Sensitivity Analysis of a Cardiorespiratory Model for the Study of Sleep Apnea

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Abstract

A novel integrated model of cardio-respiratory interactions is presented in this paper with the objective of understanding the acute physiological response due to events of sleep apneas and hypopneas in adults. A formal sensitivity analysis is proposed, focused on the chemoreflex and metabolism gas exchange components of this model, during the simulation of a 20-seconds obstructive apnea episode. During apnea, the most influent parameters were those related to metabolic rates. After the apnea, the most relevant parameters were the one related with the the amplitude gains of the central and peripheral chemoreflex. A first qualitative comparison has shown a close behaviour between experimental and simulated cardiorespiratory responses to apnea. These results highlight the influent components of chemoreflex control and the metabolic rates and provides key information towards the definition of patient-specific parameters.

1. Introduction

Sleep apnea syndrome (SAS) is a multifactorial sickness characterised by repeated episodes of cessation of breathing (apnea) or important reductions in breathing amplitude (hypopnea) during the patient 's sleep. Patients with SAS can suffer from 5 to 100 apnea or hypopnea episodes per hour of sleep, with durations going from 10 seconds to several minutes, producing acute cardiorespiratory responses and strong modifications of the sleep structure of the patient. In the long term, these acute effects increase the possibility of suffering various chronic conditions such as hypertension, stroke, heart disease and certain metabolic disorders[1].

Although 5% of the population suffers from SAS, the syndrome is highly under-diagnosed [3] [4]. The gold-standard for the diagnosis of SAS is polysomnography (PSG), which consists of a complete multi-channels recording and monitoring of cardiorespiratory and sleep signals. The interpretation of acute responses due to apneas and hypopneas could be difficult because of the variety of processes involved (autonomic regulation, respiration, chemoreflex, etc.), which should be jointly considered for an appropriate analysis. As a consequence, new methods are needed to provide a better understanding of physiological mechanisms involved in the cardiorespiratory responses to apnea. In this context, model-based approaches seems particularly adapted because it allows the integration of physiological knowledge in data processing tasks and it permits the analysis of underlying mechanisms that are difficult or impossible to observe.

This paper presents a novel integrated model of cardiorespiratory interactions. The objective is to determine the most influent parameters of chemoreflex regulation and metabolic rates before, during and after an obstructive apnea episode. The method section includes a description of the model structure, a sensitivity analysis method and the experimental data. The results section presents a comparison between simulated and experimental data for one patient and a parameter analysis.

2. Methods

2.1. Model description

The proposed model (Fig. 1) is composed of four interconnected components : i) the respiratory system, ii) the cardiovascular system, iii) the gas exchange (in the lungs and the metabolism) and iv) the neural control.

2.1.1. Cardiovascular system model

The cardiovascular system (CVS) is constituted of three coupled components: 1) the cardiac electrical activity, 2) the cardiac mechanical activity, and 3) the circulation. The proposed model of the cardiac electrical activity, is based on a set of coupled automata developed by our group [5]. The cardiac mechanical activity is represented by means of a classical elastance-based approach [6]. Finally, the circulation is divided into the pulmonary circulation and the systemic circulation as presented by [7]. In order to integrate the metabolic gas exchange sub-model, a new compartment representing the systemic peripheral vessels has been included in the systemic circulation.

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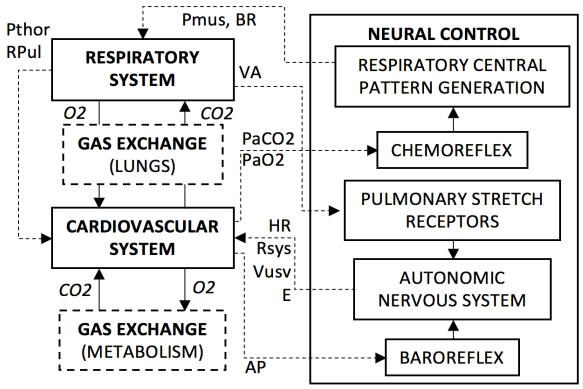

Figure 1. Cardiorespiratory model diagram. Dotted line arrows symbolyze interactions between submodels. P_{thor}, thoracic pressure; R_{pul} pulmonary capillaries resistance; P_{mus}, respiratory muscles pressure; BR, breathing rate; V_A, alveolar volume; Pa_{O2} and Pa_{CO2}, partial pressure of O_2 and CO_2 in the systemic arteries respectively; HR, heart rate; R_{sys}, systemic peripheral resistance; V_{usv}, unstressed volume of the systemic veins; E, ventricle elastances; AP, arterial pressure.

2.1.2. Respiratory model

The respiratory model was adapted from previous work of our team [8]. It includes the upper, collapsible and small airways, the alveolar compartment, the pleural cavity and the chest wall.

2.1.3. Gas exchange model

The gas exchange is composed of three components: *i)* lung gas exchange and *ii)* metabolism gas exchange and *iii)* gas transport.

2.1.3.a Lung gas exchange: The description of CO_2 and O_2 exchanges between the dead space compartment, the alveoli compartment and the pulmonary capillaries was adapted from [9]. Fractions and partial pressures of each gas are computed for each compartment, depending on the air flow to the lungs, the percentage of O_2 and CO_2 in the inspired air and the blood flow in the pulmonary capillaries.

2.1.3.b Metabolism gas exchange: A model of CO_2 production and O_2 consumption by the tissues and organs [10] was integrated in the systemic peripheral vessels compartment. The metabolic gas exchange is defined by the following equations:

$$(V_{T,sp} + V_{sp})\frac{dC_{sp,O2}}{dt} = Q_{ea}(\tilde{C}_{A,O2} - C_{sp,CO2}) - M_{O2sves} \quad (1)$$

$$(V_{T,sp} + V_{sp})\frac{dC_{sp,CO2}}{dt} = Q_{ea}(\tilde{C}_{A,CO2} - C_{sp,CO2}) + M_{CO2sves} \quad (2)$$

where Q_{ea} and V_{sp} are respectively the blood flow and volume of the systemic peripheral vessels, M_{O2sves} and M_{O2sves} are the metabolic O_2 consumption and CO_2 production, $\tilde{C}_{AO2}$ and $\tilde{C}_{ACO2}$ are the concentrations of gas from the alveoli after the gas transport in the cardiovascular circulation, and $V_{T,sp}$ is the blood supply to the tissue/organs.

2.1.4. Neural control

2.1.4.a Chemoreflex model: Peripheral and central chemoreflex submodels, adapted from [10], were integrated in the model in order to represent modulations of breathing rhythm (BR) and respiratory muscle pressure amplitude (P_{max}) in response to Pa_{O2} and Pa_{CO2} modifications.

The central chemoreceptor mechanism was represented as a combination of first-order systems defined by some gains ($G_{c,A}$ and $G_{c,f}$) and time constants $\tau_{c,f}$ and $\tau_{c,A}$. The peripheral chemoreflex is described as a two-stage transduction mechanism. First, Pa_{O2} and Pa_{CO2} are transduced into the afferent electrical activity of the peripheral chemoreceptors f_{acp} .Then, the second stage is represented a set of first-order models, defined by gains ($G_{p,A}$, $G_{p,f}$) and time constants $\tau_{p,f}$ and $\tau_{p,A}$. Contributions of each branch are summed in order to define P_{max} and BR.

2.1.4.b Baroreflex and pulmonary stretch receptors: This submodel is based on previous work of our laboratory[6]. The baroreceptors dynamical properties are represented by a first-order filter. The efferent pathways consist of normalisation functions, delays and first-order filters giving as outputs the modification of the heart rate (HR) through the vagal and sympathetic paths and modification of some other cardiovascular parameters. The pulmonary stretch receptors modulate the vagal branch of the baroreflex in relation to the changes of alveolar volume V_A.

2.2. Sensitivity analysis

A sensitivity analysis through the Morris' screening method [11] was performed to determine the most influential parameters of the chemoreflex and the metabolism submodels during and after an obstructive apnea. This method consists in generating several random trajectories through the parameter space. Each trajectory is associated with an estimation of the Elementary Effects EE_i, defined for a

parameter x_i :

$$EE_i = \frac{F(x_1, ..., x_i, ...x_k) - F(x_1, ..., x_i + \Delta, ...x_k)}{\Delta} \quad (3)$$

where F is a function of the model output variables and Δ is the variation of the parameter. EE_i are calculated r times and the mean μ_i and standard deviation σ_i of these r realisations are then computed for each parameter i. The position of each group of EE_i in the μ vs. σ plane determine the relevance and the linearity of each parameter. Two output functions *F*, with X=$\{Sa_{O2}, Pa_{O2}, Pa_{CO2}\}$, were defined in order to perform the sensitivity analysis:
1. between the start and the end of an apnea event:

$$DeltaX = \frac{X_{EndApnea} - X_{StartApnea}}{X_{StartApnea}} \quad (4)$$

2. in 15 second's window before the apnea and a 15 second's window after the apnea:

$$DeltaX_{Mean} = \frac{X_{MeanAfter} - X_{MeanBefore}}{X_{MeanAfter}} \quad (5)$$

The screening method was applied on 19 parameters of the chemoreflex and metabolism gas exchange component. Parameter ranges were selected from the nominal literature values $\pm 30\%$. The two most important parameters, deduced from the Morris method, were selected and a local sensitivity analysis was performed in order to analyse the influence of these parameters on cardiorespiratory signals.

2.3. Experimental protocol and data

A patient were selected from the database of the French ANR project PASITHEA[12].This database consists of more than 100 adults with sleep apnea syndrome on a full polysomnography. The data was annotated by an expert, blinded core-lab (CHU Grenoble, France) who scored individual events like apneas or hypopneas (start, end, duration and type) among other annotations.

3. Results

3.1. Comparison with experimental data

Experimental data were confronted to simulated signals obtained during obstructive apnea event, which was generated by increasing the resistance of the upper airways of the respiratory model to 100000 $cmH_2O \cdot s \cdot l^{-1}$ Figure 2 shows flow, oxygen saturation (Sa_{O2}) and heart rate time series during a 20 seconds' obstructive apnea obtained experimentaly (A) and synthesized by the model (B). An increase of the respiratory effort after the apnea event due to the hypoxia, can be noticed both in the observed and the simulated data. The dynamics of the Sa_{O2} time series are similar on both cases, presenting a delay of 17.3s and 18.6s respectively. Both heart rate curves possess similar order of magnitude and similar variabilities with a mean value of 52.7 bpm and 60.15 bpm.

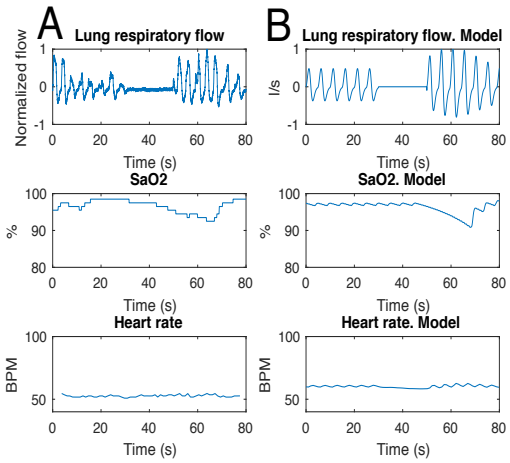

Figure 2. Comparison between observed data (A) and model output signals (B) during a 20 seconds obstructive apnea event.

4. Sensitivity analysis results

Figure 3 present the results of the sensitivity analysis for both output functions evaluated for Pa_{O2}. During apnea, the most influent parameters were those related to the metabolic O_2 consumption rate (MO_{2sves}). In the 15-second window after and before the apnea, the most relevant parameters were the amplitude gains of the central and peripheral chemoreflex ($G_{c,A}$, $G_{p,A}$). These results are consistent with the literature around the influence of the metabolic rate in the oxygen desaturations due to apneas [13] and the importance of the chemoreflex feedback loop gain to SAS [14].

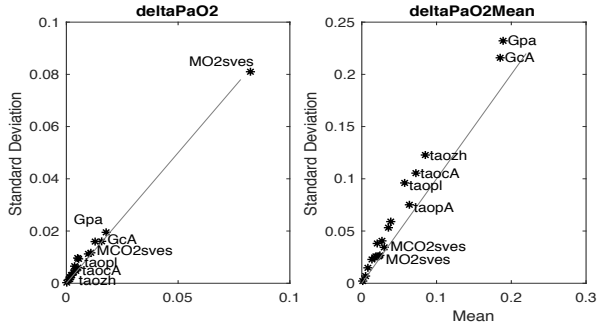

Figure 3. μ vs. σ plane for $DeltaPa_{O2}$ and $DeltaPa_{O2}Mean$

Figure 4 presents the oxygen saturation Sa_{O2} for a

20 seconds obstructive apnea for different values of: i) $MO_{2sves} \in [1, 9]$ $ml \cdot s^{-1}$ (A) and ii) $G_{c,A} \in$ [-1,-9] $cmH_2O \cdot mmHg^{-1}$ (B). During an apnea, the lack of ventilation induces the stop of O_2 and CO_2 flow and the chemoreflex cannot modify the mechanics of the respiration. Hence, the only factor that is going to affect the oxygen desaturation during an apnea is the O_2 metabolic rate. After the apnea, a higher $G_{c,A}$, will lead to an higher increment of the amplitude of the ventilation after the event, increasing the flow of O_2 into the system and the flow of CO_2 out of the body. If the gain is too big, it could generate an overcompensation, leading to abnormal breathing patterns. A small gain will lead to a slow recovery to baseline values.

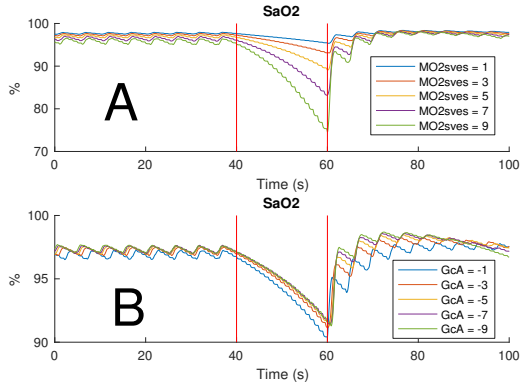

Figure 4. Local sensitivity analysis done with the parameter MO_{2sves} (A) and $G_{c,A}$ (B).The red lines represents the start and the end of the apnea event.

5. Conclusion

This work presents an integrated model of cardio-respiratory interactions for the analysis of obstructive apnea event. A formal sensitivity analysis method was applied in order to determine the influence of each model parameter on O_2 desaturation. The results highlight the influent components of chemoreflex control and the metabolic rates and provides key information towards the definition of patient-specific parameters. Further work will focus on more extended sensitivity analysis and in a patient-specific identification of parameters in order to reproduce data observed from polysomnographic studies.

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