prostaglandin enzyme to prevent its constriction.)

As can be seen in Fig. 5 the pulmonary-to-systemic flow ratio (QP/QS) changes with the two parameters. As R_{ASD} increases, this ratio decreases because the pulmonary flow keeps on decreasing since, at steady state, all the pulmonary flow passes through the ASD, and so by increasing $R_{ASD,}$ the flow decreases. As R_{PDA} increases, the systemic flow decreases since all the systemic flow passes through ductus arteriosus and hence, the ratio increases.

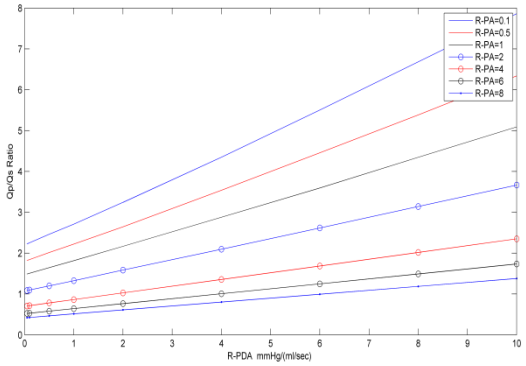

Fig. 5. Plot of pulmonary to systemic (Qp/Qs) flow for different PDA and ASD resistances. A ratio around one is optimal ratio.

Plot of changes induced in cycle-averaged pulmonary artery pressure by varying heart rate and PA resistance is shown in Fig. 6. As depicted in Fig. 6 these changes are not linear.

In this paper a cycle-averaged lumped parameter model of HLHS heart is developed. The need for physical modeling of this congenial heart disease comes from our goal to predict one of its side effects (PVL). The cycle-averaging method helps us to track trends in intercycle dynamics instead of studying instantaneous changes in hemodynamic variables.

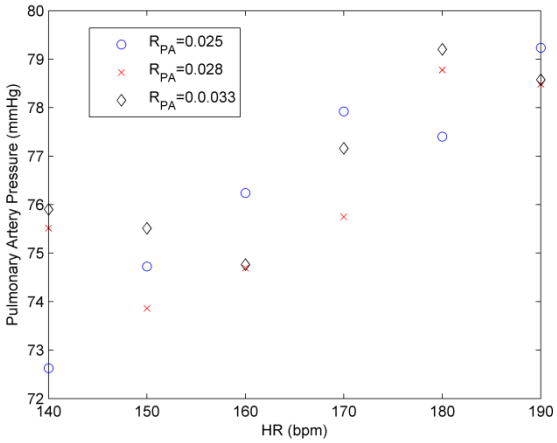

Fig. 6. Plot of changes induced in PAP due to variation of PA resistance and HR. plot shows that how changing the PA resistance affect the trend of PAP.

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