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Validation of a preterm infant cardiovascular system model under baroreflex control with heart rate and blood pressure data

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Abstract— **In this paper we present an autonomic cardiovascular model of a preterm infant of 28 weeks of gestation with a birth weight of 1000 g and a closed ductus arteriosus by the end of the first week, that is capable of describing the complex interactions between heart rate, blood pressure and respiration. The hemodynamic model consists of a pulsatile heart and several vascular compartments, and is regulated by a baroreflex control system. The model is relatively simple to allow for a mathematical analysis of the dynamics but sufficiently complex to provide a realistic representation of the underlying physiology. The model provides (beat-to-beat) values of R-R interval and blood pressure that resemble realistic signals of preterm infants. The model is validated with experimental data obtained in preterm infants.**

I. INTRODUCTION

Arterial blood pressure is controlled to ensure adequate blood flow to organs throughout the body. This is accomplished by a negative feedback system incorporating baroreceptors to sense arterial pressure. The importance of the baroreflex is to stabilize perfusion pressure in the face of disturbances of circulatory homeostasis. In sick preterm infants, a poorly developed baroreflex function may cause impaired cerebral perfusion or hemorrhage. A better understanding of the dynamics underlying the control mechanisms to regulate blood pressure may be useful to improve diagnosis of these disorders based upon analysis of heart rate and blood pressure data.

Several model approaches have been employed to describe the short-term control of blood pressure in human adults [1-3], however no cardiovascular models with appropriate baroreflex regulation exist for preterm infants. In this study we use an adaptation of a neonatal hemodynamic model used for educational simulation [4, 5]. This model was selected because, while of relatively reduced complexity, it supports realistic physiology. It can generate pulsatile blood pressure waveforms and reacts appropriately to blood loss and volume administration. The model is suitable to scale to preterm dimensions and to extend with a baroreflex control incorporating parasympathetic (vagal) and sympathetic efferent activity.

In this paper, we present a model of the autonomic cardiovascular system of a preterm infant of 28 weeks of gestation with a birth weight of 1000 g at the end of the first week with a closed ductus arteriosus. The model is capable of describing autonomous nervous system related interactions between heart rate, blood pressure and respiration. The objective is that the model is relatively simple to allow for a mathematical analysis of the dynamics, and sufficiently complex to provide a realistic representation of the underlying physiology. It provides (beat-to-beat) values of R-R interval and blood pressure that resemble realistic signals. Finally, the model is validated with experimental data obtained in preterm infants.

II. METHODS

First, the primary control mechanism that regulates blood pressure by affecting the cardiovascular system is summarized. Second, the spectral analysis technique for baroreflex control is given. Third, a time-varying cardiovascular model of a preterm infant of 28 weeks with baroreflex control is introduced that is used to describe the interactions between heart rate, blood pressure and respiration. Finally, the validation of the model with experimental data obtained in preterm infants of 28 weeks of gestation is described.

A. Control Mechanism

Within the cardiovascular system there is a complex relationship between blood pressure, heart rate and respiration. To regulate blood pressure, the heart rate may be increased by sympathetic activity or decreased by vagal activity. The competition between these two counter-acting branches of the autonomic nervous system results in beat-to-beat changes of R-R interval and blood pressure. Because of the different neuronal architecture between these branches (long versus short neurons; type of neurotransmitter), rapid onset and offset of cardiac vagal responses allow for beat-to-beat vagal regulation of heart rate, whereas the slow temporal response to sympathetic stimulation precludes such dynamic regulation [6]. For this reason it is assumed that high frequency (HF, respiratory associated) fluctuations are associated with the vagal system, whereas low frequency (LF) fluctuations are attributed to the baroreflex and related to sympathetic and vagal activity [7].

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B. Spectral Analysis

Spectral analysis (Fourier Transform) can decompose spontaneously occurring variations in blood pressure and R-R interval into LF and HF fluctuations. In human adults, LF fluctuations are in the range of 0.04 to 0.15 Hz whereas HF fluctuations are between 0.15 to 0.4 Hz [7]. As the neonatal heart rate and respiration rate differ from that of the adult, neonatal studies require a different HF spectral band definition [8]. For preterm infants, LF and HF bands were defined as 0.04-0.15 and 0.4-1.5 Hz, respectively.

Transfer function gain and phase between blood pressure and R-R interval series may be estimated from the auto- and cross spectral density functions [1, 7]. We refer to a previous paper for the details of this method [9]. Transfer gain and phase may be assessed in the LF and HF band, respectively. Transfer gain (ms/mmHg) reflects the degree to which the input signal (blood pressure) amplitude becomes manifest in the output signal (R-R interval) amplitude at a discrete frequency. The LF transfer gain may be used to estimate baroreflex sensitivity. The transfer function phase (s) indicates the temporal relationship between the fluctuations of both signals in the frequency domain.

C. The Model

The well described hemodynamic model for term newborns by Sá Couto et al [4, 5] is chosen as starting point for the preterm infant cardiovascular model. The hemodynamic parameters of this model have been validated with clinical data for a variety of conditions, including congenital heart defects. After the term model was rebuilt based on the published papers, the model is subsequently scaled to preterm dimensions. As this model lacks physiology-based baroreflex modeling, the hemodynamic model of Sá Couto is extended with a well described baroreflex model of Ursino et al [10].

1) Term hemodynamic model: The model of Sá Couto consists of two major parts: a time-varying elastance pumping heart model and seven vascular compartments [4, 5, 11]. Pressure in the compartment and flow between compartments are described with time-dependent linear equations. Change of volume in a compartment is based on the conservation of mass and described with a differential equation. One-way heart valves and inertia are included in the model. We refer to previous papers for a detailed description of the mathematics associated with implementation of the model [4, 5, 11]. Implementation was carried out in Matlab 7.5.0 (The MathWorks, Massachusetts, USA). As hemodynamic output variables were identical to the original publications, we considered our mathematical and software implementation to be correct.

2) Scaling the cardiovascular model to preterm dimensions: Neonatal unstressed volumes of systemic and pulmonary vessels, compliance and cardiac elastance were proportionally scaled from term to preterm values, considering a blood volume of 310 ml and 110 ml for a 3500 g term and 1000 g preterm infants, respectively [12]. Thus, the parameter values for unstressed volume and compliance are multiplied by 0.35, whereas the elastance values were divided by 0.35.

The term infant model used the total systemic vascular resistance (SVR) to scale the other vascular resistance components of the model [11]. For the preterm infant model we follow the same method. We found two papers with values of SVR in preterm infants with a closed ductus arteriosus [13, 14]. For this study, we used the mean values of both studies (249 and 148, respectively), yielding a SVR value of 199 mmHg $\cdot$ min $\cdot$ l^{-1}. As the SVR used by Sá Couto et al [4] for the term infant is 99 mmHg $\cdot$ min $\cdot$ l^{-1}, the other vascular resistances components in the preterm infant model are redefined by a scaling factor of 2.

With the assumption of a fully developed pulmonary system after one week [15] and no other data available, the pulmonary vascular resistance (PVR) is scaled by the same factor as SVR.

As no data is present for inertia in preterm infants, this parameter could not be redefined.

3) Baroreflex control model: To investigate how R-R interval variability reflects the action of the autonomic regulatory mechanisms, an existing mathematical model of short-term cardiovascular regulation by Ursino et al is used [3, 10]. The regulatory part of the model includes (1) two groups of receptors (arterial baroreceptors and lung stretch receptors), (2) the sympathetic and vagal efferent branches, and (3) a very low-frequency vasomotor noise. The model is validated and produces a R-R interval power spectrum with two distinct peaks as seen in human adults [7]: a HF peak at the respiratory rate and a LF peak at approximately 0.1 Hz.

The information from the receptors modulates various cardiovascular parameters: systemic peripheral resistance, venous unstressed volume, heart contractility (i.e., the end-systolic elastance in the left and right ventricles), and R-R interval. The R-R interval control involves a balance between vagal and sympathetic activities. In general, a sigmoid relation is assumed between deviations from normal in receptor signal and effector response. This response is applied after low-pass filtering and application of a time delay. In particular, dynamics of the vagal and sympathetic mechanisms are different: the vagal control is characterized by a rapid response, which is completed within two or three cardiac beats, whereas sympathetic control requires many seconds. The model includes the possibility of different gains and different dynamics for the vagal and sympathetic paths. We refer to the papers of Ursino for the mathematical equations of the regulation mechanism [3, 10].

4) Scaling the baroreflex model to preterm dimensions: The baroreflex parameters of the adult Ursino model were adjusted to fit the preterm cardiovascular model. First, boundaries of the sigmoidal function describing effector response were scaled to maintain a relative effector range equal to the adult model. Second, the effector gains were scaled. For effectors related to baroreceptors, the gain was scaled by the ratio of effector range and pressure range for the preterm infant. For the gains related to lung stretch receptors, the gains were similarly scaled by the ratio of effector range and tidal

volume of the preterm infant. The delays and time constants were not adjusted, because there are no reference values for preterm infants in literature. Exception is the vagal nerve delay, which is altered from 500 ms to 200 ms in accordance with the previous Ursino model [3] and other publications [16]. Finally, the sigmoidal function for the R-R interval was adapted to include baseline vagal nerve activity to be able to operate realistically outside homeostasis e.g. during vagal nerve blockage. This baseline value was estimated from the Ursino model describing baroreflex through nerve activity [3] and from data obtained by Levy et al [17], describing heart rate change as function of vagal and sympathetic nerve activity.

5) Preterm infant cardiovascular model with baroreflex: Finally, the models of the preterm cardiovascular system and the preterm baroreflex feedback system are combined. A few simplifications have been made to allow combination of both models.

First, atria are modeled as passive compartments because the baroreflex feedback as modeled by Ursino only affects the ventricles. Furthermore, atria have a minor contribution to circulatory parameters. Second, valve resistances are omitted because of their negligible influence on total resistance. Third, pulmonary artery inertia from the Ursino model is neglected in correspondence with Sá Couto. Fourth, splanchnic and extrasplanchnic compartments are combined. As a result, the baroreflex only adjusts one peripheral resistance. The resulting model and its interaction with the baroreflex feedback system is shown in Fig. 1. Validation is performed by examining model output 1) in homeostasis and 2) during perturbation as caused by vagal blockage resulting from atropine administration.

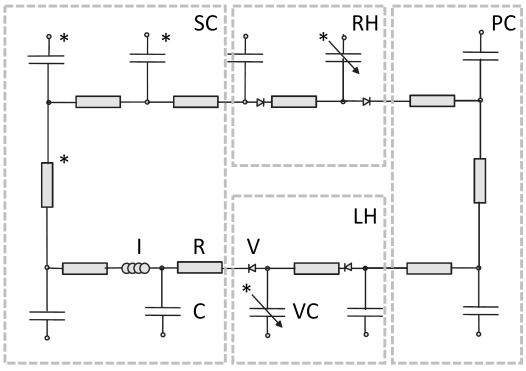

Fig. 1. Electrical equivalent of the cardiovascular model, with compartments left heart (LH), right heart (RH), systemic circulation (SC) and pulmonary circulation (PC). Model is composed of the components time-varying elastance (VC), one-way valve (V), resistance (R), compliance (C), and inertia (I). Note that components are only labeled once for clarity. Components labeled with * are affected by the baroreflex feedback system as described by Ursino [3, 10].

6) Cardiovascular validation: Homeostasis: To validate the model, homeostatic output is compared to literature. After reaching steady state (minimum of 150 beats, maximum difference of 0.2 ml between stroke volumes of two consecutive beats), pressure and flow values are quantified for one cardiac cycle. Spectral power of HR and ABP with gain and delay are also compared to literature.

TABLE I

HEMODYNAMIC OUTPUT OF THE DEVELOPED MODEL

Hemodynamic variables	Simulation	Kent [19]	Soloveychik [20]
Gestational age (wk)	28	28-29	28±3
Birth weight (g)	1000		1080±400
Systemic SBP (mmHg)	57	58 (49-63)	
Systemic MBP (mmHg)	42	42 (37-45)	37±6
Systemic DBP (mmHg)	31	32 (28-38)	
Pulmonary SBP (mmHg)	25		
Stroke volume (ml)	1.25		1.3±0.4
Cardiac output (ml/min)	177		197±80

Legend: SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure. Data are expressed as mean±sd or median (range).

7) Baroreflex validation: Atropine study: To validate the baroreflex feedback system, a simulation of atropine administration is performed. Atropine (partly) blocks vagal pathways. In a clinical study [18], blood pressure and heart rate was recorded before and after atropine administration in 12 preterm infants with gestational age of 27.8 ± 2.3 weeks and a body weight 1081 ± 514 gram. From this study, it was seen that heart rate increased, heart rate variability decreased and blood pressure (variability) remained constant. In our model, we assumed a 50% blockage of vagal activity. To validate our model, the simulation is compared with these clinical data.

III. RESULTS

The pressure and flow output of the model for the preterm infant in steady-state is shown for one heart beat in Fig. 2.

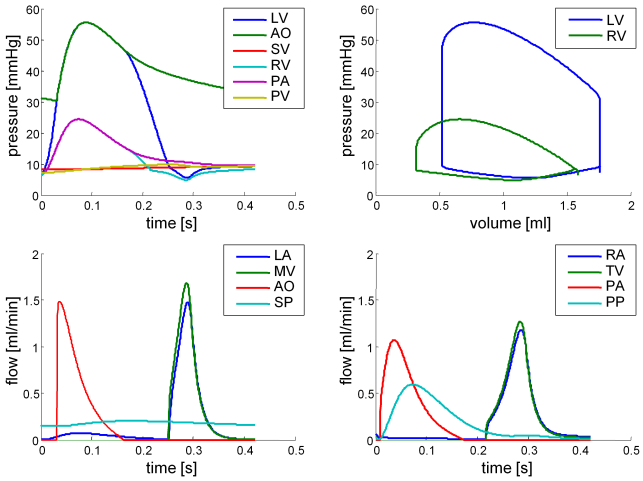

Fig. 2. Simulated blood pressure (mmHg), blood flow (ml/min) and volume (ml) for one cardiac cycle of the model for the preterm infant. Indicated are left ventricle (LV), aorta (AO), systemic vein (SV), right ventricle (RV), pulmonary artery (PA), pulmonary vein (PV), left atrium (LA), mitral valve (MV), systemic periphery (SP), right atrium (RA), tricuspid valve (TV) and pulmonary periphery (PP).

Hemodynamic model outcome as quantified by time-domain parameters, shown in Table I, is in accordance with

TABLE II

SPECTRAL ANALYSIS OF THE DEVELOPED MODEL

	Simulation		Clinical data [18]	
	Control	Atropine	Control	Atropine
R-R interval (ms)	430	383	422 (399-439)	378 (353-402)
Total power (ms^2)	125	77	135 (59-173)	22 (8-52)
- LF power (ms^2)	90	70	99 (34-155)	6 (3-35)
SBP (mmHg)	55.3	55.8	51.5 (48.4-53.8)	52.1 (48.5-52.5)
Total power ($mmHg^2$)	1.5	4.5	4.1 (2.1-6.0)	5.2 (2.7-7.6)
- LF power ($mmHg^2$)	0.5	3.5	1.8 (0.8-2.2)	1.8 (1.1-2.9)
LF gain (mmHg)	11.9	4.8	4.2 (2.6-7.0)	1.4 (0.9-2.3)
LF phase (s)	-1.9	-5.4	-3.7 (-5.8 to 0.2)	-3.6 (-5.9 to 2.8)

Legend: SBP = systolic blood pressure; LF = low frequency; Clinical data are expressed as median (interquartile range).

literature for infants of 28 weeks gestation and 1000 g body weight [19, 20]. From Table II (grey columns) the baroreceptor related spectral LF parameters are seen to correspond to reference values [18].

Atropine simulation (Fig. 3 and Table II) shows decreased R-R interval and variability, as seen clinically [18]. Mean systolic blood pressure remains constant, with a small increase in variability as seen in LF power (white columns).

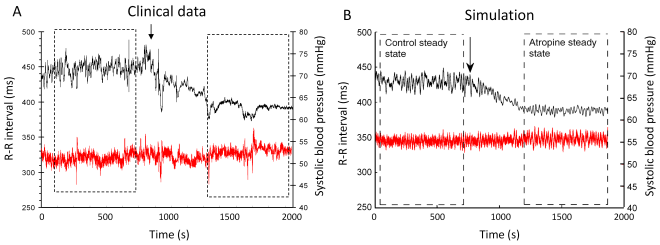

Fig. 3. R-R interval and systolic blood pressure before and after atropine administration (arrow), as seen from clinical data (A) and simulation (B).

IV. DISCUSSION

As the hemodynamic output of our model in homeostasis is comparable to literature, the cardiovascular system of the preterm infant is modeled well. Homeostatic baroregulation is also modeled adequately, as output resembles the LF fluctuations in R-R interval and blood pressure seen in clinical studies. Atropine simulation shows decreased R-R interval (variability) and unchanged blood pressure, comparable to clinical data. The model also shows increased blood pressure variability after atropine administration, as seen in LF power, which is in contrast to experimental data. This discrepancy might be caused by poor estimation of baroreflex parameters, a different balance in effector activity for preterm infants, or lack of adaptation or local regulation.

Using this model, it may be possible to quantify baroreflex maturation in preterm infants and to simulate clinically relevant interventions, e.g. vascular expansion for hypotension. The ability to measure baroreflex activity in infants during sleep may provide vital clues into pathologic conditions associated with impaired autonomic control during sleep (sudden infant death).

Limitations of this study include the use of parameter values from a variety of human and animal data, validation of the model using only R-R interval and blood pressure data, and the exclusion of e.g. chemoreceptors from the feedback system.

V. CONCLUSION

Our model is the first model describing hemodynamics and baroregulation of the preterm infant adequately, and is validated with clinical data. Future work will focus on implementation of chemoreceptors to simulate perinatal asphyxia.

REFERENCES

[1] deBoer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. *Am J Physiol*. 1987;253:H680-H689.

[2] Ottesen JT. Modelling of the baroreflex-feedback mechanism with time-delay. *J Math Biol*. 1997;36:41-63.

[3] Ursino M. Interaction between carotid baroregulation and the pulsating heart: a mathematical model. *Am J Physiol*. 1998;275:H1733-H1747.

[4] Sa Couto CD, van Meurs WL, Goodwin JA, Andriessen P. A model for educational simulation of neonatal cardiovascular pathophysiology. *Simul Healthc*. 2006;1 Spec no.:4-9.

[5] Zijlmans M, Sa-Couto CD, van Meurs WL, Goodwin JA, Andriessen P. Corrected and improved model for educational simulation of neonatal cardiovascular pathophysiology. *Simul Healthc*. 2009;4:49-53.

[6] Abboud FM, Thames MD. Interaction of cardiovascular reflexes in circulatory control. In: Shepherd JT, Abboud FM, editors. *Handbook of Physiology*. Bethesda, MD: American Physiological Society, 1983: 675-753.

[7] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93:1043-1065.

[8] Fortrat JO. Inaccurate normal values of heart rate variability spectral analysis in newborn infants. *Am J Cardiol*. 2002;90:346.

[9] Andriessen P, Koolen AM, Berendsen RC, Wijn PF, ten Broeke ED, Oei SG et al. Cardiovascular fluctuations and transfer function analysis in stable preterm infants. *Pediatr Res* . 2003;53:89-97.

[10] Ursino M, Magosso E. Role of short-term cardiovascular regulation in heart period variability: a modeling study. *Am J Physiol Heart Circ Physiol* . 2003;284:H1479-H1493.

[11] Sa-Couto CD, Andriessen P, van Meurs WL, yres-de-Campos D, Sa-Couto PM. A model for educational simulation of hemodynamic transitions at birth. *Pediatr Res*. 2010;67:158-165.

[12] Saigal S, O'Neill A, Surainder Y, Chua LB, Usher R. Placental transfusion and hyperbilirubinemia in the premature. *Pediatrics*. 1972;49:406-419.

[13] Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr*. 1996;129:506-512.

[14] S. Noori, P. Friedlich, I. Seri and P. Wong, Changes in myocardial function and hemodynamics after ligation of the ductus arteriosus in preterm infants. *J Pediatr 150*, 597-602 (2007).

[15] Dawes GS. Sudden death in babies: physiology of the fetus and newborn. *Am J Cardiol*. 1968;22:469-478.

[16] M. N. Levy, P. J. Martin, T. Iano and H. Zieske, Effects of single vagal stimuli on heart rate and atrioventricular conduction. *Am J Physiol* 218, 1256-1262 (1970).

[17] M. N. Levy and H. Zieske, Autonomic control of cardiac pacemaker activity and atrioventricular transmission. *J Appl Physiol* 27, 465-470 (1969).

[18] Andriessen P, Janssen BJ, Berendsen RC, Oetomo SB, Wijn PF, Blanco CE. Cardiovascular autonomic regulation in preterm infants: the effect of atropine. *Pediatr Res*. 2004;56:939-946.

[19] A. L. Kent, S. Meskell, M. C. Falk and B. Shadbolt, Normative blood pressure data in non-ventilated premature neonates from 28-36 weeks gestation. *Pediatr Nephrol* 24, 141-146 (2009)

[20] V. Soloveychik, A. Bin-Nun, A. Ionchev, S. Sriram and W. Meadow, Acute hemodynamic effects of caffeine administration in premature infants. *J Perinatol* 29, 205-208 (2009).