AN IMPROVED DIGITAL COMPUTER MODEL OF THE NEONATAL RESPIRATORY SYSTEM

by

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LIST OF SYMBOLS

Symbol	Definition	Units
CARB	Content of $NaHCO_3$ to infant	liters/liter blood
$CAHBO_2$	Content of oxyhemoglobin in blood	liters/liter blood
CA1	Arterial content of O_2 in heart	liters gas/liter blood
CA2	Arterial content of CO_2 in heart	liters gas/liter blood
CA3	Arterial content of N_2 in heart	liters gas/liter blood
CA5	Arterial content of HCO_3- in heart	liters gas/liter blood
CAL1	Arterial content of O_2 in lungs	liters gas/liter blood
CAL2	Arterial content of CO_2 in lungs	liters gas/liter blood
CAL3	Arterial content of N_2 in lungs	liters gas/liter blood
CAP1	O_2 capacity of blood	dimensionless
CBR	HCO_3^- content of medulla	liters gas/liter blood
CB1	Content of O_2 in brain	liters gas/liter blood
CB2	Content of CO_2 in brain	liters gas/liter blood
CB3	Content of N_2 in brain	liters gas/liter blood
CB5	Content of HCO_3^- in brain	liters gas/liter blood

Symbol	Definition	Units
CCS4	Content of hydrogen ions at central site	liters gas/liter blood
CDB1	Derivative of O_2 content in brain	liters gas/liter blood-sec
CDB2	Derivative of CO_2 content in brain	liters gas/liter blood-sec
CDB3	Derivative of N_2 content in brain	liters gas/liter blood-sec
CDT1	Derivative of O_2 content in tissues	liters gas/liter blood-sec
CDT2	Derivative of CO_2 content in tissues	liters gas/liter blood-sec
CDT3	Derivative of N_2 content in tissues	liters gas/liter blood-sec
CK5	Content of HCO_3^- leaving kidney	liters gas/liter blood
CT1	Content of O_2 in tissues	liters gas/liter blood
CT2	Content of CO_2 in tissues	liters gas/liter blood
CT3	Content of CO_2 in tissues	liters gas/liter blood
CT5	Content of HCO_3^- in tissues	liters gas/liter blood
CVB1	Venous content of O_2 in brain	liters gas/liter blood
CVB2	Venous content of CO_2 in brain	liters gas/liter blood
CVB3	Venous content of N_2 in brain	liters gas/liter blood
CVT1	Venous content of O_2 in tissues	liters gas/liter blood

Symbol	Definition	Units
CVT2	Venous content of CO_2 in tissues	liters gas/liters blood
CVT3	Venous content of N_2 in tissues	liters gas/liters blood
CV1	Venous content of O_2 leaving right heart	liters gas/liters blood
CV2	Venous content of CO_2 leaving right heart	liters gas/liters blood
CV3	Venous content of N_2 leaving right heart	liters gas/liters blood
CV5	Venous content of HCO_3^- leaving right heart	liters gas/liters blood
CZAB1	Arterial content of O_2 at brain	liters gas/liters blood
CZAB2	Arterial content of CO_2 at brain	liters gas/liters blood
CZAB3	Arterial content of N_2 at brain	liters gas/liters blood
CZAB5	Arterial content of HCO_3^- at brain	liters gas/liters blood
CZAT1	Arterial content of O_2 at tissues	liters gas/liters blood
CZAT2	Arterial content of CO_2 at tissues	liters gas/liters blood
CZAT3	Arterial content of N_2 at tissues	liters gas/liters blood
CZAT5	Arterial content of HCO_3^- at tissues	liters gas/liters blood
CZVB1	Venous content of O_2 at brain	liters gas/liters blood
CZVB2	Venous content of CO_2 at brain	liters gas/liters blood

Symbol	Definition	Units
CZVB3	Venous content of N_2 at brain	liters gas/liters blood
CZVB5	Venous content of HCO_3^- at brain	liters gas/liters blood
CZVT1	Venous content of O_2 at tissues	liters gas/liters blood
CZVT2	Venous content of O_2 at tissues	liters gas/liters blood
CZVT3	Venous content of O_2 at tissues	liters gas/liters blood
CZVT5	Venous content of O_2 at tissues	liters gas/liters blood
DAV1	Alveolar diffusion constant for O_2	Dimensionless
DAV2	Alveolar diffusion constant for CO_2	Dimensionless
DAV3	Alveolar diffusion constant for N_2	Dimensionless
DB1	Brain-Cerebrospinal Fluid diffusion constant for O_2	liter gas/sec/mmHg
DB2	Brain-Cerebrospinal Fluid diffusion constant for CO_2	liter gas/sec/mmHg
DB3	Brain-Cerebrospinal Fluid diffusion constant for N_2	liter gas/sec/mmHg
FLOW	Rate of flow of intravenous drip	liters/sec
1CAV1	Alveolar O_2 tension initial condition	mmHg
1CAV2	Alveolar CO_2 tension initial condition	mmHg

Symbol	Definition	Units
ICAV2	Alveolar CO_2 tension initial condition	mmHg
ICB1	O_2 initial condition in brain	liters gas/liters blood
ICB2	CO_2 initial condition in brain	liters gas/liters blood
ICB3	N_2 initial condition in brain	liters gas/liters blood
ICCF1	O_2 tension initial condition in CSF	mmHg
ICCF2	CO_2 tension initial condition in CSF	mmHg
ICCF3	N_2 tension initial condition in CSF	mmHg
ICQD	Cardiac output initial condition	liters/sec
ICQDB	Brain blood flow initial condition	liters/sec
ICQDT	Tissue blood flow initial condition	liters/sec
ICQDS	Shunt blood flow initial condition	liters/sec
ICT1	O_2 initial condition in tissues	liters gas/liter blood
ICT2	CO_2 initial condition in tissues	liters gas/liter blood
ICT3	N_2 initial condition in tissues	liters gas/liter blood
ICZAB1	O_2 initial condition at brain	liters gas/liter blood

Symbol	Definition	Units
ICZAB2	CO_2 initial condition at brain	liters gas/liter blood
ICZAB3	N_2 initial condition at brain	liters gas/liter blood
ICZAT1	O_2 initial condition at tissues	liters gas/liter blood
ICZAT2	CO_2 initial condition at tissues	liters gas/liter blood
ICZAT3	N_2 initial condition at tissues	liters gas/liter blood
ICZPS1	O_2 initial condition at peripheral chemoreceptors	liters gas/liter blood
ICZPS2	CO_2 initial condition at peripheral chemoreceptors	liters gas/liter blood
ICZPS3	N_2 initial condition at peripheral chemoreceptors	liters gas/liter blood
ICZVB1	O_2 initial condition at heart from brain	liters gas/liter blood
ICZVB2	CO_2 initial condition at heart from brain	liters gas/liter blood
ICZVB3	N_2 initial condition at heart from brain	liters gas/liter blood
ICZVT1	O_2 initial condition at heart from tissues	liters gas/liter blood
ICZVT2	CO_2 initial condition at heart from tissues	liters gas/liter blood
ICZVT3	N_2 initial condition at heart from tissues	liters gas/liter blood
L2	Slope of the CO_2 solubility curve	liters gas/liters blood
METR	Weight adjusted metabolic rate	liters/sec

Symbol	Definition	Units
MRB	Total metabolic rate of body	ml/min/kg
MRB1	Metabolic consumptiom of O_2 by brain	liters gas/sec
MRB2	Metabolic generation of CO_2 by brain	liters gas/sec
MRT1	Metabolic consumption of O_2 by tissues	liters gas/sec
MRT2	Metabolic generation of CO_2 by tissues	liters gas/sec
PAL1	Arterial partial pressure of O_2 in lungs	mmHg
PAL2	Arterial partial pressure of CO_2 in lungs	mmHg
PAL3	Arterial partial pressure of N_2 in lungs	mmHg
PATM	Atmospheric pressure	mmHg
PAV1	Alveolar O_2 partial pressure	mmHg
PAV2	Alveolar CO_2 partial pressure	mmHg
PAV3	Alveolar N_2 partial pressure	mmHg
PB1	Partial pressure of O_2 in brain	mmHg
PB2	Partial pressure of CO_2 in brain	mmHg
PB3	Partial pressure of N_2 in brain	mmHg
PCF1	Partial pressure of O_2 in CSF	mmHg

Symbol	Definition	Units
PCF2	Partial pressure of CO_2 in CSF	mmHg
PCF3	Partial pressure of N_2 in CSF	mmHg
PCS1	Partial pressure of O_2 at central chemoreceptor	mmHg
PCS2	Partial pressure of CO_2 at central chemoreceptor	mmHg
PDAV1	Partial pressure derivative of alveolar O_2	mmHg
PDAV2	Partial pressure derivative of alveolar CO_2	mmHg
PDAV3	Partial pressure derivative of alveolar N_2	mmHg
PDCF1	Partial pressure derivative of O_2 in CSF	mmHg
PDCF2	Partial pressure derivative of CO_2 in CSF	mmHg
PDCF3	Partial pressure derivative of N_2 in CSF	mmHg
PHAB	Arterial pH of blood at brain	pH units
PHAL	Arterial pH of blood at lungs	pH units
PHCS	pH of fluid at central chemoreceptors	pH units
PHPS	pH of fluid at peripheral chemoreceptors	pH units
PHVB	Venous pH at brain	pH units
PHVT	Venous pH at tissues	pH units

Symbol	Definition	Units
PI1	Inspired partial pressure of O_2	mmHg
PI2	Inspired partial pressure of CO_2	mmHg
PI3	Inspired partial pressure of N_2	mmHg
PPS1	Partial pressure of O_2 at peripheral site	mmHg
PT1	O_2 partial pressure at tissues	mmHg
PT2	CO_2 partial pressure at tissues	mmHg
PT3	N_2 partial pressure at tissues	mmHg
PV1	Venous partial pressure of O_2	mmHg
PV2	Venous partial pressure of CO_2	mmHg
PV3	Venous partial pressure of N_2	mmHg
PZAB1	Partial pressure of O_2 entering brain	mmHg
PZAB2	Partial pressure of CO_2 entering brain	mmHg
QD	Total cardiac output	liters/sec
QDB	Blood flow rate to brain	liters/sec
QDB1	Blood flow rate to brain due to O_2	liters/sec
QDB2	Blood flow rate to brain due to CO_2	liters/sec

Symbol	Definition	Units
QDCS	Blood flow rate to central chemoreceptors	liters/sec
QDP	Total blood flow rate per second	liters/sec/sec
PDDB	Brain blood flow rate per second	liters/sec/sec
QDL	Blood flow rate to lungs	liters/sec
QDS	Shunted blood flow rate	liters/sec
QDT	Blood flow rate to tissues	liters/sec
RFREQ	Respiratory frequency	breaths/sec
RQ	Respiratory quotient	Dimensionless
SA1	Arterial solubility of O_2	liters gas/liter blood/ATM
SA2	Arterial solubility of CO_2	liters gas/liter blood/ATM
SA3	Arterial solubility of N_2	liters gas/liter blood/ATM
SB1	O_2 solubility in brain	liters gas/liter blood/ATM
SB2	CO_2 solubility in brain	liters gas/liter blood/ATM
SB3	N_2 solubility in brain	liters gas/liter blood/ATM
SCS1	O_2 solubility at central site	liters gas/liter blood/ATM
SCS2	CO_2 solubility at central site	liters gas/liter blood/ATM
SCS3	N_2 solubility at central site	liters gas/liter blood/ATM
SCF1	O_2 solubility in CSF	liters gas/liter blood/ATM

Symbol	Definition	Units
SCF2	CO_2 solubility in CSF	liters gas/liter blood/ATM
SCF3	N_2 solubility in CSF	liters gas/liter blood/ATM
SL1	O_2 solubility in lungs	liters gas/liter blood/ATM
SL2	CO_2 solubility in lungs	liters gas/liter blood/ATM
SL3	N_2 solubility in lungs	liters gas/liter blood/ATM
ST1	O_2 solubility in tissues	liters gas/liter blood/ATM
ST2	CO_2 solubility in tissues	liters gas/liter blood/ATM
ST3	N_2 solubility in tissues	liters gas/liter blood/ATM
SV1	O_2 solubility in venous blood	liters gas/liter blood/ATM
SV2	CO_2 solubility in venous blood	liters gas/liter blood/ATM
SV3	N_2 solubility in venous blood	liters gas/liter blood/ATM
TB	Time constant for brain flow rate	seconds
TS	Time constant for cardiac output	seconds
TT	Time constant for tissue blood flow rate	seconds
VDCS4	Ventilation due to H^+ at central site	liters/sec
VDAV	Alveolar ventilation rate	liters/sec
VDDS	Dead space ventilation rate	liters/sec

Symbol	Definition	Units
VDE	Exhaled ventilation rate	liters/sec
VDPL	Pulmonary ventilation rate	liters/sec
VDPS1	Pulmonary ventilation due to O_2 at Peripheral Site	liters/sec
VDPS4	Pulmonary ventilation due to H^+ at Peripheral Site	liters/sec
VOLAB	Arterial volume from heart to brain	liters
VOLAV	Alveolar volume	liters
VOLAPS	Arterial volume from heart to Peripheral Site	liters
VOLATS	Arterial volume from heart to tissues	liters
VOLB	Volume of brain compartment	liters
VOLCF	Volume of cerebrospinal fluid compartment	liters
VOLDS	Volume of dead space in lungs	liters
VOLT	Volume of tissue compartment	liters
VOLTIO	Tidal volume	liters
VOLVB	Venous volume from brain to heart	liters
VOLVT	Venous volume from itssues to heart	liters
WAT	Percent arterial blood going to tissues	%/100
WEIGHT	Total weight of neonate	kilograms
WCS4	Percent VDPL due to H^+ at Cerebrospinal Site	%/100

Symbol	Definition	Units
WPS1	Percent VDPL due to O_2 at Peripheral Site	%/100
WPS4	Percent VDPL due to H^+ at Peripheral Site	%/100
X1	Percent of O_2 in atmospheric air	%/100
X2	Percent of CO_2 in atmospheric air	%/100
X3	Percent of N_2 in atmospheric air	%/100

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 Pco_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 Po_2 and Pco_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 Po_2 and 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 Po_2 and Pco_2 at the peripheral chemorecptors. 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

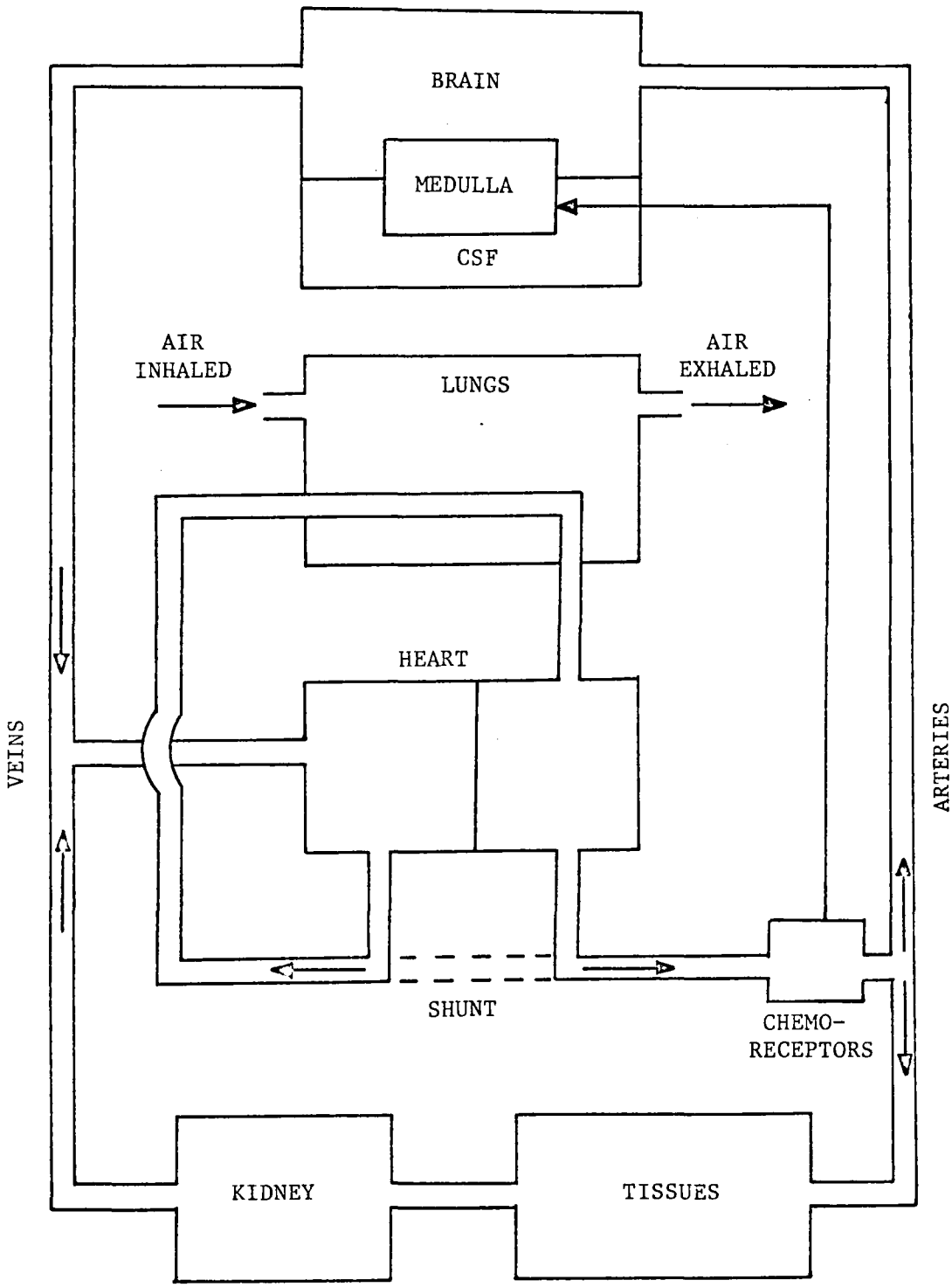

FIGURE 1. FLOW DIAGRAM OF MODEL

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:

O_2 - 1

CO_2 - 2

N_2 - 3

H^+ - 4

HCO_3^- - 5

Time Delay - Z

First Derivative - D

Second Derivative - DD

For example, the delayed arterial concentration of CO_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 Po_2 and 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, O_2, CO_2, and 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:

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

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:

$$\frac{d}{dt}\ (\text{volume x concentration}) =$$
((volume in x concentration in) -
(volume out x concentration out)) +
(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:

```
PDAV = (PATM x QDL x (CV - CAL) + VDAV x PI - VDE x PAV))/
       VOLAV,                                              (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 symbol. 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:

$$PAL = DAV \times PAV, \qquad (L2)$$

where PAL is the partial pressure of the gas in the lung arteries;

PAV is the alveolar partial pressure and;

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:

$$CDT = (QDT \times (CZAT - CVT) - MRT)/VOLT; \qquad (T1)$$

where CZAT is the arterial concentration of gas;

CVT is the venous concentration of gas;

QDT is the tissue blood flow rate;

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:

$$CDB = (QDB \times (CZAB - CVB) - MRB - DB \times (PB - PCF))/ VOLB, \quad (B1)$$

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:

$$PCF = \int PDCF \, dt, \quad (CF1)$$

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

$$PDCF = (DB/(VOLCF \times SCF)) \times (PB - PCF); \quad (CF2)$$

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:

$$CV = (QDB \times CZVB + QDT \times CZVT)/QD. \qquad (H1)$$

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:

$$CA = (QDL \times CAL + QDS \times CV)/QD. \qquad (H2)$$

The equations, of course, are written for all three species of gas. QDS is the blood flow shunted by the ductus arteriolsus and the foramen ovale. It is estimated as a function of arterial O_2 tension. It is given by the equation:

$$QDS = \int \frac{QD\ (WSHUNT) - QD}{TS}\ dt, \qquad (H3)$$

where QDS is the shunted blood flow;

QD is the total cardial output;

TS is a time constant and;

WSHUNT is the percent shunt weighing factor given by:

$$WSHUNT = (60 - 1.054595\ (PV1 - 25))/100 \qquad (H4)$$

$$2 \leq WSHUNT \leq 60$$

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:

$$C1 = CAP1 \times \frac{A}{1+A} + \frac{S1 \times P1}{PATM} \text{ , with} \qquad (D1)$$

$$A = \left(\frac{P1}{186.76 - 22.4 \times PH} \right)^{2.5}$$

where P1 is the O_2 partial pressure;

PH is the pH of the blood;

CAP1 is the O_2 transport capacity of hemoglobin;

S1 is the blood O_2 solubility and;

PATM is the atmospheric pressure.

The O_2 dissociation relationship is shown graphically in Figure 2. This relationship is used to describe O_2

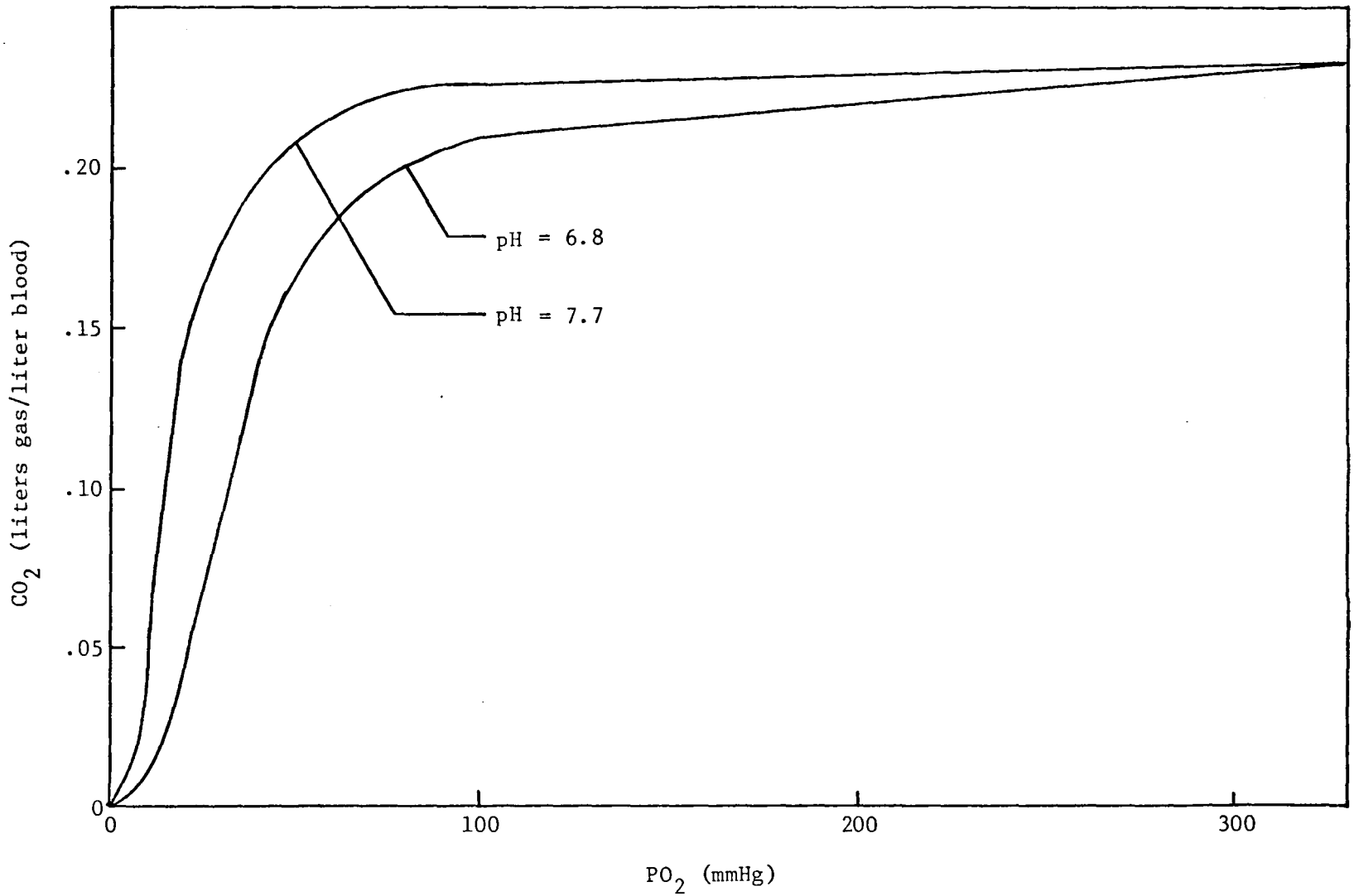

FIGURE 2. INFANT BLOOD OXYGEN DISSOCIATION CURVE

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:

$$P1 = PATM/S1 \times C1, \qquad (D2)$$

where S1 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 CO_2 dissociation relationship. Carbon dioxide forms bicarbonate ions through the following series of reactions: first, the CO_2 is hydrated to form carbonic acid,

$$CO_2 + H_2O \rightleftharpoons H_2CO_3.$$

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

$$H_2CO_3 \rightleftharpoons HCO_3^- + H^+.$$

The majority of CO_2 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:

$$H^+ + Hb^- \rightleftharpoons HHb.$$

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

$$C2 = 0.04161 \times P2^{0.6156},$$

where C2 is the CO_2 content in liters gas/liter blood and;

P2 is the partial pressure of CO_2.

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: (D3)

$$C2 = CARB + 0.375(CAP1 + CAHBO2) - (0.16 + 2.3 \times CAP1) \times \log \frac{C2 - KxS2 \times P2}{.01 \times P2} - 0.14 + K \times SA2 \times P2.$$

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,

$$CARB + 0.375\ (CAP1 - CAHBO2) - (0.16 + 2.3\ CAP1) \times \left(\log \frac{C2 - K \times S2 \times P2}{.01 \times P2} - 0.14\right),$$

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:

$$.0375 \times (CAP1 - CAHBO2),$$

where CAP1 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:

$$(0.16 + 2.3\ CAP1)$$

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

$$\log \frac{C2 - K \times S2 \times P2}{.01 \times P2} - 0.14,$$

is actually the term (PH - 7.41) where the pH is given by the Henderson-Hasselbach equation. The last term,

$$K \times S2 \times P2,$$

represents CO_2 dissolved in the blood. Where

S2 is the CO_2 solubility and

K is a conversion factor to convert atmospheres to mmHg.

Typical CO_2 dissociation curves are shown in Figure 3. This relationship is used for CO_2 dissociation in the blood. Inside the tissue, brain and CSF compartments there is no hemoglobin to affect the CO_2 dissociation. In these compartments an equation similar to this but without hemoglobin effects is used.

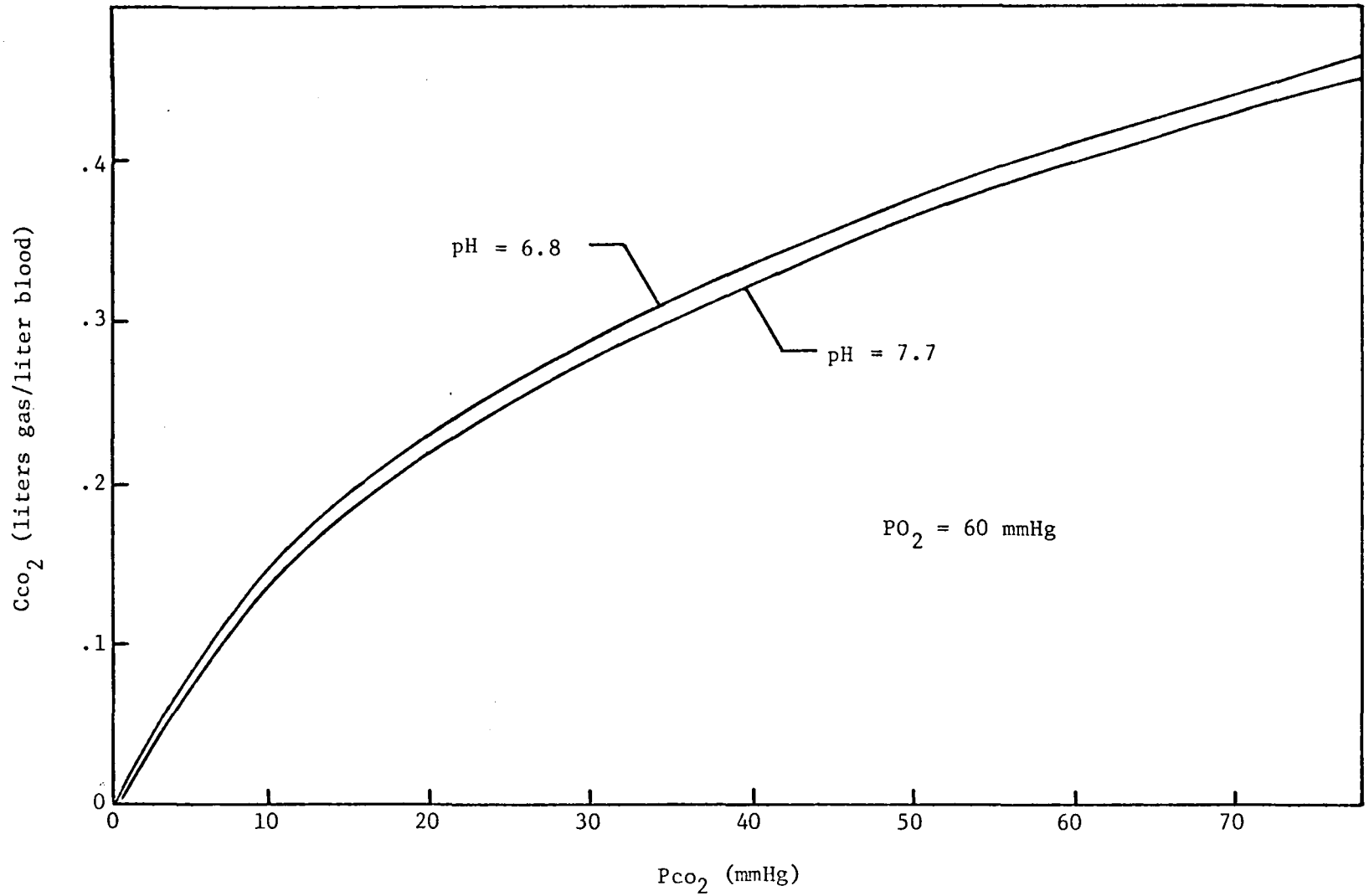

FIGURE 3. INFANT CO_2 DISSOCIATION RELATIONSHIP

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 τ 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

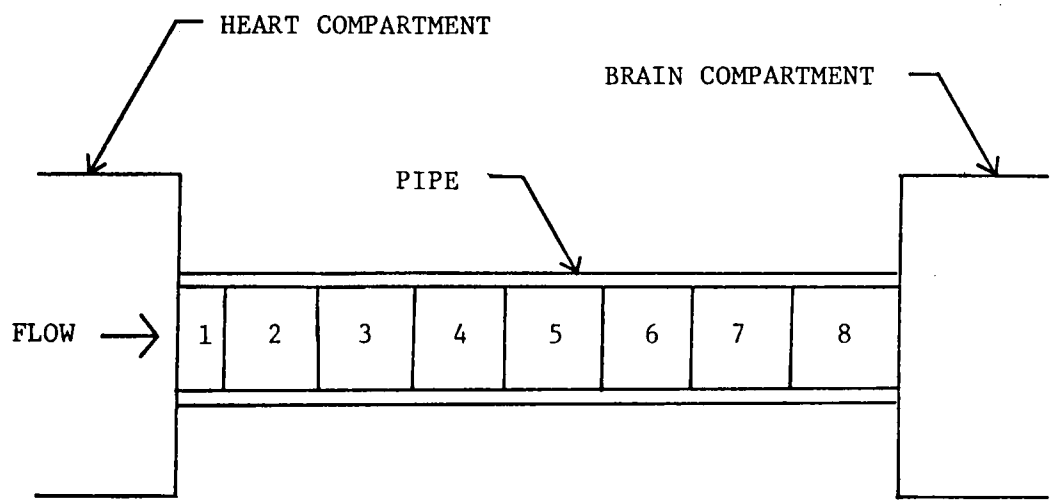

FIGURE 4a. SCHEMATIC DIAGRAM OF HEART - BRAIN TIME DELAY

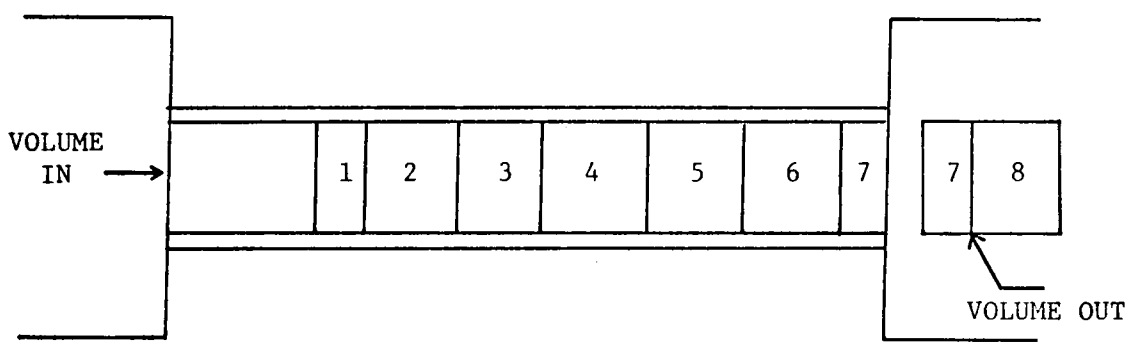

FIGURE 4b. HEART - BRAIN TIME DELAY AFTER ONE INTEGRATION STEP

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 multipled 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 occurence.

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:

$$QD = QDB + QDT, \qquad (H4)$$

where QDB is the blood flow to the brain and;
QDT is the blood flow to the tissues.

QDB, the blood flow to the brain, is a function of the O_2 and CO_2 partial pressures entering the brain compartment.

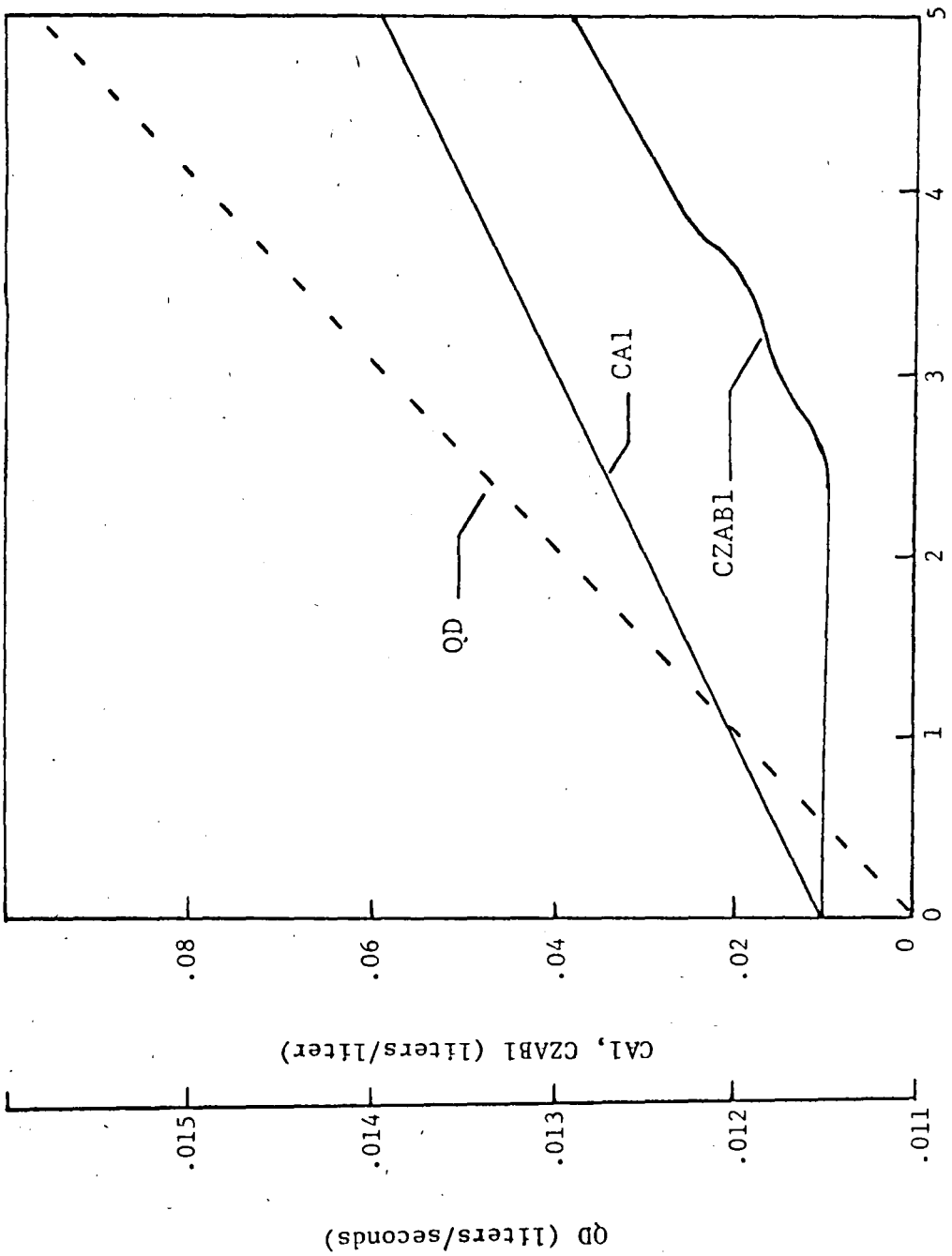

FIGURE 5. TIME DELAY TESTS

It is given by:

$$QDB = \int \frac{((ICQDB + QDB1 + QDB2 - QDB)/TB)dT}{(ICQDB + QDB1 + QDB2)/TB} \qquad (B2)$$

if QDB > .00467, QDB = .00467,

where ICQDB is the normal blood flow;

QDBI 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:

$$QDB1 = 0.0 \quad \text{if} \quad PZAB1 \geq 100 \qquad (B3)$$

$$QDB1 = 6.191(10^{-3}) - 2.941(10^{-4})\ PZAB1 + 5.7869(10^{-6}) \times PZAB1^2 - 5.1663(10^{-8})\ PZAB1^3 + 1.7019(10^{-10}) \times PZAB1^4 \quad \text{if } PZAB1 < 100. \qquad (B4)$$

QDB2 is given by:

$$QDB2 = 5.164(10^{-5}) - 6.9075(10^{-5})\ PZAB2 + 1.782(10^{-6})\ PZAB2^2 \quad \text{if } PZAB2 < 38.0$$

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

$$QDB2 = -3.4634(10^{-2}) + 1.691(10^{-3})\ PZAB2 - 2.878(10^{-5})\ PZAB2^2 + 2.0878(10^{-7})\ PZAB2^3 - 4.8346(10^{-10})\ PZAB2^4 \quad \text{if } PZAB2 > 44.0. \qquad (B5)$$

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:

$$QDT = \int ((QDTI - QDT)/TT)dT \qquad (T2)$$

if QDT > .00933, QDT = .00933

if QDT < .0045, QDT = .0045.

where QDT1 is given by:

$$QDT1 = 9.6092E\text{-}3 + 3.5E\text{-}3 \times (47.65 - PT1). \qquad (T3)$$

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 .0045 liters/sec was added. Also, a physiologically reasonable upper limit of .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

chemorecptors. The pulmonary ventilation equations used are similar in form to those of Milhorn (6).

The pulmonary ventilation is given by:

$$VDPL = WCS4 \times VDCS4 + WPS4 \times VDPS4 + WPS1 \times VDPS1 \quad (L3)$$

where WCS4, WPS4, and WPS1 are weighting factors;

VDCS4 is the contribution of H+ at the central site;

VDPS4 is the contribution of H+ at the peripheral site and;

VDPS1 is the contribution of O_2 tension at the peripheral site.

VDCS4 is given by the equations:

$$VDCS4 = 1.0E6 \times (CCS4 - 3.775E - 8) \text{ if } CCS4 > 3.9688E\text{-}8$$

$$VDCS4 = 7.5E5 \times (CCS4 - 3.685E\text{-}8) \text{ if } CCS4 \leq 3.9688E\text{-}8$$

$$\text{if } VDCS4 < 0.0,\ VDCS4 = 0.0. \quad (L4)$$

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:

$$CCS4 = EXP((-2.303)(PHCS)) \quad (B5)$$

PHPS is the pH at the central site. It is a function of the CO_2 and O_2 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 CO_2 tension at the central site, PCS2, is defined by an equation developed by Mitchell et al. (10).

$$PCS2 = PB2 + (PCF2 - PB2)\ EXP((-280(10^{-6})$$

$$(QDCS \times L2 \times PATM/DB2)^{\frac{1}{2}}) \qquad (B6)$$

280×10^6 is the distance in microns from the brain - CSF interface to the area lateralis.

L2 is the slope of the CO_2 solubility curve.

DB2 is the brain-CSF diffusion constant for CO_2.

PB2 is the CO_2 tension in the brain.

PCF2 is the CO_2 tension in the CSF.

QDCS is the blood flow to the central site.

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

$$VDPS4 = 1.0E6 \times (CPS4 - 3.387E\text{-}8)$$

$$\text{if} \quad VDPS4 < 0.0 \quad VDPS4 = 0.0 \qquad (P1)$$

The peripheral "site" is located in the aortic arch and at the bifurcation of the cartoid arteries. CPS4 is given by:

$$CPS4 = EXP\ (-2.303 \times PHPS) \qquad (P2)$$

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

VDPS1 is given by:

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

$$VDPS1 = 0.0 \quad \text{if} \quad PPS1 \geq 60. \qquad (P3)$$

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

$$VDAV = VDPL - RFREQ\ (VOLDS). \qquad (L5)$$

where RFREQ is the respiratory frequency and;
VOLDS is the respiratory deadspace.

Respiratory frequency is defined by:

$$RFREQ = VDPL/VOLTID,$$

$$\text{if} \quad RFREQ > 1.72\ , \quad RFREQ = 1.72. \qquad (L6)$$

The equations defining VOLTID and VOLDS were obtained from Milhorn (6) and modified for neonatal physiology. These expressions are:

$$VOLTID = 0.015 - 1.351857\ (0.0083 - VDPL) \qquad (L7)$$

$$VOLDS = 0.005 - 0.4333198\ (0.015 - VOLTID). \qquad (L8)$$

The exhaled ventilation rate, VDE, is given by:

$$VDE = VDAV + QDL\ ((CV2 - CAL2) + (CV1 - CAL1) + (CV3 - CAL3))\ /0.938. \qquad (L9)$$

QDL is the lung blood flow given by:

$$QDL = QD - QDS, \qquad (L10)$$

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 ($NaHCO_3$). The $NaHCO_3$ dissociates to form bicarbonate ions (HCO_3^-) and sodium ions (Na^+). Most of the CO_2 carried by the blood is in the form of bicarbonate ions (11). So, increasing the concentrations of bicarbonate is equivalent to increasing CO_2 concentration. This increase in CO_2 concentration will, because of the Bohr effect, facilitate release of O_2 at the tissues. In addition the increase in HCO_3^- will raise the pH.

Because of the advanced dissociation relationships in this model, it is possible to simulate the administration of $NaHCO_3$. To model this treatment, it is assumed that the $NaHCO_3$ dissociates completely to Na^+ and HCO_3^-. Recalling from the section explaining the dissociation relationships, the concentration of CO_2 is the sum of the CO_2 combined as bicarbonate, and the dissolved CO_2. The combined CO_2 is a function of pH and is given by a relationship of the form

$$BHCO_3 = (BHCO_3)_b + A - B\ (pH - 7.41).$$

$(BHCO_3)_b$ 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:

$$C2 - CARB + A + B * (PH - 7.41) + K \times SA2 \times P2.$$

where K and SA2 are constants and;
P2 is the CO_2 tension.

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

$$pH - pK + \log \frac{C2 - K \times SA2 \times P2}{K \times SA2 \times P2}$$

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.

$$CK5 = CB + M \times (CZAK5 - CB). \qquad (K1)$$

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 infants 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 PO_2, PCO_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 PO_2 measured in baby 'A', the alveoli were made completely permeable to O_2 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 PO_2 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 O_2 which occurs at 9200 seconds. The simulated PV1 then

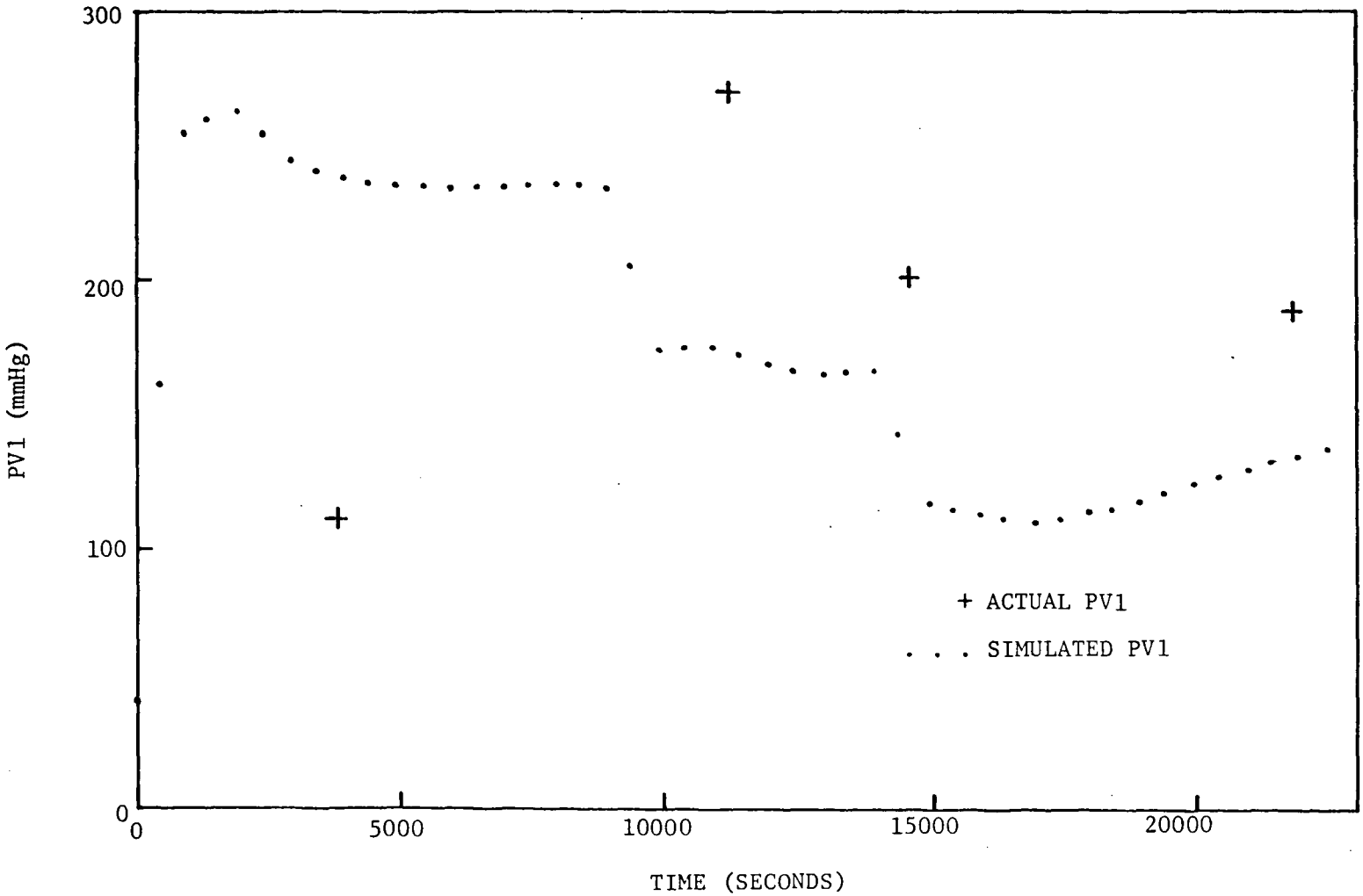

FIGURE 6. GRAPH OF ACTUAL AND SIMULATED PV1

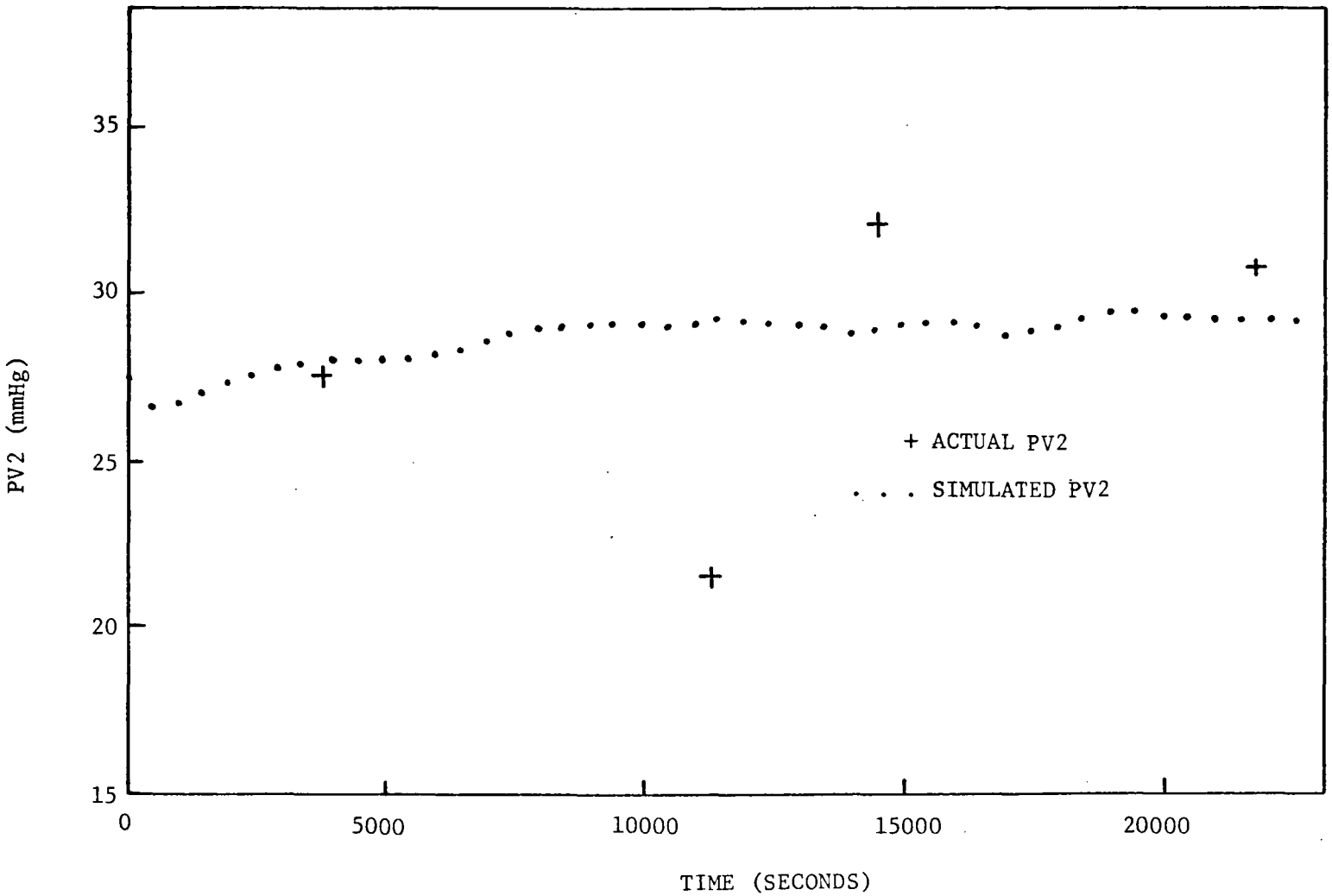

FIGURE 7. GRAPH OF ACTUAL AND SIMULATED PV2

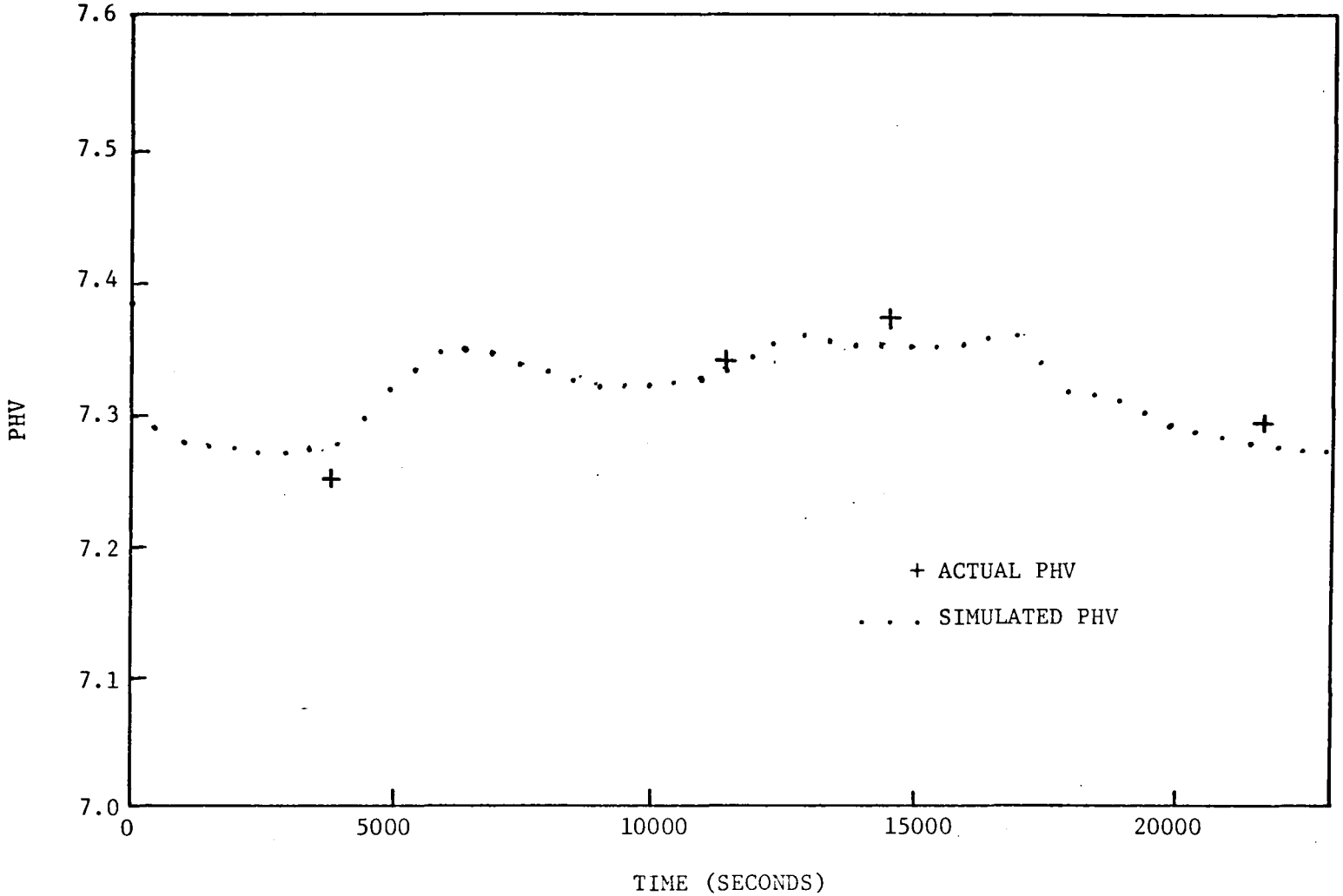

FIGURE 8. GRAPH OF ACTUAL AND SIMULATED PHV

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 occuring 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 igure 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 occuring 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 $\pm$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 CO_2. They, however, had much better results in simulating venous O_2. 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 PT1, a base rate of blood flow was provided. The controller used by Pabst and Robertshaw would shut off blood flow completely at values of PT1 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 Po_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 ouput.
   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.

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APPENDIX

COMPUTER PROGRAM LISTING

```
*****************************************************************
*                                                               *
*                    NEONAT: V      VERSION 2                   *
*                                                               *
*****************************************************************


*                    DEVELOPMENT NOTES

* DATE STARTED                  JUNE 13, 1974
* DEVELOPED BY                  H.H. ROBERTSHAW,J.J. PAUST AND G.A. CAREY


*  AN IMPROVED SIMULATION OF THE NEONATAL RESPIRATORY SYSTEM

*        CONTAINS THE DCT AND DOT LIMITS,

*        NEW CO2 DISSOCIATION RELATIONSHIPS,
*
*        UPDATED INITIAL CONDITIONS, NEW PIPE FUNCTION,
*
*        KIDNEY, AND BICARBONATE INFUSION.
*
```

```
*****************************************************************
*                                                               *
*                        TIME DELAY                             *
*                                                               *
*****************************************************************
MACRO           CZ=NEWPIP(VPARM,CD,RNCON,VOL,J,K,TIME,DELT)
                CZ=PIPEP(VPARM,CD,RNCON,VOL,J,K,TIME,DELT)
ENDMACRO
*****************************************************************


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

MACRO           PCO2=INVDSOC(C-2)
                PCO2=NLFGEN(P2TAB,CO2)
ENDMACRO
*****************************************************************
*                                                               *
*        DISSOCIATION CURVES FOR CO2 IN THE BRAIN AND TISSUES   *
*                                                               *
*****************************************************************
MACRO           CS2,PHB=BDISSOC(PS2,CBR,S2)
                A=K*S2
                CS2=NLFGEN(C2TAB,PS2)
                CAB=KP*((A+PS2)/(CS2-A+PS2))
                PHB=7.0-ALOG10(CAB)
ENDMACRO
```

```
*****************************************************************
*                                                               *
*          DISSOCIATION RELATIONSHIP FOR CO2 IN THE BLOOD       *
*                                                               *
*****************************************************************


MACRO C1,C2,PH=ITR(P2,P1,CARB,S1,S2)
PROCEDURAL
              C1=ALOG10(CGUESS,P2)
              A=K*S2
              C=0.1o2+2.3*CAP1
           21 CAH=KP*((K*S2*P2)/(C1-K*S2*P2))
              PH=3.0-ALOG10(CAH)
              AT=(P1/(1o6.75-22.4*PH))**2.5
              CAHBO2=CAP1*AT/(1.0+AT)
              C1=CAHBO2+S1*P1/P1AT*
              B=CA*3+0.375*(CAP1-CAHBO2)
              C11=C1
           25 C2=B-C*(ALOG10((C11-A*P2)/(.01*P2))-.14)+A*P2
              DIFC=C11-C2
              IF(ABS(DIFC).LE.ERRC)GO TO 38
              C11=C11-DIFC/2.
              GO TO 25
           38 IF(ABS(C2-C1).LT.ERRC)GO TO 43
              C1=C1-(C1-C2)/2.
              GO TO 21
           40 CONTINUE
ENDMACRO
```

```
*****************************************************************
*                                                               *
*          INVERSE DISSOCIATION RELATIONSHIP FOR CO2 IN BLOOD   *
*                                                               *
*****************************************************************

MACRO  P1,P2,PH2=INVIT2(C2,C1,CAR1,S1,S2)
PROCEDURAL
              P1=NLFG=N(PGUESS,C2)
              A=K*S2
              C=0.162+2.3*CAP1
              20 CAH=KP*((K*S2*PI)/(C2-K*S2*PI))
              PH2=9.0-ALOG10(CAH)
              P1=INTVAR(PLTAB,CL,PH2)
              CAH=O2=C1-S1*P1/PATM
              B=CAR1+.375*(CAP1-CAH=O2)
              PII=PI
              55    NUM=(C2-A*PII)*100.
              EX=(-C2+B+A*PII)/C+.14
              IF(EX)15,15,25
              25     DEN=10.**EX
              GO TO 95
              15   DEN=1./(10.**(-EX))
              95   P2=NUM/DEN
              DIFP=PII-P2
              IF(ABS(DIFP).LE.ERRP)GO TO 35
              IF(P2.GT.90.)GO TO 13
              PII=P2
              GO TO 12
              13 PII=PII-(PII-P2)/2.
              12 CONTINUE
```

```
                GO TO 55
                35  IF(ABS(P2-P1).LE.EPS)GO TO 55
                P1=P1-(P1-P2)/2.
                GO TO 20
                55 CONTINUE
ENDMACRO
```

```
INITIAL
*****************************************************************************
*                                                                           *
*            INITIAL CONDITIONS, CONSTANTS, AND PARAMETERS                  *
*                                                                           *
*****************************************************************************
```

```
PARAMETER       CB=.12,A=.995,MAX=1.0
PARAMETER       DAV2=5.0,DAV3=1.0,DAV1=1.0
PARAMETER       AKB1=0.00002,TBC=2.5
PARAMETER       RISE=20
CONSTANT        K=.00132,KP=700.,EPC=.01,EPRP=1.0
CONSTANT        CAP1=0.221
CONSTANT        D01=7.26835-3,D02=1.38658-7,D03=4.20670-9
CONSTANT        L2=6.71052E-4
CONSTANT        PAT1=760.
                PRE1=PAT1-47.0
CONSTANT        RG=0.75
CONSTANT        SA1=.024,SA2=0.47,SA3=.01295
CONSTANT        SB1=.024,SB2=0.47,SB3=.01295
```

```
CONSTANT        SCF1=.024,SCF2=0.47,SCF3=.01295
CONSTANT        SCS1=.024,SCS2=0.47,SCS3=.01295
CONSTANT        SL1=.024,SL2=0.47,SL3=.01295
CONSTANT        ST1=.024,ST2=0.47,ST3=.01295
CONSTANT        SV1=.024,SV2=0.47,SV3=.01295
CONSTANT        TH=5,TM=5,TT=5,TS=60
CONSTANT        VGLA0=.030005,VGLAV=.1,VGLAPS=.0135,VGLAT=.0766
CONSTANT        VGLM=.2,VGLSF=.02,VGLT=2.0,VGLVB=.049995
CONSTANT        VGLVT=.11499
CONSTANT        WAT=.4,WEIGHT=2.05,WCS4=.05,WPS1=1.0,WPS4=.12
CONSTANT        X2=.0005
                X1=0.2005
                X3=0.7009
CONSTANT        IPZPS1=60.
CONSTANT        IPZPS2=25.
CONSTANT        IPZAB1=60.
CONSTANT        IPZAB2=25.
CONSTANT        IPHAB=7.4
INCON           ICS2=.3
INCON           IPZPH=7.4
INCON           ICAV1=104,ICAV2=25.0,ICAV3=575
INCON           ICB1=.00116,ICB2=.36,ICB3=.00192
INCON           ICCF1=56.4,ICCF2=25.0,ICCF3=565
INCON           ICQDT=.0011597,ICQDS=.001645,ICQDG=.00099937
INCON           ICT1=.001591,ICT2=.25,ICT3=.0006505
INCON           ICZAB1=.22778,ICZAB2=.2,ICZAB3=.000484
INCON           ICZAT1=.22790,ICZAT2=.2,ICZAT3=.0003656
INCON           ICZPS1=.25  ,ICZPS2=.225
INCON           ICZV01=.10107,ICZV02=0.2,ICZV03=.001224
INCON           ICZVT1=0.19775,ICZVT2=0.2,ICZVT3=.0006497
```

```
*        TABULAR  DISSOCIATION RELATIONSHIP FOR CO2

FUNCTION P2TAB=(.0379,5.),(.1449,10.),(.2235,20.),...
               (.2912,30.),(.3271,40.),(.3858,50.),...
               (.3997,60.),(.4300,70.),(.4576,80.),...
               (.4830,90.)
FUNCTION C2TAB=(5.,.0379),(10.,.1449),(20.,.2235),...
               (30.,.2912),(40.,.3291),(50.,.3858),...
               (60.,.3997),(70.,.4300),(80.,.4576),...
               (90.,.4830)
*          ACTUAL INFANT DATA
FUNCTION      BB1PV1=(0.,50.),(3400.,110.),(11300.,270.),...
              (14600.,290.),(21300.,157.),(27200.,145.),...
              (30600.,88.),(34800.,53.)
FUNCTION      BB1PV2=(0.,27.5),(3400.,27.5),(11300.,21.5),...
              (14600.,32.),(21300.,31.),(27200.,28.),...
              (30600.,35.),(34800.,37.)
FUNCTION      BB1PHV=(0.,7.25),(3400.,7.25),(11300.,7.34),...
              (14600.,7.37),(21300.,7.29),(27200.,7.30),...
              (30800.,7.38),(34800.,7.34)

*      INITIAL GUESS FOR ITERATION SCHEME

FUNCTION PGUESS=(.1,4.0),(.2,10.),(.3,22.),...
                (.4,38.),(.5,63.),(.6,95.),...
                (.7,140.),(.8,196.),(.9,256.)
FUNCTION CGUESS=(4.0,.1),(10.,.2),(22.,.3),...
                (38.,.4),(63.,.5),(95.,.6),...
                (140.,.7),(196.,.8),(256.,.9)
```

```
*           TABULAR O2 DISSOCIATION RELATIONSHIP

FUNCTION PLTAB,6.3=(0.0,0.0),(.00991,10.),(.0438,20.),...
                   (.13220,40.),(.17075,60.),(.19957,80.),...
                   (.20978,100.),(.22949,300.),(.24496,760.)
FUNCTION PLTAB,7.2=(0.0,0.0),(.01976,10.),(.07867,20.),...
                   (.1682,40.),(.19965,60.),(.21156,80.),...
                   (.21715,100.),(.2300,300.),(.24495,760.)
FUNCTION PLTAB,7.3=(0.0,0.0),(.02425,10.),(.09663,20.),...
                   (.17703,40.),(.20490,60.),(.21891,80.),...
                   (.21955,100.),(.23011,300.),(.24496,760.)
FUNCTION PLTAB,7.4=(0.0,0.0),(.03021,10.),(.1044,20.),...
                   (.13547,40.),(.20795,60.),(.21991,80.),...
                   (.21973,100.),(.23019,300.),(.24493,760.)
FUNCTION PLTAB,7.5=(0.0,0.0),(.03829,10.),(.11946,20.),...
                   (.19533,40.),(.21144,60.),(.21785,80.),...
                   (.22064,100.),(.23025,300.),(.2448,760.)
FUNCTION PLTAB,7.6=(0.0,0.0),(.04934,10.),(.13709,20.),...
                   (.20043,40.),(.21444,60.),(.21935,80.),...
                   (.22175,100.),(.23031,300.),(.2449,760.)
FUNCTION PLTAB,7.7=(0.0,0.0),(.05427,10.),(.1230,20.),...
                   (.19426,40.),(.21555,60.),(.22154,80.),...
                   (.22363,100.),(.2309,300.),(.2491,760.)
**********************************************************************

*          DYNAMIC SECTION OF MODEL
DYNAMIC
               PI1=X1*PWCT
               PI2=X2*PWCT
               PI3=X3*PWCT
```

```
G
**********************************************************************
*                                                                    *
*              METABOLIC RATE EQUATIONS                              *
*                                                                    *
**********************************************************************

      MR=MRX*MRB
      METR=(MR*WGHT)/60000.
      MR42=MR01
      MRT1=(METR-MR81)
      MRT2=(METR*BSA-MR82)


**********************************************************************
*                                                                    *
*                        BRAIN COMPARTMENT                           *
*                                                                    *
**********************************************************************

*  TIME DELAY EQUATIONS FOR ARTERIAL FLOW FROM HEART TO BRAIN

      CZAB1=DELAYPIP(CA1,2DB,ICZAB1,VOLAB,3,1,TIME,DELT)
      CZAB2=DELAYPIP(CA2,2DB,ICZAB2,VOLAB,3,2,TIME,DELT)
```

```
              CZAB3=NCWPIP(CA3,QDB,ICZAB3,VOLAB,3,5,TIME,DELT)
              CZAB5=NCWPIP(CA5,QDB,C5,VOLAB,3,25,TIME,DELT)
              PZAB1=NCWPIP(PA1,QDB,IPZAB1,VOLAB,3,4,TIME,DELT)
              PZAB2=NCWPIP(PA2,QDB,IPZAB2,VOLAB,3,5,TIME,DELT)

*   MASS BALANCE EQUATIONS

              CQB1=(QDB*(CZAB1-CVB1)-PRB1-QB1*(PB1-PCF1))/VOLB
              CB1=INTGRL(IC81,CQB1)
              PB1=PATM/SB1*CB1
              CQB2=(QDB*(CZAB2-CVB2)+PRB2-QB2*(PB2-PCF2))/VOLB
              CB2=INTGRL(IC82,CQB2)
              CQB3=(QDB*(CZAB3-CVB3)-QB3*(PB3-PCF3))/VOLB
              CB3=INTGRL(IC83,CQB3)
              PB3=PATM/SB3*CB3
              PB2=IDOSUC(CB2)
              CVB3=SV3*PB3/PATM
              CVB1,CVB2,PHVB=ITER(PB2,PB1,CZAB5,SV1,SV2)
              CB5=REALPL(CB,.75,CZAB5)
*   TIME DELAY EQUATIONS FOR VENOUS FLOW FROM BRAIN TO HEART

              CZVB1=NCWPIP(CVB1,QDB,ICZVB1,VOLVB,3,7,TIME,DELT)
              CZVB2=NCWPIP(CVB2,QDB,ICZVB2,VOLVB,3,6,TIME,DELT)
              CZVB3=NCWPIP(CVB3,QDB,ICZVB3,VOLVB,3,4,TIME,DELT)
              CZVB5=NCWPIP(CB5,QDB,C5,VOLVB,3,25,TIME,DELT)


*   BLOOD FLOW TO BRAIN EQUATIONS

              QDB=(IQDB+QB1+QB2-QB3)/TB
              QDBI=INTGRL(IQDB,QDB)
PROCEDURE     QB3=FN(QDBI)
```

```
                QDB=QDB1
                IF(QD.GT..00467)QDB=.00467
                IF(QDB.LT..001)QDB=.001
ENDPROCEDURE
PROCEDURE       QDB1,QDB2=VASSO(PZAB1,PZAB2)
                IF(PZAB1.LT.100.)GO TO 100
                QDB1=0.0
                GO TO 200
                100 QDB1=6.191E-3-2.941E-4*PZAB1+5.730E-6*PZAB1**2...
                -5.1662E-8*PZAB1**3+1.7012E-10*PZAB1**4
                200 IF(PZAB2.GE.300.)GO TO 300
                QDB2=5.194E-5-6.9375E-5*PZAB2+1.702E-6*PZAB2**2
                GO TO 500
                300 IF(PZAB2.GT.400.)GO TO 400
                QDB2=0.0
                GO TO 500
                400 QDB2=-5.4634E-2+1.691E-3*PZAB2-2.670E-5*PZAB2**2...
                +2.087E-7*PZAB2**3-4.8246E-10*PZAB2**4
                500 CONTINUE
ENDPROCEDURE
```

```
*                                                                      *
*                    CEREBROSPINAL FLUID COMPARTMENT                   *
*                                                                      *
************************************************************************
*  MASS BALANCE EQUATIONS
      PDCF1=(QB1/(VOLCF*SCF1*K))*(PB1-PCF1)
      PCF1=INTGRL(ICCF1,PDCF1)
      PDCF2=(QB2/(VOLCF*SCF2*K))*(PB2-PCF2)
      PCF2=INTGRL(ICCF2,PDCF2)
      PDCF3=(QB3/(VOLCF*SCF3*K))*(PB3-PCF3)
      PCF3=INTGRL(ICCF3,PDCF3)
************************************************************************
*                                                                      *
*                         LUNG COMPARTMENT                             *
*                                                                      *
************************************************************************
*  MASS BALANCE EQUATIONS
      PAV1=INTGRL(ICAV1,PDAV1)
      PDAV1=(PATM*QOL*(CV1-CAL1)+VDAV*PI1-VDS*PAV1)/VOLAV
      PAV2=INTGRL(ICAV2,PDAV2)
      PDAV2=(PATM*QOL*(CV2-CAL2)+VDAV*PI2-VDS*PAV2)/VOLAV
      PAV3=INTGRL(ICAV3,PDAV3)
      PDAV3=(PATM*QOL*(CV3-CAL3)+VDAV*PI3-VDS*PAV3)/VOLAV

*  ALVEOLAR PERMEABILITY EQUATIONS

      PAL1=PAV1*CAV1
      PAL2=PAV2*CAV2
      PAL3=PAV3*CAV3
```

```
*  ARTERIAL GAS CONCENTRATIONS LEAVING THE LUNGS

              CAL1,CAL2,PHAL=ITR(PAL2,PAL1,CV5,SA1,SA2)
              CAL3=PAL3*SA3/PATM

*  VENTILATION RATE EQUATIONS

              VDAV=VDPL-VDDS
              VDE=VDAV+VDL*((CV2-CAL2)+(CV1-CAL1)+(CV3-CAL3))/0.9381S8
              VDDS=RFR=0*VDLDS
              VDLDS=0.005-0.4333193*(0.015-VOLTID)
PROCEDURE     VOLTID,RFRQ=RF(VDPL)
              VOLTID=0.015-1.351357*(0.0083-VDPL)
              IF(VOLTID.GT..0416)VOLTID=.0416
              RFRQ=VDPL/VOLTID
              IF(RFRQ.GT.1.72)RFRQ=1.72
ENDPROCEDURE

              VDPL=VDCS4+VDPS1+VDPS4

*  PULMONARY VENTILATION DUE TO CENTRAL CHEMORECEPTORS

PROCEDURE     VDCS4=CS(CCS4,WCS4)
              IF(CCS4.GT.3.0038E-2)GO TO 600
              VDCS4=.795*(CCS4-3.605E-2)
              GO TO 700
  600         VDCS4=.187*(CCS4-3.775E-2)
  700         IF(VDCS4.LT.0.0)VDCS4=0.0
              VDCS4=VDCS4*WCS4
ENDPROCEDURE

*  PULMONARY VENTILATION DUE TO PERIPHERAL CHEMORECEPTORS
```

```
PROCEDURE     VDPS1,VDPS4=PS(PPS1,CPS4,WPS1,WPS4)
              VDPS1=0.002083*(60.-PPS1)
              IF(VDPS1.LT.0.0)VDPS1=0.0
              VDPS1=VDPS1*WPS1
              VDPS4=1.0E06*(CPS4-3.387E-3)
              IF(VDPS4.LT.0.0)VDPS4=0.0
              VDPS4=VDPS4*WPS4
ENDPROCEDURE

*  LUNG BLOOD FLOW RATE EQUATION

              QDL=QD-VDS

**********************************************************************

**********************************************************************
*                                                                    *
*                          HEART COMPARTMENT                         *
*                                                                    *
**********************************************************************

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

              CV1=(VDS*CZV3L+QDT*CZVT1)/QD
```

```
                CV2=(QDD*CZVB2+QDT*CZVT2)/QD
                CV3=(QDS*CZVB3+QDT*CZVT3)/QD
                CV5=(QDS*CZVB5+QDT*CZVK5)/QD

*   VENOUS PARTIAL PRESSURES
                PV1,PV2,PHV=INITR(CV2,CV1,CA5,SA1,SA2)
*   AORTIC GAS CONCENTRATIONS LEAVING LEFT VENTRICLE

                CA1=(QDL*CAL1+QDS*CV1)/QD
                CA2=(QDL*CAL2+QDS*CV2)/QD
                CA3=(QDL*CAL3+QDS*CV3)/QD
                CA5=(CV5*QD+CARB*FLOW)/(QD+FLOW)
                PA1,PA2,PHA=INITR(CA2,CA1,CA5,SA1,SA2)
*   CARDIAC OUTPUT AND SHUNTING EQUATIONS

PROCEDURE       QD=AFLOW(QDT,PDB)
                QD=QDT+QDM
                IF(QD.GT.0.0)GO TO 710
                QD=0.00001
                WRITE(6,709)
                709 FORMAT(' CARDIAC OUTPUT ZERO.  RESET TO 1E-5.')
                710 CONTINUE
ENDPROCEDURE
PROCEDURE       WSHUNT=SHUNT(PPS1)
                WSHUNT=60.-1.0545*(PPS1-25.0)
                IF(WSHUNT.GT.60.)WSHUNT=60.
                IF(WSHUNT.LT.2.)WSHUNT=2.
                WSHUNT=WSHUNT/100.
ENDPROCEDURE
                QDDS=(QD*WSHUNT-QDS)/TS
                QDS=INTGRL(IQDS,QDDS)
```

```
*****************************************************************************
*                                                                           *
*                          TISSUE COMPARTMENT                               *
*                                                                           *
*****************************************************************************

*  TIME DELAY EQUATIONS FOR ARTERIAL FLOW FROM HEART TO TISSUES

      CZAT1=NEWPIP(CA1,QDT,ICZAT1,VOLAT,3,11,TIME,DELT)
      CZAT2=NEWPIP(CA2,QDT,ICZAT2,VOLAT,3,11,TIME,DELT)
      CZAT3=NEWPIP(CA3,QDT,ICZAT3,VOLAT,3,12,TIME,DELT)
      CZAT5=NEWPIP(CA5,QDT,CB,VOLAT,3,27,TIME,DELT)

*  MASS BALANCE EQUATIONS

      CDT1=(QDT*(CZAT1-CVT1)-MRT1)/VOLT
      CT1=INTGRL(ICT1,CDT1)
      PT1=PATM/ST1*CT1
      CDT2=(QDT*(CZAT2-CVT2)+MRT2)/VOLT
      CT2=INTGRL(ICT2,CDT2)
      CVT1,CVT2,PHVT=ITER(PT2,PT1,CZAT5,SV1,SV2)
      PT2=IGLOO(CT2)
      CDT3=(QDT*(CZAT3-CVT3))/VOLT
      CT3=INTGRL(ICT3,CDT3)
      PT3=PATM/ST3*CT3
      CVT5=SV3*PT5/PATM
      CT5=REALPL(CB,.75,CZAT5)
```

```
*  TIME DELAY EQUATIONS FOR VENOUS FLOW FROM TISSUES TO HEART

                CZVT1=NEWPIP(CVT1,QDT,ICZVT1,VOLVT,3,13,TIME,DELT)
                CZVT2=NEWPIP(CVT2,QDT,ICZVT2,VOLVT,3,14,TIME,DELT)
                CZVT3=NEWPIP(CVT3,QDT,ICZVT3,VOLVT,3,15,TIME,DELT)

*  TISSUE BLOOD FLOW EQUATION

PROCEDURE       QDT=VASQT(PT1,TT,ICQDT)
                QDT1=9.6052E-3+3.5E-3*(47.65-PT1)
                IF(QDT1.LT.0.0)QDT1=0.0
                QDDT=(QDT1-QDT)/TT
                QDT=INTGRL(ICQDT,QDDT)
                IF(QDT.LT..0045)QDT=.0045
                IF(QDT.GT..02)QDT=.02
ENDPROCEDURE

*****************************************************************************
*                                                                           *
*                                  KIDNEY                                   *
*                                                                           *
*****************************************************************************

                CZAKS=CTS
                CKS=CS+1.*(CZAKS-CS)
                CZVKS=NEWPIP(CKS,QDT,CS,VOLVT,3,28,TIME,DELT)

*****************************************************************************
*                                                                           *
*                              CHEMORECEPTORS                               *
*                                                                           *
*****************************************************************************
```

```
*   PERIPHERAL CHEMORECEPTORS

                PPS4=NEWPIP(PA4,QDR,IPZPS4,VCLAPS,3,22,TIME,DELT)
                CPS4=EXP(-2.303*PHPS)
                PHPS=NEWPIP(PHA,QDR,IPZPH,VCLAPS,3,24,TIME,DELT)
*   CENTRAL CHEMORECEPTORS

                CCS2,PHCS=BOISOC(PCS2,CBR,SL2)
                CCS4=EXP(-2.303*PHCS)
                PCS2=PB2+(PCF2-PB2)*EXP(-260.05-6*SQRT(QDCS*L2*PATM/DB2))
                QDCS=QDB

*****************************************************************************

PROCEDURE       CARB,FLOW=BIC(TIME)
                CALL BICARB(TIME,CARB,FLOW)
ENDPROCEDURE
PROCEDURE       X1,X3=INHALE(TIME,RISE)
                CALL RESP(TIME,RISE,X1,X3)
ENDPROCEDURE

                ACTPV1=AFGEN(SB1PV1,TIME)
                ACTPV2=AFGEN(SB1PV2,TIME)
                ACTPHV=AFGEN(SB1PHV,TIME)
```

```
NOSORT
CALL DEBUG(1,0.0)
CALL DEBUG(1,5.0)
CALL DEBUG(1,10.)
CALL DEBUG(1,1000.)
CALL DEBUG(1,2000.)
CALL DEBUG(1,5000.)
CALL DEBUG(1,10000.)
CALL DEBUG(1,15000.)
CALL DEBUG(1,20000.)
CALL DEBUG(1,22000.)
CALL DEBUG(1,23000.)
CALL DEBUG(1,24000.)
CALL DEBUG(1,25000.)
CALL DEBUG(1,26000.)
CALL DEBUG(1,27000.)
CALL DEBUG(1,28000.)
CALL DEBUG(1,29000.)
TERMINAL


  METHOD  RKSFX


TIMER      FINTIM=24000.,DELT=.75,OUTDEL=200.

OUTPUT WSHUNT
OUTPUT  CK5,CT5,CR
PAGE GROUP(0.,.8)
OUTPUT FLOW,X1,MAX
```

```
OUTPUT VOAV
OUTPUT RFREQ (0.0,1.75)
OUTPUT VOPL
OUTPUT  CA5,CV5,CB
PAGE GROUP(0.0,.8)
OUTPUT CA55
OUTPUT PA1,PA2
PAGE GROUP(0.0,600.)
OUTPUT  PV2,ACTPV2
PAGE GROUP(0.0,300.)
OUTPUT PV1,ACTPV1
PAGE GROUP(0.0,500.)
OUTPUT PCF1,PCF2
PAGE GROUP(0.0,600.)
OUTPUT PCS2
OUTPUT PAL1,PAL2
PAGE GROUP(0.0,600.)
OUTPUT QOT,QOS
OUTPUT QO (0.0,.025)
OUTPUT PHV,ACTPHV
PAGE GROUP(6.5,7.8)
OUTPUT PHPS,PHCS
PAGE GROUP(6.5,7.8)
OUTPUT PS2 (0.0,500.)
OUTPUT PHA,PHAL
PAGE GROUP(6.5,7.8)
OUTPUT PPS1
PAGE GROUP(0.0,600.)
OUTPUT  PG1,PT1
PAGE GROUP(0.0,600.)
OUTPUT CCS2
OUTPUT VOPS1,VOPS4,VOCS4
```

```
      SUBROUTINE BICARB(TIME,CARB,FLOW)
      REAL DTIME(14)/0.0,3300.,6500.,9200.,11300.,
     *13100.,14600.,16400.,23600.,25400.,27200.,
     *29000.,30800.,50000./
      REAL DCARB(13)/0.0,2.69,2.69,2.69,2.69,2.69,2.69,
     *0.0,2.69,2.69,2.69,2.69,0.0/
      REAL DFLOW(13)/0.0,.005,.001,.002,.003,.001,.004,.01,
     *.006,.006,.003,.003,0.0/
      I=1
  100 I=I+1
      IF(TIME.LE.DTIME(I))GO TO 2
      GO TO 100
    2 CARB=DCARB(I-1)
      DEL=DTIME(I)-DTIME(I-1)
      FLOW=DFLOW(I-1)/DEL
      RETURN
      END
00
      SUBROUTINE RESP(TIME,RISE,X1,X3)
      REAL DTIMES(20)/200.,2000.,9200.,14600.,20000.,25400.,
     *                27200.,999999.,12*0.0/
      REAL PDEL(21)/20.95,100.,93.,77.,62.,54.,40.,20.95,13*0.0/
      I=0
  100 I=I+1
      IF(TIME.LE.DTIMES(I))GO TO 200
      IF((TIME-RISE).LE.DTIMES(I))GO TO 300
      GO TO 100
  200 X1=PDEL(I)/100.
      X3=1.0-X1
      RETURN
  300 X1=((PDEL(I+1)-PDEL(I))/RISE*(TIME-DTIMES(I))+PDEL(I))/100.
      X3=1.0-X1
```

```
      FUNCTION PIPEP(VPARM,QD,RNCON,VOL,J,K,TIME,DELT)
      DIMENSION PARAM(300,3,30),NTOT(30)
      IF(TIME.NE.0.0)GO TO 100
      TOLD=TIME
      KOLD=0
      VIN=QD*DELT
      NI=VOL/VIN
      RN=VOL/VIN
      DV=(RN-NI)*VIN
      NTOT(K)=NI+1
      NT=NI+1
      PARAM(1,1,K)=DV
      DO 1 I=2,NT
1     PARAM(I,1,K)=VIN
      DO 2 I=1,NT
2     PARAM(I,J,K)=RNCON
      PIPEP=RNCON
      GO TO 200
100   VOLIN=QD*DELT
      M=-1
      VOLT=0.0
      PX=0.0
      NT1=NTOT(K)
4     M=M+1
      NT1=NT1-M
      VOLT=VOLT+PARAM(NT1,1,K)
      IF(VOLT.LE.VOLIN)GO TO 3
      GO TO 5
 3    PX=PX+PARAM(NT1,J,K)*PARAM(NT1,1,K)
      GO TO 4
5     PXX=PARAM(NT1,J,K)*(PARAM(NT1,1,K)-(VOLT-VOLIN))
      PIPEP=(PX+PXX)/VOLIN
```

```
      NTOT(K)=NTOT(K)-M+1
      NTOTI=NTOT(K)
      INT=NTOTI-1
      PARAM(NTOTI,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)=VPARM
      IF(TIME.EQ.TOLD)GO TO 11
      TOLD=TIME
      KOLD=K
      GO TO 12
11    IF(KOLD.EQ.K)GO TO 200
      KOLD=K
12    DO 7 NN=2,INT
      N=NTOTI+1-NN
7     PARAM(N,1,K)=PARAM(N-1,1,K)
      PARAM(1,1,K)=VOLIN
      PARAM(NTOTI,1,K)=VOLT-VOLIN
200   CONTINUE
      RETURN
      END
```

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AN IMPROVED DIGITAL COMPUTER SIMULATION OF THE NEONATAL RESPIRATORY SYSTEM

by

George Alfred Carey

(ABSTRACT)

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 contentration 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.