A MODEL OF THE RESPIRATORY SYSTEM IN THE NEWBORN INFANT

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Abstract A dynamic mathematical model is presented which successfully simulates the respriatory control system of the newborn infant in different physiological conditions. The primary objective in constructing this model has been to provide a simulation aid in the investigation of maturation of the respiratory system, and the respiratory disorders during the newborn period, without the need for invasive measurements. The model comprises a continuous plant and a discrete controller. The controller incorporates as key elements, a non-linear multiple regression element and an energy minimization routine for the determination of ventilation and breathing frequency. The plant consists of lungs, body tissue, brain tissue, a cerebrospinal fluid compartment and central and peripheral receptors. The effect of shunt in the lungs is included in the model and the lung volume and the dead space are time varying. The effects of Hering-Breuer type reflexes are embodied to accomplish respiratory synchronization. The model is examined and simulation results of its performance for test conditions in hypoxia and hypercapnia are presented.

چکیده در این مقاله یک مدل ریاضی برای مشابه سازی سیستم کنترل تنفس یک طفل نوزاد ارائه می شود. هدف از مدل ایجاد تسهیلات مشابه سازی، برای انجام بررسی های مربوط به سیستم تنفسی نوزادان بدون نیاز به اندازه گیریهای مستقیم است. سیستم اصلی پیوسته و سیستم کنترل کننده منفصل درنظر گرفته شده است. پس از تحلیل مدل نتایج مشابه سازی از کارکرد مدل در شرایط آزمایشی مربوط به هیپوکسیا و هیپرکاپنیا ارائه می شود.

INTRODUCTION

The human respiratory system can be described as a sensitive feedback regulator which determines the level of ventilation by receiving the chemical and neural stimuli and controls the pH and gas concentrations of the blood. If anything upsets the balance of this system, the ventilation level is adjusted to counter the disturbance and minimize the effects on the blood chemistry. Different mathematical models have been presented to simulate the respiratory system since 1954. Among many researchers in this area the names of Gray, Horgan, Lange, Milhorn, Guyton, Longobardo and Yamamoto easily come to mind. Fincham and Tehrani [2] presented a model which included many dynamic aspects of the system and reproduced both the low and high frequency effects of different physiological stimuli under transient and steady state conditions. The main applications of these simulation models have been in clinical research and diagnosis. The development of a reliable mathematical model for the respiratory system is particularly significant in the investigation of the behavior of the pulmonary system in the newborn infant. Due to prematurity of the respiratory system of newborn infants, they have a tendency to lapse into respiratory failure because of fluctuations in their lung function such as unpredictable changes in minute ventilation and shunt effect. Revow et al. [3] presented a model which could simulate the respiratory system of the newborn infant during epochs of quiet sleep. This model was based on an earlier system developed by Milhorn [4].

The main purpose of the research work presented here was constructing a model as a simulation aid in the investigation of the behavior and maturation of the respiratory system of the newborn infant without invasive measurments and experimentations. An earlier model of Fincham and Tehrani [2] has been used

as the basic structure of this model and further developed to include the characteristics of the respiratory system in the newborn period. The new model can successfully simulate the respiratory system of the newborn infant under different test conditions and be used in the investigation of maturation of the system, and infant respiratory disorders.

The solution of the model equations was achieved by using the "Interactive Simulation Language" (ISL) which is a block oriented simulation software, on a digital computer.

MODEL DESCRIPTION

A block diagram of the model is shown in Figure 1. The plant consists of lungs, body and brain tissues, a cerebrospinal fluid compartment, and the peripheral and central medullary receptors. The effects of shunt in the lungs is included and a blood transport time delay is interposed on blood gas concentrations between the lungs and the peripheral receptors. Cardiac output and cerebral blood flow are considered to be constant.

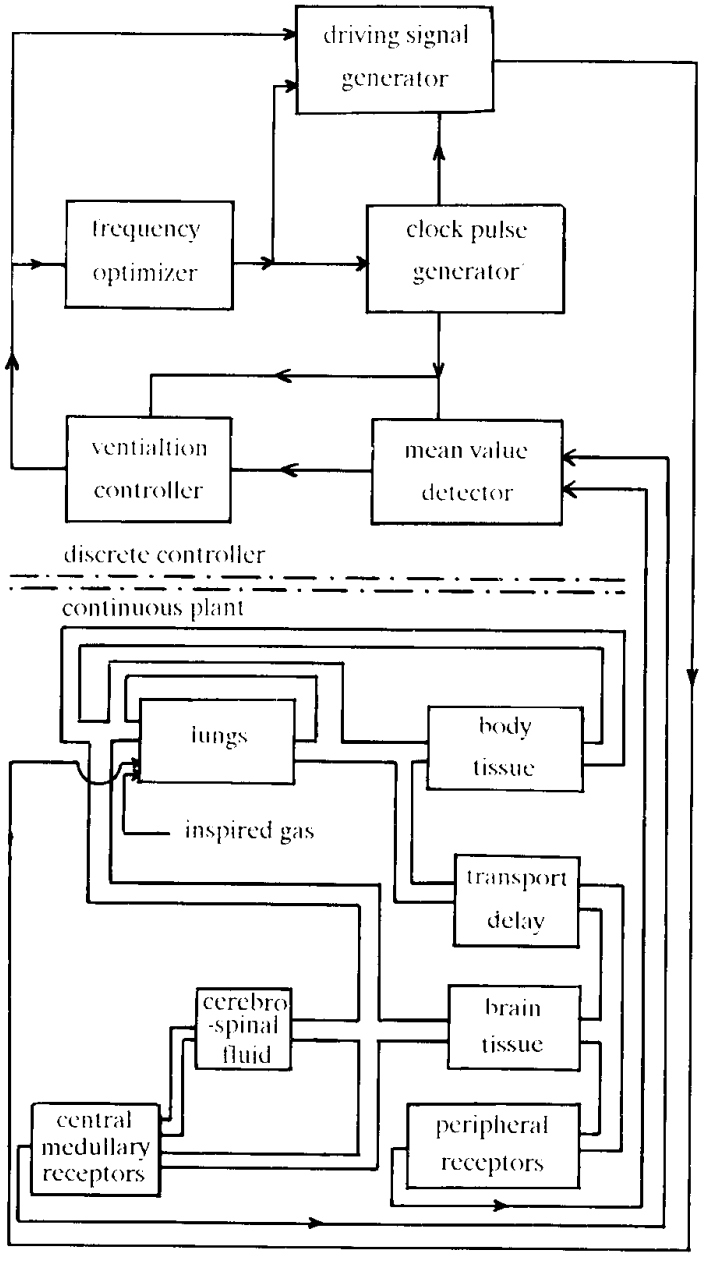

Figure 1. Model Block Diagram.

The controller receives the information about gas tensions in the neighborhoods of the arterial and central receptors continuously, and adjusts the tidal volume and the respiratory frequency at the end of every breath. Respiratory work is minimized and the effects of lung compliance, airway resistance in the lungs and a varying dead space are included in determination of breathing frequency.

PLANT DESCRIPTION: SPECIFIC

Mass flow equations for CO_2 and O_2 in the lungs are described as:

$$(CVT_j - Ca_j)Q_T(1-R_s) + (CVB_j - Ca_j)Q_B(1-R_s) = \frac{V}{P_b - 47} \cdot \frac{dP_{Aj}}{dt} + \text{FACT}$$

where $\text{FACT} = \frac{P_{Aj} - P_{Ij}}{P_b - 47} \cdot \frac{dV}{dt}$ during inspiration and FACT = 0 in expiration

$$\text{Cam}_j = (1-R_s)Ca_j + \frac{R_s Q_T CVT_j}{Q} + \frac{R_s Q_B CVB_j}{Q}$$

In these equations, j = CO_2 and O_2 and CVT, CVB, and Ca are gas concentrations in the body tissue, brain tissue, and arterial blood, respectively. V is the volume of the alveolar space, Q_T, is blood flow in the body tissues, Q is cardiac output, Q_B is cerebral blood flow, P_b is the barometric pressure, C_{am} is the gas concentration in the mixed arterial blood, R_s is the lung shunt ratio and P_A and P_I represent gas partial pressures in the alveolar space and the inspired gas, respectively.

Mass balance equations for the body tissues and brain are the same as equations for these compartments in [2] with mixed arterial gas concentrations used to include the effect of shunt

in the lungs. A transport delay on concentration is included between main arterial blood and the blood at the site of the carotid body. Partial pressure of CO_2 at the site of central receptors is obtained by using an equation from the paper of Mitchell et al. [5] and is a function of CO_2 tensions in the brain and cerebrospinal fluid. The equation for the cerebrospinal fluid compartment is described as:

$$\frac{K dP_{CSFCO_2}}{dt} = (P_{VBCO_2} - P_{CSFCO_2})$$

Where P_{CSFCO_2} and P_{VBCO_2} are the partial pressures of CO_2 in the cerebrospinal fluid and the brain tissue, respectively, and k is a constant representing the diffusion time constant across the blood brain barrier. Aveolar and arterial tensions of CO_2 are considered to be equal and for oxygen, a difference of 10-20 mmHg is assumed between aveolar and arterial tensions.

CONTROLLER DESCRIPTION

The information about gas concentrations at the sites of the arterial and central receptors is supplied to a discrete controller. The mean values of the gas concentrations over a breath interval are sent to a ventilation controller which determines the level of ventilation for the next breath using the following equation:

$$\frac{V'_A}{V'_A(\text{rest})} = 0.22 H^+ + 0.262 Pa'_{mCO_2} + \text{FACT1} - k'$$

where $\text{FACT1} = 4.72 \times 10^{-9} (104 - Pa'_{mO_2})^{4.9}$ if $Pa'_{mO_2} < 104$ mmHg

and $\text{FACT1} = 0$ if $Pa'_{mO_2} > 104$ mmHg

In the above equation which is derived on the basis of the multiple factor theory of Gray [1] V'_A represents alveolar ventilation in (1/s), H^+ is blood hydrogen ion concentration (in nmoles/l), Pa'_m is gas partial pressure at the entrance of the brain compartment (in mmHg), FACT1 is the response of arterial chemoreceptors to hypoxia and k′ is a constant.

Considering half of the ventilatory response to CO_2 and H^+ to be due to the arterial receptors and the other half via central receptors, ventilation equation can be rewritten as:

$$\frac{V'_A}{V'_A(\text{rest})} = 0.11 H^+ a + 0.131 Pa'_{mCO_2} + 0.11 H^+_{CSF} + 0.131 P_{CSFCO_2} + \text{FACT1} - K'$$

Where H^+a and H^+_{CSF} are hydrogen ion concentrations at the sites of arterial receptors and the cerebrospinal fluid compartment, respectively, and are specified in terms of CO_2 partial pressures in these regions by:

$$H^+ a = 0.65 Pa'_{mCO_2} + 13.5$$

and $$H^+_{CSF} = \frac{\alpha.\beta}{(BH CO_3)CSF} \cdot P_{CSFCO_2}$$

$RHCO_3$ represents standard bicarbonate concentration, α is the solubility factor of CO_2 and β is carbonic acid dissociation constant in the cerebrospinal fluid. The ventilation equation is used to determine the alveolar ventilation for every breath. Since there is evidence that peripheral receptors are premature at birth and mature to adult functionality later, different versions of the ventilation equation should be used at different stages in the newborn period.

The frequency optimizer determines the optimum breathing frequency for every breath by minimizing the respiratory work. The minization formula and procedure presented by Otis et al. [6] is used in the frequency optimizer. The driving signal generator is a sine wave oscillator which is synchronized with clock pulse. The output of this generator, which provides the neural drive signal to the lungs, is controlled for every breath by having the alveolar ventilation and the optimum frequency.

The clock pluse generator receives the frequency from the frequency optimizer and generates a pulse at the end of the period of every breath. This generator represents the mechanism of the Hering-Breuer reflexes in the model.

RESULTS AND DISCUSSION

The performance of the model was investigated under different test conditions. The simulation

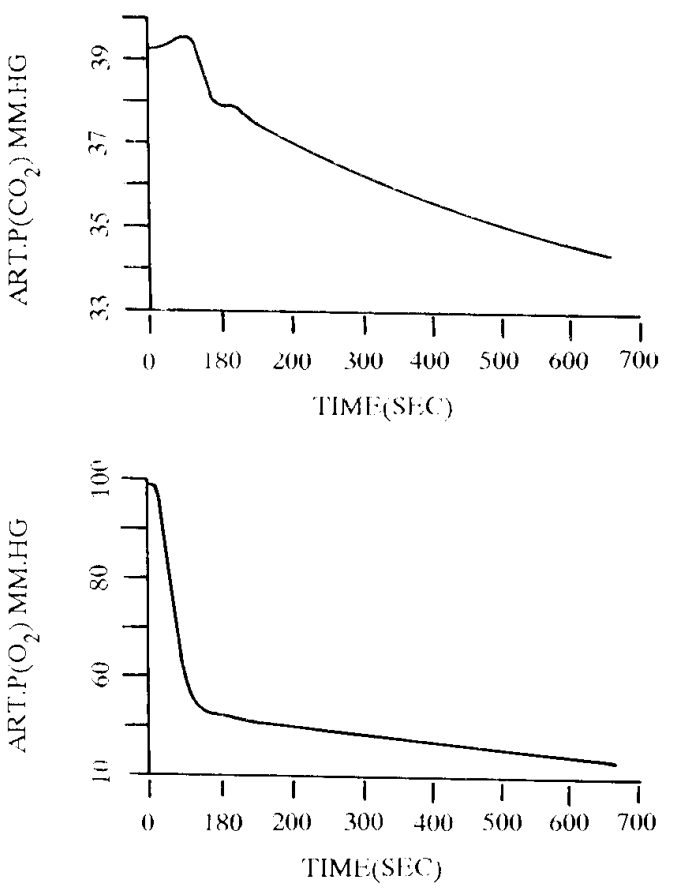

Figure 2. Simulation results of model in 10% oxygen breathing.

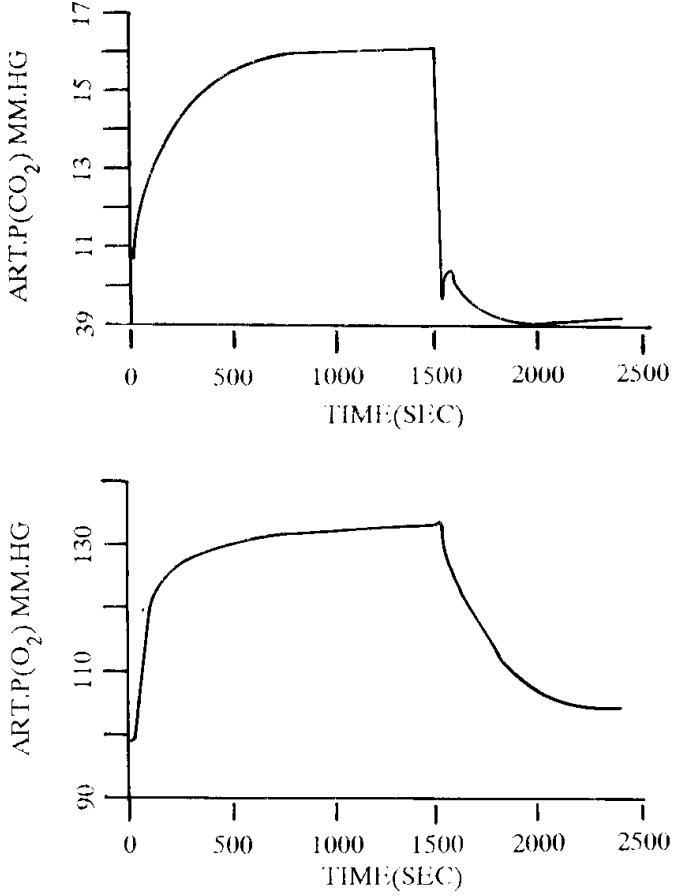

Figure 2. Simulation results of model in 5% CO_2 breathing and recovery.

results were always stable and in close agreement with the experimental observations available in the literature.

The effect of 10% oxygen breathing on arterial pressures of carbon dioxide and oxygen is shown in Figure 2.

It can be seen in this figure, that at the beginning of hypoxia, arterial pressure of oxygen falls rapidly due to decrease in inspired oxygen fraction. As a result of the rapid reduction in arterial oxygen pressure, the oxygen concentration in the body tissues decreases and finally, by physiological intervention of the respiratory controller and increase in ventilation, arterial level of oxygen gradually reaches the steady state. Arterial pressure of CO_2 falls rapidly in hypoxia due to increase in ventilation. The reduction in arterial pressure of carbon dioxide has a strong antagonistic effect against the lack of oxygen in control of ventilation. Therefore, as a part of the excitatory effect of reduction in arterial oxygen tension on ventilation is compensated by the inhibitory effect of low CO_2 partial pressure at the sites of the peripheral and central receptors, the system reaches the steady state as shown in Figure 2. In Figure 3, the simulation results of the model for CO_2 and O_2 arterial pressures are shown in 5% CO_2 breathing and recovery.

A rapid rise in arterial pressure of CO_2 is observed at the beginning of hypercapnia. This rise is due to the increase in inspired fraction of CO_2 and is followed by a further and slower increase in the transition region. At the beginning of exposure to normal air, there is an abrupt fall in the arterial pressure of CO_2 due to the sharp decrease in the concentration of inspired carbon dioxide. The response later approaches the steady state after a slight undershoot.

The arterial pressure of oxygen increases at the beginning of hypercapnia due to the rapid increase in ventilation and later falls during the recovery period as ventilation approaches its normal steady state level.

The responses of peripheral receptors to

hypoxia and hypercapnia were included in the ventilation equation to obtain the illustrated results of Figures 2 and 3.

CONCLUSIONS

A mathematical model has been presented which can simulate the respiratory system of the newborn infant under different test conditions. The model includes both the peripheral and central receptors and can be used to investigate the effects of prematurity of peripheral receptors on the respiratory function in the newborn period. The effects of shunt in the lungs and a varying dead space are included in the model. The respiratory work is minimized and the effects of lung compliance and airway resistance are included in the determination of the rate of breathing. Due to relative sophistication and structural isomorphism of the model with the real system, it offers considerable flexibility in simulation of a relatively wide range of stimuli on the respiratory function of the newborn infant.

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