

# Model-Based Analysis of Apnea-Bradycardia events in Newborns

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## Abstract

*In preterm infants, recurrent episodes of apnea, bradycardia and severe intermittent hypoxia are mainly related to cardiorespiratory immaturity. These episodes are associated with major risks during the first weeks of life. Cardiorespiratory data consisting of a continuous 12 hours recording of transthoracic impedance and ECG signals were acquired in 18 preterm neonates. 106 isolated apnea events (>10 sec) were manually annotated from the database, of which 19 apneas with bradycardia. A system-level physiological model of cardio-respiratory interactions in the newborn is proposed and used to reproduce simulations of mixed apneas with and without bradycardia, by modifying the functional residual capacity. A first qualitative comparison between the simulations and the clinical data shows a close match between the experimental and simulated heart rate series during apnea with bradycardia (RMSE 4.96 bpm) and without (RMSE 2.02 bpm).*

## 1. Introduction

Recurrent episodes of apnea, bradycardia and severe intermittent hypoxia are observed in 10% to 85% of preterm infants, depending on their gestational age and are mainly related with cardiorespiratory immaturity. Apnea events on preterm infants are defined as respiratory pauses of at least 20 seconds, or more than 10 seconds if coupled with bradycardia and/or oxygen desaturation [1, 2]. Apneas can be followed by bradycardia, defined in this context as a decrease in heart rate of at least 33% compared to the previous mean value and lasting more than 5 seconds [3]. Apnea-bradycardia (AB) episodes are considered as clinically significant when a decrease in oxygen saturation (SpO<sub>2</sub>) of at least 10% is observed. AB events are mainly attributed to a stimulation of arterial chemoreceptors in response to cessation of pulmonary ventilation and hypoxia [4].

The interpretation of acute responses due to mixed apneas can still be difficult because several physiological processes (autonomic regulation, ventilation, chemoreflex, etc.) are involved and the underlying mechanisms that gen-

erate the occurrence of bradycardia in relation with apneas are still not completely elucidated. In this context, a physiological modeling approach seems particularly interesting to improve the interpretability of clinical data acquired in neonatal intensive care units (NICU).

The literature on cardio-respiratory modeling for infants and neonates remains particularly poor when compared to that of adult cardiorespiratory models. Indeed, a limited number of cardiovascular models, integrating the baroreflex [5–7], and the respiratory function [8], inspired from adult models, have been adapted to preterm newborns. We have recently proposed an integrated cardio-respiratory model adapted to the physiology of preterm neonates [9]. This model is an adaptation of an adult model previously proposed by our team [10–12]. Structural modifications were made as well as parameter adjustments based on the preterm infants literature [6, 13], by scaling method [7] and manual adaptations.

This paper presents a model-based analysis of the cardio-respiratory interactions during mixed apnea events in newborns using such an integrated cardio-respiratory model. The objective of this paper is to propose a first qualitative comparison between simulations and clinical data acquired in NICU during apnea-bradycardia events.

## 2. Methods

### 2.1. Experimental protocol and data

The study was conducted within the prospective clinical study "CARESS-Premi" (NCT01611740) registered at ClinicalTrials.gov, and recruitment occurred from June 2012 through January 2019. Data from a subset of 18 preterm newborns of this study, including continuous recordings of an average of 12 hours of transthoracic impedance and ECG signals (3 channels) were studied. Newborns presented a gestational age of 24–30 weeks and birth weight of 620–1595 g, around their 7th day of life. For each subject, an echocardiography was performed to determine the status of the ductus arteriosus (open or closed) when recording the signals.

The qualitative comparison described in this article is based on one subject with gestational age of 27 weeks, a

birth weight of 920 g and an open ductus arteriosus.

Transthoracic impedance signals were annotated manually by experts. Annotations included the instant of apneas occurrence. In this work, the analysis was focused on selected annotated mixed apnea events, with a minimum apnea duration of 10 seconds and no other events over a window of  $-/+ 20$  seconds before and after apnea, in order to minimize the cardio-respiratory effects due to the other respiratory episodes.

## 2.2. Signal processing

The RR interval time series of each subject was extracted from ECG signals, using a QRS complex detector developed by our team [14], in order to observe heart rate dynamics during apnea.

The minimum ( $\min(HR)$ ) and the average of HR before apnea ( $\text{mean}(HR_{before})$ ) were calculated. Bradycardia was detected when HR was less than 33% of  $\text{mean}(HR_{before})$  for more than 2 heartbeats, and its duration is reported. Finally,  $\Delta HR$  was calculated as follows:

$$\Delta HR = \frac{\min(HR) - \text{mean}(HR_{before})}{\text{mean}(HR_{before})}. \quad (1)$$

## 2.3. Model description

The proposed model (Fig. 1) is composed of four interconnected components: i) the cardiovascular system (CVS), ii) the respiratory system, iii), the gas exchange (in the lungs and metabolism) and iv) the neural control. The model corresponds to the anatomy and physiology of a preterm newborn with gestational age of 28 weeks, post-menstrual age of 29 weeks and weight of 1 kg.

*Cardiovascular system model:* The cardiac electrical activity submodel is based on a set of coupled automata [15]. The cardiac mechanical activity is represented by an elastance-based method [9]. The model includes the pulmonary and systemic circulations [16], with the presence of the interventricular septum. The ductus arteriosus was integrated according to [5]. The blood flow through it can be activated in various directions or not, depending on the desired study.

*Respiratory model:* The submodel, adapted from previous works of our team [16], includes the upper, intermediate and lower airways, the alveolar compartment, the pleural cavity, the chest wall and the respiratory muscles.

*Gas exchange model:* It is composed of three components: i) the lung gas exchange, ii) the metabolism gas exchange and iii) the gas transport. The lung gas exchange, adapted from [17], corresponds to the exchange of  $CO_2$  and  $O_2$  between the dead space compartment, the alveoli compartment and the pulmonary capillaries. Fraction and partial pressure of both gases were computed for each

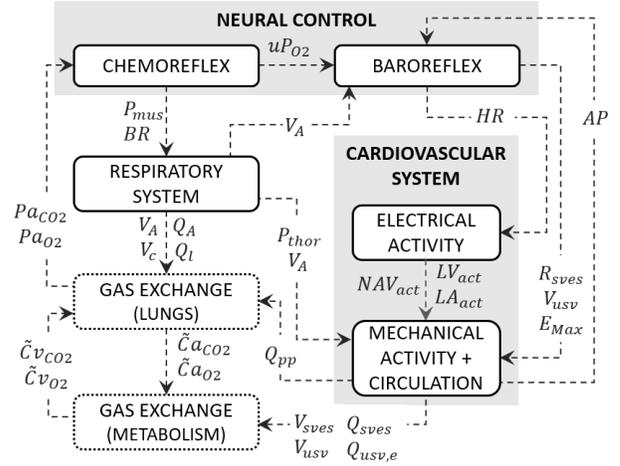


Figure 1. Cardio-respiratory model diagram. Dotted line arrows symbolize interactions between submodels.  $uP_{O_2}$ , peripheral chemoreceptors activity;  $P_{mus}$ , respiratory muscle pressure;  $BR$ , breathing rate;  $V_A$ , lung volume;  $HR$ , heart rate;  $AP$ , arterial pressure;  $P_{aO_2}$  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;  $Q_l$ , lung respiratory flow;  $P_{thor}$ , thoracic pressure;  $\tilde{C}v_{CO_2}$  and  $\tilde{C}v_{O_2}$ , delayed gas concentrations of  $O_2$  and  $CO_2$  in the venous blood;  $\tilde{C}a_{CO_2}$  and  $\tilde{C}a_{O_2}$ , 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.

compartment. The metabolism gas exchange model was integrated in the systemic peripheral vessels compartment in CVS model. It corresponds to the  $CO_2$  production and  $O_2$  consumption by the tissues and organs [18]. Finally, the gas transport describes the  $CO_2$  and  $O_2$  circulation through the CVS model. The time of gas transport from the pulmonary capillaries to the systemic peripheral vessels, and from the extra-thoracic veins to the pulmonary capillaries, are defined by pure delays [18].

*Neural control:* The baroreflex model is based on previous work of our team [15]. It includes the baroreceptors and efferents pathways, the cardiovascular control center, the efferent pathway and the pulmonary stretch receptor. The efferent pathway, depending on the activity of peripheral chemoreceptors ( $uP_{O_2}$ ), control the heart rate through the vagal and sympathetic paths. Dependence on  $uP_{O_2}$  al-

lows the generation of apnea-bradycardia. The pulmonary stretch receptors, activated by alveolar volume, also modulate the vagal branch of the baroreflex. The chemoreflex model is composed of the peripheral and central chemoreflex models, adapted from [18]. It represents modulations of breathing rhythm and respiratory muscle pressure, in response to  $P_{aO_2}$  and  $P_{aCO_2}$  modulations.

## 2.4. Simulation of apnea-bradycardia events

Mixed apnea is the most frequent type of long apnea among preterm infants [19]. A mixed apnea usually starts as a central apnea and ends as an obstructive apnea. The first period of central apnea is simulated by setting respiratory muscle pressure ( $P_{mus}$ ) to 0 in order to stop the movement of the respiratory muscles. The obstructive apnea part was induced at half apnea by increasing the resistance of the upper airways ( $R_u$ ) of the respiratory model to 10,000  $cmH_2O.s.l^{-1}$  to mimic a complete obstruction of the airways.

Simulations were performed with two initial values of lung volume ( $V_A$ ),  $V_{A_0} = 24$  ml and  $V_{A_0} = 60$  ml. A manual adjustment of some parameters of the model was performed to fit clinical data obtained from patients: the basal heart rate, the duration of apnea and the parameter  $D_p$  delay which stands for the transport of information between the systemic arteries and the peripheral chemosensitive area.

## 2.5. Signal comparisons

To compare the clinical and simulated data, the root mean square error (RMSE) between them can be quantified:

$$RMSE = \sqrt{\frac{1}{N} \sum_{t_e=0}^{N-1} (HR^{exp}(t_e) - HR^{sim}(t_e))^2} \quad (2)$$

where  $t_e$  corresponds to the current sample of the time series,  $HR^{sim}$  and  $HR^{exp}$  are, respectively, the simulated and experimental heart rate,  $N$  is the number of samples of the time series. The RMSE between clinical and simulated HR signals were calculated over a window of  $\pm 40$  seconds before and after apnea.

## 3. Results

### 3.1. Database analysis

106 isolated apnea events were identified, with an average of 6 apneas per subject. Among these, 19 events were associated with bradycardia, with a  $\Delta HR$  average of  $-53\%$ . Two apnea events, 5 min apart, were selected for one representative patient, in order to analyze specifically

the association of apnea with bradycardia. Event 1 showed a 15.38 seconds apnea followed with bradycardia. Event 2 showed a duration of 11.04 seconds and did not present bradycardia.

### 3.2. Simulation of apnea events

Figure 2 illustrates the experimental and simulated signals. The clinical transthoracic impedance signal is shown, to highlight the duration of the apnea. Table 1 shows  $\min(HR)$ ,  $\text{mean}(HR_{before})$ , and the  $\Delta HR$  for event 1. The duration of clinical bradycardia is 5.3 seconds and 5.8 seconds for simulated bradycardia. Event 2 is not associated with bradycardia and  $\text{mean}(HR)$  is equal to 138 bpm. For event 1, the RMSE was 4.96 bpm and for event 2, the RMSE was 2.02 bpm.

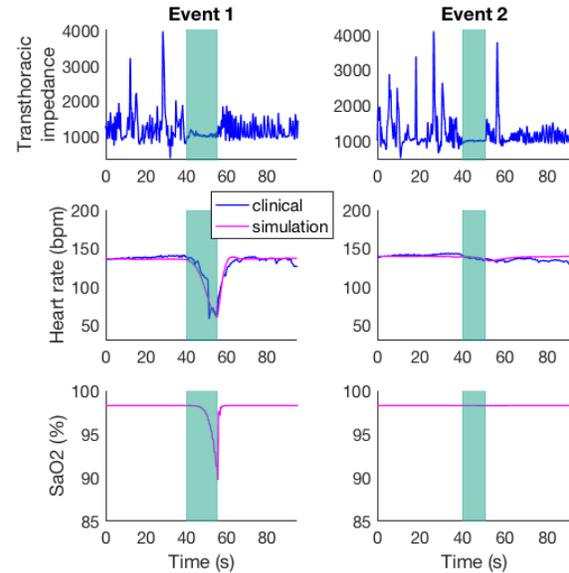


Figure 2. Comparison of clinical (blue) and simulated data (pink) during apnea with (left) and without bradycardia (right). On top the transthoracic impedance signal, on the middle the heart rate signal and on the bottom the oxygen saturation. The green rectangle corresponds to the duration of apnea.

Table 1. HR values from clinical and simulated data for event 1.

	$\text{mean}(HR_{before})$	$\min(HR)$	$\Delta HR$
Clinical	138.34 bpm	58.25 bpm	$-57.89\%$
Simulated	135.97 bpm	60.42 bpm	$-55.56\%$

## 4. Discussion

In this work, we propose a model-based approach for the analysis of apnea-bradycardias events in preterm newborns. The database analysis shows that some apneas could be associated with bradycardia, while others did not imply any modification of heart rate. The results highlighted also the model ability to generate mixed apneas of different durations associated or not with bradycardia, and more generally, the event-specific capacity of the model. A close match was observed between the clinical and simulated HR for both events, with RMSE lower than 5 bpm.

The model was able to reproduce different profiles of HR modifications observed in the experimental mixed apneas. Bradycardia dynamics, in relation with apnea, are mainly explained by the influence of peripheral chemoreceptors activity on efferent parasympathetic pathway of the baroreflex [20]. In fact, hypoxemic stimulation of arterial chemoreceptors in response to cessation of pulmonary ventilation could be related to apnea-bradycardia [4].

The bradycardia level was adjusted by modifying the  $V_{A_0}$ . This influenced the HR output of the baroreflex sub-model from the vagal branch, and thus the cardiac electrical impulses.  $V_{A_0}$  is associated with the lungs air volume at the end of passive expiration, which is defined by the Functional Residual Capacity (FRC). The presence of desaturation when  $V_{A_0}$  is low is consistent with [21], who describe that low FRC was related to high desaturation.  $V_{A_0}$  large variations in the same patient can be explained by the presence of sighs which impact the FRC [22].

## 5. Conclusion

To our knowledge, this work represents the first integrated representation of the cardiorespiratory interactions during apnea of prematurity with and without bradycardia. A qualitative comparison has shown a close match between clinical and simulated heart rate during apnea event. Further work, will focus on the model validation through patient-specific identifications of model parameters in order to reproduce clinical data observed in NICU.

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