

Sensitivity Analysis of a Cardio-respiratory Model in Preterm Newborns for the Study of Patent Ductus Arteriosus

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Abstract—This paper proposes an integrated model of cardio-respiratory interactions in preterm newborns, focused on the study of the patent ductus arteriosus (PDA). A formal model parameter sensitivity analysis on blood flow through the PDA is performed. Results show that the proposed model is capable of simulating hemodynamics in right-to-left and left-to-right shunts. For both configurations, the most significant parameters are associated with mechanical ventricular properties and circulatory parameters related to left ventricle loading conditions. These results highlight important physiological mechanisms involved in PDA and provide key information towards the definition of patient-specific parameters.

I. INTRODUCTION

Patent ductus arteriosus (PDA) is a large vessel that connects the main pulmonary trunk with the descending aorta [14]. Ductus arteriosus normally closes quickly after birth, however, in some preterm infants, it remains patent beyond the first few days of life. With the decrease of pulmonary vascular resistance, the fetal right-to-left ($R \rightarrow L$) shunt becomes a left-to-right ($L \rightarrow R$) shunt, resulting in pulmonary over-circulation and systemic hypoperfusion [1]. The presence of a hemodynamically significant PDA is commonly associated with increased risk of pulmonary edema, ventilator dependence, intraventricular hemorrhage or death. Currently, there is no consensus on the treatment of PDA in preterm infants. New methods such as percutaneous transcatheter closure emerge [7], but are still poorly documented. PDA status and direction induce strong hemodynamic perturbations and highly affect interactions between cardiovascular, respiratory and nervous systems. As a consequence, the analysis of cardio-respiratory interactions requires taking into account ductus arteriosus circulation, in order to better document the cardio-respiratory adaptation due to the presence or the closure of a PDA.

In this context, a model-based method seems particularly adapted, because it allows the integration of physiological knowledge in data processing tasks, and it permits the analysis of underlying physiological mechanisms. A limited number of cardiovascular models, integrating the baroreflex [13] [2] [10], and the respiratory function [5], inspired from adult models, have been adapted to preterm newborns. In particular, Sa Couto's model [13] introduced a representation of the PDA. The influence of a sudden closure on hemodynamics and the associated autonomic responses was analyzed in [15]. However, to our knowledge, no complete integrated

cardio-respiratory model, adapted to preterm infants and including PDA, exists in the literature.

Our team has proposed an integrated cardio-respiratory model [8], but it is not suitable for neonates and does not incorporate a representation of the PDA. In this paper, we adapt the above-mentioned model to the physiology of preterm newborns, including the integration of the PDA. We also perform a parameter sensitivity analysis on this model, focused on the physiological consequences of the PDA for both $R \rightarrow L$ and $L \rightarrow R$ shunt directions.

II. METHODS

A. Model description

The integrated model proposed on this paper is composed of four interconnected components (Fig. 1): i) the cardio-vascular system (CVS), ii) the respiratory system, iii) the gas exchange (in the lungs and the metabolism) and iv) the neural control. The model, proposed by our team [8], was adapted to the anatomy and physiology of preterm newborn with a gestational age of 28 weeks, post-menstrual age of 29 weeks and weight of 1 kg. Modifications of the structure were made concerning the cardiovascular, gas exchange and neural control submodels. Most parameters were taken from the literature for preterm infants [2] [21]. Some parameters were adapted following the scaling methods presented by [10] or by manual adjustments.

1) *CVS model*: The model of cardiac electrical activity is based on a set of coupled automata [17]. The cardiac mechanical activity is represented by an elastance E_X associated with left (l) and right (r) atrium (a) and ventricles (v):

$$E_X(t) = E_{MIN,X} + (E_{MAX,X} - E_{MIN,X}) \times e_X(t) \quad (1)$$

where $X \in \{ra, la, rv, lv\}$, $E_{MIN,X}$ and $E_{MAX,X}$ stand respectively for minimal and maximal elastance, and

$$e_{la}(t) = \sin\left(2\pi \frac{0.25}{C_{la}} t\right) \times e^{-B_{la}(t-C_{la})^2} \quad (2)$$

$$e_{lv}(t) = \begin{cases} \sin\left(2\pi \frac{0.25}{C_{lv}} t\right) \times e^{-B_{lv1}(t-C_{lv})^2} & \text{if } t < C_{lv} \\ e^{-B_{lv2}(t-C_{lv})^2} & \text{otherwise,} \end{cases} \quad (3)$$

B_{la} , C_{la} , B_{lv1} , B_{lv2} and C_{lv} are parameters associated with the elastance shape. Similar elastance expressions were defined for e_{rv} and e_{ra} with parameters B_{rv1} , B_{rv2} , C_{rv} , B_{ra} and C_{ra} .

The CVS model includes the pulmonary and systemic circulations (Fig. 2) [11]. The volume of each cardiac

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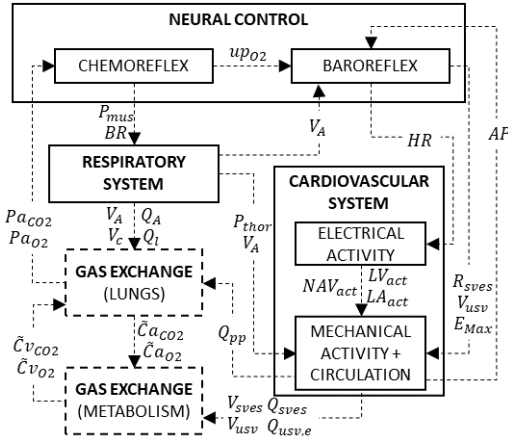


Fig. 1. Cardio-respiratory model diagram. Dotted line arrows symbolize interactions between submodels. up_{O_2} , peripheral chemoreceptors activity; P_{mus} , respiratory muscle pressure; BR , breathing rate; V_A , alveolar volume; HR , heart rate; AP , arterial pressure; P_{aO_2} and P_{aCO_2} , partial pressure of O_2 and CO_2 in the systemic arteries; V_c , intermediate airway volume; Q_A , alveolar flow; Q_I , lung respiratory flow; P_{thor} , thoracic pressure; $\check{C}v_{O_2}$ and $\check{C}v_{CO_2}$, delayed gas concentrations of O_2 and CO_2 in the venous blood; $\check{C}a_{O_2}$ and $\check{C}a_{CO_2}$, delayed gas concentrations of O_2 and CO_2 in the arterial blood; Q_{pp} , pulmonary peripheral circulation flow; LV_{act} , LA_{act} and NAV_{act} , electrical activation of left ventricle (LV), atrium and atrioventricular node; R_{sves} , systemic peripheral vessel resistance; V_{usv} , unstressed volume of the systemic veins; E_{Max} , ventricle maximum systolic elastances; V_{sves} , systemic peripheral vessel volume; V_{usv} , systemic vein volume; Q_{sves} , systemic peripheral vessel blood flow; $Q_{usv,e}$, systemic extrathoracic vein blood flow.

chamber or vessel is calculated from the net flow: $V(t) = \int (Q_{in}(t) - Q_{out}(t))dt$, where the flows are defined by the pressure gradient across chambers and a resistance: $Q(t) = \frac{\Delta P(t)}{R}$. The pressure of cardiac cavities, arterial and venous vessels are defined as an elastance linear relationship: $P(t) = E(t)(V(t) - V_u) + P_{thor}$, where V_u is the unstressed volume and P_{thor} is the thoracic pressure. Flow across cardiac valves is represented as diodes.

2) *Ductus Arteriosus*: A ductus arteriosus was integrated according to [13]. Flow rate through the ductus arteriosus (Q_{da}) was included, as a new state variable:

$$\frac{dQ_{da}(t)}{dt} = \frac{P_{sa,i}(t) - R_{da} \times Q_{da}(t) - P_{pa}(t)}{L_{da}} \quad (4)$$

where $P_{sa,i}$ and P_{pa} are respectively intrathoracic systemic and pulmonary arterial pressures, parameter R_{da} is the resistance to blood flow in the PDA and L_{da} the inertia.

3) *Respiratory model*: The respiratory model was adapted from previous work of our team [11] and includes the upper, intermediate and lower airways, the alveolar compartment, the pleural cavity, the chest wall and the respiratory muscles.

4) *Gas exchange model*: The gas exchange submodel is composed of three components: i) lung gas exchange, ii) metabolism gas exchange and iii) gas transport.

a) *Lung gas exchange*: The exchanges of CO_2 and O_2 between the dead space compartment, the alveoli compartment and the pulmonary capillaries was adapted from [4]. For each compartment, fraction and partial pressure of both gases were computed.

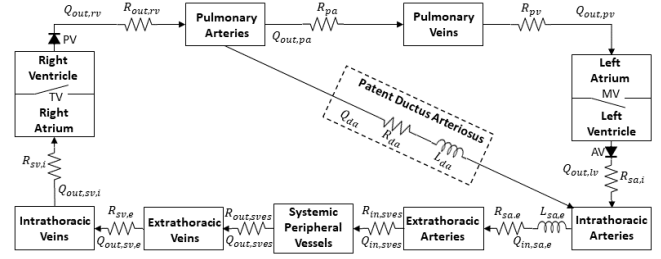


Fig. 2. Cardiovascular model, including ductus arteriosus. P: pressure, Q: flow, R: resistance, L: inductance, da: ductus arteriosus, sa: systemic arteries, sv: systemic veins, pa: pulmonary arteries, pv: pulmonary veins, sves: systemic peripheral vessels, i: intrathoracic, e: extrathoracic

b) *Metabolism gas exchange*: A model of CO_2 production and O_2 consumption by the tissues and organs [3] was integrated in the systemic peripheral vessels compartment in CVS model.

c) *Gas transport*: O_2 and CO_2 circulate through the CVS model. The time taken by a given volume of blood to transport the gases from the pulmonary capillaries to the systemic peripheral vessels, and from the extra-thoracic veins to the pulmonary capillaries are defined by pure delays [3].

5) *Neural control*:

a) *Baroreflex model*: This submodel is based on previous work of our team [17]. It includes the baroreceptors and afferent pathways, the cardiovascular control center, the efferent pathways and the pulmonary stretch receptors. The efferent pathways, depending on the activity of peripheral chemoreceptors (up_{O_2}), control the heart rate through the vagal and sympathetic paths. The pulmonary stretch receptors, activated by alveolar volume V_A , also modulate the vagal branch of the baroreflex.

b) *Chemoreflex model*: Peripheral and central chemoreflex models, adapted from [3], represent modulations of breathing rhythm (BR) and respiratory muscle pressure (P_{mus}), in response to P_{aO_2} and P_{aCO_2} modifications.

B. PDA shunt direction

Three shunt configurations were defined (Table I):

- $R \rightarrow L$ shunt: Fetal circulation is characterized by a high pulmonary peripheral vessel resistance (R_{pp}). During the fetal circulation and first seconds of life [14], blood circulates from the pulmonary arteries to the systemic intrathoracic arteries.
- $L \rightarrow R$ shunt: The fetal $R \rightarrow L$ shunt becomes $L \rightarrow R$ shunt, with the decrease of R_{pp} due to maturation.
- no PDA: The closure of the ductus is accompanied by an increase of R_{da} , until the total PDA closure.

TABLE I

R_{da} AND R_{pp} VALUES FOR EACH SHUNT CONFIGURATION.

	$R \rightarrow L$ Shunt	$L \rightarrow R$ Shunt	No PDA
R_{da}	1.0051	1.0051	$+\infty$
R_{pp}	40	1.7086	1.7086

C. Sensitivity analysis

A sensitivity analysis was applied to determine the most influent parameters, on maximum absolute value of blood flow through the PDA. The Morris' screening method [18] explores the parameter space and calculates elementary effects EE_i for each parameter x_i :

$$EE_i = \left| \frac{F(x_1, \dots, x_i, \dots, x_k) - F(x_1, \dots, x_i + \Delta, \dots, x_k)}{\Delta} \right| \quad (5)$$

where F is defined as $\max(|Q_{da}|)$, and Δ is the variation associated with each parameter. EE_i are calculated r times, the median χ_{i^*} and the interquartile range q_i are computed for each parameter x_i . The screening method was applied to the 159 parameters of the cardio-respiratory model. Parameter ranges were defined as the nominal values $\pm 30\%$ and important parameters were ranked according to their sensitivity indices D_i :

$$D_i = \sqrt{(\chi_{i^*})^2 + (q_i)^2}. \quad (6)$$

Local sensitivity analysis were applied to most important parameters of each PDA shunt, obtained from the Morris method.

III. RESULTS AND DISCUSSION

A. Simulated signals

Fig. 3 shows the PDA blood flow, as well as ventricular and arterial pressures, for the three shunt configurations, during a cardiac cycle.

Concerning $R \rightarrow L$ shunt, maximum blood flow is around 90 mL/s during systole. Pulmonary arterial pressure P_{pa} is higher than intrathoracic systemic arterial pressure $P_{sa,i}$. In fact, it has been reported that $R \rightarrow L$ shunt is usually associated with pulmonary hypertension [20]. Maximum ΔP , which is directly related to Q_{da} [9] [16], is around 9 mmHg and is consistent with reported values [16].

For $L \rightarrow R$ shunt, the maximum blood flow is around 260 mL/s during systole and $P_{sa,i}$ is higher than P_{pa} . The systolic $P_{sa,i}$ is 60 mmHg, whereas the systolic P_{pa} is approximatively equal to 50 mmHg in accordance with [6]. Maximum ΔP value is around 30 mmHg.

During transition from $L \rightarrow R$ shunt to PDA closure, right ventricular pressure declines due to R_{pp} decrease and R_{da} increase. After PDA closure, the systolic $P_{sa,i}$ is around 55 mmHg, whereas systolic P_{pa} is equal to 24 mmHg. This decrease is mainly due to reduction of left ventricular preload [12].

B. Sensitivity analysis results

Fig. 4 presents 10 most influential parameters deduced from the sensitivity analysis, for $R \rightarrow L$ and $L \rightarrow R$ shunts. The most significant parameters were mainly related to ventricular elastances. In fact, C_{lv} and C_{rv} are respectively associated with instants of maximum LV and RV elastances. B_{lv1} and B_{rv1} control the rise of LV and RV pressures during systole. Q_{da} also showed significant dependences on $E_{MIN,ra}$, $E_{MIN,la}$, $E_{MIN,lv}$ and $E_{MIN,rv}$, which stand for

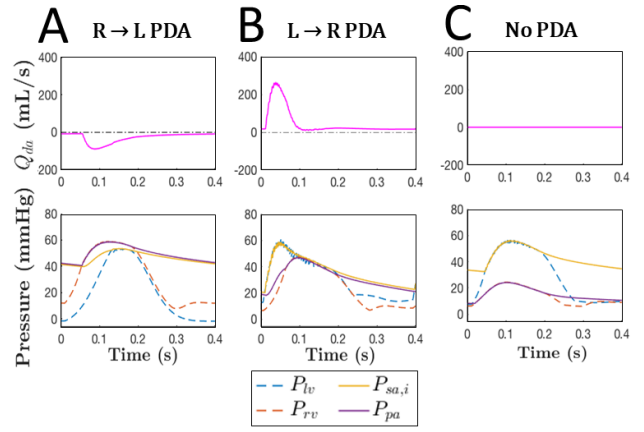


Fig. 3. Simulated signals during a cardiac cycle, representing blood flow through the PDA (Q_{da}), ventricular pressures (P_{lv} and P_{rv}) and pressures of the intrathoracic and pulmonary arteries ($P_{sa,i}$ and P_{pa}), for a $R \rightarrow L$ shunt (A), $L \rightarrow R$ shunt (B) and when the ductus arteriosus is closed (C).

diastolic properties associated with each cardiac cavity. Variations of diastolic parameters induce modifications in loading conditions, and involve changes in systemic and pulmonary arterial pressures. As a consequence, pressure gradient across PDA is directly affected by ventricular elastance properties.

Concerning $R \rightarrow L$ shunt (Fig. 5.A), pulmonary arterial pressure, which is directly driven by C_{rv} , $E_{MIN,ra}$ and $E_{MIN,rv}$, rises slightly earlier and appears as more elevated than aortic pressure. In opposition, the pulsatile patterns associated with $L \rightarrow R$ shunt (Fig. 5.B) shows an earlier and significant increase of aortic pressure, that is highly influenced by C_{lv} , $E_{MIN,la}$ and $E_{MIN,lv}$. The model is able to reproduce modifications of pressure profiles associated with each shunt configuration. These modifications have already been reported in [16] and are attributed to the coupling between ventricular mechanical functions and loading conditions.

R_{da} also appears as an important parameter. In fact, flow resistance is related to vessel diameters and the size of the PDA affects the pulsatile flow. The importance of R_{da} is in directly related with the decision to perform ductal ligation, which is primarily based on the PDA size or presence of cardiovascular dysfunction [12].

Other circulatory parameters are also influent. Unstressed volumes represent blood volume reserves associated with each circulatory compartment. Modifications of unstressed volumes are related to variations of vessel pressure. In particular, V_{upv} (unstressed volume of pulmonary veins) can modify LV preload conditions, whereas $V_{usa,e}$ and V_{usves} (unstressed volumes of the extrathoracic arteries and systemic peripheral vessels) are associated with LV afterload. Extrathoracic arteries resistance ($R_{sa,e}$) also appeared important as it directly affects systemic arterial pressure.

The most influent parameters are related to circulatory properties because the parameter ranges, defined for the Morris method, include mainly physiological values. However, in newborns with respiratory distress, the presence of a large shunt through a PDA is highly related to respiratory out-

