AN IMPROVED DIGITAL COMPUTER MODEL OF THE
NEONATAL RESPIRATORY SYSTEM

by

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<td>Alveolar O₂ partial pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>PAV2</td>
<td>Alveolar CO₂ partial pressure</td>
<td>mmHg</td>
</tr>
<tr>
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<td>Alveolar N₂ partial pressure</td>
<td>mmHg</td>
</tr>
<tr>
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<td>Partial pressure of O₂ in brain</td>
<td>mmHg</td>
</tr>
<tr>
<td>PB2</td>
<td>Partial pressure of CO₂ in brain</td>
<td>mmHg</td>
</tr>
<tr>
<td>PB3</td>
<td>Partial pressure of N₂ in brain</td>
<td>mmHg</td>
</tr>
<tr>
<td>PCFl</td>
<td>Partial pressure of O₂ in CSF</td>
<td>mmHg</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
<td>Units</td>
</tr>
<tr>
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</tr>
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</tr>
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<td>PCF3</td>
<td>Partial pressure of N₂ in CSF</td>
<td>mmHg</td>
</tr>
<tr>
<td>PCS1</td>
<td>Partial pressure of O₂ at central chemoreceptor</td>
<td>mmHg</td>
</tr>
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<td>PCS2</td>
<td>Partial pressure of CO₂ at central chemoreceptor</td>
<td>mmHg</td>
</tr>
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<td>Partial pressure derivative of alveolar CO₂</td>
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<td>Partial pressure derivative of alveolar N₂</td>
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<td>mmHg</td>
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<td>Partial pressure derivative of CO₂ in CSF</td>
<td>mmHg</td>
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<td>Partial pressure derivative of N₂ in CSF</td>
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<td>PHAL</td>
<td>Arterial pH of blood at lungs</td>
<td>pH units</td>
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<td>pH of fluid at central chemoreceptors</td>
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</tr>
<tr>
<td>PHPS</td>
<td>pH of fluid at peripheral chemoreceptors</td>
<td>pH units</td>
</tr>
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<td>PHVB</td>
<td>Venous pH at brain</td>
<td>pH units</td>
</tr>
<tr>
<td>PHVT</td>
<td>Venous pH at tissues</td>
<td>pH units</td>
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<td>Symbol</td>
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</tr>
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<td>Inspired partial pressure of CO₂</td>
<td>mmHg</td>
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<td>PI3</td>
<td>Inspired partial pressure of N₂</td>
<td>mmHg</td>
</tr>
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<td>Partial pressure of O₂ at peripheral site</td>
<td>mmHg</td>
</tr>
<tr>
<td>PT1</td>
<td>O₂ partial pressure at tissues</td>
<td>mmHg</td>
</tr>
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<td>PT2</td>
<td>CO₂ partial pressure at tissues</td>
<td>mmHg</td>
</tr>
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<td>PT3</td>
<td>N₂ partial pressure at tissues</td>
<td>mmHg</td>
</tr>
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<td>Venous partial pressure of O₂</td>
<td>mmHg</td>
</tr>
<tr>
<td>PV2</td>
<td>Venous partial pressure of CO₂</td>
<td>mmHg</td>
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<td>Venous partial pressure of N₂</td>
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<td>Partial pressure of O₂ entering brain</td>
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</tr>
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<td>Partial pressure of CO₂ entering brain</td>
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<tr>
<td>QD</td>
<td>Total cardiac output</td>
<td>liters/sec</td>
</tr>
<tr>
<td>QDB</td>
<td>Blood flow rate to brain</td>
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</tr>
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<td>Blood flow rate to brain due to O₂</td>
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<td>Blood flow rate to brain due to CO₂</td>
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<td>--------</td>
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<td>QDCS</td>
<td>Blood flow rate to central chemoreceptors</td>
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</tr>
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<td>QDP</td>
<td>Total blood flow rate per second</td>
<td>liters/sec/sec</td>
</tr>
<tr>
<td>PDDB</td>
<td>Brain blood flow rate per second</td>
<td>liters/sec/sec</td>
</tr>
<tr>
<td>QDL</td>
<td>Blood flow rate to lungs</td>
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</tr>
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<td>QDS</td>
<td>Shunted blood flow rate</td>
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<tr>
<td>QDT</td>
<td>Blood flow rate to tissues</td>
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</tr>
<tr>
<td>RFREQ</td>
<td>Respiratory frequency</td>
<td>breaths/sec</td>
</tr>
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<td>RQ</td>
<td>Respiratory quotient</td>
<td>Dimensionless</td>
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<td>Arterial solubility of O₂</td>
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<td>Arterial solubility of CO₂</td>
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<td>Arterial solubility of N₂</td>
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</tr>
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<td>O₂ solubility in brain</td>
<td>liters gas/literblood/ATM</td>
</tr>
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<td>SB2</td>
<td>CO₂ solubility in brain</td>
<td>liters gas/literblood/ATM</td>
</tr>
<tr>
<td>SB3</td>
<td>N₂ solubility in brain</td>
<td>liters gas/literblood/ATM</td>
</tr>
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<td>O₂ solubility at central site</td>
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</tr>
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<td>CO₂ solubility at central site</td>
<td>liters gas/literblood/ATM</td>
</tr>
<tr>
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<td>N₂ solubility at central site</td>
<td>liters gas/literblood/ATM</td>
</tr>
<tr>
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<td>O₂ solubility in CSF</td>
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</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
<td>Units</td>
</tr>
<tr>
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<td>-----------------------------------------------</td>
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</tr>
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<td>$CO_2$ solubility in CSF</td>
<td>liters gas/liter blood/ATM</td>
</tr>
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<td>$N_2$ solubility in CSF</td>
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<td>$O_2$ solubility in lungs</td>
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</tr>
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<td>$CO_2$ solubility in lungs</td>
<td>liters gas/liter blood/ATM</td>
</tr>
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<td>$N_2$ solubility in lungs</td>
<td>liters gas/liter blood/ATM</td>
</tr>
<tr>
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<td>$O_2$ solubility in tissues</td>
<td>liters gas/liter blood/ATM</td>
</tr>
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<td>ST2</td>
<td>$CO_2$ solubility in tissues</td>
<td>liters gas/liter blood/ATM</td>
</tr>
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<td>ST3</td>
<td>$N_2$ solubility in tissues</td>
<td>liters gas/liter blood/ATM</td>
</tr>
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<td>$O_2$ solubility in venous blood</td>
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</tr>
<tr>
<td>SV2</td>
<td>$CO_2$ solubility in venous blood</td>
<td>liters gas/liter blood/ATM</td>
</tr>
<tr>
<td>SV3</td>
<td>$N_2$ solubility in venous blood</td>
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</tr>
<tr>
<td>TB</td>
<td>Time constant for brain flow rate</td>
<td>seconds</td>
</tr>
<tr>
<td>TS</td>
<td>Time constant for cardiac output</td>
<td>seconds</td>
</tr>
<tr>
<td>TT</td>
<td>Time constant for tissue blood flow rate</td>
<td>seconds</td>
</tr>
<tr>
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<td>Ventilation due to $H^+$ at central site</td>
<td>liters/sec</td>
</tr>
<tr>
<td>VDAV</td>
<td>Alveolar ventilation rate</td>
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</tr>
<tr>
<td>VDDS</td>
<td>Dead space ventilation rate</td>
<td>liters/sec</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
<td>Units</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
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<tr>
<td>VDE</td>
<td>Exhaled ventilation rate</td>
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<tr>
<td>VDPL</td>
<td>Pulmonary ventilation rate</td>
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<td>Pulmonary ventilation due to O$_2$ at Peripheral Site</td>
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<td>Pulmonary ventilation due to H$^+$ at Peripheral Site</td>
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</tr>
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<td>Arterial volume from heart to brain</td>
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<td>VOLAV</td>
<td>Alveolar volume</td>
<td>liters</td>
</tr>
<tr>
<td>VOLAPS</td>
<td>Arterial volume from heart to Peripheral Site</td>
<td>liters</td>
</tr>
<tr>
<td>VOLATS</td>
<td>Arterial volume from heart to tissues</td>
<td>liters</td>
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<tr>
<td>VOLB</td>
<td>Volume of brain compartment</td>
<td>liters</td>
</tr>
<tr>
<td>VOLCF</td>
<td>Volume of cerebrospinal fluid compartment</td>
<td>liters</td>
</tr>
<tr>
<td>VOLDS</td>
<td>Volume of dead space in lungs</td>
<td>liters</td>
</tr>
<tr>
<td>VOLT</td>
<td>Volume of tissue compartment</td>
<td>liters</td>
</tr>
<tr>
<td>VOLTIO</td>
<td>Tidal volume</td>
<td>liters</td>
</tr>
<tr>
<td>VOLVB</td>
<td>Venous volume from brain to heart</td>
<td>liters</td>
</tr>
<tr>
<td>VOLVT</td>
<td>Venous volume from tissues to heart</td>
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</tr>
<tr>
<td>WAT</td>
<td>Percent arterial blood going to tissues</td>
<td>%/100</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Total weight of neonate</td>
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<tr>
<td>WCS4</td>
<td>Percent VDPL due to H$^+$ at Cerebrospinal Site</td>
<td>%/100</td>
</tr>
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<td>Definition</td>
<td>Units</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>WPS1</td>
<td>Percent VDPL due to O\textsubscript{2} at Peripheral Site</td>
<td>%/100</td>
</tr>
<tr>
<td>WPS4</td>
<td>Percent VDPL due to H\textsuperscript{+} at Peripheral Site</td>
<td>%/100</td>
</tr>
<tr>
<td>X1</td>
<td>Percent of O\textsubscript{2} in atmospheric air</td>
<td>%/100</td>
</tr>
<tr>
<td>X2</td>
<td>Percent of CO\textsubscript{2} in atmospheric air</td>
<td>%/100</td>
</tr>
<tr>
<td>X3</td>
<td>Percent of N\textsubscript{2} in atmospheric air</td>
<td>%/100</td>
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</table>
CHAPTER 1

INTRODUCTION

1.1 PURPOSE OF STUDY

The purpose of this study is to develop a digital computer simulation of the human neonatal cardiovascular and respiratory systems. The model simulates gas transfer in the lungs, transport of blood gases to the body via the circulatory system as well as the control of pulmonary and cardiovascular functions by the nervous system. This model represents the third in a series of neonatal simulations. The first model in this series is the analog computer model developed by MacIndoe and Robertshaw (1). This work was later expanded by Pabst and Robertshaw (2) who used a digital computer simulation. This third model is an attempt to improve on the work of Pabst and Robertshaw.

There are several reasons why a simulation of this nature is needed. The most important is that it could provide great insight into the methods by which the body controls the respiratory and cardiovascular systems. A computer is, in some sense, a "transparent" infant which can be observed and modified easily. The model could also be used to simulate neonatal respiratory diseases. Then, the effectiveness of various treatments could be evaluated. Another use of the model would be as a "dummy" patient.
which could be used to train doctors and nurses in infant care. Finally, the model could be used to simulate actual infants, using faster-than-real-time simulations, the progress of infant patients could be predicted.

1.2 REVIEW OF LITERATURE

Although cardiovascular and respiratory control have been studied for several centuries, only since the early 1950's have attempts been made to simulate these systems with computers. Earlier theories of cardiovascular and respiratory control, prior to 1950, have been discussed by both Pabst (2) and MacIndoe (1) and will not be discussed here.

Probably the first important simulation study was done by Grodins et al. (3) in 1954. He developed an analog simulation of the respiratory control mechanism. This model consisted of three physiologic compartments: Blood, tissues, and lungs. Ventilation was assumed to be a function of $P_{CO_2}$. In 1965, Milhorn et al. (4) developed a model of the respiratory system. It also had three physiologic compartments. Ventilation was assumed to be a function of $P_{O_2}$ and $P_{CO_2}$ at the peripheral chemoreceptors. The cardiac output was held constant. A major improvement occurred in 1967. A new model was developed by Grodins et al. (5). This model had four compartments: brain, lungs,
tissues, and cerebrospinal fluid. It also had a variable cardiac output. Ventilation was a function of hydrogen ion concentration in the cerebrospinal fluid compartment and peripheral chemoreceptors. In 1972, Milhorn (6) improved on Grodin's model. Milhorn developed an improved respiratory controller using the results of Mitchell (7) which showed a chemosensitive site in the medulla.

The first neonatal simulation was done by Robertshaw and MacIndoe (1) in 1973. It was an analog computer model with constant cardiac output. Ventilation was a function of \( \text{Po}_2 \) and \( \text{Pco}_2 \) at the peripheral chemoreceptors. In 1974, Robertshaw and Pabst (2) developed a digital simulation. It included six compartments: lungs, brain, tissues, muscles, heart, and cerebrospinal fluid. The model had a variable cardiac output, and ventilation was considered a function of hydrogen ion concentration at central chemoreceptors as well as \( \text{Po}_2 \) and \( \text{Pco}_2 \) at the peripheral chemoreceptors. This represents the most advanced neonatal simulation to date and it is the basis for much of the work done in this study.
CHAPTER 2

DEVELOPMENT OF PRESENT MODEL

2.1 BACKGROUND

The original developmental work on this model was done by Pabst and Robertshaw (2). The basic model developed by them remains the same, although major changes have been made in the dissociation relationships, time delays, blood buffer systems, the ability to simulate bicarbonate administration, as well as the addition of a rudimentary kidney.

The model is divided into five physiologic compartments: brain, lungs, heart, tissues, and cerebrospinal fluid compartment. A flow diagram for the model is shown in Figure 1. Gases are exchanged among these compartments as well as between the lungs and the atmosphere.

As can be seen in Figure 1, the heart compartment contains shunts. These are to model the flow of blood through the ductus arteriosus. This shunt allows blood to flow from the pulmonary artery to the aorta, bypassing the lungs. This is believed by some to be a major factor in infant respiratory distress (12).

2.2 PHYSIOLOGICAL NOTATION

In order to simplify the programming of this simulation a convenient method of naming physiologic variables is used in the model. Each variable is assigned a symbol. Each
FIGURE 1. FLOW DIAGRAM OF MODEL
symbol consists of not more than six characters, each of which has a function in identifying the variable. These characters do four things:

1. Classify the variable as a concentration, pressure, etc.
2. Tell whether it is a time derivative and/or time delayed.
3. Establish its location in the model.
4. Establish the species of gas or ion to which it applies.

Gas species and ions are signified by numbers, while derivatives and time delays are noted with letters according to the following key:

\[
\begin{align*}
o_2 & \quad 1 \\
c_{o_2} & \quad 2 \\
_n_2 & \quad 3 \\
_{h^+} & \quad 4 \\
_{hco_3^-} & \quad 5 \\
\text{Time Delay} & \quad Z \\
\text{First Derivative} & \quad D \\
\text{Second Derivative} & \quad DD
\end{align*}
\]

For example, the delayed arterial concentration of \(c_{o_2}\) at the brain is given by \(CZAB2\). Variables which are not gases or ions have been given names which are
descriptive. For example, the symbol representing respiratory frequency is "RFREQ".

2.3 ASSUMPTIONS

The neonatal cardiovascular and respiratory systems are, without a doubt, extremely complex. Any attempt to simulate them exactly as they are would result in a mathematical model that is so large and complicated that it would be extremely hard to understand and also to program. For these reasons several simplifying assumptions have been made. They make the derivation of equations easier and, hopefully, do not significantly affect the validity of the model. These assumptions are listed below.

1. The model is divided into five physiological compartments: the lungs, the brain, the heart, the tissues, and the cerebrospinal fluid compartment.

2. Atmospheric air consists of O$_2$, CO$_2$ and N$_2$ at BTPS.

3. Venous Po$_2$ and Pco$_2$ equal tissue PO$_2$ and PCO$_2$ respectively. This assumes that equilibrium occurs during capillary blood gas-tissue exchange.

4. The effects of temperature and neonate age on the oxygen-hemoglobin curve are ignored.

5. The arterial PO$_2$ of blood in the lungs is equal to the alveolar PO$_2$ times the permeability.

6. The arteries and veins have constant volume.

7. No storage of blood occurs in any compartment.
8. Blood flow at the central chemoreceptor site is equal to the cerebral blood flow.

9. Cardiac output is a function of arterial $\text{Po}_2$ and $\text{Pco}_2$. Cerebral blood flow is a function of arterial blood gas chemistry at the brain.

10. Not all of the blood leaving the right ventricle is oxygenated in the lungs. A certain portion of the blood is shunted away by the ductus arteriosus.

2.4 DERIVATION OF EQUATIONS

2.4.1 Mass Balance Equations

Three gas species, $\text{O}_2$, $\text{CO}_2$, and $\text{N}_2$ are considered in the model mass balance equations. The amount of any of these gases in any one compartment can be mathematically described by a first-order differential equation of the general form:

$$\frac{d}{dt} \text{mass of gas} = \text{mass flow of gas in} - \text{mass flow of gas out} + \text{gas exchanged via metabolism}. \quad (1)$$

The exact form of this equation will be different for each compartment because each exchanges gases differently.

The lung compartment exchanges gas with the atmosphere via respiration and also with blood brought in by the pulmonary circulation. For convenience, the mass balance is written in terms of volume rate of flow using the following relationship:
mass flow = volume flow x concentration x density. (2)

Combining this equation with equation 1 and cancelling the density which is constant at BTPS (body temperature, pressure, saturated with water vapor) yields:

\[
\frac{d}{dt} (\text{volume} \times \text{concentration}) = \\
((\text{volume in} \times \text{concentration in}) - \\
(\text{volume out} \times \text{concentration out})) + \\
(\text{volume of gas exchanged via metabolism}).
\] (3)

By making use of the fact that the partial pressure of a gas is proportional to its concentration in the alveoli and by considering the average alveolar volume to be constant, the mass balance equations for the lungs can be written as follows:

\[
P_{DAV} = \frac{(P_{ATM} \times Q_{DL} \times (C_{V} - C_{AL}) + V_{DAV} \times P_{I} - V_{DE} \times P_{AV})}{V_{OLAV}},
\] (L1)

where PDAV is the derivative of the gas partial pressure;
PATM is the atmospheric pressure;
QDL is the blood flow rate to the lungs;
CV is the gas concentration in venous blood;
CAL is the gas concentration in arterial blood;
VDAV is the alveolar ventilation rate;
PI is the partial pressure of gas in inspired air;
VDE is the exhaled ventilation rate;
PAV is the alveolar partial pressure of gas and;
VOLAV is the average alveolar volume.

This equation can be written for all three gas species
by placing the appropriate number at the end of each sym-
bol. The transfer of gas across the alveolar membrane is
modeled by assuming a permeability for each gas across the
membrane. This yields equations of the form:

\[ \text{PAL} = \text{DAV} \times \text{PAV}, \]  \hspace{1cm} (L2)

where \( \text{PAL} \) is the partial pressure of the gas in the
lung arteries;
\( \text{PAV} \) is the alveolar partial pressure and;
\( \text{DAV} \) is the diffusion coefficient.

The tissue compartment has mass balance equations which
are slightly different from the lung compartment. The
tissue compartment exchanges gas with blood flowing through
it. It also loses oxygen and gains carbon dioxide via
metabolism. These equations have the form:

\[ \text{CDT} = (\text{QDT} \times (\text{CZAT} - \text{CVT}) - \text{MRT})/\text{VOLT}; \]  \hspace{1cm} (T1)

where \( \text{CZAT} \) is the arterial concentration of gas;
\( \text{CVT} \) is the venous concentration of gas;
\( \text{QDT} \) is the tissue blood flow rate;
\( \text{MRT} \) is the gas exchanged by metabolism and;
VOLT is the tissue compartment volume.

This equation is the same for all three gas species.

The equations for the brain are similar except the brain also exchanges gas with the CSF compartment via diffusion. These equations have the form:

$$CDB = \frac{(QDB \times (CZAB - CVB) - MRB - DB \times (PB - PCF))}{VOLB},$$

where

- DB is the brain-CSF diffusion constant;
- PB is the brain gas partial pressure;
- PCF is the CSF gas partial pressure and;
- VOLB is the volume of the brain compartment.

The mass balance equations for the CSF and the heart are somewhat different. The CSF compartment exchanges gas only through diffusion of gas to and from the brain. The partial pressure of gas in the CSF is given by:

$$PCF = \int PDCF \, dt,$$

where

- PDCF is the derivative of the partial pressure given by an equation developed by Grodins (5).

$$PDCF = \frac{DB}{(VOLCF \times SCF)} \times (PB - PCF);$$

where

- DB is the brain-CSF diffusion constant;
- VOLCF is the volume of the CSF compartment;
SCF is the solubility of the gas in cerebrospinal fluid and;
PB is the partial pressure in the brain.

The heart compartment is divided into two parts. The right heart receives blood returning from the brain and tissues, and the left heart receives blood from the lungs and the fetal shunting pathways. The concentration of gases in the right heart is determined by the mixing of blood returning from the various compartments. It is given by the equation:

\[ CV = \frac{(QDB \times CZVB + QDT \times CZVT)}{QD}. \quad (H1) \]

QDB and QDT are the blood flows from the brain and tissues respectively. CZVB and CZVT are the concentrations of gas in these flows.

The blood flows from the right heart to the left heart through both the lungs and the shunts. The concentration of gases in the left heart is determined by the mixing of these flows:

\[ CA = \frac{(QDL \times CAL + QDS \times CV)}{QD}. \quad (H2) \]

The equations, of course, are written for all three species of gas. QDS is the blood flow shunted by the ductus arteriosus and the foramen ovale. It is estimated as a function of arterial $O_2$ tension. It is given by the equation:
\[ Q_{DS} = \int \frac{QD (WSHUNT)}{TS} - QD \, dt, \quad \text{(H3)} \]

where
- \( Q_{DS} \) is the shunted blood flow;
- \( QD \) is the total cardiac output;
- \( TS \) is a time constant and;
- \( WSHUNT \) is the percent shunt weighing factor given by:

\[ WSHUNT = \frac{(60 - 1.054595(PV1 - 25))/100}{2 \leq WSHUNT \leq 60} \quad \text{(H4)} \]

### 2.4.2 Dissociation Relationships

The concentration of a gas in any location is given by the mass balance equations. However, it is necessary to know the partial pressure of \( O_2 \) and \( CO_2 \) at several places in the model to drive control equations and to determine gas transfer from tissues to venous blood. The concentration of a gas is related to its partial pressure by a dissociation relationship. An important aspect of this work is the development of more realistic representations of the dissociation of the various gases in the blood and tissues. The dissociation relationship for \( CO_2 \) which was used by Pabst and Robertshaw (2) has several inadequacies. It's major fault is that it does not take into account the Haldane effect, which is explained later in this section.
It also assumes that the blood is a simple buffer system which can be described by the Henderson-Hasselbach equation. The new dissociation relationship takes into account the Haldane effect and has a more complex buffer system. The relationship used were developed by Grodins (5).

2.4.2.1 Oxygen Dissociation Relationship

Oxygen is transported by the blood in two ways, dissolved in the plasma and bound with hemoglobin. The $O_2$ dissociation relationship used in this model is basically Hill's equation as given by Altman (8) which has been modified for neonatal blood. The $O_2$ concentration is given by:

$$ C_l = C_{AP} \times A \times S_l \times P_l , \text{ with} \quad (D_1) $$

$$ A = \left( \frac{P_l}{186.76 - 22.4 \times P_H} \right)^{2.5} $$

where

- $P_l$ is the $O_2$ partial pressure;
- $P_H$ is the pH of the blood;
- $C_{AP}$ is the $O_2$ transport capacity of hemoglobin;
- $S_l$ is the blood $O_2$ solubility and;
- $P_{ATM}$ is the atmospheric pressure.

The $O_2$ dissociation relationship is shown graphically in Figure 2. This relationship is used to describe $O_2$
FIGURE 2. INFANT BLOOD OXYGEN DISSOCIATION CURVE
dissociation in the blood throughout the model. Inside the tissue and brain compartments, where no hemoglobin is present, the $O_2$ dissociation is represented by a linear relationship given by:

$$P_l = \frac{P_{ATM}}{S_l} \times C_l,$$

where $S_l$ is the $O_2$ solubility in the appropriate compartment.

2.4.2.2 CO$_2$ Dissociation Relationship

Carbon dioxide is transported in several ways. Most of the CO$_2$ is present as bicarbonate ions in the erythrocytes and plasma. A smaller, but still significant fraction of CO$_2$ combines with hemoglobin to form carbamino-hemoglobin compounds in the erythrocytes. A very small amount remains dissolved in the erythrocytes and plasma and a very small amount forms carbamino compounds with plasma proteins.

The amount of CO$_2$ that combines with hemoglobin is dependent upon the extent of oxygenation of the hemoglobin. This is known as the Haldane effect. The more oxygenated the hemoglobin is, the less CO$_2$ it can carry. This effect is taken into account in the new CO$_2$ dissociation relationship.

Since most of the CO$_2$ in the blood is present as bicarbonate ions, it is evident that the bicarbonate content of
the blood is a big factor in the CO₂ dissociation relationship. Carbon dioxide forms bicarbonate ions through the following series of reactions: first, the CO₂ is hydrated to form carbonic acid,

\[ \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3. \]

The carbonic acid then ionizes to form hydrogen ions and bicarbonate ions,

\[ \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+. \]

The majority of CO₂ undergoes this reaction inside the erythrocytes. These two reactions proceed because most of the bicarbonate ions formed in the erythrocytes diffuses out into the plasma and the accompanying hydrogen ions are taken up by hemoglobin according to the reaction:

\[ \text{H}^+ + \text{Hb}^- \rightleftharpoons \text{HHb}. \]

The dissociation relationship used by Pabst and Robertshaw (2) was obtained from data gathered by Smith (9). It is given by:

\[ \text{C}_2 = 0.04161 \times \text{P}_2^{0.6156}, \]

where \( \text{C}_2 \) is the CO₂ content in liters gas/liter blood and;

\( \text{P}_2 \) is the partial pressure of CO₂.
It is simply a mathematical representation of a typical neonatal CO$_2$ dissociation curve.

The dissociation relationship presently used in the model was developed by Grodins in 1967 (5). To define the concentration of CO$_2$ in the blood, Grodins gives the following equation:

\[
C_2 = \text{CARB} + 0.375(CA_1 + CAHBO2) - (0.16 + 2.3 \times CA_1) \times \log \frac{C_2 - K \times S_2 \times P_2}{0.01 \times P_2} - 0.14 + K \times SA_2 \times P_2.
\]

This equation assumes that the CO$_2$ carried by the blood is either combined in bicarbonate ions or protein or dissolved. The first three terms of the equation,

\[
\text{CARB} + 0.375 \times (CA_1 - CAHBO2) - (0.16 + 2.3 \times CA_1) \times \log \frac{C_2 - K \times S_2 \times P_2}{0.01 \times P_2} - 0.14,
\]

represent the combined CO$_2$. The combined CO$_2$ is a linear function of pH. "CARB" is the bicarbonate ion concentration, which includes natural bicarbonate plus any administered during treatment of the infant. The second term represents the "hemoglobin unsaturation". It is given by:

\[
.0375 \times (CA_1 - CAHBO2),
\]

where $CA_1$ is the blood oxygen capacity and;

$CAHBO2$ is the concentration of oxyhemoglobin.
These first terms determine the intercept of the linear relationship. The slope is determined by the term:

\[(0.16 + 2.3 \text{ CAP1})\]

The constant 0.16 represents the concentration of plasma protein. The term given by:

\[\log \frac{C2 - K \times S2 \times P2}{0.01 \times P2} - 0.14,\]

is actually the term \((\text{PH} - 7.41)\) where the \text{pH} is given by the Henderson-Hasselbach equation. The last term, \(K \times S2 \times P2\), represents \(\text{CO}_2\) dissolved in the blood. Where \(S2\) is the \(\text{CO}_2\) solubility and \(K\) is a conversion factor to convert atmospheres to \(\text{mmHg}\).

Typical \(\text{CO}_2\) dissociation curves are shown in Figure 3. This relationship is used for \(\text{CO}_2\) dissociation in the blood. Inside the tissue, brain and CSF compartments there is no hemoglobin to affect the \(\text{CO}_2\) dissociation. In these compartments an equation similar to this but without hemoglobin effects is used.
FIGURE 3. INFANT CO₂ DISSOCIATION RELATIONSHIP

\[
\begin{align*}
\text{\(C_{\text{CO}_2}\)} & \text{ (liters gas/liter blood)} \\
\text{\(P_{\text{CO}_2}\)} & \text{ (mmHg)}
\end{align*}
\]

\[
\begin{align*}
\text{\(\text{pH} = 6.8\)} \\
\text{\(\text{pH} = 7.7\)} \\
\text{\(P_{\text{O}_2} = 60 \text{ mmHg}\)}
\end{align*}
\]
2.5 TIME DELAY EQUATIONS

2.5.1 Background

Within the model it is necessary to simulate the transport of certain quantities from one point in the body to another via blood flow. For example, the arterial CO$_2$ at the brain is actually that which has been transported there by blood flow from the heart.

It is evident that the speed of transport of these substances will depend on the cardiac output as well as the distance between the sites. In the first neonate model (1) this was simulated by using a constant time delay, e.g., the concentration of CO$_2$ in the brain at time $t$ was equal to the concentration of CO$_2$ leaving the heart at time $t - \tau$, where $\tau$ is an appropriate time delay based on an average blood flow to the brain and an estimate of the volume of the arteries connecting the heart and brain. While this method was simple, it could not account for the changes in cardiac output. This is necessary for an accurate simulation of the actual process since cardiac output does vary significantly.

The model developed by Robertshaw and Pabst (2) contained a variable time delay. This time delay was extremely complex and increased the time requirements of the simulation greatly. There is also some indication that this time delay was not functioning properly. An effort was made to
develop a variable time delay which would not increase the simulation time by a great deal.

2.5.2 Development of Present Time Delay

The present time delay is simple in principle. It is capable of simulating the transport of six different parameters between five physiological compartment sites in the body. To simplify the procedure it is assumed that the compartments are connected by only one blood vessel. This vessel is assumed to have a constant volume equal to the total volume of all the vessels involved in the transport. For example, the vessel or pipe from the heart to the brain would have a volume equal to the total volume of all the arteries connecting the two sites. The pipe going from the brain back to the heart would have a volume equal to the total volume of the veins connecting the two sites.

To simplify the explanation of the time delay, refer to the schematic diagram in Figure 4. Each pipe is divided into segments. When the simulation begins (time equals zero) all but one of these segments has a volume which is equal to the initial cardiac output multiplied by the integration time step. The pipe is divided into as many segments with this volume as possible. Any remaining volume becomes the first segment.

When time equals zero, the value of each parameter to be transported through the pipe is the same in all segments
FIGURE 4a. SCHEMATIC DIAGRAM OF HEART - BRAIN TIME DELAY

FIGURE 4b. HEART - BRAIN TIME DELAY AFTER ONE INTEGRATION STEP
and equal to a specified initial value. During each integration step more blood enters the pipe in the form of a new segment. It enters the pipe in front of the first segment. Its volume is equal to the current cardiac output multiplied by the integration step size. The values of parameters in this segment are equal to the current values in the compartment from which the flow originates. Since the volume of the pipe remains constant the same amount of blood must go out the other end of the pipe. Segments are pushed out the end of the pipe until their total volume pushed out equals the volume which entered the pipe. The value of the parameter coming out of the pipe is a weighted average of the parameter in each segment pushed out. For example, the volume of parameter 'A' coming out of the pipe in Figure 4b is computed in the following manner. The value of 'A' in segment 7 is multiplied by the ratio of the volume of segment 7 pushed out to the total volume pushed out. This is added to the product of the value of 'A' in segment 8 and the ratio of the volume of segment 8 to the total volume pushed out.

With each new integration step, a new segment is added to the pipe. All of the segments already inside the pipe are pushed farther along and more segments are pushed out. In this manner the segments march along the pipe and emerge at some time later. The time it takes for the blood to
flow through the pipe is determined by the cardiac output.

2.5.3 Evaluation and Verification

This is a rather simple representation of the transport process. It does not take into account any mixing of the parameters between the segments while they are inside the pipe. While this would make a more realistic simulation, this extra computing time needed to accurately simulate this mixing would probably offset any benefits derived from it. The time delay does provide an accurate representation of the time required for the blood to flow from one site to another.

Large variations in cardiac output and/or integration step size can cause problems with the time delay subroutine. A combination of a small integration step and a very small cardiac output results in a very large number of segments in each pipe. If this number is large enough, the allocated computer storage space for the simulation may be exceeded. Also a combination of a large step size and a large cardiac output could result in a segment being added which has a volume greater than the pipe. The time delay subroutine is unable to handle this occurrence.

In order to verify the time delay subroutine, it was programmed separately and tested. Typical values of cardiac
output and integration step size were chosen and several parameters were sent through the pipes. Figure 5 shows the results of one of these tests. It shows the flow of arterial oxygen through the pipe connecting the heart to the brain.

2.6 CONTROLLERS

2.6.1 Introduction

In order to complete the system of equations it is necessary to provide for the control of cardiac output and respiration. The equations used in this model to define the control of these functions are basically adaptations of these found in the recent research of Grodins and Milhorn.

2.6.2 Control of Cardiac Output

In this simulation, the cardiac output is based on the demand for blood of the tissues and the brain.

The cardiac output is given by the equation:

\[ Q_D = Q_{DB} + Q_{DT}, \]  \hspace{1cm} (H4)

where

- \( Q_{DB} \) is the blood flow to the brain and;
- \( Q_{DT} \) is the blood flow to the tissues.

\( Q_{DB} \), the blood flow to the brain, is a function of the \( O_2 \) and \( CO_2 \) partial pressures entering the brain compartment.
Figure 5: Time Delay Tests
It is given by:

\[ QDB = \int \frac{((ICQDB + QDB1 + QDB2 - QDB)/TB)\,dT}{(ICQDB + QDB1 + QDB2)/TB} \]  

(B2)

if \( QDB > 0.00467 \), \( QDB = 0.00467 \),

where

- \( ICQDB \) is the normal blood flow;
- \( QDB1 \) is the blood flow caused by \( O_2 \) tension;
- \( QDB2 \) is the blood flow caused by \( CO_2 \) tension and
- \( TB \) is a time delay.

The second equation serves to realistically limit the brain blood flow. \( QDB1 \) is defined by the following equations:

\[ QDB1 = 0.0 \quad \text{if} \quad PZAB1 \geq 100 \]  

(B3)

\[ QDB1 = 6.191(10^{-3}) - 2.941(10^{-4}) PZAB1 + 5.7869(10^{-6}) \times \]

\[ PZAB1^2 - 5.1663(10^{-8}) PZAB1^3 + 1.7019(10^{-10}) \times \]

\[ PZAB1^4 \quad \text{if} \quad PZAB1 < 100. \]  

(B4)

\( QDB2 \) is given by:

\[ QDB2 = 5.164(10^{-5}) - 6.9075(10^{-5}) PZAB2 + \]

\[ 1.782(10^{-6}) PZAB2^2 \quad \text{if} \quad PZAB2 < 38.0 \]

\[ QDB2 = 0.0 \quad \text{if} \quad 38.0 \leq PZAB2 \leq 44.0 \]

\[ QDB2 = -3.4634(10^{-2}) + 1.691(10^{-3}) PZAB2 - \]

\[ 2.878(10^{-5}) PZAB2^2 + 2.0878(10^{-7}) PZAB2^3 - \]

\[ 4.8346(10^{-10}) PZAB2^4 \quad \text{if} \quad PZAB2 > 44.0. \]  

(B5)
TB is a constant time delay. It is necessary to simulate the physiological reaction time associated with changes in flow. The brain blood flow equations are basically those of Grodins (5), modified for neonates.

QDT is a function of local $O_2$ tension. It is given by:

\[
QDT = \frac{(QDTI - QDT)}{TT}dT \tag{T2}
\]

if $QDT > 0.00933$, $QDT = 0.00933$

if $QDT < 0.0045$, $QDT = 0.0045$.

where $QDTI$ is given by:

\[
QDTI = 9.6092E-3 + 3.5E-3 \times (47.65 - PTI). \tag{T3}
\]

This differs from the controller used by Pabst and Robertshaw (2) in that a minimum and maximum blood flow has been added. The original controller provided no blood flow when tissue oxygen tension was greater than 47.65 mmHg. To be realistic, a minimum blood flow of 0.0045 liters/sec was added. Also, a physiologically reasonable upper limit of 0.00933 was established. These values were estimated from data given by Smith (9).

2.6.3 Ventilation Control

Ventilation is considered to be a function of hydrogen ion concentration at the central and peripheral chemoreceptors and oxygen concentration at the peripheral
chemoreceptors. The pulmonary ventilation equations used are similar in form to those of Milhorn (6).

The pulmonary ventilation is given by:

\[ V_{DPL} = W_{CS4} \times V_{DCS4} + W_{PS4} \times V_{DPS4} + W_{PS1} \times V_{DPS1} \quad (L3) \]

where \( W_{CS4}, W_{PS4}, \) and \( W_{PS1} \) are weighting factors;

- \( V_{DCS4} \) is the contribution of H+ at the central site;
- \( V_{DPS4} \) is the contribution of H+ at the peripheral site and;
- \( V_{DPS1} \) is the contribution of O_2 tension at the peripheral site.

\( V_{DCS4} \) is given by the equations:

\[
V_{DCS4} = \begin{cases} 
1.0E6 \times (CCS4 - 3.775E-8) & \text{if } CCS4 > 3.9688E-8 \\
7.5E5 \times (CCS4 - 3.685E-8) & \text{if } CCS4 \leq 3.9688E-8 
\end{cases} 
\]

\[ \text{if } V_{DCS4} < 0.0, V_{DCS4} = 0.0. \quad (L4) \]

The central chemoreceptors are located in the area lateralis in the medulla. They are responsive to changes in the H+ concentration in the cerebrospinal fluid compartment. The H+ concentration at the central site, \( CCS4 \), is given by:

\[ CCS4 = \exp \left( (-2.303) \times PHCS \right) \]  
\[ \text{ (B5) } \]
PHPS is the pH at the central site. It is a function of the CO₂ and O₂ tensions in the cerebrospinal fluid. The pH is found using an iteration scheme similar to the one described in the section on the dissociation relationships with the hemoglobin effects removed because there is no hemoglobin at the central site. The CO₂ tension at the central site, PCS₂, is defined by an equation developed by Mitchell et al. (10).

\[
\text{PCS}_2 = \text{PB}_2 + (\text{PCF}_2 - \text{PB}_2) \exp \left(\left(-280 \times 10^{-6}\right) \left(\text{QDC}_2 \times \text{L}_2 \times \frac{\text{PATM}}{\text{DB}_2}\right)^{\frac{1}{2}}\right)
\]

(B6)

280 x 10⁶ is the distance in microns from the brain-CSF interface to the area lateralis.
L₂ is the slope of the CO₂ solubility curve.
DB₂ is the brain-CSF diffusion constant for CO₂.
PB₂ is the CO₂ tension in the brain.
PCF₂ is the CO₂ tension in the CSF.
QDC₂ is the blood flow to the central site.

VDPS₄ is the contribution of the H⁺ concentration at the peripheral site. It is given by:

\[
\text{VDPS}_4 = 1.0 \times 10^6 \times (\text{CPS}_4 - 3.387 \times 10^{-8})
\]

if \( \text{VDPS}_4 < 0.0 \) \( \text{VDPS}_4 = 0.0 \) (P1)
The peripheral "site" is located in the aortic arch and at the bifurcation of the cartoid arteries. CPS4 is given by:

\[ CPS4 = \text{EXP} (-2.303 \times \text{PHPS}) \]  

(P2)

PHPS is the delayed value of the pH leaving the left heart. 

VDPSl is given by:

\[ VDPS1 = 0.002083 (60 - \text{PPS1}) \quad \text{if} \quad \text{PPS1} \leq 60 \]

\[ VDPS1 = 0.0 \quad \text{if} \quad \text{PPS1} > 60. \]  

(P3)

Once pulmonary ventilation is known, alveolar ventilation is defined by the relationship

\[ VDAV = VDPL - \text{RFREQ} (\text{VOLDS}). \]  

(L5)

where  

\text{RFREQ} is the respiratory frequency and; 

\text{VOLDS} is the respiratory deadspace.

Respiratory frequency is defined by:

\[ \text{RFREQ} = \frac{VDPL}{\text{VOLTID}}, \]

if  

\[ \text{RFREQ} > 1.72 \quad \text{RFREQ} = 1.72. \]  

(L6)

The equations defining VOLTID and VOLDS were obtained from Milhorn (6) and modified for neonatal physiology. These expressions are:
VOLTID = 0.015 - 1.351857 (0.0083 - VDPL) \hspace{1cm} (L7)

VOLDS = 0.005 - 0.4333198 (0.015 - VOLTID). \hspace{1cm} (L8)

The exhaled ventilation rate, VDE, is given by:

\[
VDE = VDAV + QDL \left( (CV2 - CAL2) + (CV1 - CAL1) + (CV3 - CAL3) \right) / 0.938. \hspace{1cm} (L9)
\]

QDL is the lung blood flow given by:

\[
QDL = QD - QDS, \hspace{1cm} (L10)
\]

where QDS is the blood flow through the shunt.
CHAPTER 3

BICARBONATE ADMINISTRATION

One of the most important treatments used on infants with respiratory distress is the administration of sodium bicarbonate (NaHCO₃). The NaHCO₃ dissociates to form bicarbonate ions (HCO₃⁻) and sodium ions (Na⁺). Most of the CO₂ carried by the blood is in the form of bicarbonate ions (11). So, increasing the concentrations of bicarbonate is equivalent to increasing CO₂ concentration. This increase in CO₂ concentration will, because of the Bohr effect, facilitate release of O₂ at the tissues. In addition the increase in HCO₃⁻ will raise the pH.

Because of the advanced dissociation relationships in this model, it is possible to simulate the administration of NaHCO₃. To model this treatment, it is assumed that the NaHCO₃ dissociates completely to Na⁺ and HCO₃⁻. Recalling from the section explaining the dissociation relationships, the concentration of CO₂ is the sum of the CO₂ combined as bicarbonate, and the dissolved CO₂. The combined CO₂ is a function of pH and is given by a relationship of the form

\[ \text{BHCO}_3 = (\text{BHCO}_3)_b + A - B \ (pH - 7.41) \]

\((\text{BHCO}_3)_b\) is the bicarbonate concentration at \(pH = 7.4\).
A & B are functions of the hemoglobin saturation.

The bicarbonate administered to the infant is added directly to the first term of this equation. In the simulation this term appears as the variable 'CARB'. It represents the bicarbonate concentration at pH = 7.4 plus any bicarbonate which has been added. The equation for the concentration of CO$_2$ takes the form:

$$\text{C}_2 - \text{CARB} + A + B \times (\text{PH} - 7.41) + K \times \text{SA2} \times \text{P2}.$$

where $K$ and $\text{SA2}$ are constants and;

$\text{P2}$ is the CO$_2$ tension.

The effect of the bicarbonate on pH is also taken into account because the pH is given by:

$$\text{pH} - \text{pK} + \log \frac{\text{C}_2 - K \times \text{SA2} \times \text{P2}}{K \times \text{SA2} \times \text{P2}}$$

and C2 has administered bicarbonate included in it.

The bicarbonate is assumed to be added into the left ventricle. This is because HCO$_3^-$ is mostly administered via intravenous drip into the umbilical artery. The added HCO$_3^-$ is carried via time delays to various other compartments. From the hospital records it is possible to obtain a time schedule of the bicarbonate administration. Thus, flow rates and concentrations of HCO$_3^-$ throughout the treatment of the infant can be modeled.
In simulations of several hours it was found that the bicarbonate concentration increased above reasonable levels. This was due to the lack of a kidney compartment in the model to filter the blood. To correct this a rudimentary kidney was added to filter only bicarbonate. This kidney is located in the tissue compartment and filters blood flowing from the tissues to the heart. The kidney lowers bicarbonate concentration that is too high by the following equation.

\[ CK5 = CB + M \times (CZAK5 - CB) \]  \hspace{1cm} (K1)

where

- CK5 is bicarbonate concentration leaving kidney;
- CB is the normal bicarbonate concentration and;
- M is a constant \( < 1.0 \) and;
- CZAK5 is the bicarbonate concentration entering the kidney.

This was developed using the assumption that the kidney will try to keep bicarbonate level near normal. The constant 'CB' which represents the normal bicarbonate level was estimated from data given by Grodins (5).
CHAPTER 4

INFANT SIMULATIONS

4.1 INTRODUCTION

For a model of this nature to be useful it must be able to accurately simulate the behavior of an actual infant's physiological systems. Such a simulation was attempted with this model. The success of the simulation was determined by the extent the model could match certain infant variables available from clinical data.

Actual clinical data was available from hospital records of an infant that was treated for respiratory distress. For identification purposes the infant shall be known as baby "A". Baby "A" was born with Pulmonary Hyaline Membrane Disease. The baby underwent ventilation therapy for nine hours using an Arp Infant Respirator. It was also treated with periodic infusion of sodium bicarbonate to regulate blood gas chemistry. During this period, the infant's venous $P_0^2$, $P_{CO_2}$, and pH were monitored, providing the data to which the model was compared.

A six hour simulation was attempted. The gas concentrations provided by the respirator and the sodium bicarbonate administration were both simulated. To make the model accurately simulate baby 'A' three parameters, metabolic rate, alveolar permeability,
and kidney effectiveness were adjusted until the model most closely matched the actual data.

4.2 RESULTS

The success of the simulation was evaluated by comparing simulated values of three variables, PV1, PV2, and PHV with the actual values measured during the treatment of the infant. During the time of the infants life simulated by the model, actual data was taken four times. This gives four values of each variable to compare with the model. The simulated time histories of each variable are shown in Figures 6, 7, 8.

Figure 6 shows the history of PV1. In order to achieve the high values of venous P02 measured in baby 'A', the alveoli were made completely permeable to O2 and the metabolic rate was lowered to 2.5 ml/min-kg (compared to a normal value of 6.6 ml/min-kg). From figure 6 it is evident that the model had some difficulty in simulating the venous P02 of the infant. The model reaches a high value of PV1, 232 mmHg, quickly and remains relatively constant at that value for 6000 seconds. This puts the simulated PV1 considerably higher than the first actual value of 110 mmHg. At 9200 seconds the simulated PV1 drops abruptly from 232 mmHg to 167 mmHg. This is evidently due to a decrease in the concentration of inspired O2 which occurs at 9200 seconds. The simulated PV1 then
FIGURE 6. GRAPH OF ACTUAL AND SIMULATED PV1
FIGURE 7. GRAPH OF ACTUAL AND SIMULATED PV2
FIGURE 8. GRAPH OF ACTUAL AND SIMULATED PHV
remains constant at 167 mmHg until 14600 seconds where it drops abruptly to 105 mmHg then remains relatively constant at about 110 mmHg for the remainder of the simulation. The second drop is also in response to a decrease in concentration of inspired $O_2$ occurring at 14600 seconds. As a result of these responses, the simulated values of PV1 are lower than the last three actual values. At 11600 seconds baby A's PV1 is 270 mmHg while the simulated PV1 is 169 mmHg. This represents -37% error. At 14600 seconds the actual PV1 is 200 mmHg. The simulated PV1 is 167 mmHg for a -16.5% error. At 21800 seconds baby A has a PV1 of 187 mmHg; the simulated PV1 is 97.0 mmHg, resulting in a 98% error.

Although the simulated PV1 behaves predictably it does not duplicate the actual values. It does, however, seem to match the general trends of the actual data in the latter half of the simulation. This can be explained by considering the representation of alveolar premeability in the model. The permeability of the alveoli to $O_2$ and $CO_2$ in the model is considered constant. Its value was adjusted at the start of the simulation to give the best results. For the simulation attempted, the alveoli were made completely permeable to $O_2$ in order to obtain the high values of PV1 exhibited in the middle of the simulation. This is not accurate when simulating an infant with
Respiratory Distress Syndrome. Such an infant would initially have impaired alveolar permeability which, with successful treatment, would approach normal values.

The simulation of PV2 is shown in figure 7. The model seems to simulate PV2 more accurately than PV1. The simulated value of PV2 remains relatively constant around 29 mmHg throughout the course of the simulation. This results in an error of only 2.5% at the first actual value. At 11600 seconds the actual PV2 is 21.5 mmHg and the resulting error is 28.2%. At 14600 seconds the error is again low at -8.1% and at 21900 seconds the error is 5.4%. Except for the low values occurring around 11000 seconds the model follows the infants PV2 quite closely.

Like PV2, the simulated values of PHV are close to the actual ones. At 3800 seconds the actual PHV is 7.25 and the simulated value is 7.27 giving an error of +.27%. At 11600 seconds, the actual value is 7.34. The simulated value is 7.33 or -.13% error. At 14600 seconds the error is -.54%, and at 21800 seconds the error is only -.12%. At all points the model is in good agreement with the actual data.

The results of the simulation represent a significant improvement over the simulation attempts of Pabst and Robertshaw (2). They also attempted to simulate baby 'A'. Their attempts to simulate PV1 resulted in errors ranging
from 60% to 80% when compared to the actual values. The error in simulating PV1 with the present model ranged from -16.5% to 111%. Improvement can be seen in the simulation of PV2. The results of Pabst and Robertshaw show a minimum error of about 12% and a maximum of 60%. The maximum error in the present simulation was 28% while all other error measurements were less than 10%. The error values in simulating PHV of Pabst and Robertshaw were within ±1%. Values for the model were within .5%, so a slight improvement can be seen here.

A comparison of this model with the analog model MacIndoe and Robertshaw (1) reveals some interesting things. The present model compares well to that of MacIndoe and Robertshaw in its ability to simulate venous CO2. They, however, had much better results in simulating venous O2. A major difference in the two models is the ability of MacIndoe and Robertshaw to vary permeability during the course of the simulation. This suggests that an ability to simulate variable permeability would improve the models' ability to simulate PV1.

This simulation seems to be an improvement over previous attempts to simulate neonates. The model fails to simulate accurately the infant's venous oxygen behavior. This is probably due to the inability to model the variability of alveolar permeability to oxygen. The model does
seem to accurately simulate the behavior of venous $P_{CO_2}$ and pH. This seems to indicate that the factors that have the greatest effect on these variables, namely $CO_2$ dissociation and blood bicarbonate level have been accurately represented in the model.
CHAPTER 5

CONCLUSIONS

Several important modifications have been made in the model of Pabst and Robertshaw (2). By far the most important change is the improvement of the CO$_2$ dissociation curve in both the blood and tissues. The new dissociation relationship contains a more complex and realistic buffer system. It includes both bicarbonate and protein buffers and is able to simulate the Haldane effect. With this new dissociation relationship it is possible to model the effects of sodium bicarbonate infusion often used in treatment of infants with respiratory distress. In conjunction, sodium bicarbonate infusion was simulated during the modeling of baby "A". Another modification is the addition of a rudimentary kidney. This kidney models the renal effects on bicarbonate levels in the blood. Changes have also been made in the cardiac and ventilatory controllers. The tissue blood flow controller was changed so that at higher levels of PTl, a base rate of blood flow was provided. The controller used by Pabst and Robertshaw would shut off blood flow completely at values of PTl greater than 43.65 mmHg. This prevented the venous O$_2$ levels from reaching the high levels required to simulate baby "A". The ventilation controller was changed to allow the model
to simulate pH values exhibited by baby "A". The changes consist of shifting the curves so normal ventilation occurs at pH of 7.4 and lower the slope of the curves so less ventilation occurs at low values of pH.

In addition, two changes were made to simplify the model. The time delay used by Pabst and Robertshaw was replaced with one much simpler but equally effective. Also, the muscles were removed as a separated compartment and included in the lumped tissue compartment.

Several minor changes were also made. Physiologically realistic limits were placed on cardiac output and ventilation. The initial conditions of the variables were adjusted to more realistic values.

The results of the baby "A" simulation show that the model is only partially successful in simulating the infant. It is evident, from these results, that the additions and modifications listed above have resulted in a model that is better able to simulate baby "A" than its predecessor, the model developed by Pabst and Robertshaw (2). However, any attempt to evaluate the ability of this model to simulate neonates other than baby "A" would be speculation. Many more infant simulations should be attempted in order to accurately evaluate the model. The simulation of baby "A" does suggest that, while the model is an improvement over previous attempts, it still has deficiencies which
prevent it from accurately modeling the neonatal respiratory and circulatory systems.
CHAPTER 6

RECOMMENDATIONS

The results of the infant simulation reveals several areas in which improvement can be made. These involve both the physiological aspects of the model as well as the programming aspects. These recommendations are listed below.

1. An accurate modeling of the tissue blood flow control must be added. The simulation reveals that the present controller is not active at the high levels of $P_{O_2}$ experienced, providing only a constant minimum level of blood flow throughout the course of the simulation.

2. An improved renal system must be added. The simulation of the bicarbonate injections indicates that modeling of the kidney is necessary. The present representation is extremely rudimentary and possibly inaccurate.

3. The simulation shows that constant alveolar membrane permeabilities are inadequate. The ability to model changes in permeability would be a big improvement.
4. The present simulation of the metabolic functions is poor. Improvements can be made especially accounting for temperature effects.

5. Modifications in the time relay should be made. These should include adapting it to handle variable STEP integration routines and low levels of cardiac output. This would result in a better simulation time to real time ratio.

6. More data from actual infants must be obtained so that a complete evaluation of the model can be made.
REFERENCES


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AN IMPROVED SIMULATION OF THE HUMAN RESPIRATORY SYSTEM

CONTAINS THE FOLLOWING LIMITS:

- NEW O2 DISSOCIATION RELATIONSHIPS,
- UPDATED INITIAL CONDITIONS, NEW PIPE FUNCTION,
- KIDNEY, AND BICARBONATE INFUSION.
**TIME DELAY**

**MACRO**

\[ C_Z = \text{DEP}(V_{PA}, r, \text{Com}, V_J, K, \text{TE}, G, \text{LT}) \]

\[ C_Z = \text{DIP}(V_{PA}, r, \text{Com}, V_J, K, \text{TE}, G, \text{LT}) \]

**END MACRO**

---

**INVERSE DISSOCIATION CURVE FOR CO2 IN THE BRAIN AND TISSUES**

**MACRO**

\[ P_{O_2} = \text{POC}(C_{O_2}) \]

\[ \phi_2 = \text{NEP}(P_{\text{C1A3}}, C_{O_2}) \]

**END MACRO**

---

**DISSOCIATION CURVE FOR CO2 IN THE BRAIN AND TISSUES**

**MACRO**

\[ C_{S_2}, P_{O_2} = \text{DSC}(P_{S_2}, C_{S_2}, C_{S_2}) \]

\[ A = K_{S_2} \]

\[ C_{S_2} = \text{KFS}(C_{T_{A3}}, P_{S_2}) \]

\[ C_{O_2} = K_{S_2}((A+P_{S_2})/(C_{S_2}-A+P_{S_2})) \]

\[ P_{\phi_2} = 9.3 - 0.6 \log_{10}(A_{\phi_2}) \]

**END MACRO**
MACRO C1, C2, P1 = ITA (P2, P1, C x n, S1, S2)

PROCEDURAL

C1 = (L <= 0) \cdot (C1 <= S2, P2)

A = K + S2

C = 0.10 + 2.5 \cdot C1

C1 = K \cdot P1 \cdot ((K \cdot S2 + P2) / (C1 - K \cdot S2 + P2))

P1 = 0.1 - A \cdot L \cdot (S1 \cdot C1)

A1 = (0.1 / (1.0 \cdot 7 + 2.2 \cdot 4 \cdot P1)) \cdot 2.6

C1 = C1 + 0.375 \cdot (CAH + x - S1 \cdot P1 / P1 \cdot T)

C1 = CAH + 0.3 \cdot 375 \cdot (CAH - CAH + x - 2)

C1 = C1

2 \cdot C2 = -1 \cdot (CAH + x - (C1 + A \cdot P2) / (C1 + A \cdot P2) - 1.) + 5 \cdot P2

C1 = C1 - C2

IF (ABS(C2) > 5.0) GO TO 30

C1 = C1 - 0.1 \cdot C2

GO TO 20

30 IF (ABS(C2 - C1) > 20) GO TO 40

C1 = C1 - (C1 - C2) / 2.

GO TO 20

GO TO 40

ENDMACRO
MACRO PL, P2, P3 = 1 (C2, S1, CAR = SL, S2)

PROCEDURAL

\[ P1 = \text{IFG} = 4 (P5, Q5, S1, S2) \]

\[ A = K = 52 \]

\[ C = 0.152 + 2.3 \times CP1 \]

\[ 20 \quad \text{CAH} = K P1 (K + S2 \times P2) / (C2 - K \times S2 \times P1) \]

\[ P3 = 9.1 - \text{ALOS10} (C4) \]

\[ P1 = 1.115 \times (P1 + 1, S1, P2) \]

\[ \text{CAH} = 0.2 = C1 = S1 = P1 / P4 \]

\[ S = \text{CAR} = 0.375 \times (C2 - \text{CAH} \times S2) \]

\[ P1 = P2 \]

\[ S = 40 : = (C2 - A \times P1) / 100 \]

\[ C = (-C2 + A \times P2) / 50 + 14 \]

\[ \text{IF} (C3) 1, 10, 25 \]

\[ \text{ENDIF} = 1 \]

\[ 90 \text{ TO } 95 \]

\[ 15 \quad \text{DEN} = 1. / (1. + 4 \times (-C3)) \]

\[ 95 \quad P3 = 1. \times 10 \times \text{DEN} \]

\[ \text{IFP} = P2 - P1 \]

\[ \text{IF} (\text{ASS}(\text{IFP}) \times 5.5) \text{ TO } 35 \]

\[ \text{IF} (P2 = 9.0) \text{ TO } 13 \]

\[ P1 = P2 \]

\[ 60 \text{ TO } 92 \]

\[ 13 \quad P1 = P1 - (P1 - 0.1) / 2. \]

\[ 12 \quad \text{CONTINUE} \]
G1 TO 55
35 IF(ABS(P2-P1) .LE. 0.001) GO TO 55
P1=P1-(PI-P2)/2.
GO TO 20
55 CONTINUE
ENDMACRO

INITIAL

* INITIAL CONDITIONS, constants, and parameters

PARAMETER    CB = 1.0,  z = -9.15, Mx = 1.0
PARAMETER    CAVE = 0.3, DAY=1.0, DAY1=1.0
PARAMETER    Mxe=9.99992,  MPE=2.5
PARAMETER    RISE = 20
CONSTANT     K = 0.0132, Kp = 7.05,  TEC = 0.91,
              KSP = 1.0
CONSTANT     C41 = 0.221
CONSTANT     D1=7.2665e-3, D0=1.36656-7, D13=4.7287e-6
CONSTANT     L2 = 0.719526 =4
CONSTANT     PAX = 100.
              P13 = PAX 47.0
CONSTANT     p6 = 2.75
CONSTANT     S41 = 9.38, S42 = 0.47, S43 = 0.163
CONSTANT     S41 = 0.24, S42 = 0.47, S43 = 0.1295
## Tabular Dissociation Relationship for COP2

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* Actual Input Data

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* Initial Guess for Iteration Scheme

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<td>Table 02 Dissociation Relationship</td>
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**FUNCTION PITA~ 7.3**
(0.9, 0.9) (0.834, 0.85) (0.851, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

**FUNCTION PITA~ 7.2**
(0.9, 0.9) (0.854, 0.85) (0.867, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

**FUNCTION PITA~ 7.1**
(0.9, 0.9) (0.834, 0.85) (0.851, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

**FUNCTION PITA~ 7.4**
(0.9, 0.9) (0.834, 0.85) (0.851, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

**FUNCTION PITA~ 7.5**
(0.9, 0.9) (0.834, 0.85) (0.851, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

**FUNCTION PITA~ 7.6**
(0.9, 0.9) (0.834, 0.85) (0.851, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

**FUNCTION PITA~ 7.7**
(0.9, 0.9) (0.834, 0.85) (0.851, 0.76)...
(0.732, 1.0) (0.735, 0.53) (0.778, 0.73)...
(0.797, 0.76) (0.849, 0.76) (0.890, 1.0)...

---

**DYNAMIC SECTION OF MODEL**

DYNAMIC

\[
P1 = x1 \times P2 \times T
\]

\[
P2 = x2 \times P3 \times T
\]

\[
P3 = x3 \times P4 \times T
\]
CZA85 = UC4wIP(CAS, DOB, ICZ85, VAL4, 3, 4, TIME, DELT)
CZA86 = UC4wIP(CAS, DOB, CS, VCLAB, 3, 2, TIME, DELT)
PZA81 = UC4wIP(PA1, DOB, IPZA81, VCL4, 3, 4, TIME, DELT)
PZA32 = UC4wIP(PA2, DOB, IPZA32, VCL4, 3, 5, TIME, DELT)

* MASS BALANCE EQUATIONS

C681 = (G681 + (C681 - CV61) - 0.01 - 0.01v(P61 - P61)) / VCL6
C61 = INTCL(1C61, C681)
P61 = PAT / S61 + C61
C682 = (C682 + (C682 - CV62) + 0.02 - 0.02v(P62 - P62)) / VCL6
C62 = INTCL(1C62, C682)
C683 = (C683 + (C683 - CV63) - 0.02v(P63 - P63)) / VCL6
C63 = INTCL(1C63, C683)
P63 = PAT / S63 + C63
C682 = V63 + P63 / PAT
CV61, CV62, P61, V61 = IMP(C681, NV1, C685, VCL6, 61)
C65 = REALPL(63, EV, CZA65)

* TIME DELAY EQUATIONS FOR VENOUS FLOW FROM AORTA TO GUT

C681 = UC4wIP(CV61, 16, IC681, VCL4, 3, 4, TIME, DELT)
C682 = UC4wIP(CV62, 16, IC682, VCL4, 3, 4, TIME, DELT)
C683 = UC4wIP(CV63, 16, IC683, VCL4, 3, 4, TIME, DELT)
C684 = UC4wIP(63, 16, IC684, VCL4, 3, 4, TIME, DELT)

* BLOOD FLOW TO BRAIN EQUATIONS

C681 = (1C681 + 1C681 + 1C682 - 1C682) / 76
C61 = INTCL(1C61, 76)
PROCEDURE: C681 = 1(I641)
_PROCEDURE
    QD8 = 0.081
    IF (QD8 .GT. 0.9467) QD8 = 0.9467
    IF (QD8 .LT. 0.091) QD8 = 0.091
ENDPROCEDURE

PROCEDURE
    QD81, QD82 = VAS90 (PZAB1, PZAB2)
    IF (PZAB1 .LT. 150.) Go To 100
    QD81 = 0.9
    Go To 200
100 QD81 = 1.191E-3 - 2.941E-3 * PZAB1 + 5.755E-4 * PZAB1 * PZAB1 * QD81
     - 5.166E-3 * PZAB1 * PZAB1 + 3.171E-4 * PZAB1 * PZAB1
200 IF (PZAB2 .EQ. 3.) Go To 300
    QD82 = -1.191E-3 - 6.192E-3 * PZAB2 + 1.725E-4 * PZAB2
     + 2.934E-3 - 7 * PZAB2 + 3.934E-4 * PZAB2
    Go To 400
300 IF (PZAB2 .GT. 100.) Go To 400
    QD82 = 0.9
    Go To 500
400 QD82 = -9.403E-4 - 2.610E-2 * PZAB3 + 2.476E-2 * PZAB3 * PZAB3
     + 2.248E-3 - 7 * PZAB3 + 3.46E-4 * PZAB3 * PZAB3
    Go To 500
500 ENDPROCEDURE
CEREBROSPINAL FLUID COMPARTMENT

**MASS BALANCE EQUATIONS**

\[
PDCF1 = \frac{dL1}{VCLCF} \times SCF1 \times K \times (P_{BF} - P_{CF1})
\]

\[
PCF1 = \text{Integral} \left( ICCF, PDCF1 \right)
\]

\[
PDCF2 = \frac{dL2}{VCLCF} \times SCF2 \times K \times (P_{BF} - P_{CF2})
\]

\[
PCF2 = \text{Integral} \left( ICCF2, PDCF2 \right)
\]

\[
PDCF3 = \frac{dL3}{VCLCF} \times SCF3 \times K \times (P_{BF} - P_{CF3})
\]

\[
PCF3 = \text{Integral} \left( ICCF3, PDCF3 \right)
\]

**LUNG COMPARTMENT**

**MASS BALANCE EQUATIONS**

\[
PAV1 = \text{Integral} \left( ICAV1, PAV1 \right)
\]

\[
PDAV1 = \frac{P_{AV1} \times VCL}{(VCL1 - CAL1 + VCLAV} \times P_{IL - VCL} + PAV1) / VCLAV
\]

\[
PAV2 = \text{Integral} \left( ICAV2, PAV2 \right)
\]

\[
PDAV2 = \frac{P_{AV2} \times VCL}{(VCL2 - CAL2 + VCLAV} \times P_{IL - VCL} + PAV2) / VCLAV
\]

\[
PAV3 = \text{Integral} \left( ICAV3, PAV3 \right)
\]

\[
PDAV3 = \frac{P_{AV3} \times VCL}{(VCL3 - CAL3 + VCLAV} \times P_{IL - VCL} + PAV3) / VCLAV
\]

**ALVEOLAR PERMEABILITY EQUATIONS**

\[
PALL = PAV1 \times CAV1
\]

\[
PALL2 = PAV2 \times CAV2
\]

\[
PALL3 = PAV3 \times CAV3
\]
* AERIAL GAS CONCENTRATIONS LEAVING THE LUNGS

\[ \text{CAL}1, \text{CAL}2, \text{PAL} = 1 \text{f} (\text{PAL}2, \text{PAL}1, \text{G}5, \text{S}1, \text{S}2) \]
\[ \text{CAL}2 = \text{PAL}1 \times \text{CAL}1 \]

* VENTILATION RATE EQUATIONS

\[ V_{DAV} = V_{DPL} - V_{DO} \]
\[ V_{DO} = V_{DAV} + 3.46 \times ((G_2 - G_4) + (G_1 - G_2)^2) / 0.938136 \]
\[ V_{DOL} = 0.330 - 0.433193 (V_{DOL} - V_{DO}) \]

PROCEDURE

\[ V_{DOL} = \text{PID} \times (0.315 - 1.35157 \times (V_{DOL} - V_{DO})) \]
\[ \text{IF} (V_{DOL} \geq 0.0418) V_{DOL} = 0.0418 \]
\[ \text{IF} (V_{DOL} \leq 0.07) V_{DOL} = 0.07 \]

ENDPROCEDURE

\[ V_{DOL} = V_{DOL} + V_{DS} + V_{DS}4 \]

* PULMONARY VENTILATION DUE TO CENTRAL CHEMOREPETORS

PROCEDURE

\[ V_{DCS}4 = 0.0 (C_{CS}4, W_{CS}4) \]
\[ \text{IF} (C_{CS}4 > 0.08) V_{DCS}4 = 0.0 \]
\[ \text{IF} (V_{DCS}4 \geq 0.7) V_{DCS}4 = 0.7 \]

ENDPROCEDURE

* PULMONARY VENTILATION DUE TO PERIPHERAL CHEMOREPETORS

\[ V_{DCS}4 = 0.0 \]
PROCEDURE VOPS1, VOPS4 = P3(PPS1, CPS4, VPS1, VPS4)
VOPS1 = 3.02023 * (6) * PPS1
IF (VOPS1 LT 0.0) VOPS1 = 0.0
VOPS1 = VOPS1 * VOPS1
VOPS4 = 1.0 + (CPS4 - 3.3875 - 0)
IF (VOPS4 LT 0.0) VOPS4 = 0.0
VOPS4 = VOPS4 * VOPS4
ENDPROCEDURE

* LUNG BLOOD FLOW RATE EQUATION

JBL = 0.0 - JPS

* HEART COMPARTMENT

* VENOUS MIXING OF BLOOD OCCURRING IN RIGHT ATRIUM AND RIGHT VENTRICLE

\[ \dot{V}_1 = (J_{03} + CZV31 + 0.0T CZV31) / 30 \]
\[
\begin{align*}
CV_2 &= (QD + CZV_2 \cdot QD + CZV_3) / 60 \\
CV_3 &= (QD + CZV_3 \cdot QD + CZV_4) / 60 \\
CV_5 &= (QD + CZV_5 \cdot QD + CZV_6) / 60
\end{align*}
\]

* VENOUS PARTIAL Pressures

\[
PV_1, PV_2, PV_3 = \text{INIT}(CV_2, CV_1, CAL, SAL, SA)
\]

* AORTIC GAS Concentrations LEAVING LEFT VENTRICLE

\[
\begin{align*}
CA_1 &= (QD + CAL_1 \cdot QD + CV_1) / 60 \\
CA_2 &= (QD + CAL_2 \cdot QD + CV_2) / 60 \\
CA_3 &= (QD + CAL_3 \cdot QD + CV_3) / 60 \\
CA_5 &= (QD + CAL_5 \cdot QD + FLOW) / (QD + FLOW) \\
PA_1, PA_2, PA_3 &= \text{INIT}(CA_2, CA_1, CAL, SAL, SA)
\end{align*}
\]

* CARDIAC OUTPUT AND SHUNTING EQUATIONS

PROCEDURE QD = FLOW(QD, QD)
  QD = QD + QD
  IF(QD + QD > 1000) GOTO 710
  QD = QD
  WRITE(2, 709)
  709 FORMAT('CARDIAC OUTPUT ZERO. RESET TO 1E-5.1')
  710 CONTINUE
ENDPROCEDURE

PROCEDURE WSHUNT = SHUNT(PPS)
  WSHUNT = 0.1 \cdot 0.1 + 5 \times (PPS - 25.1)
  IF(WSHUNT \geq 0.5) WSHUNT = 0.5
  IF(WSHUNT \leq 2.0) WSHUNT = 2.0
  WSHUNT = WSHUNT / 100
ENDPROCEDURE

\[
\begin{align*}
\text{QDS} &= \text{INT}\{\text{QD} - \text{WSHUNT} - 0.15\} / 15 \\
\text{QDS} &= \text{INT}\{\text{QD} - \text{WSHUNT} - 0.15\} / 15
\end{align*}
\]
TISSUE COMPARTMENT

TIME DELAY EQUATIONS FOR ARTIFICAL FLOW FROM HEART TO TISSUES

\[ C_{AT1} = \text{EXP}(C_{AT1}, \text{DT}, 1, \text{C}_{LAT1}, \text{VOLAT}, 3, 12, \text{TIME}, \text{DELT}) \]
\[ C_{AT2} = \text{EXP}(C_{AT2}, \text{DT}, 1, \text{C}_{LAT2}, \text{VOLAT}, 3, 11, \text{TIME}, \text{DELT}) \]
\[ C_{AT3} = \text{EXP}(C_{AT3}, \text{DT}, 1, \text{C}_{LAT3}, \text{VOLAT}, 3, 12, \text{TIME}, \text{DELT}) \]
\[ C_{AT5} = \text{EXP}(C_{AT5}, \text{DT}, 3, \text{VOLAT}, 3, 27, \text{TIME}, \text{DELT}) \]

MASS BALANCE EQUATIONS

\[ C_{T1} = \left( C_{T1} - C_{AT1} - C_{VT1} - M_{T1} \right) / \text{VOLT} \]
\[ C_{T1} = \text{INTGREL}(C_{T1}, C_{T1}) \]
\[ P_{T1} = \text{PAT}/\text{ST} \]
\[ C_{VT2} = \left( C_{VT2} - C_{AT2} - C_{VT2} + M_{VT2} \right) / \text{VOLT} \]
\[ C_{T2} = \text{INTGREL}(C_{T2}, C_{T2}) \]
\[ C_{VT1}, C_{VT2}, P_{VT1} = \text{INTGREL}(P_{T1}, P_{T1}, C_{VT2}, S_{VT1}, S_{VT2}) \]
\[ P_{T2} = S_{VT2}/S_{VT1} \]
\[ C_{VT3} = \left( C_{VT3} - C_{AT3} - C_{VT3} \right) / \text{VOLT} \]
\[ C_{T3} = \text{INTGREL}(C_{T3}, C_{T3}) \]
\[ P_{T3} = \text{PAT}/S_{T3} = C_{T3} \]
\[ C_{VT5} = S_{VT5}/\text{ATM} \]
\[ C_{T5} = \text{ALDL}(C_{T5}, C_{AT5}, P_{T5}) \]
TIME DELAY EQUATIONS FOR VENOUS FLOW FROM TISSUES TO HEART

\[ CVVT_1 = NEAP(CVT_1, VT, ICVT_1, VELVT, 3, 13, TIME, DELT) \]
\[ CVVT_2 = NEAP(CVT_2, VT, ICVT_2, VELVT, 3, 11, TIME, DELT) \]
\[ CVVT_3 = NEAP(CVT_3, VT, ICVT_3, VELVT, 3, 15, TIME, DELT) \]

TISSUE BLOOD FLOW EQUATION

PROCEDURE
\[ QVT = VASOT(TL, TT, ICQDT) \]
\[ QLT = 0.60525 - 3 + 3.57 - 3 \times (47.55 - PT) \]
\[ IF(QLT \cdot LT \cdot 0) QDT = 0.0 \]
\[ QDT = (QVT - QDT) / TT \]
\[ QST = JAVGRL(1CQOT, VT) \]
\[ IF(QST \cdot ST \cdot 0.35) QST = 0.045 \]
\[ IF(QST \cdot ST \cdot 0.21) QST = 0.2 \]
ENDPROCEDURE

KIDNEY

\[ CVAK5 = CT \]
\[ C5 = C3 + 1 \times (CVAK5 - C3) \]
\[ CVK5 = NEAP(C5, 0.0, IC, VELVT, 2, 2, TIME, DELT) \]

CHAMPRECEPTORS

...
* PERIPHERAL CHEMORECEPTORS

\[
\begin{align*}
PPS_1 &= \text{NEWPIP}(\text{PAL}, \text{QD}, \text{IPZPS1}, \text{VCAPS}, 3, 24, \text{TIME}, \text{DELT}) \\
CPH_4 &= \exp(-2 \cdot 3 \cdot \text{PHOS}) \\
PHPS &= \text{NEWPIP}(\text{PHA}, \text{QD}, \text{IPZPH}, \text{VCAPS}, 3, 24, \text{TIME}, \text{DELT})
\end{align*}
\]

* CENTRAL CHEMORECEPTORS

\[
\begin{align*}
CGS_2, PHCS &= 30 \text{ISOG}(\text{CGS2}, \text{CGS3}, \text{CGS2}) \\
CGS_3 &= \exp(-2 \cdot 3 \cdot \text{PHOS}) \\
CGS_2 &= \text{PBZ} + (\text{PCP2} - \text{PBZ}) \times \exp(-2 \cdot 0.05 - 6 \times \text{SUG}(\text{QCS} - \text{LC} \cdot \text{PATM} / \text{CGS2})) \\
QCS &= \text{QDC}
\end{align*}
\]

PROCEDURE \( \text{CARO}, \text{FLOW} = \text{IC}(\text{TIME}) \)
CALL \( \text{ICARO}(\text{TIME}, \text{CARO}, \text{FLOW}) \)
ENDPROCEDURE

PROCEDURE \( \text{X1, X3} = \text{ICHAL} (\text{TIME}, \text{RIS}) \)
CALL \( \text{ICSP} (\text{TIME}, \text{RIS}, \text{X1, X3}) \)
ENDPROCEDURE

ACTPV1 = \text{AFGEN}(\text{S1PV1, TIME})
ACTPV2 = \text{AFGEN}(\text{S1PV2, TIME})
ACTPHV = \text{AFGEN}(\text{S1PHV, TIME})
METHOD RKSEX

TIMER PINTIM=24000.,DELT=.15,(OUTDEL=70).

OUTPUT USHUNT
OUTPUT CK5,CT5,CH
PAGE GROUP(0,3)
OUTPUT FLAX,X1,4RX
OUTPUT V04V
OUTPUT RFB1,0 (0.0,1.75)
OUTPUT V3PL
OUTPUT CAS5,CVS,CS
PAGE GROUP (0.0,4.)
OUTPUT CAR5
OUTPUT PA1,PA2
PAGE GROUP (0.0,690.)
OUTPUT PV2,ACTPV2
PAGE GROUP (0.0,300.)
OUTPUT PV1,ACTPV1
PAGE GROUP (0.0,300.)
OUTPUT PCF1,PCF2
PAGE GROUP (0.0,600.)
OUTPUT PCS2
OUTPUT PA1,PA2
PAGE GROUP (0.0,690.)
OUTPUT JUT,JS1
OUTPUT JD (0.0,0.025)
OUTPUT PHV,ACTPHV
PAGE GROUP (6.5,7.3)
OUTPUT PHS,PHCS
PAGE GROUP (6.5,7.3)
OUTPUT PS2 (0.0,500.)
OUTPUT PHA,PHAL
PAGE GROUP (6.5,7.3)
OUTPUT PPS1
PAGE GROUP (0.0,600.)
OUTPUT P61,PT1
PAGE GROUP (0.0,600.)
OUTPUT GCS2
OUTPUT V0PS1, V0PS4, V0CS4
SUBROUTINE BICARB(TIME, CARB, FLOW)
REAL DTIME(14) /0.0, 3.300, 6.500, 9.200, 11.300,
* 13.00, 14.00, 16.400, 23.600, 25.400, 27.200,
* 29.00, 3.300, 5.300/,
REAL DCARB(13) /0.0, 2.69, 2.69, 2.69, 2.69, 2.69,
* 2.69, 2.69, 2.69, 2.69, 2.69,
REAL DFLOW(13) /0.0, 0.005, 0.005, 0.003, 0.001, 0.004, 0.01,
* 0.006, 0.005, 0.003, 0.0/,
I=1
100  I=I+1
IF (TIME .LE. DTIME(1)) GO TO 2
GO TO 100
2    CARB = DCARB(I-1)
DEL = DTIME(I) - DTIME(I-1)
FLOW = DFLOW(I-1) / DEL
RETURN
END

SUBROUTINE GESP(TIME, RISE, X1, X3)
REAL DTIMES(20) /200, 200, 200, 200, 200, 200, 200, 200, 200,
* 27.200, 27.909, 16.0* 1.12*, 0.0*,
REAL PDDEL(21) /23.95, 1.55, 0.9, 0.7, 0.4, 0.0, 0.0, 0.0,
I=0
100  I=I+1
IF (TIME .LE. DTIMES(1)) GO TO 200
IF ((TIME - RISE) .LE. DTIMES(1)) GO TO 200
GO TO 100
200  X1 = PDDEL(I) / LOG.
X3 = 10.0 - X1
RETURN
300  X1 = ((PDDEL(I+1) - PDDEL(I)) / RISE - (TIME - DTIMES(I)) + PDDEL(I)) / 100,
X3 = 10.0 - X1
FUNCTION PIPEP(VPARM, GD, ENGNEN, VOL, J, K, TIME, DALT)
DIMENSION PARM(3JO, 3, 3), NTOT(3)
IF(TIME .GT. J, 0) GO TO 100
TOLD=TIME
KOLD=J
VIN=GO * DALT
NI=VOL/VIN
RN=VOL/VIN
OV=(RN-AI)*VIN
NTOT(K)=NI+1
NT=NI+1
PARAM(1,1,K)=OV
DO 1 1=2, NT
1 PARAM(I,1,K)=VIN
DO 2 I=1, NT
2 PARAM(I,J,K)=ENGNEN
PIPEP=ENGNEN
GO TO 200
100 VOLT=GO * DALT
M=-1
VOLT=0.0
PX=0.0
NT1=NTOT(K)
4 M=M+1
NT1=NT1-M
VOLT=VOLT+PARAM(N1,1,K)
IF(VOLT.LE.VIN(NG)) GO TO 3
GO TO 5
3 PX=PX+PARAM(N1,1,K)-PARAM(N1,1,K)
GO TO 4
5 PXX=PARAM(N1,1,K)*(PARAM(N1,1,K)-(VOLT-VOLT))
PIPEP=(PX+PXX)/VIN
NTOT(K) = NTOT(K) - N + 1
NTOT1 = NTOT(K)
INT = INT1 - 1
PARAM(NTOT1, J, K) = PARAM(NT1, J, K)
DO 6 II = 2, INT
I = NTOTI + 1 - II
6 PARAM(I, J, K) = PARAM(I - 1, J, K)
PARAM(1, J, K) = VPAE
IF (TIME.EQ.40.0) GO TO 11
TIME = TIME
KOLD = K
GO TO 12
11 IF (KOLD.EQ.K) GO TO 200
KOLD = K
12 DO 7 N = 2, INT
N = NTOTI + 1 - NM
7 PARAM(N, 1, K) = PARAM(N - 1, 1, K)
PARAM(1, 1, K) = VELIN
PARAM(NTOT1, 1, K) = VELT - VELIN
200 CONTINUE
RETURN
END
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An improved digital computer model of the neonatal respiratory system was developed. Using previous models as a basis, important improvements were made in order to accurately simulate infant blood gas chemistry and its effect on respiratory and circulatory control.

The model is divided into five physiologic compartments: heart, brain, lungs, tissues, and cerebrospinal fluid compartment. Respiration is a function hydrogen ion concentration in the medulla and oxygen tension and hydrogen ion concentration in the aorta. Cardiac output is a function of oxygen and carbon dioxide tension in the brain and oxygen tension at the tissues.

Major improvements in this model include an advanced carbon dioxide dissociation relationship and a complex blood buffer system. It also is able to simulate treatment of respiratory distressed infants with bicarbonate infusion and respirator therapy. In addition, it has a simplified variable time delay.
In order to evaluate the model, an attempt was made to simulate an actual infant. Results indicate that while the model is an improvement over previous attempts, it is still deficient in some areas in its ability to simulate actual infants. More comparisons with actual data must be made to accurately evaluate the model.