

Modeling of Neonatal Hemodynamics during PDA Closure *

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Abstract— The transition of the fetus at birth to extrauterine life is an extremely complex process. As part of the hemodynamic transition, the closure of ductus arteriosus, a fetal shunt, is among the key steps to achieve normal postnatal cardiovascular function. However, significant gaps remain in our knowledge pertaining to the hemodynamics of normal ductal closure, and in case of failure of closure, to the hemodynamic consequences and treatment of the patent ductus arteriosus (PDA) in preterm infants. This paper presents a mathematical model of a newborn's cardiovascular system with five peripheral organ systems, the ductus arteriosus, and the baroreceptor reflex. We present the hemodynamic findings during simulation of sudden ductal closure, an event seen in real life when the PDA is closed surgically. The results of our model match the clinical data.

I. INTRODUCTION

Upon entering the world, a newborn begins the challenging journey of adjusting to life outside the uterus. The infant's first breath causes a fall in pulmonary vascular resistance and an increase in the surface area available for gas exchange. The ensuing increase in blood oxygenation serves as an important signal to initiate further steps in the transitional process, starting with the constriction of the umbilical vessels. The reduction in placental blood flow and the simultaneous increase in pulmonary blood flow result in changes in pressure and flow patterns in the circulation. These changes, in conjunction with endocrine and paracrine factors stimulate the closure of the fetal circulatory shunts, the foramen ovale and the ductus arteriosus [1].

The ductus arteriosus closes in the majority of term infants within the first 48 hours after delivery. However in about 50-70% of the extremely low birth weight infants (birth weight <1000g), the ductus arteriosus remains open. In such cases, concerns about the consequences of the associated increases in pulmonary blood flow and decrease in systemic perfusion, and the controversy over the approach to the treatment of the PDA have made the management of PDA a

major focus in the care of preterm infants. A PDA, if sustained and hemodynamically significant, affects left ventricular output and systemic and pulmonary flow and may lead to hemodynamic compromise. It is the changes in systemic and pulmonary flow that are thought to be the culprit for the morbidities and mortality associated with a hemodynamically significant PDA. Indeed, PDA has been shown to be associated with peri/intraventricular hemorrhage (P/IVH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC) in the very preterm neonate [1]. The PDA may be closed using medications or by surgical ligation. However, both approaches carry risk of short- and long-term adverse effects. For example, about 30% of preterm infants develop significant deterioration in cardiovascular and respiratory function after PDA ligation [1]. As such, there is controversy over whether the PDA in very preterm infants should be treated at all, and if so, what treatment should be used and when [2].

In light of the uncertainties and controversies, computer simulation of the neonatal cardiovascular system modeling the effects of PDA on systemic and organ blood flow along with the hemodynamic changes that occur with the closure of the PDA, would be beneficial in improving our understanding of neonatal cardiovascular physiology [3]. In addition, computer simulation would also provide hypothesis-generating information on the suspected role of PDA in the pathogenesis of various diseases.

Mathematical models have historically been used to quantify characteristics of experimental results from various sources and combine them in a single entity with the goal to improve our understanding of biological systems. Many models simulating the cardiovascular and respiratory systems have been published for adults [4]-[7], and a few for infants and neonates [8]-[10]. However, in the existing newborn models, distinction between organ systems does not exist and the baroreceptor control of autonomic activity has not been modeled.

This paper presents a model of a newborn's cardiovascular system with five peripheral organ systems, the ductus arteriosus, and the baroreceptor reflex. The major changes from the previous adult models [6], [7] include 1) addition of the ductus arteriosus to the vascular compartment, 2) adjustments to represent newborn parameters in the cardiovascular model, and 3) the baroreflex model. The model has been validated against clinical measurements. Simulation of the sudden closure of the PDA was also accomplished, and comparison of the results to a lamb animal model [11] is presented.

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II. METHOD: MODEL DESCRIPTION

The present mathematical model represents a significant extension and adjustment of the cardiovascular and baroreflex model described by Ursino and Magosso [6], [7] modified for a newborn infant of approximately 3.5kg in body weight on its second to third day of postnatal life. The model was built using Simulink, (Matlab; MathWork, Natick, MA), based on work by Cheng et al. [4].

A. Vascular System

The electrical analog of the vascular system is described in Fig. 1 modified from [7]. It includes vascular components representing the pulmonary circulation, systemic circulation, and the ductus arteriosus. In the systemic circulation, five different compartments arranged in parallel describe the peripheral circulation of the brain, coronary, skeletal muscle, and splanchnic and extra-splanchnic vascular beds. Representation of the different organs allows for the modeling of the distinct regulatory mechanisms characteristic for each organ system. Compartments are modeled using a resistor (R) representing the resistance to flow, capacitor (C) representing the compliance of the vasculature, and inductance (L) representing the inertia of blood flow in large arteries.

The ductus arteriosus was modeled using a resistor and inductor and added as a parallel circuit connecting the aorta to the pulmonary artery.

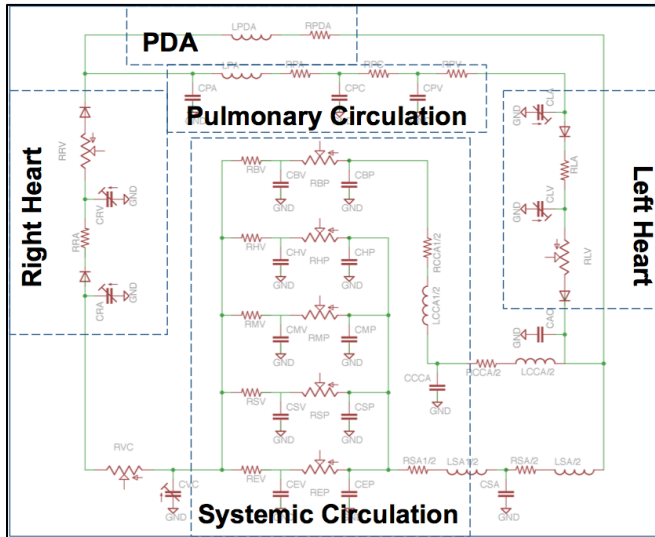


Figure 1. Electrical analogue of the newborn's cardiovascular system. R, resistance to flow; C, compliance; L, inductance; AO, aorta; CCA, ascending aorta; SA, systemic arteries; BP and BV, brain peripheral and venous circulation; HP and HV, heart peripheral and venous circulation; MP and MV, skeletal muscle peripheral and venous circulation; SP and SV, splanchnic peripheral and venous circulation; EP and EV, extrasplanchnic peripheral and venous circulation; VC, vena cava; PA, pulmonary arteries; PC and PV, pulmonary peripheral and pulmonary venous circulation; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; P, ductus arteriosus ductus arteriosus patent ductus arteriosus.

B. Heart

The model of the pulsating heart is based on the work by Ursino [6] where the atrium is represented by passive compliance while ventricular activity is simulated by means

of a variable-elastance model. The heart rate and slope of the end-systolic pressure-volume curve are modified by efferent neural activities. The atrioventricular, aortic and pulmonary valves are mimicked as ideal diodes.

C. Baroreceptor Reflex

The baroreceptor reflex response is described in three parts similar to the work by Ursino [6]. First, the *afferent pathway*: the dynamic relationship between aortic pressure and the activity of the carotid sinus nerve is described as a first order linear differential equation and rate-dependent gain in series with a sigmoidal static function. Second, the *efferent autonomic pathway*: the relationship between the frequency of sinus nerve firing and the autonomic activity is described as an exponential decreasing curve for the sympathetic efferent and as an increasing exponential curve for the vagal efferent pathway. Third, the *effector response* to sympathetic activity and the *sympathovagal control* of the heart rate are represented.

III. METHOD: PARAMETER ASSIGNMENT

A. Vascular System

The resistances in the model were scaled such that the value for baseline systemic and pulmonary vascular resistance matches the reference in literature [Table 1]. The distribution of resistance across the five systemic compartments was set such that the percent flow distribution matches the values reported in the lamb model [11] adjusted for the newborn infant [12]. The resistance of the PDA was set to achieve the desired PDA flow to left ventricular output (LVO) ratio of 40-60%, clinically classified as a moderate PDA [1].

B. Heart

Atrial compliance was calculated using end-diastolic and end-systolic pressure and volume data from literature [13], [14].

Ventricular elastance was calculated based on the end-diastolic and end-systolic pressure volume relationship (EDPVR and ESPVR, respectively). EDPVR is the ventricular compliance and was estimated based on an exponential function with parameters fitted using data from the newborn lamb [15]. ESPVR is the maximal pressure developed at any given ventricular volume and was estimated as a linear function fitted using data from the ventilated fetal sheep model [16].

C. Baroreceptor Reflex

Blanco et al. studied a single carotid baroreceptor afferent response in anesthetized fetal lambs [17]. They found that the baroreceptor afferents were all physically active and increased discharge as pressure was raised as seen in adults. They also noticed that basal discharge did not change significantly despite the increase in mean arterial blood pressure with gestational or postnatal age. This indicates that a reset of the baroreceptors resulting in shifting of the curve to the right with increase in age. Based on this study, the sigmoidal curve representing the afferent sinus nerve-firing rate versus the aortic pressure was shifted to the right to represent the new reset systemic mean blood pressure value.

No data were available for the efferent autonomic pathway; thus, the ratio used in adults [6] was implemented. The gain values for the various effector organs were set and heart rate was adjusted based on data in the literature studying autonomic blockade in fetal lambs [18], [19].

IV. RESULTS

Computer simulations of hemodynamic variables during basal conditions and PDA closure were performed.

A. Baseline value

Comparison of baseline parameters of our computer simulations to data obtained in term neonates is presented in Table 1. Simulation of the left ventricular pressure volume loop is presented in Fig. 2.

TABLE 1. Baseline hemodynamic parameters in term neonates and simulated hemodynamic variables

Hemodynamic Variables	Newborn Infant*	Computer Simulation
Cardiac Output (L/min)	0.5 - 1.02 (N=47)	0.59
Heart Rate (beat/min)	114-150 (N=68)	123
Calculated Stroke Volume (mL)	3.3 - 8.9	5
Systemic Mean Blood Pressure (mmHg)	46-74 (N=129)	57
Pulmonary Mean Blood Pressure (mmHg)	20-22 (N=2)	16
Calculated Systemic Vascular Resistance (mmHg s/mL)	2.7-8.9	4.7

* Literature values for term infants with closed ductus arteriosus, birth weight 3.5kg, 2-3 day of life. The range listed is calculated based on mean \pm standard deviation of various studies. For pulmonary mean blood pressure both available data points are listed. Number in parenthesis represents total number of infants studied. Stroke volume was calculated based on cardiac output/ heart rate. Systemic vascular resistance was calculated using systemic mean blood pressure/ systemic blood flow, with the assumption that right atrial pressure is zero. References: [20]-[25]

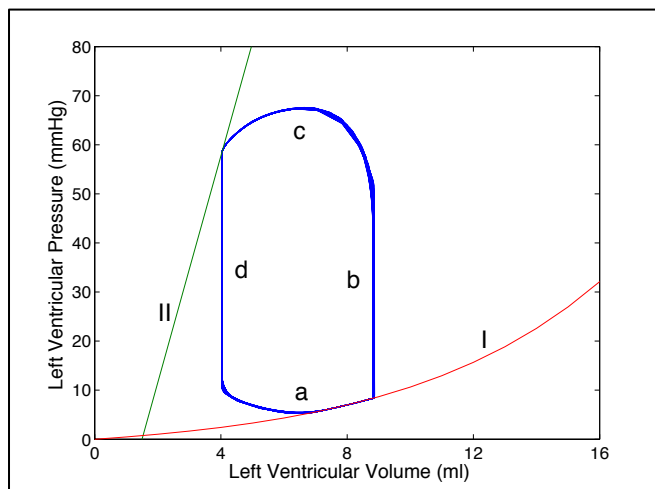


Figure 2. Computer simulation of left ventricular pressure volume loop. Simulation of pressure-volume function during ventricular filling (a), isometric contraction (b), ventricular ejection (c), and isometric relaxation (d). The line marked by I represents the end-diastolic pressure volume relationship (EDPVR) and II represents the end-systolic pressure volume relationship (ESPVR).

B. PDA Closure

The cardiovascular and autonomic simulation, designed to mimic surgical, sudden closure of the PDA was accomplished by changing the resistive properties of the PDA [Fig. 3]. A study of the cardiovascular effects of PDA in lambs with respiratory distress was performed by Clyman et al. [11] and Table 2 compares percent change in various hemodynamic variables following PDA closure in lambs to those of our computer simulation using a moderate PDA simulation model.

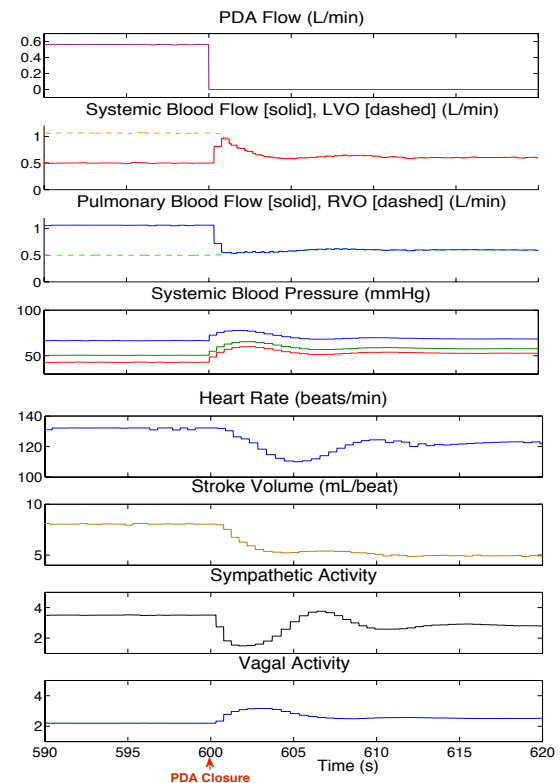


Figure 3. Computer simulation of the acute hemodynamic and autonomic changes of sudden closure of a moderate PDA. LVO, left ventricular output; RVO, right ventricular output. Systolic, mean, and diastolic blood pressure is represented in the systemic blood pressure panel. See text for details.

Immediately after PDA closure, systemic blood flow increases as left ventricular output (LVO) is now directed only to the systemic circulation. The increase in systemic blood flow causes a sudden rise in blood pressure, which, in turn, triggers a baroreceptor reflex response. The ensuing vagal activation decreases heart rate and sympathetic drive resulting in a decrease in systemic vascular resistance. With the removal of the shunt, pulmonary blood flow also decreases, leading to gradual decreases in left ventricular preload during the subsequent cardiac cycles followed by decreases in left ventricular stroke volume and systemic blood flow. Thus, the initial immediate post-closure rise in systemic blood flow is followed by a subsequent decrease in systemic blood flow due to decrease in preload. Except for the sudden increase in blood pressure, the significant and short-lived alterations in hemodynamics cannot be seen in animal models or human neonates using the available monitoring systems.

TABLE 2. Percent change during PDA closure in physiologic model (lamb) [11] and the computer simulation

Variable (% change)	Physiological Model	Computer Simulation
PDA:LVO flow ratio	50% → 0%	53% → 0%
Left Ventricular Output	-41%	-39%
Systemic Blood Flow	19%	18%
Stroke Volume	-40%	-29%
Heart Rate	-3%	-7%
Systemic Mean Blood Pressure	20%	12%
Pulmonary Mean Blood Pressure	-29%	-41%
Brain Blood Flow	19%	16%

V. CONCLUSION

The modified mathematical model provides qualitative and quantitative representations of the newborn infant's hemodynamic response to the presence of a PDA and its closure. In addition, the model has revealed short-lived yet clinically relevant hemodynamic changes not seen with the present monitoring capability in the clinical practice. The findings of the simulation match the data published in the literature in the newborn lamb model and the human infant. We speculate that, after appropriate modification of the parameters for the preterm infant and validation based on clinical data, the model can be used for quantitative analysis and prediction of the hemodynamic events associated with PDA ligation or pharmacological closure of the PDA. Limitations of our model and parametric modeling in general include the assumptions and simplifications made in order to make modeling possible.

We propose that this model will complement other techniques toward a holistic understanding of the effects of PDA on neonatal hemodynamics in particular and system physiology in general. These efforts might eventually lead to the development of a prediction tool that can aid physicians in deciding if the given patient would or would not benefit from PDA closure or what approach would be the best to use.

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