CARDIORESPIRATORY SYSTEM MODELING IN PATIENTS INTOXICATED WITH ORGANOPHOSPHORUS COMPOUNDS

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Abstract

The management of toxicity by poisoning with organophosphorus compounds is difficult for medical personnel due to the lack of knowledge about the clinical feature evolution and the low percentage of therapeutic efficiency used, which leads to patients to require long and expensive recovery periods in an intensive care unit. In the current work, an extended cardiorespiratory model considering the respiratory muscle activity was proposed to improve the determining of the appropriate timing for initiating extubation maneuvers in patients intoxicated with organophosphorus compounds. This opens the possibility of exploring and using surface electromyography as tool for understanding the cardiorespiratory response in these patients. According to the experimental data and optimization results, this muscular response is correlated with the parasympathetic- sympathetic action measured through the heart rate. This can be very important in diagnosis of health and disease states. Having more knowledge about the balance of these systems allows evaluating the efficiency of pharmacological treatment, given the clinical condition of the intoxicated patient.

Keywords: parasympathetic system; mechanical ventilation; sympathetic system

Resumen

El manejo de la toxicidad por intoxicación con compuestos organofosforados es difícil para el personal médico debido a la falta de conocimiento sobre la evolución de las características clínicas y el bajo porcentaje de eficiencia terapéutica utilizada, lo que hace que los pacientes requieran largos y costosos períodos de recuperación en una unidad de cuidados intensivos. En el trabajo *actual, se propuso un modelo cardiorrespiratorio extendido que considera la actividad muscular respiratoria para mejorar la determinación del momento adecuado para iniciar maniobras de extubación en pacientes intoxicados con compuestos organofosforados. Esto abre la posibilidad de explorar y utilizar la electromiografía de superficie como herramienta para comprender la respuesta cardiorrespiratoria en estos pacientes. Según los datos experimentales y los resultados de optimización, esta respuesta muscular se correlaciona con la acción parasimpática y simpática medida a través de la frecuencia cardíaca. Esto puede ser muy importante en el diagnóstico de estados de salud y enfermedad. Conocer mejor el equilibrio de estos sistemas permite evaluar la eficacia del tratamiento farmacológico, dado el estado clínico del paciente intoxicado.*

Palabras clave*: sistema parasimpático; ventilación mecánica; sistema simpático.*

1. Introduction

Organophosphorus compounds (OC) are pesticides derived from phosphoric acid, which irreversibly inhibit the cholinesterase's action, specifically acetylcholinesterase (AChE) and butyrylcholinesterase, whose function is the degradation of acetylcholine (ACh) in the synaptic gap; such inhibition causes a cholinergic over stimulation and subsequent blockade of a neurotransmission process (Sungur and Güven 2001).
Pesticides are used in the world as insecticides in agricultural, industrial and domestic activities (Sharma and Singh 2000), whose exposure can be by air, oral and/or physical contact. The severity of the intoxication depends on the dose and the exposure's period to the pesticide (Mew et al. 2017). In developing countries, OC are considered one of the types of agents most involved in intoxications due to their toxicity (Pose, Benz, and Delfino 2000). Colombia is a country with significant agricultural and industrial production, which means that the use of chemical substances is high as well as the risk of intoxication. In fact, according to the Epidemiological Bulletin, in 2016 there were 34,869 chemical poisonings, of which 8,663 (25.8%) were secondary to pesticides, being the second cause of intoxication in our country (Instituto Nacional de Salud de Colmbia 2016).

The lack of knowledge concerning the muscular state after poisoning conducts to the standardization of the treatment and usually the patients require long and expensive recovery periods in an Intensive Care Unit (ICU), presenting a high incidence of patients with mechanical ventilation and muscular weakness (Takasu et al. 2005). The therapeutic treatment in these patients is highly complex due to the high variability of results in clinical practice (Eddleston et al. 2005).

Experimental studies performed by several authors (Sungur and Güven 2001) have demonstrated that failures in the respiratory system, by intoxication, are the result of neuromuscular blockade due to the stimulation of cholinesterase enzyme, which triggers changes at the cardiovascular level. Breathing depends on the muscle function involved in ventilation and whose control is performed by the Autonomic Nervous System (ANS). The respiratory process requires that the oxygen bonded to the red blood cells must be transported to the tissues and organs. The heart modifies the stroke volume and generates the pressure in the arteries, which allow the transportation of the oxygen according to human body physiological needs. Respiratory and cardiovascular systems are coupled; therefore, the blocking of any of them produces direct effects in the other system.

This work was motivated by the possibility of finding a relationship between the cardiorespiratory system and muscle activity measured by surface electromyography during a spontaneous breathing test. This relation could give light in improving the efficiency of therapeutic treatment, more specifically in the ventilatory strategy. It is possible to achieve a shorter time of mechanical ventilation, performing a continuous (non-subjective) evaluation of muscle weakness caused by OC.

2. Materials and Methods

2.1. Patients

Patients with OC poisoning were admitted and managed in the Hospital San Vicente Foundation (Medellin, Colombia); they were included in the study according to the following inclusion criteria: i) intoxication with OC, ii) requirement of mechanical ventilation, iii) absence of myopathy and thoracic trauma, iv) older than 16 and v) nonpregnant. This study was conducted under the approval of the Ethical Review Committee (Acta 001, 2014) of the Hospital and written informed consent was obtained from the patient's family for publication of this study.

2.2. Identification problem

Given a mathematical model of cardiovascular regulation and a set of values of the model parameters, the system's identification was made through a set of candidate models (DiStefano and Landaw 2010) for autonomic nervous system. The cardiovascular regulation model was identified in loop-closed, considering that the new mathematical formulations for these systems should characterize the input-output properties, mainly in LF and HF bands, bearing in mind fit criteria. The best model structure was a second-order system:

$$G(s) = \frac{k\omega_n^2}{s^2 + 2\xi\omega_n s + \omega_n^2} \qquad (1)$$

The parameters are three: the static gain, k, the damping factor, ξ, and the natural frequency, ω_n (It is equal to $2\pi f_n$). These parameters describe the gain of the system, type of system response, and dynamic delay, respectively.

2.3. Optimization Algorithm

The algorithm used for the optimization phase is the Sequential Quadratic Programming (SQP) (Gill et al. 1984) algorithm, which according to a recent study in which several optimization techniques were compared, Serna et al. found that the SQP showed the best performance and convergence speed (Serna et al. 2016). The SQP is a deterministic and gradient-based algorithm for nonlinear optimization. With this optimization algorithm, the objective was to minimize the cost function J [see (1)].

$$J = \sum_{k=0}^{p-1}\left(\frac{|H_{EXP}(w_k)| - |H_{SIM}(w_k)|}{|H_{EXP}(w_k)|}\right)^2 + \left(\frac{Phy(H_{EXP}(w_k)) - Phy(H_{SIM}(w_k))}{Phy(H_{EXP}(w_k))}\right)^2 \qquad (2)$$

Where $|H\ (w_k)|$ represent magnitude, $Phy\ (w_k)$ is the phase, *k* is the samples number of the data in frequency both for simulated - *SIM* - and experimental – *EXP* - data.

2.4. Statistical analysis

A hierarchical clustering using Ward method and Squared Euclidean distance was performed. The inconsistency coefficient was used for the clustering selection, providing a measure of the distance among groups relative to the mean distance of the nearest neighbor, in a way that higher values of this coefficient represent better differentiated groups (Zahn 1971):

$$I = \frac{d - \bar{d}}{\sigma} \qquad (3)$$

3. Results and Discussion

Both in time and frequency domain, real-time monitoring of respiratory muscles activity by surface electromyography, taking into account the pharmacological treatment and the cholinesterase enzyme activity evaluated in blood. The recorded signals of the patient during six respiratory cycles are shown in Figure 1, where the increase of the airway pressure and the decrease of esophageal pressure occur when airflow goes to the lungs through airways.

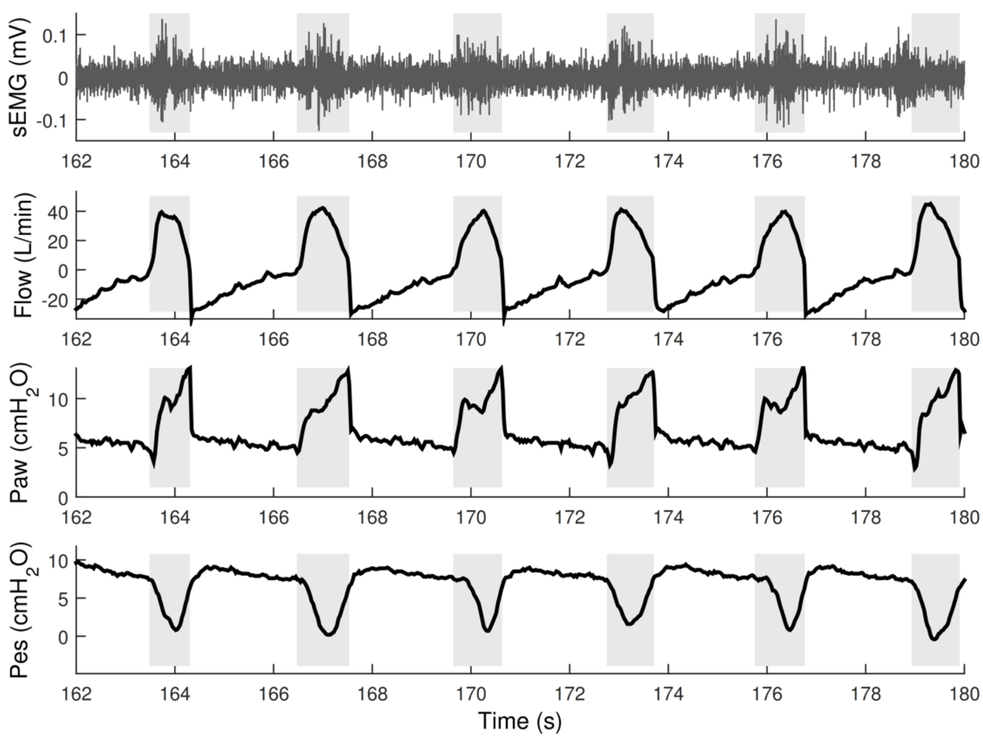

Figure 1. Signals recorded during the successful weaning test: surface electromyography (sEMG) from diaphragm muscles, airflow (Flow), airway pressure (Paw) and esophageal pressure (Pes). The shaded area corresponds to the inspiratory phase.

Contraction can be evidenced as an increase in amplitudes of the sEMG signal, particularly during the inspiratory phases (shaded areas). The patients were subjected to spontaneous breathing tests (weaning test). Different muscle coordination levels were obtained. The low synchronism between airway pressure and sEMG can be attributed to the fact that it was the machine which supports breathing instead of the respiratory muscles. In the case of the fourth test, the higher correlation coefficient was for airway pressure and the diaphragm muscle associated with the muscle effort of the patient.

Figure 2 shows Campbell diagrams (pressure-volume loops), which permit to calculate respiratory and pulmonary compliances, as quantified by the slopes of blue and red lines, respectively. Given the high level of poisoning during the first weaning (WT1), the patient required a lot more effort to fill his lungs with fresh air (Fig. 2A, 2E). Patient achieved an average of 0.57 liters to 17 breaths/min. In the third weaning (WT3), the pressure difference was lower than WT1, the patient mobilized a volume of 0.39 liters at 20 breaths/min (Fig. 2A, 2C). This reflects a decreased distensibility of the respiratory system (see the blue slope change) and the discomfort of the patient with respect to spontaneous breathing. A closer inspection of Figure 2 evidences that considerable changes in volume are easily reached with rather small changes in pressure. This can be further supported measuring the loop slopes. The highest observed slope is for the fourth test (WT4) followed by WT3, WT2 and finally WT1. WT4 exhibited the lowest airway and esophageal pressure differences; this suggests that elastic WOB was lower in WT4. The patient mobilized 0.45 liters at 21 breaths per minute. The darkened regions in can be associated with the patient's breathing work during inspiration. The results showed a high correlation between the respiratory muscles pattern and the patient's response during the spontaneous breathing test. The Paper I enabled us to meet the specific target III.

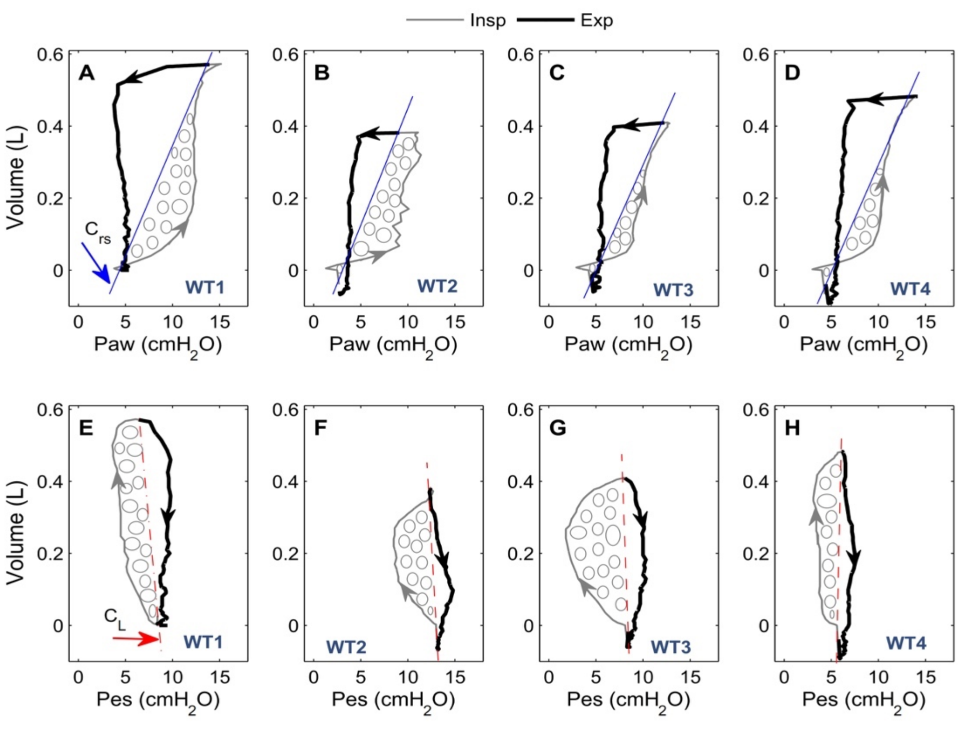

Figure 2. Tidal volume as a function of the airway pressure (Paw) during the different weaning tests (pressure-volume loops at the top): (A) WT1, (B) WT2, (C) WT3 and (D) WT4. Tidal volume as a function of the esophageal pressure (Pes) during the different weaning tests at the bottom: (E) WT1, (F) WT2, (G) WT3 and (H) WT4. Inspiratory and expiratory cycles are shown in gray and black; respectively. The straight line in each case describes lung compliance, CL, and respiratory system compliance, Crs.

Several studies have demonstrated the importance of modeling the cardiorespiratory system response in the diagnosis and clinical treatment (Batzel, Ellwein, and Olufsen 2011; Cheng et al. 2010; Topor, Pawlicki, and Remmers 2004), this has provided an excellent starting point for a research focused on the assessing the patient clinical condition with specific clinical manifestations (Cheng et al. 2010). Given the complexity in the clinical treatment and the lack of tools for medical training prior to the care of patients intoxicated with organophosphate, in this work modifications were proposed to a cardiovascular mathematical model published in 1991 by Saul et. al (Saul et al. 1991), implementing changes to predict the response of the cardiorespiratory system in our patients, including the respiratory muscle activity. We suggested to change the transfer function, its order and structure (see Figure 3), with the aim of modeling the frequency response measured through the heart rate in these patients (according to experimental results), which was not possible with a first-order system. The transfer function of the sympathetic (SNS) and parasympathetic (PNS) systems were selected as the focus of the optimization through parameters $\{K_p, A_p, f_p, \xi_p, K_s, A_s, f_s, \xi_s\}$ because these systems are directly affected to inhibition of acetylcholinesterase enzymes by OC poisoning.

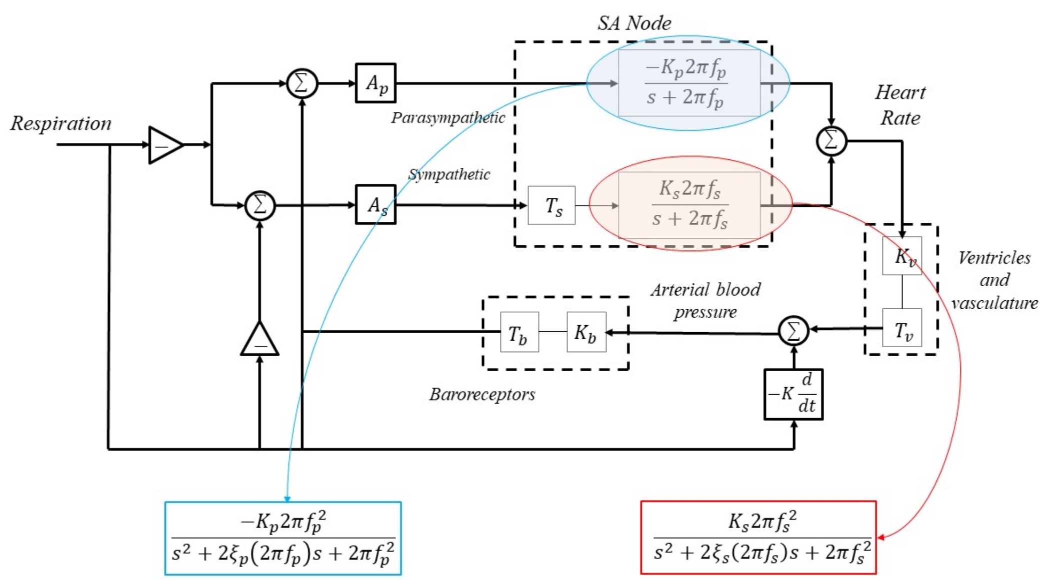

Figure 3. Cardiovascular model proposed (blue and red rectangles) considering the model published by Saul et al (Saul et al. 1991). Constant K_v and fixed delay T_v of the vasculature and ventricles. Constant K_b and fixed delay T_b of the baroreflex control. Subscript (P) Parasympathetic and (S) sympathetic system (its Latency T_s). Constant A_p and A_s in relation with the baroreflex control. Corner frequency (f_p, f_s) and constants gains (K_p, K_s). Damping constant ξ_p and ξ_s (Saul et al. 1991).

The optimal parameters, both temporal and frequency domain were considered. It was found that there is a high correlation among the energy ($RMS_{i/e}$) and engagement of diaphragm and sternocleidomastoid muscles ($r^2_{Dia,\ Strn}$) and sympathovagal balance. Like Figure 4 illustrates, the diaphragm's contraction during inspiration is related to high energy values in the inspiratory in comparison to energy on expiratory semi-cycle. According to the experimental data, this response is high correlated with the sympathetic frequency increase. A contrary pattern occurs in the vagal activity, A_p decreases and f_p decreases in relation to the increase of $r^2_{Dia,\ Strn}$, suggesting that when the low correlation coefficient between Dia and Strn is more dependent of the absence of muscle contraction of diaphragm for action of the parasympathetic system. This reflects the importance of the respiratory muscles activity on ventilation, because the use of the main and accessory respiratory muscles at the same time implies that the parasympathetic system decreases its action to support the load of the respiratory muscles.

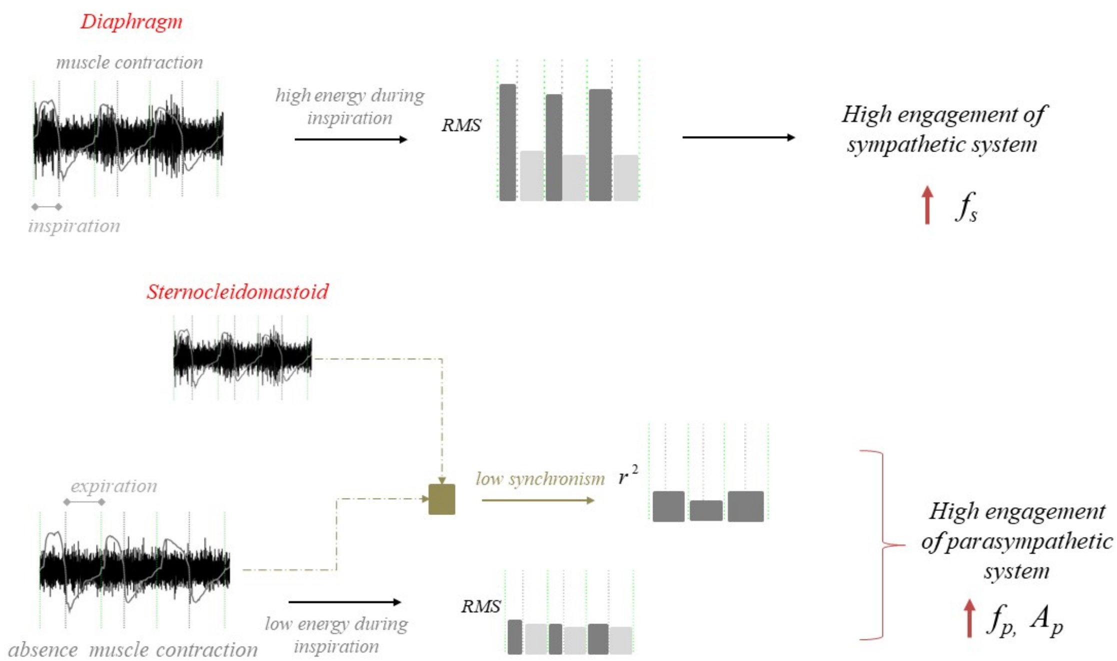

Figure 4. Framework of relationship between the optimal parameters and electromyographic information. The root mean square (RMS), inspiratory (bars dark gray) and expiratory (bars light gray) half-cycle. The squared Pearson correlation coefficient (r^2); f_p: parasympathetic corner frequency; A_p: parasympathetic weight factors of baroreflex control; and f_s: sympathetic corner frequency.

Conclusions

It is known that the management of toxicity is difficult for the medical staff, nowadays therapeutic treatment used is a diffuse process, in some cases iterative between application of drug doses and medical observation. Therefore, there is a growing need for developing of new tools as the proposal in this work, to characterize and provide information about the interaction processes in these physiological conditions by medicine students, physicians, nurses, and critical care therapist in clinical practice.

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