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Abstract

This paper presents a model-based method for the analysis of respiratory signals specifically adapted to newborns. The model includes a description of upper airways, distensible and lower airways, lungs, chest wall, alveoli, pleura and respiratory muscle activity. The model was used in stationary and non-stationary conditions to simulate respiratory signals obtained in one newborn lamb in various physiological conditions. An identification algorithm was used to adapt the model parameters to lamb data. Finally, the identified parameters were compared to values previously reported in adult humans.

MESH Keywords Animals ; Animals, Newborn ; Computer Simulation ; Lung ; physiology ; Models, Biological ; Pulmonary Ventilation ; physiology ; Respiratory Mechanics ; physiology ; Sheep

Introduction

Respiratory problems are particularly frequent in the neonatal period, due to the critical changes necessary for adaptation to air breathing [1]. While respiratory disorders are often restricted to the neonatal period, they can be life-threatening or the first manifestation of a chronic cardiopulmonary problem, especially in extremely premature infants [2]. To our knowledge, while numerous studies on neonatal respiration have been published, no mathematical modeling of the neonatal respiratory system is yet available.. Mathematical modeling, which integrates interacting physiological processes, would be of great help in understanding the complex mechanisms involved in newborn respiratory dynamics.

Functionally, the mammalian respiratory system is made of three components: i) ventilation, which includes the airways and lung mechanics; ii) lung perfusion by the pulmonary circulation and iii) O_2 and CO_2 gas exchange. The present article focuses on ventilation, along with the chest wall and respiratory muscle activity.

Models of breathing mechanics previously proposed can be classified in four categories: i) One-compartment models: The simplest models of respiratory mechanics are linear and mono-alveolar. Other non-linear models differentiate the inspiratory and expiratory phases [3]; ii) Two-compartment models: Otis et al [4] proposed a two-compartment model, which takes into account differences of ventilation between various regions of the lung. Mead [5] considered a serial arrangement of compartments by differentiating distensible central airways and ventilated lung periphery. Mount [6] added visco-elastic properties. More recent models integrate non-linear effects, to account for dynamic airway [7, 8] compression and non-linear behavior of airway resistances; iii) Two-compartment models that integrate the chest wall: These two-compartment models include a description of chest wall mechanics to simulate pleural pressure [9–12]; iv) Multi-compartment models: Multi-compartment models simulate inhomogeneous lung ventilation [13]. Some are based on the Weibel's scheme of the tracheobronchial tree that includes 24 ventilation zones [14, 15].

All of the above models are adapted to human adult physiology and integrate adult parameters. Thus, the aim of our study is to propose a model adapted to newborns. First, a description of the respiratory model is provided, followed by a description of the experimental protocol used in one newborn lamb. Secondly, simulation of stationary and non-stationary conditions and the identification algorithm are reported. Finally, identified parameters are discussed in light of specificity of ventilatory mechanics previously documented in the mammalian newborn.

Respiratory Model Description

Respiratory mechanics are often represented through lumped parameter models. Figure 1 depicts the electrical analog of the model. The global structure is based on two-compartment models, which include chest wall dynamics [9–12]. The model includes a description of airway resistance, lung and chest wall compliance and lung viscoelasticity:

- The upper airways are represented by a non-linear Rohrer resistance that depends on flow Q [16]:

$$Ru = K1 + K2\,|\,Q\,|$$

where K1 is the resistance component for laminar flow and K2 is the resistance component that describes turbulence.

- The distensible, central airways are modeled by a non-linear resistance and compliance. The resistance varies inversely with the square of airway volume [17]:

$$Rc = K3(Vc_{\max} / Vc)^2$$

where K3 is the resistance value when airway volume Vc is equal to its maximum $Vc_{\max}$. The volume Vc depends on transmural pressure:

$$Vc = Vc_{\max} / 1 + \exp(-a(p_{tm} - b))$$

where a and b are constants and p_{tm} is the transmural pressure. This relation has been determined from experimental data [18].

- The lower airway resistance is linear:

$$Q_A = (P_c - P_A) / Rs$$

where Q_A and P_A are respectively flow and pressure in the alveoli. Rs is lower airway resistance and P_c is pressure in distensible airways.

- The lung and chest wall are modeled by linear compliances:

$$Pel = V_A / C_l$$

$$Pcw = V_u / C_{cw}$$

where Pel and Pcw are respectively lung elastic recoil and chest wall pressure. C_l and C_{cw} are lung and chest wall compliances. V_A and V_u are respectively alveolar and total respiratory system volume.

- The alveolar pressure is computed as the sum of the lung elastic recoil pressure Pel, the visco-elastic pressure Pev and the pleural pressure Ppl:

$$Pa = Pel + pev + Ppl$$

- The pleural pressure is driven by respiratory muscles (Pmus):

$$Ppl = Pcw - Pmus$$

where Pmus is described by the following relation:

$$Pmus = \begin{cases} A_{\max} . \sin^N(\pi.Fr.t) & t \le T_I \\ A_{\max} . \sin^N(\pi.Fr.t). \exp(-B(t - T_I)) & t > T_I \end{cases}$$

where $A_{\max}$ corresponds to maximum muscle activity, T_I is inspiration duration, N and B characterize respiratory muscle activity.

The model includes a representation of the respiratory system that allows simulation of physiological signals (flow, pleural pressure, …). Simulated signals must be compared to experimental data in stationary and non-stationary conditions in order to adapt the model parameters to newborn lamb physiology.

Experimental protocol

The study involved one newborn lamb, which was born at term. The study protocol was approved by the ethics committee for animal care and experimentation of the University of Sherbrooke. Surgery was first performed under general anesthesia for chronic instrumentation, including thoracic electrodes to record electrocardiogram (ECG) and catheters to monitor systemic arterial pressure (AP) and central venous pressure (CVP). In addition, a microtip pressure transducer catheter (Millar) was inserted into the esophagus to monitor esophageal pressure variations (Pes), which are equal to pleural pressure variations (Ppl ≈ Pes)[19, 20].

Non-calibrated respiratory inductance plethysmography was used to record lung volume variations semi-quantitatively. On the experimental day, pressure (Pmask) and flow (Qmask) were both measured in a nasal mask placed on the lamb's muzzle.

All data were first measured under stationary conditions to determine both the amplitude and shape of experimental signals. Then, several levels of pressure were applied into the nasal mask, in an attempt to assess the effects of a Valsalva-like maneuver on respiratory signals.

Simulation of stationary and non-stationary conditions

The lamb experimental protocol was simulated by applying different levels of pressure at nasal level. For simulation of stationary conditions, nasal pressure was equal to zero, i.e., atmospheric pressure. For simulation of non-stationary conditions, three levels of positive pressure were successively applied to reproduce experimental conditions: Phase 1) 8.5 mmHg during 25 seconds; Phase 2) 30 mmHg during 22 seconds; Phase 3) 6.5 mmHg during 23 seconds.

Identification Method

A model-based process was used to analyze respiratory signals. The method consists in adapting the model parameters to experimental data and interpreting the identified parameters.

The objective is thus to obtain an optimal set of patient-specific parameters P*, which minimizes an error function between simulated and experimental signals. This error function must include stationary and non-stationary conditions. It has been defined here as the sum of absolute values of the difference between: i) experimental and simulated flow and pleural pressure calculated for one respiratory cycle; ii) experimental and simulated mean pleural pressure calculated for the three levels of positive pressure applied into the nasal mask during 70 seconds:

$$\epsilon = \sum_{cycle}^{Respiratory} |Flow^{sim}(t) - Q_{mask}(t)| +$$
$$\sum_{cycle}^{Respiratory} |Ppl^{sim}(t) - Pes^{obs}(t)| +$$
$$\sum_{70s} |Ppl_{mean}^{sim}(t) - Pes_{mean}^{obs}(t)|$$

This error function is not differentiable and can have multiple local optima. This kind of problem can be solved using Evolutionary Algorithms (EA), which are optimization methods adapted for identification of complex nonlinear problems, characterized by a poorly-known state-space. EA are stochastic search techniques, inspired by the theories of evolution and natural selection, which can be employed to find an optimal configuration for a given system within specific constraints [21].

Each individual EA represents an example of the whole model and is characterized by 10 parameters, to be identified: lung and chest wall compliances (C_l and C_{cw}), airway resistances (K1, K2, K3), initial value of total respiratory system volume (V_{u_init}), maximum muscle activity (A_{max}), duration of inspiration (T_I) and parameters characterizing respiratory muscle activity (N and B).

Results

Figure 3 shows both the simulated signals obtained after parameter adaptation and experimentally recorded signals under stationary conditions for flow and pleural pressure.

Figure 4 depicts the simulated and experimental mean pleural pressure when three levels of positive pressure are applied into the lamb nasal mask.

Figures 3 and 4 show the similarities between simulated and experimental signals. In stationary conditions, the mean square error is equal to 0.00022 and 3.65 respectively for flow and pleural pressure. In non-stationary conditions, the mean square error is equal to 0.846 for mean pleural pressure.

While the lungs are more compliant than the chest wall in adult life, the reverse is observed in the newborn lamb. Moreover, the overall airway resistance is greater in the newborn lamb. Those characteristics are known to be specific to the neonatal period [22].

The identified value of the lamb lung compliance is physiologically plausible as it is close to other values taken from other studies (table 2), The difference existing between values can be explained by the diversity of experimental protocols (nasal mask, anesthesia, number of days after birth, …). In addition, the identified value is specific to the lamb, whereas the theoretical value has been computed as the average of several lung compliances.

Conclusion

A model of the respiratory system is proposed in the newborn lamb. The model includes upper airways, distensible and lower airways, lungs, chest wall, alveoli and pleura. The approach is original as the model includes a new analytic law that describes the respiratory muscles dynamics and the model parameters are specific to newborn lamb.

An experimental protocol was used to obtain physiological signals in one newborn lamb: i) under stationary conditions in order to determine both the amplitude and shape of experimental signals; ii) under non-stationary conditions, during successive application of three levels of positive airway pressure. An identification algorithm was used to obtain an optimal set of parameters, which minimize the difference between simulated and experimental signals. Results illustrate the similarity between experimental data and simulations following identification. The identified parameters show that lung compliance is lower than chest wall compliance and that airway resistance is high in the newborn lamb.

The results are encouraging as the identified parameter values are coherent with physiological knowledge. The proposed model-based method must now be further validated with signals obtained in additional lambs. Thereafter, the present respiratory model will integrate a cardiovascular/autonomic nervous system model. Ultimately, the overall cardio-pulmonary model should allow a better understanding of the influences of various ventilatory modes on arterial pressure and heart rate variability in the newborn.

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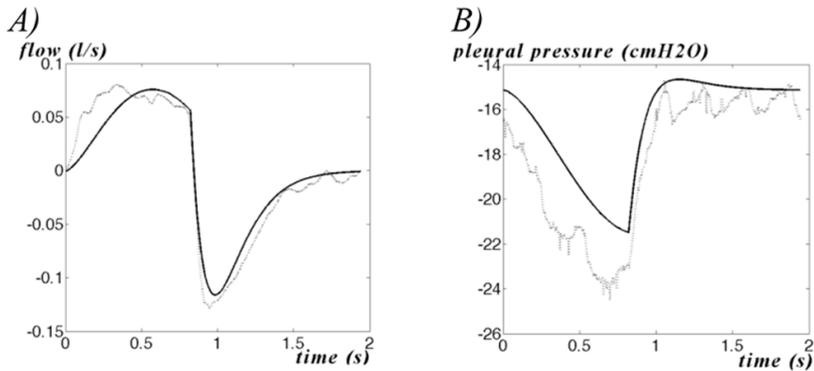
Fig. 1

schematic representation of the respiratory system model and electrical analog of the model.
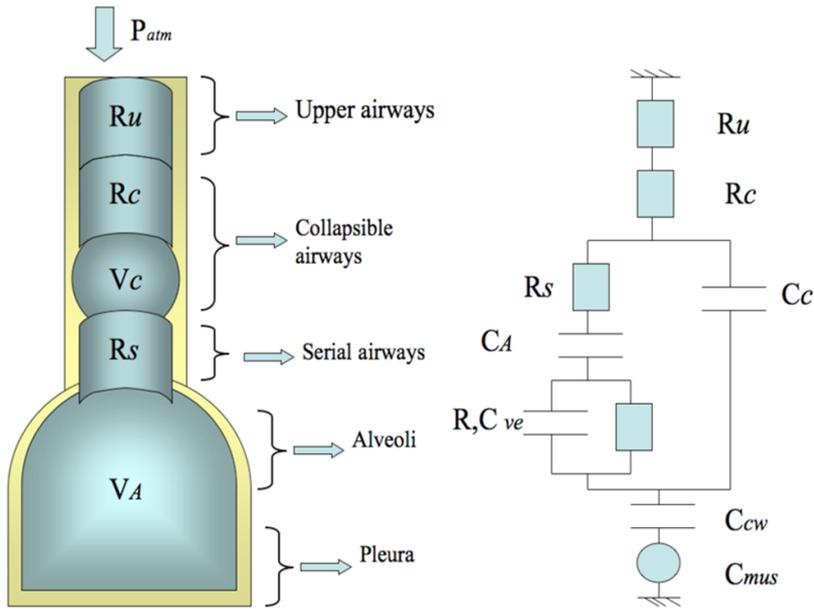
Fig. 2

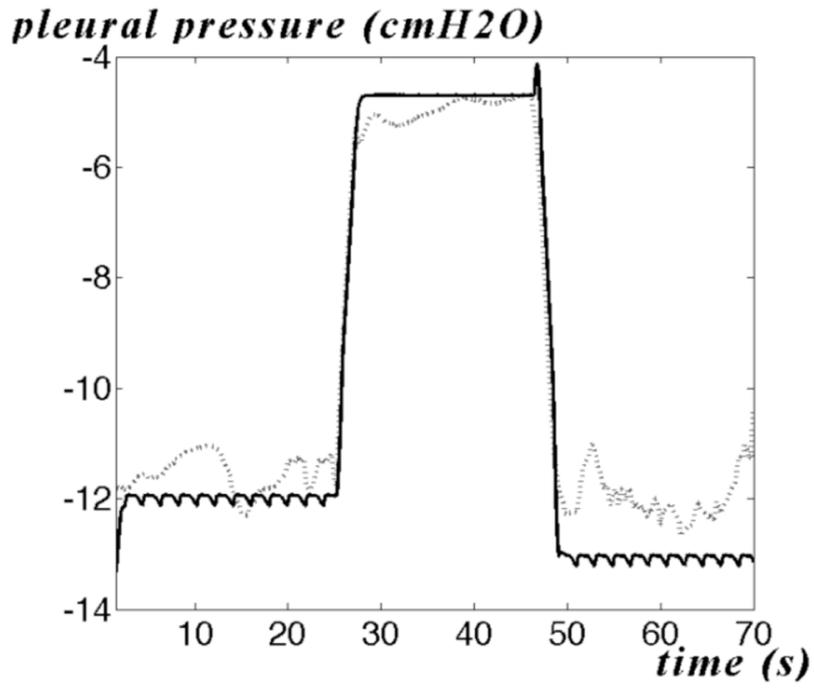Three levels of positive pressure applied into the lamb nasal mask
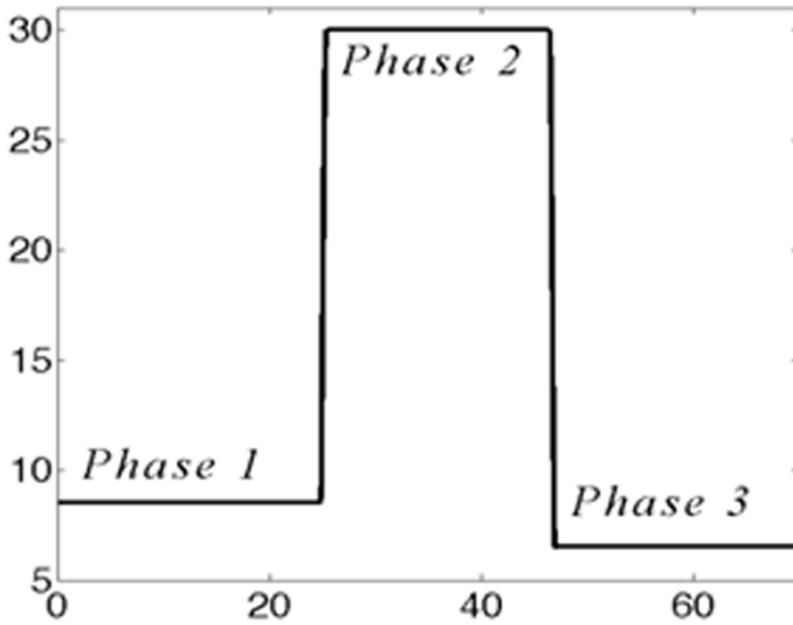
Fig. 3

Comparison between experimental (grey curve) and simulated signals (black curve): A) flow (l/s); B) pleural pressure (cmH$_2$O).

Fig. 4
Comparison between experimental (grey curve) and simulated (black curve) mean pleural pressure (cmH$_2$O) in non-stationary conditions.

Table 1

Comparison of parameter values identified for newborn lambs and previously reported for adult humans [8].

	Newborn Lamb	Adult human
C_l (l/cmH$_2$0)	0.009	0.1
C_{cw} (l/cmH$_2$0)	0.013	0.0667
K1 (cmH$_2$O.s/l)	12.96	0.5
K2 (cmH$_2$O.s/l)	2.388	0.2
K3 (cmH$_2$O.s/l)	14.99	0.2

Table 2

Lamb lung compliance values. Comparison between the identified value and values taken from other studies [23, 24, 25]

References	Identified value	[23]	[24]	[25]
C_l (l/cmH$_2$0)	0.009	0.0076	0.0075	0.0066