AN ANALYTICAL AND EXPERIMENTAL INVESTIGATION OF RESPIRATORY DYNAMICS USING P/D CONTROL AND CARBON DIOXIDE FEEDBACK

by

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ABSTRACT

This thesis addresses the problem of defining the control law for human respiration. Seven different drivers have been identified as possibly having an input to the respiratory controller. These seven represent a combination of feedforward and feedback inputs arising from neural and humoral mechanisms.

Using the assumption that carbon dioxide concentrations in the arterial blood have the strongest effect, a control equation with proportional and derivative components based on this driver was evaluated. The methodology for the evaluation was to create a model of the respiratory system incorporating the P/D controller, obtain experimental data of one test subject's respiratory response to exercise, then compare model generated output with experimental data, and adjust the parameters in the control equation to yield optimal model performance.

The usual practice of testing controller performance has been to apply single step loads to a model and evaluate its response. A multi-step protocol was used here to provide a better, more generalized test of controller performance. This thesis may represent the first documented use of an approach of this type for evaluating respiratory controller performance.

Application of a multi-step protocol revealed a non-linear controller was needed to keep pace with system changes. Respiratory system operation was effectively managed using a controller of the form:

$$\text{VENTILATION} = F(dCO2/dT,Q) + F(CO2,Q) + \text{CONSTANT}.$$

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I would like to extend a special thanks to Dr. H.H. Robertshaw. I came to VPI with one very short year to pursue graduate study, a grace period to revitalize a mind saturated with the 9 to 5. I asked for something different from classical mechanical engineering; something I had never done before. He answered with an endeavor that was a combination of control theory and biomedical engineering. It was exactly what I needed.

I would like to finish with a thanks and so long to all the people I met at VPI and in Blacksburg that made my year away from the rat-race a very special one.

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NOMENCLATURE

SUBSCRIPTED VARIABLES

CHARACTER	SUBSCRIPTS LOCATION	SUBSCRIPTS SPECIES	DEFINITION	UNITS
C	i	j	Concentration of gas	L/L
	a	O2	In arterial blood	
		CO2		
	A	O2	In alveolar gas	
		CO2		
	V	O2	In venous blood	
		CO2		
CDOT	i	j	Time rate of change of C	L/(L*t)
	a	O2	In arterial blood	
		CO2		
	A	O2	In alveolar gas	
		CO2		
	V	O2	In venous blood	
		CO2		
F	i	j	Fractional concentration of gas	L/L
	I	O2	In inspired air	
		CO2		
	E	O2	In expired air	
FDOT	i	j	Time rate of change of F	L/(L*t)
	I	O2	In inspired air	
		CO2		
	E	O2	In expired air	
M	i		Mass of CO2	L
	in		Entering lung	
	out		Leaving lung	
	lung		Storage	
MDOT	i		Time rate of change of M	L/sec
	in		Entering lung	
	out		Leaving lung	
	lung		Storage	
P	i	j	Partial pressure of gas, arterial blood	mmHG
	a	CO2		
		O2		
	A	CO2	In alveolar air	
		O2		
PDOT	i	j	Arterial blood gas, derivative	mmHG
	a	CO2		
		O2		
	A	CO2	In alveolar air	

NON-SUBSCRIPTED VARIABLES

CHARACTER	DEFINITION	UNITS
CC	Gain, proportional	None
CO2	Carbon dioxide	None
CONV	Conversion, dry to saturated air	None
F	Breathing frequency	Cyc/min
H+	Hydrogen ion	None
O2	Oxygen	None
PATM	Barometric pressure	mmHG
Q	Blood flow rate	L/sec
SAT	Percent saturation of hemogloben	None
SCV	Saunder's control value, gain	None
TV	Tidal Volume	L
t	Time	Sec
VBL	Volume of blood in lung	L
VBLDOT	Time rate of Change of VBL	L/sec
VD	Volume dead space	L
VDALV	Volume of alveoli dead space	L
VDAN	Volume of anatomical dead space	L
VL	Lung Volume	L
VLDOT	Time rate of change of VL	L/sec

1.0 INTRODUCTION

Any dynamic system has either an implicit or explicit control mechanism that manages its operation. In the simplest of systems the control mechanism receives an input coming to the system and sets parameters for plant operation based only on what has been received. This is open-loop control, see Fig. #1.

The open-loop design is not a forgiving means of control. It assumes that system operation is not susceptible to any variations. For example, an open-loop automobile speed control system would control engine output at one power level regardless of whether the car was going uphill, downhill, or around a curve. In the case of respiration, an open-loop controller would set a breathing rate corresponding to a work level. It would ignore altitude, temperature effects, or air quality.

When the control mechanism also monitors system performance and uses this information to help direct system operation, it is termed closed-loop control, see Fig. #2. Closed-loop control monitors system output and adjusts system operation to ensure the output is correct. When a system is affected by a disturbance it is moved from its steady-state operation. The closed-loop controller can respond to the disturbance. This is the major advantage of feedback. The output is less sensitive to variations and, therefore, precise knowledge of system characteristics is not necessary. Closed-loop control can make corrections in operation using feedforward or a feedback control.

In a feedforward mode, the controller estimates the effect of a disturbance and then modulates operation. In feedback, the controller must wait until the disturbance appears in the system output before making adjustments. Feedforward improves system speed at the expense of increasing the error between desired and actual output. Feedback is slower, but improves accuracy.(1) Feedback can also adversely impact on system

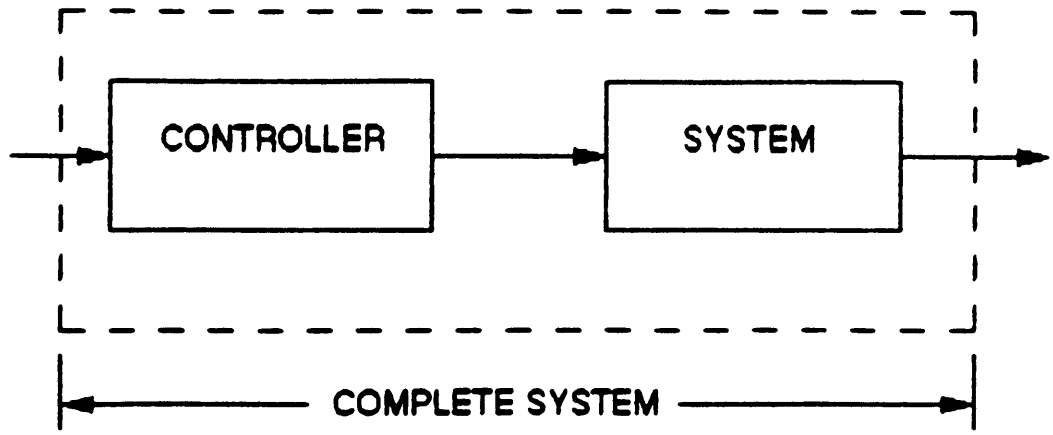


FIGURE 1 TYPICAL OPEN-LOOP CONTROL SYSTEM

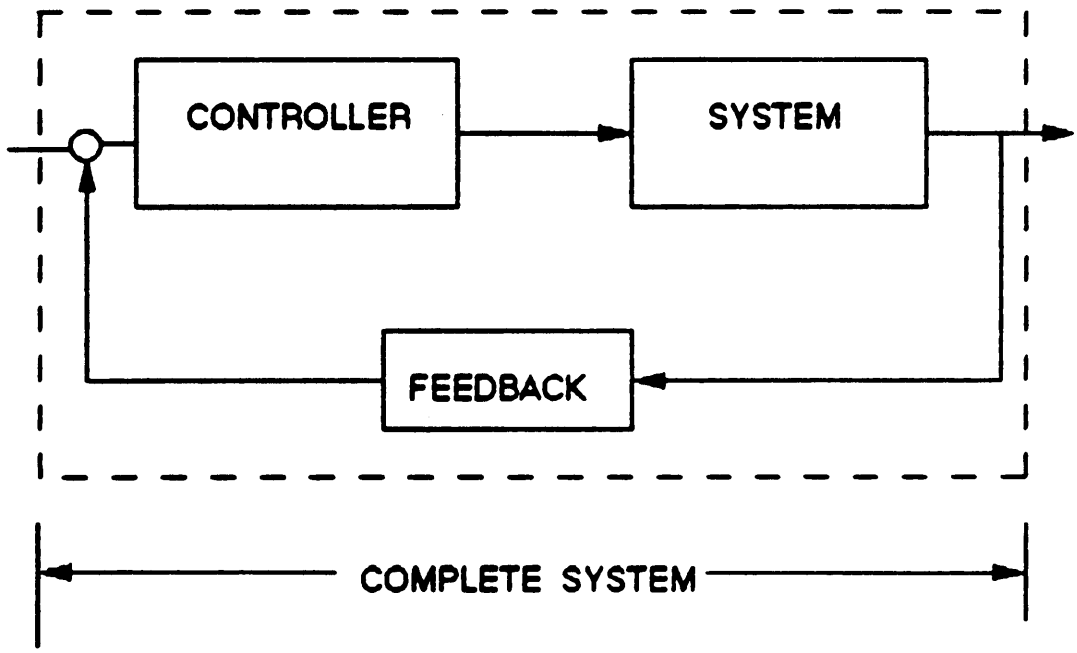


FIGURE 2 TYPICAL CLOSED-LOOP CONTROL

stability. The controller senses the feedback signal, changes plant operation, and then re-evaluates the output. Cycling can arise when the controller reads a signal that is too high, then too low, then too high again, etc.

In some systems an equation can be derived that relates the output to the input. When the output is a function of time and a first order function of the input the system is linear. The output can be twice the input, the time derivative of the input, or some other combination of functions. If a system is linear, tools of modern control theory can be applied and more often then not, the control law can be established.

When the output is a function of time and other than a first order function of the input, then the system is non-linear and analysis becomes much more complex. Unfortunately, most biological systems, including the respiratory system, are non-linear. The method to attack non-linear systems is to assume they behave linearly, find an area in their performance that is close to linear to find general results, or simulate each specific response.

The mission of the respiratory system is to maintain proper blood chemistry by bringing in oxygen and liberating carbon dioxide. Blood chemistry norms are disrupted when the body undergoes an energy transient where metabolism is increased or decreased. Going from sitting to standing and from walking to running are examples of energy transients. The respiratory system modulates breathing frequency and depth of breath to regulate the oxygen and carbon dioxide gas levels.

The control law governing respiration is assumed to be neural (pertaining to the brain) and humoral(pertaining to the blood). Early models depicted the respiratory system as either one or the other. The neural theory was championed by Kao who said exercise stimulated nerve endings in the working muscle.(2) These nerves generated a signal notifying the respiratory control center to increase breathing. Kao's cross-circulation

experiments were the basis of the neural theories. Experimental results showing changes in ventilation before any "affected" blood returning from a working muscle could reach known sensors and be read by the brain proved the existence of a neural component. Whipp and others sponsored the humoral theories of respiratory control.(3) The basis for the humoral theory was that changes in metabolism, blood chemistry, and ventilation tracked each other too closely, temporally and quantitatively, to disregard a blood-borne component in the control law. Research has shown respiratory control as a combination of these two mechanisms.(4)

One way the body maintains correct blood gas levels is by monitoring carbon dioxide. The primary sensing mechanism (there are secondaries) are the carotid bodies. They are located in the carotid artery and are the transducers that convert carbon dioxide concentrations to nerve impulses. The respiratory center of the brain senses these nerve impulses and directs the involuntary muscles of the lungs to adjust breathing accordingly.

Research for this thesis was conducted under the premise that the main sensor providing feedback for respiratory control is the carotid body. This was not to say the carotid body was the only sensor. It means that a system model incorporating just humoral control and using carotid body output as feedback, can act as a partial state sensor and satisfactorily control blood chemistry during exercise transients.

Saunders postulated the humoral control law containing a proportional component (based on the average carbon dioxide concentrations) and derivative component (based on how fast carbon dioxide concentrations were changing).(30) Ellis and Villiger expanded on this.(35,36) The model in Villiger's work included allowances for time delay for blood reaching different portions of the body, sinusoidal breathing, and a lung dead space.

The intent of the research in this thesis was to investigate the mechanism that governs

respiration. More specifically the intent was to determine, if given every possible advantage, would the Saunders control law satisfactorily control respiratory through an exercise transient. Saunders had only applied single step loads to his respiratory controllers. He never published evidence of the effects of multi-step protocols.

All experimentation was non-intrusive. Actual blood chemistry was never measured. Inspired and expired air gas concentrations were used to estimate blood chemistry. Corrections made in the model were based on comparing ventilation generated by the model and generated from testing (ventilation is a function of breathing frequency and depth of breath).

Throughout this thesis the term "physiologically correct" is often used. The model is a combination of what is known from human physiology, experimentation, and automatic controls engineering. Physiologically correct implies adjustments to the model based on what is known from physiology. This means incorporating such things as time delays for blood traveling from the working muscles to the lungs and the proper relationship between breathing frequency and depth of breath.

This thesis contains chapters outlining model development, a literature search, experimental procedures and results, and a conclusion. It also contains a chapter on physiology germane to respiratory control. This was included under the premise that a little bit of physiology helps considerably in understanding of respiratory control. A chapter on units is included to help explain conversion factors and some of the bizarre units respiratory physiologists use.

This introduction purposely does not contain vocabulary unfamiliar to the layperson. Beginning with the next section, terms associated with respiratory physiology will be used. Appendix A is a glossary of terms peculiar to this type of work.

2.0 GENERAL PHYSIOLOGY

This chapter explains the general principles of physiology that pertain to respiratory control. It consists of four sections: cell metabolism, circulatory system structure, respiratory system structure, and the carotid body structure. It provides the foundation for the chapter on model development. Key words and phrases to watch for in this chapter that will be used in discussing model development are dissociation curves, partial pressure, metabolic production of carbon dioxide, tidal volume, minute volume, breathing frequency, and dead space. Readers familiar with human physiology can easily skip this chapter and still retain continuity. When reading this chapter, recognize that the work levels talked about in this thesis are quite low. There is a reason for this. At low levels, the respiratory response to changes in work is linear. At high levels, it is not. The next section explains why. Specific references are not cited in this chapter. The general references 37 through 41 apply.

2.1 CELL METABOLISM

All of man's internal biological processes are powered with the energy-rich compound adensine triphosphate, ATP. ATP reacts with water within the cell in a hydrolysis reaction that cleaves one phosphate molecule. Adensine diphosphate, ADP, and free energy are the by-products. The free energy is not all lost as heat and can be applied directly to a receptor site of another compound. This second compound receives an energy boost that enables it to perform a biological function such as a muscle contraction. The conversion of ADP back to ATP is called phosphorylization.

Because ATP is the only fuel the body uses for all of its biological processes, maintaining sufficient levels of ATP is a critical bodily function. Additionally, when discussing any

process occurring within the body that involves the transfer of energy, its important to remember every process ultimately involves ATP one way or another. As will be explained presently, both oxygen and carbon dioxide play an integral role in the production of ATP.

The bodies store of ATP is limited. Normal basal rates would consume these stores in a manner of minutes. The body has three methods of producing ATP. They are the hydrolysis of the energy storage compound, creatine phosphate, anaerobic glycolysis, and aerobic glycolysis.

2.1.1 CREATINE PHOSPHATE

Creatine phosphate, CP, stores and releases energy in a reaction similar to that of ATP's in that a phosphate bond is made or broken. The body maintains larger stores of CP than ATP. The free energy associated with the release of phosphate from the CP molecule is higher than the energy associated with ATP. As a result, released energy from the hydrolysis of CP can be applied directly to the conversion of ADP to ATP.

2.1.2 ANAEROBIC GLYCOLYSIS

The glycolysis reaction synthesizes ATP through the break down of carbohydrates, fats, and proteins. As an energy source, carbohydrates are the most versatile of the three groups. Breakdown of carbohydrates to yield energy occurs in a two-step process. The first is anaerobic (without oxygen present). The second is aerobic (with oxygen present). Sufficient energy is produced during this first step to produce ATP. Carbohydrates are the only nutrients that can be used to produce ATP anaerobically.

Some carbohydrates can be metabolized directly by the body, but most are first con verted to glucose. The complete degradation of glucose to extract energy for ATP is called glycolysis. Glycolysis begins with an ATP kick. Two molecules of ATP are used as catalysts to initiate glycolysis. Glycolysis is then a ten-step process during which one molecule of glucose yields two molecules of ATP, two molecules of hydrogen ions, H^+, four molecules of nicolinamide adenine dinucleaoide, NADH, and two molecules of pyruvic acid. The H^+, NADH, and pyruvic acid can undergo further degradation to yield additional ATP molecules. However, to this point, no oxygen has been needed to complete any of the ten chemical reactions. Thus, the first stage of glycolysis occurs anaerobically. The additional processes that incorporate the H^+, NADH, and pyruvic acid all must be carried out in the presence of oxygen. When the body has low reserves of both ATP and oxygen, ATP demands can be met by glycolysis.

2.1.3 LACTIC ACID

Biological processes within the body must conform to chemical laws. Continued glycolysis reactions would result in a build up of the reactants. Concentrations of the reactants would eventually slow and then halt glycolysis. The biological answer to this is, that when concentrations are too high, the glycolysis by-products, H^+, NADH, and pyruvic acid, react to form lactic acid and NAD. Formation of lactic acid from these components does not require oxygen. Lactic acid is readily transported from the cell by the blood and allows for the glycolysis reaction to continue. The lactic acid produced in this reaction is not a waste product. It is eventually converted back to pyruvic acid, NADH, and H^+ in the liver. The production of lactic acid is what drives respiratory response to work level changes non- linear. The affects of lactic acid on the acid-buffer system is covered in a later section.

2.1.4 AEROBIC GLYCOLYSIS

Anaerobic glycolysis releases only about 5% of the energy in the glucose molecule. Additional energy is extracted beginning with an eleven step chemical process called the Krebbs cycle. To initiate the cycle, pyruvic acid from the anaerobic glycolysis reaction, is converted to acetyl coenzyme A. Acetyl coenzyme A enters the Krebb cycle and combines with the enzyme, oxaloacetic acid. The net reaction of one glucose molecule (which has split into two pyruvic acid molecules) is two molecules of ATP, eight molecules of NADH, two molecules of flavin adenine dinucleatide, FADH, and six molecules of H^+.

To this point, three by-products of the degradation of a carbohydrate (glucose) molecule, NADH, FADH, and H^+ have not been discussed. Each of these contain energy that can be extracted and used for ATP phosphorylization. This occurs in a process called electron transport. Electron transport only takes place within the mitochondria in the cells. The free H^+ radical and the hydrogen extracted from the NADH and FADH combine with oxygen in a hydrolysis reaction to produce water and energy for conversion of ADP to ATP. The Krebb cycle and electron transport constitute aerobic glycolysis, the third method the body has of producing ATP. Its the only one of the three methods that needs oxygen to proceed. Ironically, the only requirement for the oxygen is as the final electron receptor. Yet, it is often the limiting factor in exercise.

Of the three methods the body has of creating ATP, the glycolysis-Krebb cycle-electron transport method is the body's long term solution to ATP synthesis. The other two methods, CP hydrolysis and anaerobic glycolysis, respond only when time or stress limits the full reaction from taking place. Recognize that extracting ATP from anaerobic glycolysis is just an abridged version of the whole process. It can be envisioned as a fall-back measure when insufficient oxygen is present to allow for the complete process to electron transport to be completed

2.1.5 FATS AND PROTEINS

The degradation of fats and proteins occur along different pathways than carbohydrates. Both fats and proteins metabolized in a series of steps that spin off products that fit into glycolysis-Krebb cycle-electron transport mechanism. One important distinction is that no protein and only the glycerol portions of fats can be used to generate ATP from anaerobic glycolysis. This means that fats and proteins are only burned during the aerobic synthesis of ATP.

Fats are catabolized; that is, broken-down and metabolized in a process that begins the separation of the molecule into glycerol and fatty acids. The glycerol is incorporated in anaerobic glycolysis reaction as just stated. The fatty acids break-down via a process called the beta oxidation cycle. Useable by-products of this are hydrogen and coenzyme A. Energy from the hydrogen is trapped by electron transport. The coenzyme A molecules enter the Krebb cycle just as the coenzyme A molecules produced during carbohydrate catabolism did. The NADH, FADH, and H^+ that generate from the Krebb cycle processing of a fat molecule also undergo electron transport just as the carbohydrate Krebb Cycle by-products.

Proteins are broken down in a process that divides the protein substrate into its amino acid building blocks. The body then denitrifys the amino acids. The denitrified products are usually one of the reactants that are part of the glycolysis or the Krebb cycle and can be used to generate ATP without any other synthesis.

2.1.6 ENERGY CONTENT OF CARBOHYDRATES, FATS, AND PROTEINS

The amount of energy the body gains from the catabolism of a carbohydrate is approx-

imately 36 molecules of ATP. From a triglyceride fat molecule the body generates approximately 463 ATP molecules. The energy produced from protein is difficult to establish since the many types of proteins yield different levels of energy. The disparity in energy production between carbohydrates (36 ATP) and fats (463 ATP) shows how the body utilizes these energy storage schemes. Fats contain vast quantities of energy that can be converted only during a slow burn type of process. Carbohydrates, however, yield less then a tenth of the energy yield and can be catabolyzed in a quick burn type of process during which oxygen may or may not be present.

During energy demands of 1-2 seconds, the body hydrolyzes CP to obtain energy for ATP production. For energy transients on the order of minutes, the anaerobic catabolism of carbohydrates fulfills the ATP demands. During steady-state energy consumption, aerobic energy production burning carbohydrates, fats, and proteins takes place.

There is an increased level of steady state energy consumption where aerobic ATP production is not sufficient to fulfill ATP demands. This is the anaerobic threshhold. Above this level, anaerobic ATP production supplements aerobic methods.

It is also important for understanding the energy transfer mechanisms that CP hydrolysis and anaerobic glycolysis be recognized as supplemental forms of energy production for use during work transients that produce sudden ATP demands. Whereas aerobic production of ATP can occur virtually indefinitely as long as nutrients are available to feed the reactions.

2.1.7 CARBON DIOXIDE'S ROLE

Missing from this discussion to this point has been the role of carbon dioxide in the energy transfer process. Carbohydrates, fats, and proteins are hydrocarbon chains that

are chemically degraded into essentially carbon dioxide, water and energy for the phosphorylization of ATP.

The ratio of the amount of carbon dioxide produced to the amount of oxygen consumed is called the respiratory quotient. The respiratory quotients for the catabolism of carbohydrates, fats, and proteins are 1.00, 0.70, and 0.82 respectively. The respiratory quotient can be used to determine the type of energy transfer process that is occurring within the body during a specified test period. By measuring inspired oxygen and expired carbon dioxide, an estimate of the respiratory quotient can be made. This indicates the type of nutrients being consumed. The varying levels of carbon dioxide that are produced with the break down of the different nutrients complicates the problem of controlling respiration. Different amounts of carbon dioxide can be produced for identical work loads depending on the type of nutrients being consumed.

Carbon dioxide and oxygen are not only used in the energy transfer process that culminates in the phosphorylization of ATP. Both compounds as well as the other participants in the energy transfer mechanism are produced or consumed in other chemical reactions in other biological processes in the body. However, for the purposes of this thesis, any changes in oxygen demand or carbon dioxide production are assumed to be the result of an exercise transient.

Important to the understanding of the processes that go on within the body, is the concept that biological reactions are virtually always two-way reactions that are in equilibrium. Therefore, the concentrations of the products are as equally important as the concentrations of the reactants when considering the direction and rate of a process. This is especially true in respiratory system control where carbon dioxide has a stronger influence on breathing rate than oxygen.

2.2 RESPIRATORY SYSTEM STRUCTURE

The main structures of the lungs are the trachea, bronchi, alveoli, and chest cavity. The chest cavity surrounds the lungs on all but the bottom side. This lower surface is the diaphragm. No physical connection exists between the lungs and the chest cavity. Surface tension created by moisture that exists on the outside of the lung causes the lung to cling to the chest cavity. Expansion of the chest cavity increases the volume of the lung. Air is pulled into the lung because of the vacuum created. Expansion of the chest cavity is accomplished via two sets of muscles, the diaphragm and intercostal muscles. The diaphragm is a sheet of muscle that, when relaxed, is a concave shape. Diaphragm contraction causes the muscle to flatten and the chest cavity to expand. The intercostal muscles are used during heavy ventilation demands. They essentially lift the chest cavity up and outward. This also increases the chest cavity volume.

These muscle sets are controlled by the respiratory center of the medulla within the brain. Expanding the chest cavity brings air into the lungs. Expiration of air in all but the heaviest ventilation demands is caused by just the relaxation of the muscle sets.

The alveoli are where gas exchange takes place. The alveoli are extremely small air sacs. The lung is made up of approximately three hundred million of them. The walls of the alveoli are thin and contain blood capillaries. The close proximity of the capillaries to the air in the alveoli allows mass transport of oxygen and carbon dioxide to take place between the blood and the lung air.

Normal breathing is a cyclic process making the lung volume vary almost sinusoidally. Inspiration and expiration times are not equal. Expiration times are about one-third longer in a normal adults at rest breathing.

The volume of air cycled through the lung during each breath is the tidal volume. The

amount of air brought in and then out of the lung in one minute is the minute volume. The product of breathing frequency and tidal volume, therefore, is the minute volume.

Fig #3 shows other terms associated with pulmonary ventilation used in this thesis.

The last item that needs mentioning in this section concerns lung dead space. Dead zones in the lung where no gas exchange takes place appear in two areas. Gas exchange does not take place across the trachea and bronchial tubes. This is the anatomical dead space. Its about one-fifth of the tidal volume. At the end of inspiration, the dead space contains all ambient air. At the end of exhalation, the dead space contains end-tidal air.

The alveoli sacs are efficient handlers of oxygen and carbon dioxide. Concentration of the two gases in the blood equalize with the lung air concentrations long before the blood completes its transit through the pulmonary capillary. However, even in healthy people, a certain percentage of alveoli sacs do not function. The physiologic dead space is this volume of idle alveoli. The amount of air exposed to active alveoli is the alveoli volume. Total lung volume less the anatomical and physiologic dead spaces is the alveoli volume. Dead space volumes play a large role in respiratory models.

2.3 GAS EXCHANGE

Exchange of oxygen and carbon dioxide takes place across the alveoli membrane. Diffusion of the two gases occurs passively. That is, no active mechanism carries the gas molecules across the compartment boundaries. The concentration gradient is the driving force. The transfer of gas molecules obeys Henry's law --the movement of molecules is a function of gas solubility and pressure gradient. Oxygen has poor solubility when compared to carbon dioxide. It is approximately twenty-five times less soluble than carbon dioxide. As already mentioned, gas concentrations across the alveoli wall

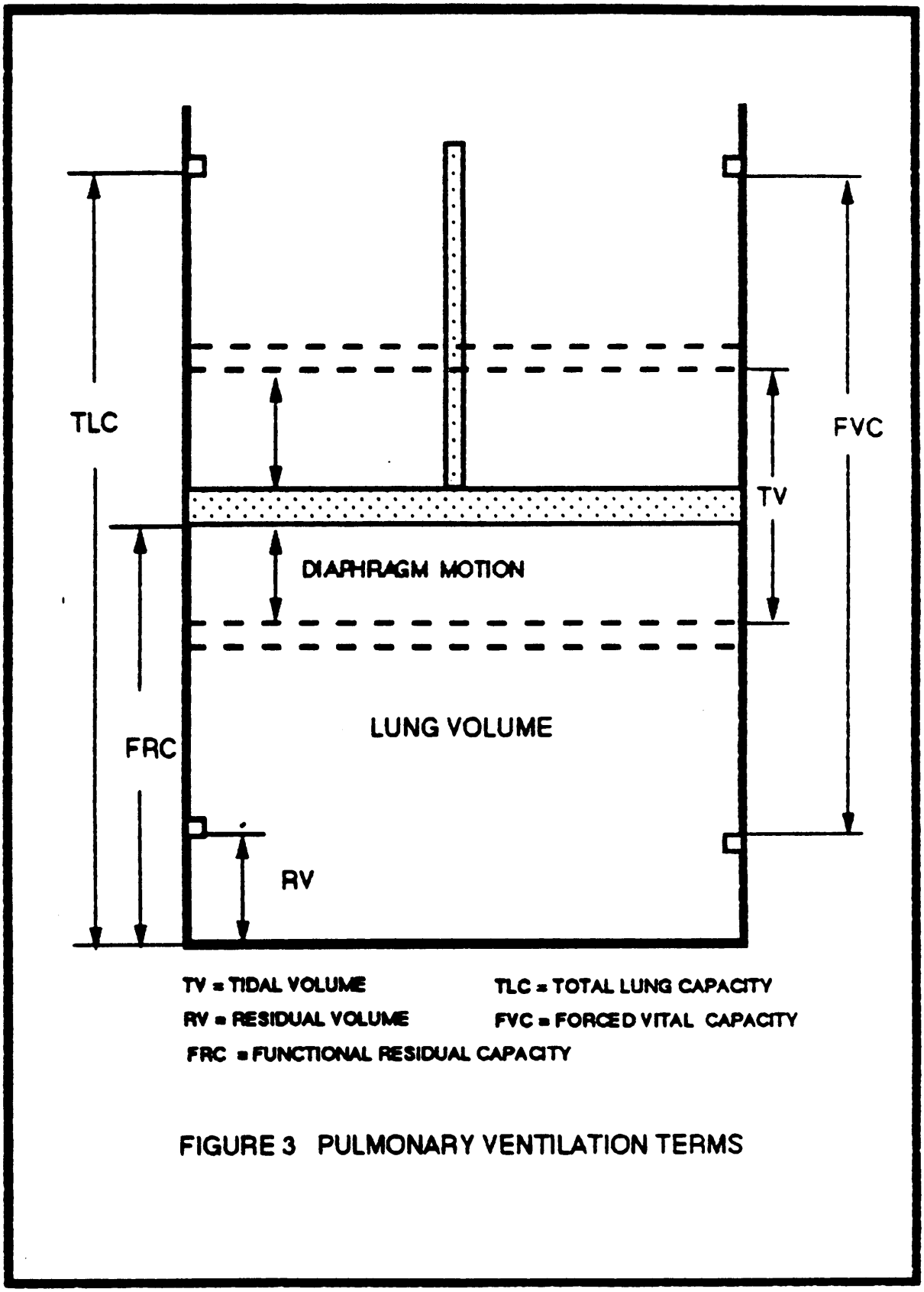


FIGURE 3 PULMONARY VENTILATION TERMS

equalize long before the blood finishes its travel through the alveolar capillary. The carbon dioxide achieves this because of its high solubility. Oxygen concentrations in the capillaries and alveoli reach equilibrium because its poor solubility is balanced by high pressure gradients between the two compartments.

Ambient air concentrations of oxygen and carbon dioxide are 20.93 and 0.04 per cent. This equates to partial pressures of 159 and 0.3 mmHG. Air brought into the lungs becomes saturated with water during its passage through the trachea and bronchial tubes. Its temperature also reaches equilibrium with the body's temperature, nominally 37°C. The moisture and temperature changes produce oxygen and carbon dioxide concentrations in the alveoli of 100 and 40 mmHG. Resting gas levels in the muscle tissue are on the order of 40 mmHG for oxygen and 46 mmHG for carbon dioxide. Again, pressure equalizes across the lung-pulmonary capillary boundary. As an indication of the minimum pressure gradients the respiratory system works with, pressure differences are about 60 mmHG for oxygen and 6 mmHG for carbon dioxide in both the lungs and muscles, see Fig #4.

In the dialogue above, the partial pressures used were the average values of gas concentrations. In actuality, the concentrations of oxygen and carbon dioxide vary cyclically over time. The scenario is complicated. Partial pressures still equalize across the pulmonary capillary membrane, but the oxygen and carbon dioxide concentrations vary depending on whether its the beginning, middle, or end of the breath. The cyclic variation of carbon dioxide is one of the bases of the control law for the model used in this thesis.

2.3.1 OXYGEN TRANSPORT

Oxygen's low solubility precludes any appreciable amount from being transported by the

blood in the dissolved state. Only five percent is carried as dissolved, free oxygen. However, this five percent plays an important role in the transportation mechanism. It establishes the partial pressure of the oxygen in the blood. The pressure gradient in the lung and muscle is a function of this partial pressure.

The balance of the oxygen being transported combines with the iron protein hemoglobin in the red blood cells. The oxygen is very loosely held by the hemoglobin. The ability of hemoglobin to hold onto oxygen depends entirely on the partial pressure of the dissolved, free oxygen in the plasma. Hemoglobin is approximately 95% saturated with oxygen with partial pressures as low as 90 mmHG (remember nominal lung air has an oxygen concentration of 100 mmHG). Hemoglobin's ability to hold oxygen does not seriously degrade until surrounding partial pressures drop below 60 mmHG. As partial pressure drops further, hemoglobin's ability to hold oxygen falls dramatically. Remember now that resting oxygen levels in the muscle are approximately 40 mmHG. During intense exercise, oxygen partial pressures in the tissues can drop to 5 mmHG. At partial pressure in this range, hemoglobin has jettisoned virtually all of its bound oxygen.

Increased temperature and acidity adversely affects hemoglobin's affinity for oxygen. This is known as the Bohr effect.

2.3.2 CARBON DIOXIDE TRANSPORT

Carbon dioxide transport by the blood is accomplished by a different mechanism. Ten percent of transported carbon dioxide exists as dissolved, free molecules in blood plasma. The red blood cells carry the remaining ninety percent. Five of that ninety exists as free carbon dioxide within the red blood cell. The balance is carried as bicarbonate. As with oxygen, the dissolved, free molecules in the plasma establishes the partial pressure of the carbon dioxide.

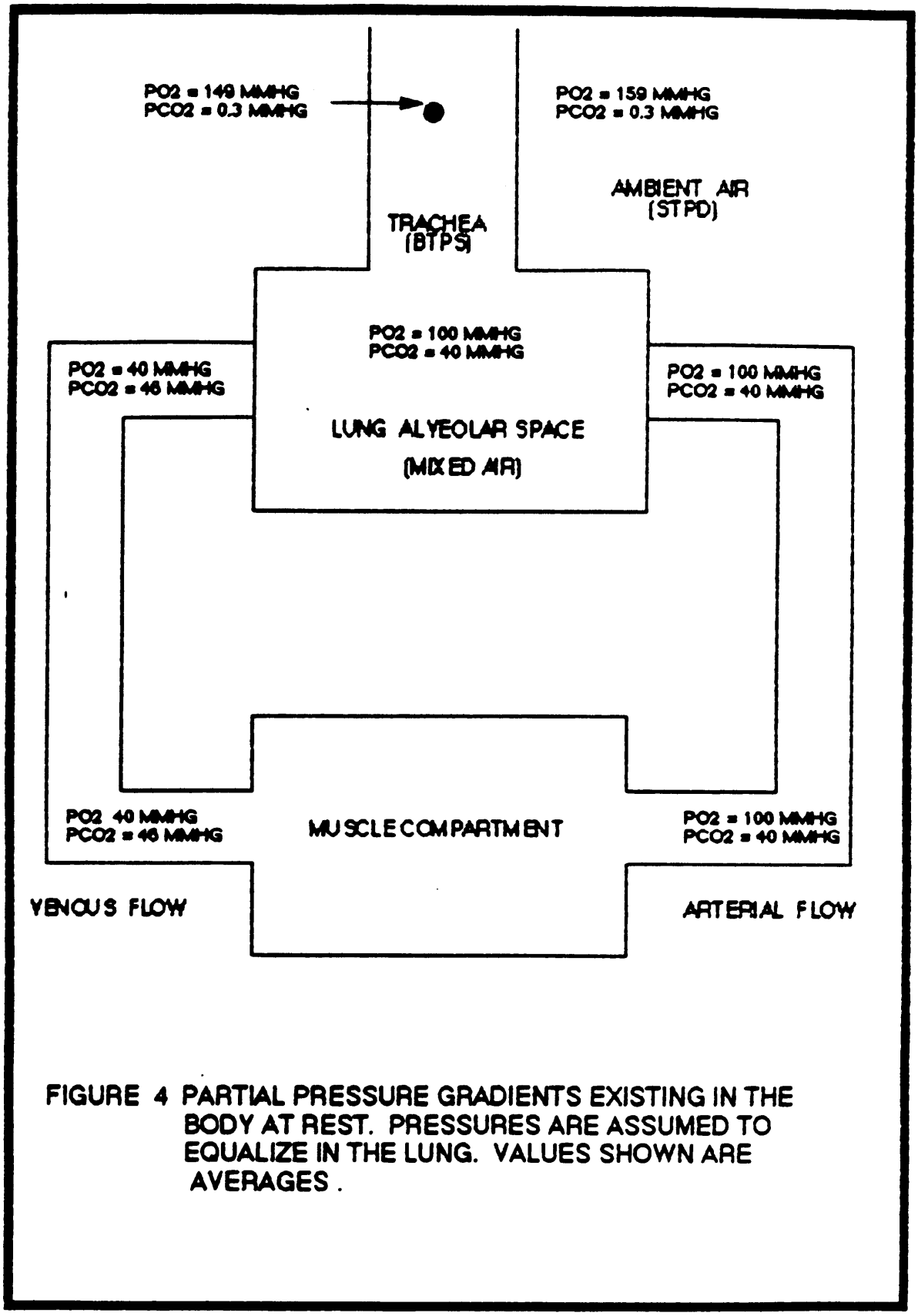


FIGURE 4 PARTIAL PRESSURE GRADIENTS EXISTING IN THE BODY AT REST. PRESSURES ARE ASSUMED TO EQUALIZE IN THE LUNG. VALUES SHOWN ARE AVERAGES .

Carbon dioxide from the tissues combines with water to form carbonic acid. The process is normally quite slow. The presence of the catalyzing enzyme, carbonese anhydrase, makes the reaction almost immediate. Most of the carbonic acid dissociates into hydrogen ions and bicarbonate ions. The bicarbonate ion is the form in which sixty per cent of the carbon dioxide is carried by the blood.

The transformation of carbon dioxide to bicarbonate has tremendous physiological significance. The concentration of hydrogen ions determines the PH in the blood. The body keeps tight reign on acid-base quality of the blood because metabolism is highly sensitive to PH.

2.3.3 LACTATE PRODUCTION, WHEN THINGS GO NON-LINEAR

As mentioned in the section on cell metabolism, high demands for ATP, can initiate lactic acid production. Lactic acid reacts in solution to form sodium lactate and carbonic acid. The carbonic acid dissociates just as it did before into hydrogen and bicarbonate ions. Exercise levels that force lactate production affect blood acidity greatly because of this extra infusion of acid. Lactic acid is buffered; however, its effect disrupts the simple linear relationship between work level and carbon dioxide concentrations in the blood. Work levels used in thesis are set to stay below the point where lactic acid is formed.

3.0 BASIC LAWS AND UNITS

Four basic gas laws have importance in respiratory physiology. The four are Boyle's Law, Charles' Law, Dalton's Law, and Fick's Law. Each will be explained briefly and then a paragraph will sum their applications to this thesis.

3.1 BOYLE'S AND CHARLES' LAWS

Boyle's Law states gas volumes vary indirectly with changes in pressure; increasing pressure decreases the volume. Charles' Law states gas volumes vary directly with changes in temperature; increasing temperature increases the volume.

Metabolic calculations are almost always expressed as standard temperature and pressure, dry, STPD. Experimental data are often expressed as body temperature and pressure, saturated, BTPS. STPD implies 760 mmHG, 273°K, with dry conditions. BTPS implies ambient pressure, 273°K + 37°K, with saturated water vapor conditions.

3.2 DALTON'S LAW

In a mixture of gases, each gas exerts a pressure that is a portion of the total pressure. This partial pressure is the pressure each gas would exert if it were the only gas present in the volume. Dalton's Law establishes the partial pressure of each gas as being a direct function of its concentration.

$$P_G = F_G \times P_T \tag{3.1}$$

P_G = partial pressure of the gas, mmHG

F_G = volumetric fraction of the gas, liters/liters

P_T = total pressure of the mixture, mmHG

P_T must reflect the total pressure in the correct units of BTPS or STPD. In BTPS, P_T is ambient pressure less the saturation pressure of water at the body's temperature of 37°C. That is, (750 - 47) mmHG with an ambient pressure of 750 mmHG or (742 - 47) mmHG if ambient pressure is 742 mmHG.

3.3 FICK'S LAW OF DIFFUSION

The last fundamental law to be presented is Fick's Law of Diffusion. It provides the mathematical relationship defining the rate at which gases move across a permeable membrane.

$$W = A * (P_2 - P_1) \tag{3.2}$$

W = amount of gas diffused per unit time

A = diffusion capacity (function of surface area and solubility)

$P_2 - P_1$ = pressure gradient gas across the separating membrane

This function describes the rate at which oxygen and carbon dioxide cross the pulmonary and muscle-tissue capillaries.

3.4 SUMMARY

Each of these four laws plays a part in a model of the respiratory system. Boyle's and Charles' Laws combine to form the conversion factor relating metabolic rates, expressed STPD, and experimental results, expressed BTPS. The conversion is

$$\text{VOL BTPS} = \text{VOL STPD} * \frac{T(\text{BTPS})}{T(\text{STPD})} * \frac{P(\text{STPD})}{P(\text{BTPS})} \tag{3.3}$$

Dalton's Law allows for the conversion of gas concentrations to partial pressures. Model development, as will be shown in chapter 5, begins with mass balance around the lung using concentrations to determine mass in and mass out.

Fick's Law is important because it provides the platform on which to make the assumption that diffusion rates need not be considered in the simulation of the respiratory system. One of the fundamental assumptions made in respiratory models is that the diffusion rate goes to zero before the blood reaches the end of the pulmonary capillary. This means the quantity $P_2 - P_1$ becomes zero or the partial pressures across each boundary reach equilibrium.

The time it takes for blood to travel the pulmonary capillary is on the order of 0.75 seconds. The partial pressure of carbon dioxide in the capillary falls rapidly, but does not reach equilibrium for approximately 0.4 seconds or about halfway across. Oxygen reaches equilibrium in about 0.25 seconds. This means that although carbon dioxide dissolves much more readily in blood, it takes a longer time to reach equilibrium then oxygen.(38)

4.0 LITERATURE REVIEW

4.1 INTRODUCTION

This literature search documents the published research germane to respiratory system modelling. A series of topics is presented concerning the development of models and evaluating experimental data. The last section discusses actual respiratory models published.

A who's who of respiratory control is easily formulated by examining the published literature. Cummins, Cunningahm, Grodins in England and Whipp, Wasserman, and Yamamoto here in the United States are by far the leading publishers in this field.

The majority of work in respiratory control takes place in just three places: St. George's Hospital Medical School, London; University of Southern California, Los Angeles, California; and UCLA School of Medicine, Torrence, California. Many investigators have made contributions to the problem of determining the respiratory control law, but the vast majority of papers published are generated in one of these laboratories.

Douglas in 1905 and Haldane in 1908 published findings of a humoral- based respiratory control system.(5,6) Both recognized a linear relationship between expired carbon dioxide and ventilation.

In 1933, Haymans reported his findings concerning the role of the carotid body as a peripheral chemoreceptor. Haymans received a Nobel prize for his extraordinary work on the nature of the carotid body.(7)

In the 1940's, the higher flying aircraft of World War II created a need for a better understanding of respiration. Investigations spawned as a result of this need were the

beginning of modern respiratory physiology.(8)

In 1945, Gray assimilated the current views of respiratory control and published his Multiple Factor Theory.(9) In this publication, Gray postulated respiratory control as being a function of the three ingredients of metabolism: oxygen, carbon dioxide, and hydrogen ions. Gray did not attempt to establish a quantitative description of the respiratory system, but left his model as a black box with an input and output.

In 1960, Yamamoto created a model of the gas exchange process within the lung.(10) He provided quantitative relationships between lung dynamics and arterial blood quality. Yamamoto was the first to document the oscillation of arterial blood gases over time.

These key milestones mentioned above set the stage for research in respiratory control. A tremendous amount of effort has been applied to the problem of establishing the control law for respiration over the last three decades, but the scientific community has as of yet been unable to explain it satisfactorily.

4.2 NEURAL - HUMORAL DEBATE

The steady-state relationship between ventilation and work load has been established as linear for mild and moderate exercise, see Fig. #5.(40) However, the transition from one steady-state level of ventilation when plotted against time is not linear and has been the subject of much debate. Most of the discussion centers on the two general ventilation profiles that can result. The two profiles differ by the existence or non-existence of a fast component of ventilation change, see Fig. #6.

A typical response which includes a fast component consists of an immediate increase, followed by a plateau, followed by a gradual rise to a steady-state.(11) The widely

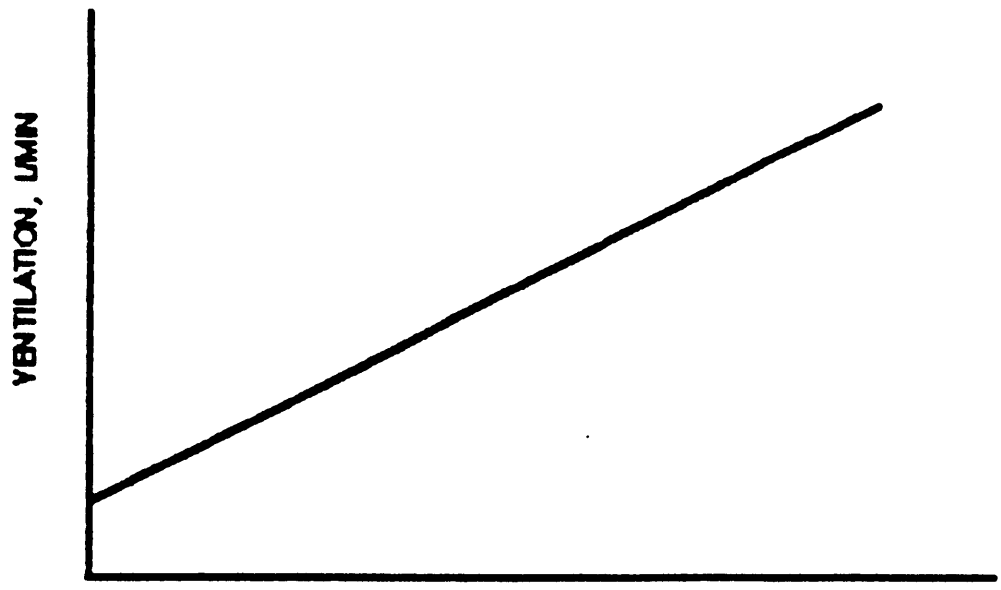


FIGURE 5 TYPICAL RELATIONSHIP BETWEEN VENTILATION AND WORK. LINEAR AT LOW WORK LEVELS

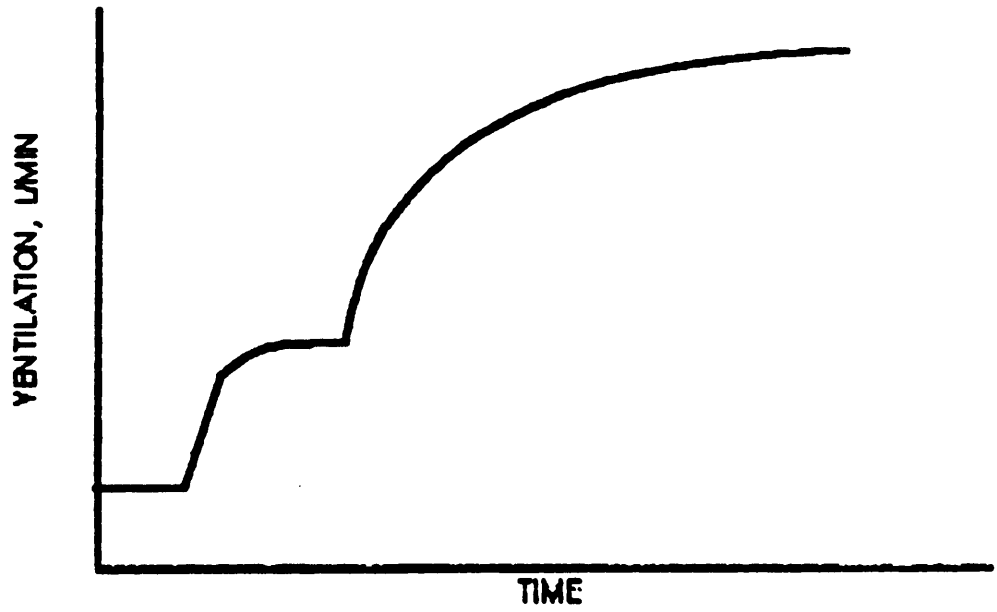


FIGURE 6 TYPICAL VENTILATION PROFILE OF AN EXERCISE TRANSIENT

accepted interpretation of this profile is the neural-humoral respiratory control theory. The fast component, because it occurs before any blood from an active muscle has time to reach any known sensor, must be a result of a neural response. This neural input may be generated in two places. The first, in the working muscle where a local mechanism sends a message to the respiratory center to increase ventilation. The second, in the higher centers of the brain where a signal for a muscle to work is accompanied by a simultaneous, parallel signal informing the respiratory controller to increase breathing.(12)

The short plateau in the profile is the neural subsystem maintaining control. The gradual rise that follows is interpreted as the assumption of control by the humoral subsystem. The time lag associated with the start of the gradual rise coincides with the time lag of blood from working muscles reaching a chemoreceptor.

How the neural and humoral signals may combine has also been the subject of much research. One theory has the two components existing simultaneously, the final steady-state ventilation being a summation of the two signals.(11) The second describes the control as two distinct mechanisms, an initial neural ventilation bump to compensate for the lag before the humoral subsystem can assume control.(13)

Some investigators have refuted the existence of a fast component in a ventilation transient. Breath-by-breath data must be used to isolate the fast component that occurs within the first one or two breaths of an exercise transient. As explained in his report of 1968, Beaver conducted a multitude of tests and time averaged the data.(14) Averaging of the data allowed Beaver to eliminate the inconsistencies that can arise from this breath- by-breath of data collection. He reported not finding evidence to support a fast component. Beaver did not attempt to suggest a neural component did not exist, only that it did not manifest itself as a fast component in a ventilation transient.

The neural-humoral dilemma cannot be properly discussed without presenting the work of Kao in his cross-circulation experiments.(2) In one of his experiments, Kao used two anesthetized dogs, a "neural dog" and a "humoral" dog. The neural dog's hind limbs were electrically stimulated to induce muscle action. Blood from the neural dog's active muscles was routed to the humoral dog. Ventilation in both dogs increased as a result of the induced exercise. Kao concluded the increase in ventilation was evidence of a neural pathway existing between working muscles and the respiratory control center.

4.3 CARDIODYNAMICS

Cummin, Wassermann, and others have proposed an alternate hypothesis to the neural component of respiratory control.(15,16,17) Their research has been directed towards establishing the fast component of ventilation and any other neural effect as the result of a humoral reaction. The theory is based on the findings that heart rate increases almost immediately with exercise (1-2 secs). Increased blood velocity without a concomitant change in lung action can alter the chemical quality of the blood leaving the lung. The changes are coded in the oscillations of the blood gases. Chemoreceptors can interpret these changes in oscillations and modulate ventilation accordingly. Experimentation has shown a strong correlation between cardiodynamics and ventilation.(16,17)

4.4 VENTILATION, THE PRODUCT OF TIDAL VOLUME AND FREQUENCY

Small increases in ventilation are accomplished by adjustments to tidal volume. Higher ventilation demands are met by a combination of tidal volume and frequency increases. During extreme demands, tidal volume reaches a maximum and ventilation requirements are met by increasing breathing frequency only.

The product of tidal volume and frequency is the ventilation. The split between tidal volume and frequency is the same for a given ventilation. This holds true whether the ventilation drive arises from exercise, hypercapnia, or asphyxia.(18) This pattern also holds true for the shape of a breath. That is, mean inspiration and expiration times are unique for a given ventilation.

The relationship between tidal volume and frequency has importance in the development of the respiratory model. The model in this thesis calculates ventilation demand and an algorithm is used to determine the associated tidal volume and frequency.

4.5 UNSTEADY STEADY-STATE

One of the handicaps of investigating respiratory dynamics is breathing is not uniform even when work or exercise levels are constant. Fig. #23 and 24 show experimental ventilation profiles of 75 and 100 watt step loads. The sections of the profiles are defined as steady-state since ventilation transients have ended, yet tidal volume and breathing frequency vary constantly from breath to breath.

Lamarra has solved part of this problem by developing a method to statistically remove noise from experimental breath-by-breath data (19).

What is left of this unsteady, steady-state problem is how to establish nominal ventilation rates from experimental data. Mathematically deriving nominal rates by averaging raw data can be accomplished only if irregularities such as coughs, sighs, and swallows are removed from the data and the data smoothed to cover the deletion. Lamarra's data reduction method does not accomplish this. The most effective method of determining nominal ventilation rates during steady-state breathing is to graph the experimental output, lay a ruler over the data, and pick the best fit. Its fast, simple and as effective

as any more scientific method.

4.6 BREATH-BY-BREATH GAS EXCHANGE

Within the normal breath, oxygen and carbon dioxide are continuously transferred to and from the blood. The rate of transfer is dependent on the pressure gradients that exist between the blood and the lung air. If lung volume were constant the gas exchange dynamics could be easily modelled. However, cyclic lung action complicates modelling by not only changing the concentrations of carbon dioxide and oxygen through inspiration and expiration, but also changing the lung volume as well. Additionally, not all of the air in the lungs is exchanged during a ventilation cycle and in the lung dead spaces air is not exposed to gas exchange. If the scenario were not bad enough, the breath-by-breath fluctuations that occur even in natural, steady-state breathing seem to make the problem of gas exchange modelling wholly impossible. Solutions to this problem have been reported by Beaver.(14) His model recognizes all the variations that can occur and can be used for estimating breath-by-breath gas exchange.

4.7 EXPIRED GAS CONCENTRATIONS

One fundamental assumption often used in respiratory physiology is that the partial pressures across the alveolar membrane equalize. Variations in alveolar carbon dioxide concentrations over time thus mirrors arterial blood concentrations. Measuring gas concentrations at the mouth is the most convenient method of measuring respiratory dynamics. However, expired gas concentrations do not reflect what is happening at the blood-air boundary. The last portion of each breath, end-tidal air, has been assumed to be the one point where data measured at the mouth equalled values in the lung and therefore in the blood. However, deviations of 5 mmHG have been reported between end-tidal and arterial carbon dioxide tensions.(20,21)

A correlation between expired and arterial carbon dioxide concentrations was established by Whipp in a report published in 1984.(22) Whipp used expired carbon dioxide data to reconstruct the alveoli carbon dioxide profile. He then calculated an average alveolar carbon dioxide level and compared that to arterial levels measured at the brachial artery. The two differed by an average of only 0.5 mmHG. Whipp concluded his report by stating end-tidal data cannot be used to accurately estimate arterial concentrations with out some yet-to-be-determined correction factor, but expired carbon dioxide concentrations serve as a valid, non-invasive estimator of arterial carbon dioxide in man.

4.8 FREQUENCY RESPONSE METHOD

A method of gathering information on the characteristics of an unknown controller is to evaluate its response to known inputs. Because carbon dioxide has been generally assumed to be the principle driver in the respiratory system, much research has been devoted to applying known carbon dioxide signals into the respiratory system. Carbon dioxide inputs can be applied by injecting carbon dioxide into the veins or by increasing inspired carbon dioxide concentrations. The non-invasive method is usually selectedas the volume of published data indicates.

A powerful tool in control engineering for examining the behavior of a system controller is to generate frequency response data for it. Frequency response data is created by applying a time varying signal into the controller and measuring the magnitude and phase shift of the resulting output. Sinusoidal signals are the favored test inputs.

Many respiratory tests have been run during which carbon dioxide is mixed with the inspired air at a sinusoidally varying rate. The magnitude and phase angle of the corresponding ventilation response is collected and used for describing respiratory

controller's characteristics.(23)

Frequency response experiments are not without problems. Data gathered from this type of experimentation are cloudy because the cyclic breathing affects the signal applied to the inspired air. Alison has developed a method of linear carbon dioxide loading.(24) This deviates from the preferred sinusoidal inputs normally used in frequency response work. However, this method approximates the carbon dioxide loading the body is

exposed to during exercise. Alison's technique simulates exercise by superimposing the carbon dioxide load on the inspired air. This differs from metabolically produced carbon dioxide loading since it is added to the blood on the wrong side of the lung, but is a good non-intrusive method of adding known carbon dioxide loads.

4.9 SUMMATION OF RESPIRATORY CONTROL DRIVERS

In his report published in 1987, Cunningham presented a listing of the principal routes by which metabolic rate may be signaled to the respiratory controller.(25) They are grouped as feedback and feedforward mechanisms, see Fig. #6.

The distinction between feedforward and feedback is different in respiratory physiology and controls engineering. Respiratory literature designates feedforward controller inputs as those which affect ventilation rates before blood from exercising muscles reaches any known chemoreceptors. Feedback drivers are designated as those which arise from deviations in hydrogen ion, oxygen, or carbon dioxide concentrations from their regulation set points. Controls engineering designates controller signals generated from the system input as feedforward and those generated from the system output as feedback.

Arterial blood gas oscillations is the respiratory driver that generates confusion. Arterial

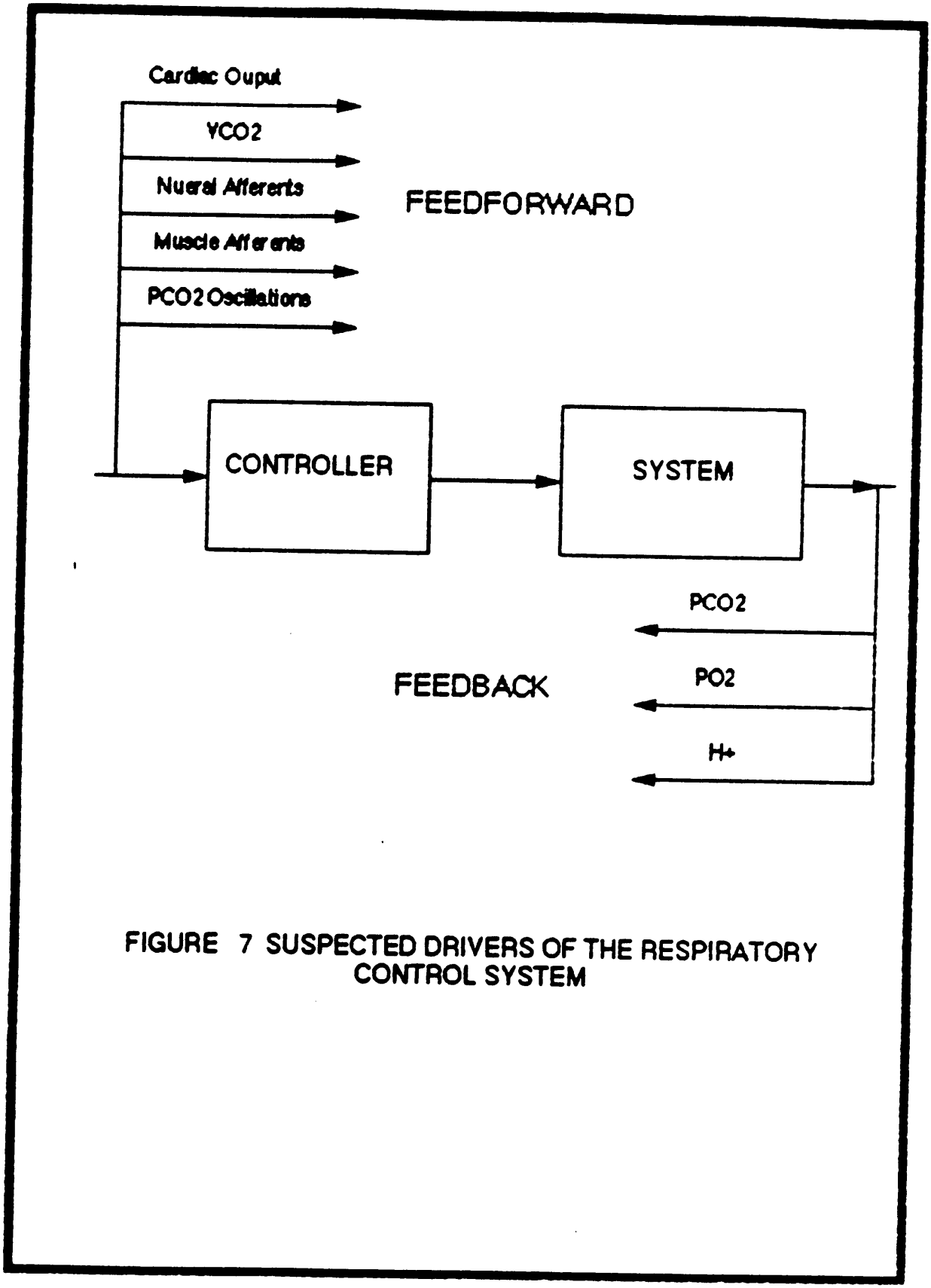


FIGURE 7 SUSPECTED DRIVERS OF THE RESPIRATORY CONTROL SYSTEM

blood oscillations change in amplitude as a result of the increased heart rate that accompanies exercise. These changes can be realized before any blood from working muscles reach known chemoreceptors. Respiratory literature therefore, designates this as feedforward. Controls engineering designates this driver as feedback since it originates from the system output. This thesis defines blood gas oscillations as feedforward for no other reason then to conform to respiratory literature.

4.9.1 FEEDBACK

The chemical reactants of metabolism (oxygen, carbon dioxide, and hydrogen ions) have been suspected of supplying feedback information to the respiratory controller since the beginning days of respiratory physiology.(9) Hydrogen ion and carbon dioxide concentration in the blood have been the subject of a tremendous amount of research mostly because their levels are so closely coupled to ventilation. Investigation into the role of oxygen concentrations in the blood have taken place to a lesser extent. The blood oxygen concentration to ventilation relationship is more loosely coupled and no chemoreceptors have been identified that tie oxygen concentration to respiration.

4.9.2 FEEDFORWARD

Possible feedforward mechanisms of respiratory control have been identified as muscle afferent, signals from the brain, expired carbon dioxide concentrations, cardiac-output, and blood gas oscillations. Afferents generated by local actuators in the muscles were the first feedforward mechanisms to appear in the respiratory control literature. Kao theorized the existence of this driver as a result of his cross-circulation experiments in the late fifties.(2) The oscillations of arterial blood gases first quantitatively documented by Yamamoto in 1960 have been postulated as the mechanism by which the body adjusts

ventilation rates to maintain isocapnia. The possibility that cardiac-output and expired carbon dioxide levels may provide a signal to the respiratory controller has only been investigated in the last decade. Mechanisms that sense these levels have not been identified. However, the relationship between cardiac-output (pressure) and ventilation rate and also expired carbon dioxide and ventilation is very tightly correlated.

4.10 SUMMARY OF RECEPTORS

The carotid body's role as a peripheral chemoreceptor, especially of carbon dioxide concentrations, has been generally accepted by respiratory physiologists. The mechanism by which the carotid body converts gas concentrations into nerve impulses has yet to be established. Nonetheless, its effect on respiration receives intense research. The aortic bodies may serve as chemoreceptors possibly in a backup role to the carotid bodies.(25) The may also read blood pressure and provide information to the respiratory center as part of the cardiac-output driver.(17) The existence of local sensors in the muscle that issue neural signals in response to muscle activity have been theorized, but never discovered.(2) There is also evidence for the existence of receptors capable of detecting carbon dioxide flux in the lung airways and in the walls of the heart.(25) The surface of the medulla has been identified has having chemosensitive areas that respond to changes in hydrogen ion or carbon dioxide concentrations in the cerebral spinal fluid.(9)

4.11 MODELS

Models appearing in the respiratory literature have the general structure shown in Fig. #8. Each includes a controlled plant, a controller, an input, and an output. The plant represents the respiratory system and is arranged in compartments. The simplest layout is a two-compartment plant containing a muscle compartment and a lung compartment.

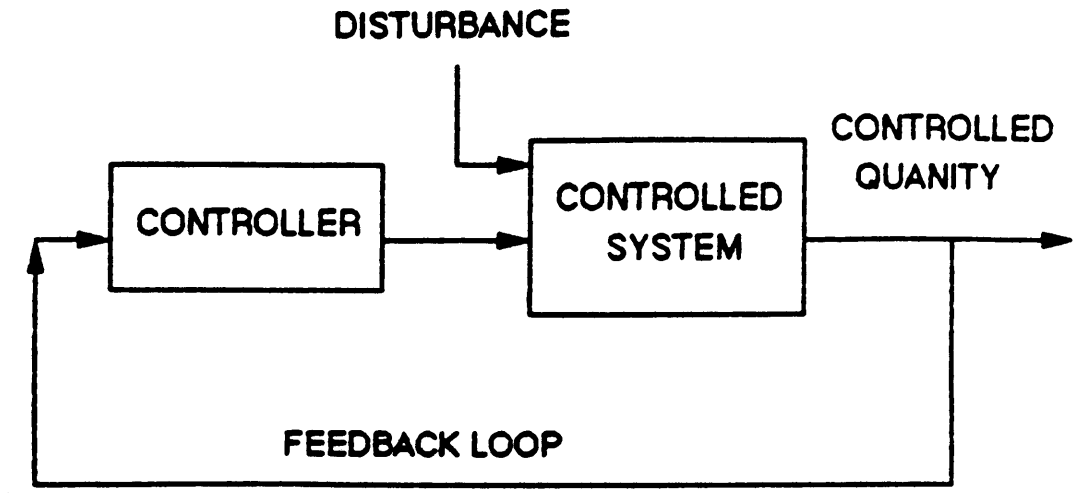


FIGURE 8 GENERAL STRUCTURE OF A RESPIRATORY CONTROL SYSTEM BLOCK DIAGRAM

The type of controller reflects the driver(s) assumed to affect respiration in each model. Drivers can be feedforward (neural, VCO2, high centers, gas oscillations) or feed back (PCO2,PO2, hydrogen ions). The controller can also have derivative control, proportional control, or both. Derivative control would be based on how fast the state variable is changing. Proportional control would be based on comparing the system output to a known set point.

Eight of the models listed in the references are discussed below.

Grodin's in 1954 published the first respiratory model (26). It was a simple model that contained two compartments: lung and muscle, see Fig. #9 and #10. Air flow into the lung was assumed non-cyclic. Blood flow was also constant regardless of metabolic rate. No time lags were considered between the muscle and lung. The controller used proportional, CO2 feedback. The sensing location for the arterial CO2 was left ambiguously as the lung.

Grodins published an expanded version of his model in 1964. The revised model included a brain compartment along with the lung and muscle compartments. The ventilation was assumed to be a constant non-cyclic flow. Blood flow was modified to be a function of metabolic rate. Bohr and Haldane effects were included to better simulate oxygen and carbon dioxide transfer rates. Grodins purposed a controller with this model that used proportional feedback. The feedback was hydrogen ion concentration in the cerebral spinal fluid, CSF, and hydrogen ion and oxygen concentrations at the carotid body. The CSF component incorporated the then recent findings in respiratory physiology.

Milhorn in 1972 published a model of similar complexity as Grodin's second model(27). Milhorn added dead space to the simulation of lung dynamics (still linear, non-cyclic flow however). Milhorn also changed the controller. Milhorn's controller used propor

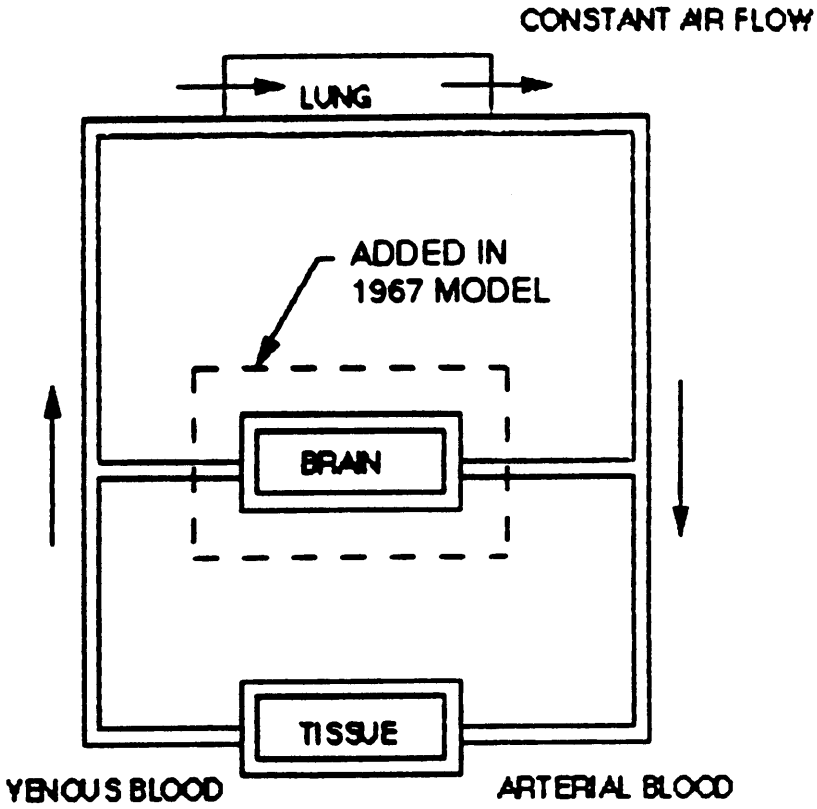


FIGURE 9 GRODIN'S 1954 RESPIRATORY MODEL
WITH 1967 MODIFICATION SHOWN

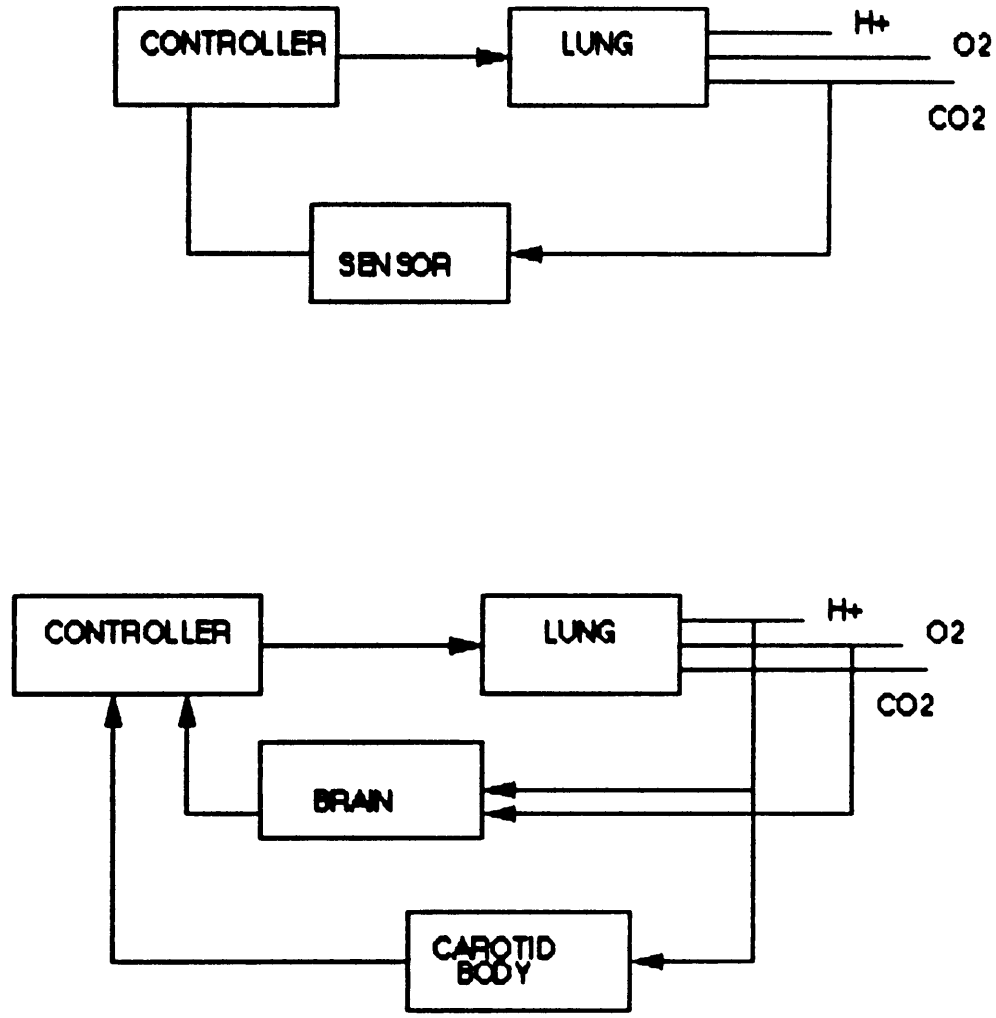


FIGURE 10 GRODINS CONTROL SYSTEM MODELS. TOP IS ORIGNAL 54' MODEL. BOTTOM IS 67' MODIFIED MODEL.

tional feedback based on hydrogen ion concentrations at the central and peripheral chemoreceptors, see Fig. #11. Milhorn did not postulate the physical characteristics of the chemoreceptors, other then to say the ventilation drive was comprised of 88% central and 12% peripheral chemoreceptor output.

Yamamoto published a complex model in 1978(28). Yamamoto's model had the main compartments representing the lung, muscle, and brain, see Fig. #12. However, each compartment was further divided to include cellular space, extra-cellular space, and capillary blood volume. Lung dynamics were modelled as cyclic and included dead space. The cardiovascular system was approximated as 60 slugs of blood, each 100ml. The discretizing of the blood volume allowed Yamamoto to model the changes in blood gas concentrations resulting from the cyclic lung volume. Why he chose 100ml slugs was not explained in the paper. The model's blood flow rate varied according to experimentally derived data. The proposed controller was relatively complex. It used proportional feed back from three signals: 1) Negative feedback from carbon dioxide concentrations in the brain. 2) Negative feedback based on the size of the arterial carbon dioxide oscillations monitored by a peripheral chemoreceptor. 3) Positive feedback from carbon dioxide gradients in the brain cells. The positive feedback concerned the size of the CO2 gradient and the ability of CO2 flux to migrate within the brain cells.

In 1981, Yamamoto published a revised model using the same layout as his 1978 model except adding a neural component to the controller.(29) Yamamoto postulated a neural signal proportional to the derivative of the metabolic rate.

Saunders published two models in 1980.(30,31) Each used the same physiological description of the respiratory system, see Fig. #13 and #14. Ventilation was modelled as cyclic and included dead space. Blood flow and metabolic rate were functions of work load extracted from experimental data. The controller for each model was based on the arterial oscillations of oxygen and carbon dioxide. The first was a modification of the

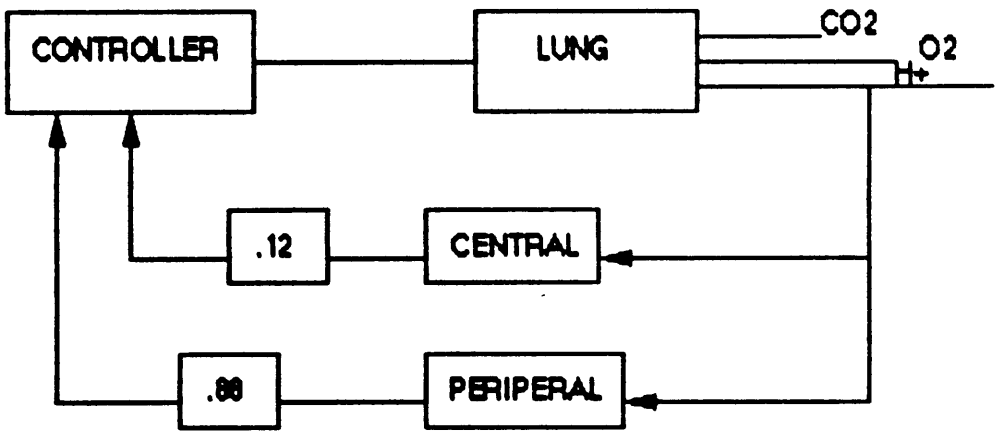
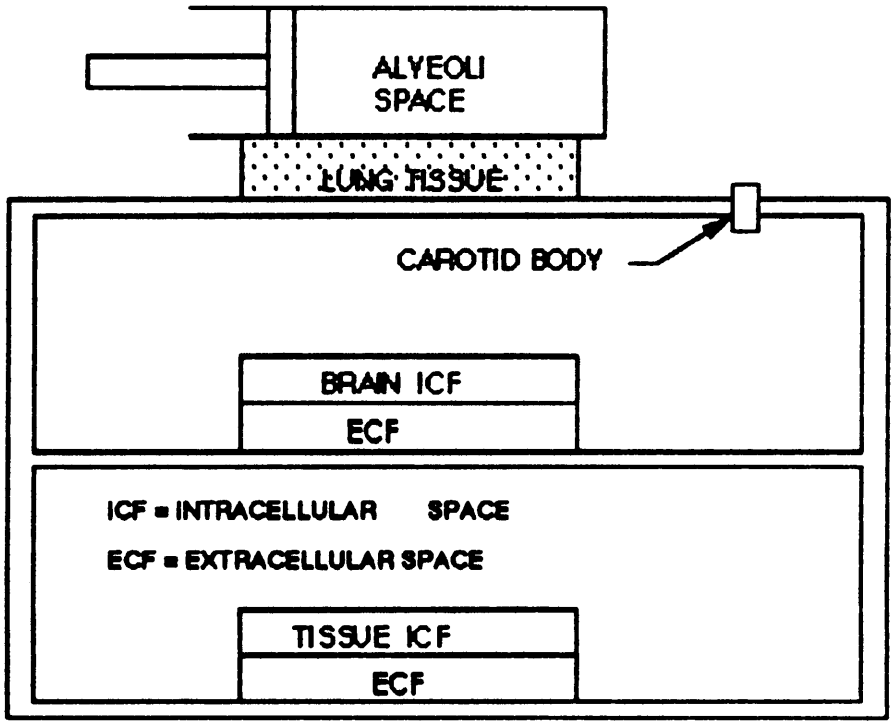


FIGURE 11 MILHORN'S CONTROL SYSTEM. PROPORTIONAL FDBCK SIGNALS GENERATED AT CENTRAL AND PERIPHERAL SENSORS



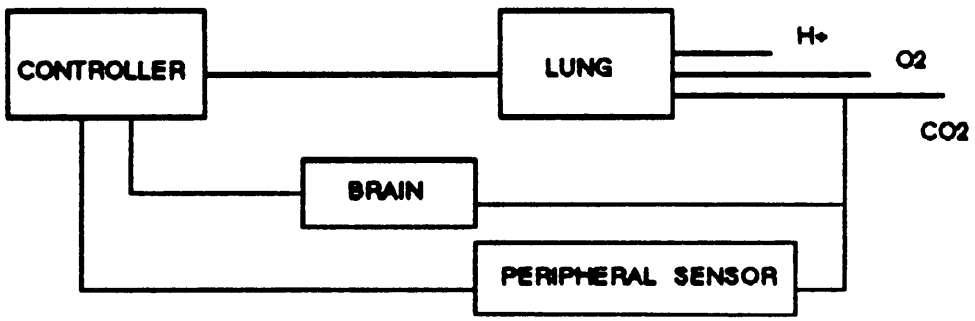


FIGURE 12 YAMAMOTO'S 1978 AND 1981 MODELS. 1978 MODEL BASED ON A FDBCK CONSISTING OF SEVERAL SIGNALS. NEURAL FEED-FORWARD SIGNAL ADDED IN THE 1981 MODEL. THREE COMPARTMENT MODEL SHOWN ABOVE.

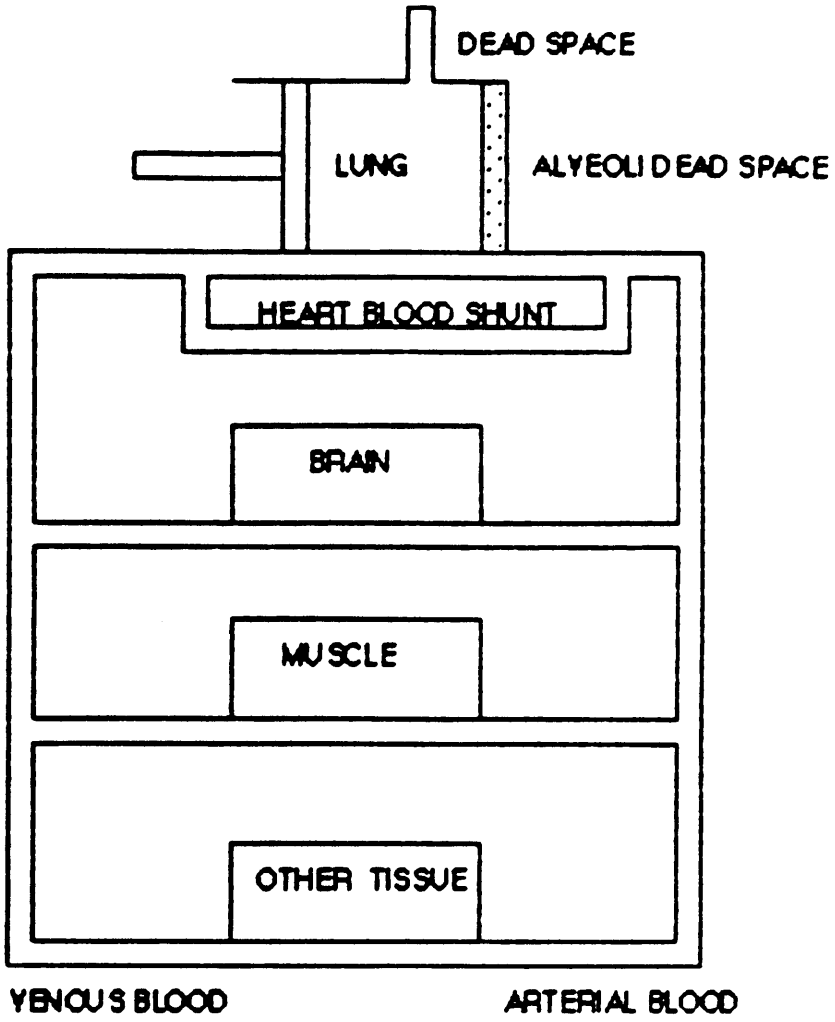


FIGURE 13 SAUNDERS THREE COMPARTMENT MODEL WITH BLOOD SHUNT, DEAD SPACE, AND CYCLIC VENT.

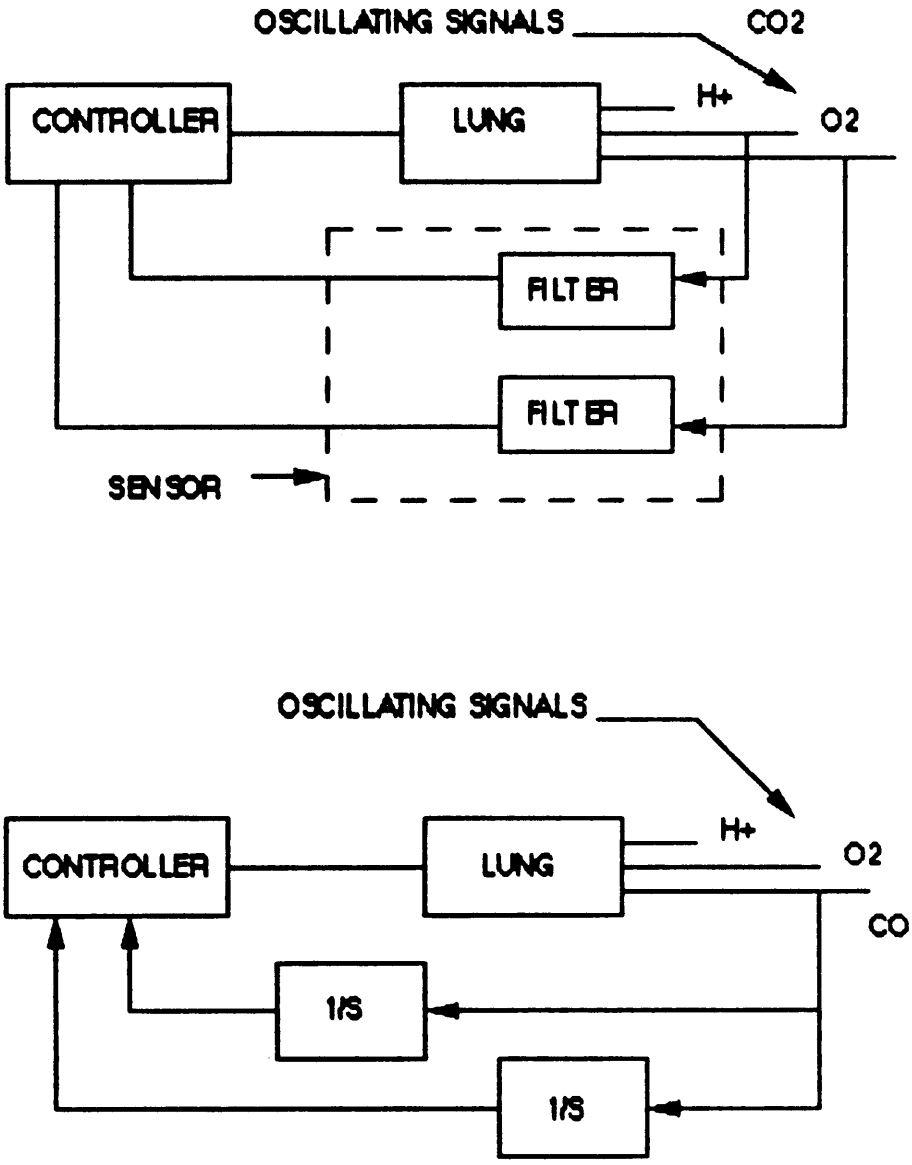


FIGURE 14 SAUNDERS CONTROL SYSTEM BLOCK DIAGRAMS. PROPROTIONAL CONTROL USING FILTERED O2 AND CO2 SIGNALS SHOWN TOP. DERIVATIVE CONTROL SHOWN BOTTOM.

controller proposed by LLoyd, Jukes, and Cunningham. Instead of the steady-state values of oxygen and carbon dioxide for proportional feedback, Saunder's used filtered values of the oscillating signals. In Saunder's second model, he proposed a feedforward control law based on the derivative of the oxygen and carbon dioxide oscillations.

At the end of the second publication, Saunders suggested a control law based on a combination of his two schemes: A derivative and proportional control law.

Khoo published a model in 1982 that lacked the sophistication of Saunder's model, however, it included a mixing feature not simulated before.(32) Khoo's model included lung, muscle, and brain compartments. Cyclic ventilation, dead space, and time delays. The controller used proportional feedback based on carbon dioxide concentrations at the brain and carotid body. The difference in Khoo's model is that he simulates mixing of the arterial blood in the heart and vasculature, see Fig. #15.

The last model to be discussed was published by Poon in 1987.(33) Poon took advantage of experimental data relating ventilation and expired carbon dioxide. The control law Poon uses is based on proportional carbon dioxide feedback and an optimizing controller, see Fig. #16. The optimizing controller adjusts the ventilation signal to achieve a minimum work level. A balance is made between the chemical work of regulating hydrogen ion, carbon dioxide, and oxygen concentrations and muscular work in the chest.

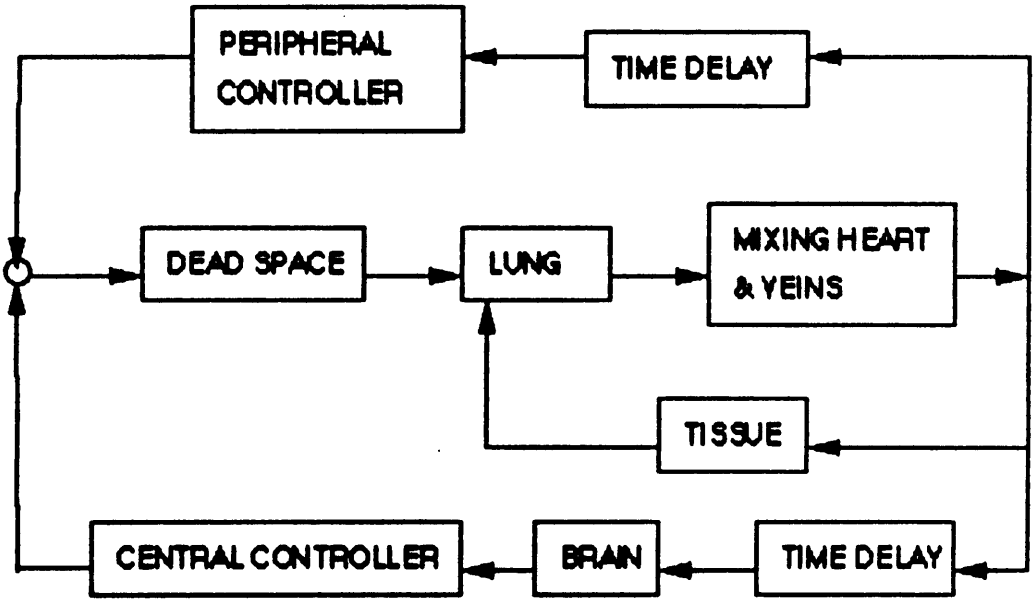


FIGURE 15 BLOCK DIAGRAM KHOO'S MODEL WHERE VENTI - LATION IS THE SUM OF PERIPHERAL AND CENTRAL COMPONENTS

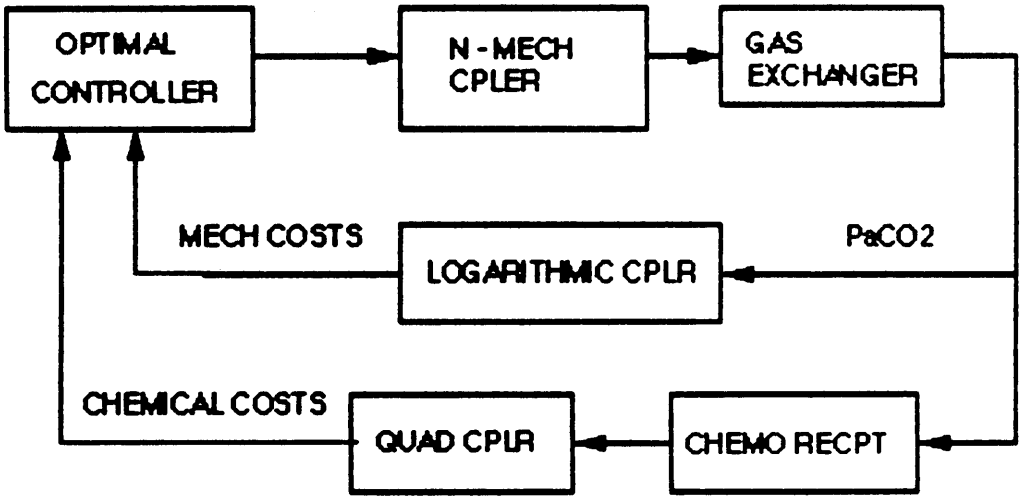


FIGURE 16 POON'S OPTIMIZATION MODEL. MINIMIZES THE SUM OF THE MECH. AND CHEMICAL COSTS OF RESPRIRATION.

5.0 MODEL DEVELOPMENT

5.1 INTRODUCTION

The respiratory system modelled in this thesis is shown in Fig. #17. The controller uses a combination of derivative feedforward control and proportional feedback control following the work of Saunders.(30) The system driver is carbon dioxide concentration in the blood. The feedforward control is based on the derivative of arterial dioxide oscillations. Feedback uses the mean of the arterial carbon dioxide oscillations.

The confusion over what constitutes feedforward and what constitutes feedback was discussed in Section 4.9. To reemphasize the difference, respiratory literature has labeled controller input arising from neural mechanisms as feedforward. Since changes in carbon dioxide oscillations appear at the carotid body before any blood from exercising muscles has time to reach there, carbon dioxide oscillations are grouped with the neural mechanisms as feedforward. However, from a controls engineering standpoint, the change in oscillations are read in the arterial blood downstream of the lung compartment and therefore would be feedback. This thesis adopts the convention used in the respiratory literature by labelling the effect of oscillations as feedforward.

The model assumes a carbon dioxide production rate that is a function of work load. Partial pressures of carbon dioxide in the blood and lung air are assumed to equalize in the pulmonary capillary. Blood gas concentration of the arterial blood leaving the lung is assumed isocapnic with a mean concentration of 40 mmHG carbon dioxide.

Nomenclature used in equations appears on pages x and xi.

The model represents breath-by-breath respiratory dynamics. It is breath-by-breath because the tidal volume and breathing frequency are updated at the end of each breath.

Expired carbon dioxide concentrations are assumed to follow alveoli concentrations. The model ignores effects arising from variations in lung volume, see section 4.6.

The model is idealized as having a known input, metabolic production of carbon dioxide. The ability of the model to generate the correct ventilation determines whether the controller has the right form.

The model is run by translating the equations developed in this chapter to a FORTRAN code called Advance Simulation Language, ACSL. ACSL has built in functions for integration, time delays, filters, graphing, and others. The ACSL program code for the respiration model is presented in Appendix B.

5.2 MODEL OF GAS EXCHANGE

The simulation of human respiration begins with a mass balance of carbon dioxide entering and leaving the lung, see Fig. #18. Mathematically, it means

(NOTE: XXDOT IMPLIES DERIVATIVE OF XX)

$$MDOT_{IN} - MDOT_{OUT} = MDOT_{LUNG} \tag{5.1}$$

$$MDOT_{IN} = C_{VCO2}*Q + F_{ICO2}*VLDOT \tag{5.2}$$

$$MDOT_{OUT} = C_{ACO2}*Q + F_{ECO2}*VLDOT \tag{5.3}$$

$$M_{LUNG} = C_{ACO2}*VBL + F_{ACO2}*VL$$

$$MDOT_{LUNG} = (CDOT_{ACO2}*VBL + CACO2*VBLDOT) + (MDOT_{ACO2}*VL + F_{ACO2}*VLDOT) \tag{5.4}$$

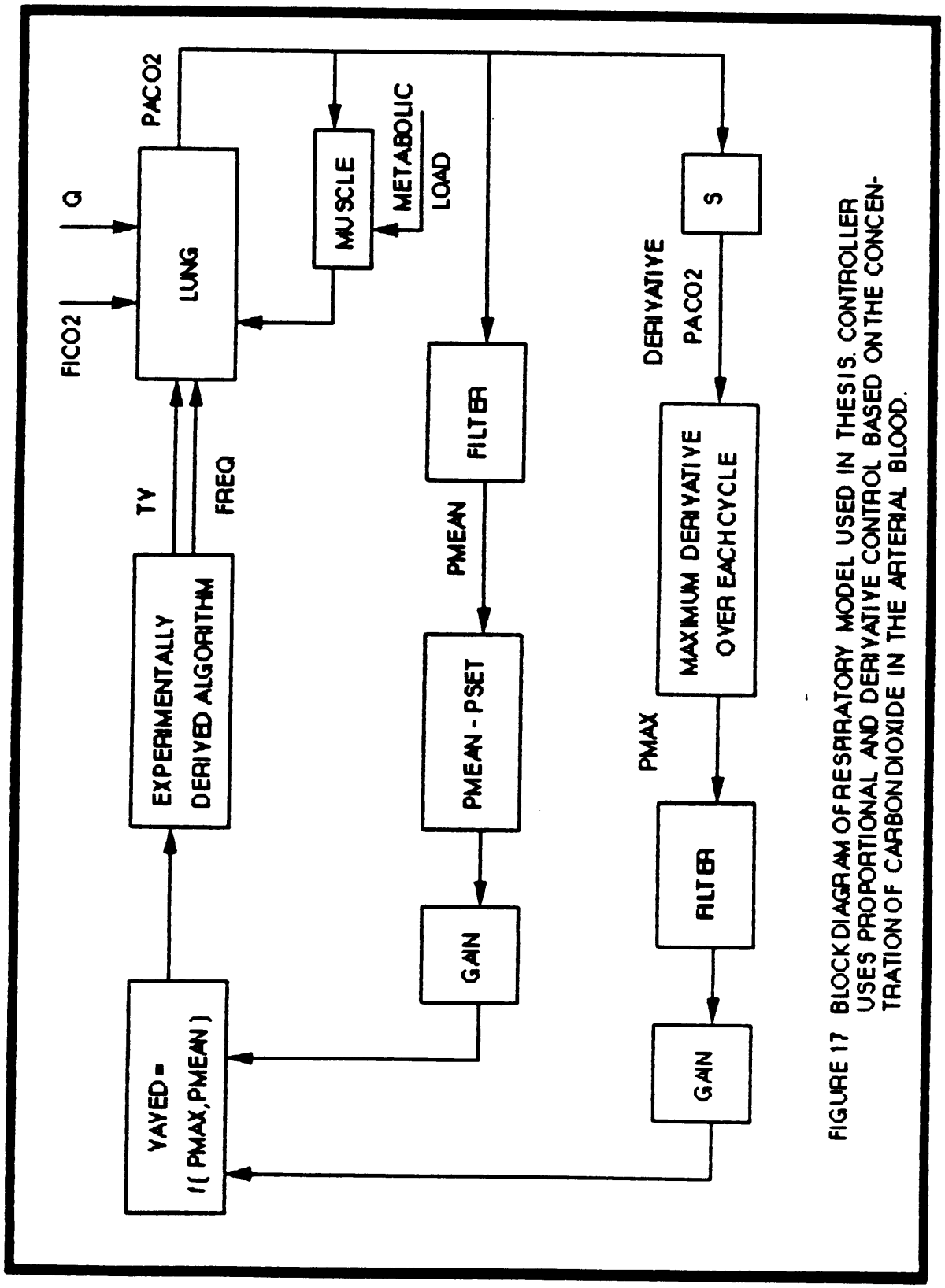


FIGURE 17 BLOCK DIAGRAM OF RESPIRATORY MODEL USED IN THESIS. CONTROLLER USES PROPORTIONAL AND DERIVATIVE CONTROL BASED ON THE CONCENTRATION OF CARBON DIOXIDE IN THE ARTERIAL BLOOD.

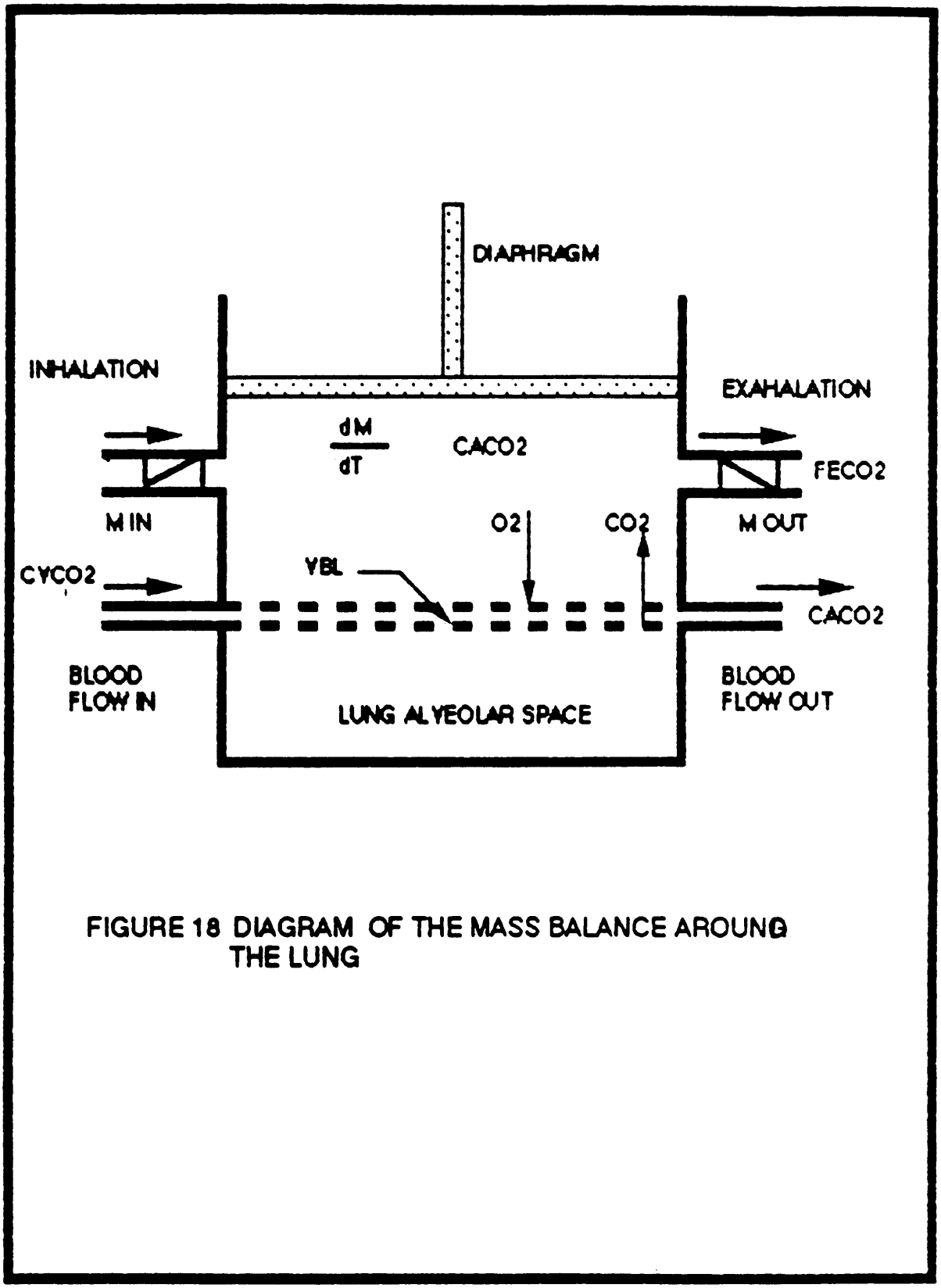


FIGURE 18 DIAGRAM OF THE MASS BALANCE AROUND THE LUNG

The amount of carbon dioxide in the lung blood is not truly CaCO2 * VBL. There is some length of time before the concentration of carbon dioxide is decreased in the pulmonary capillary from its venous to arterial levels. Two assumptions justify the approximation of CaCO2 * VBL. First, the quantity is small compared to the other terms in the equation. Second, the mass transfer rate of carbon dioxide is high. The transfer is not instantaneous, but occurs rapidly.(37)

The quantity of blood in the lung is fixed making the derivative of the lung blood volume zero.

Carbon dioxide content of inspired air is nominally 0.05% of the total air. Neglecting the inspired carbon dioxide concentrations is justified.

Additionally, expired carbon dioxide only exists during the expiration phase of ventilation. To account for this, a switch is added to the expired carbon dioxide term that is zero during inhalation and one during exhalation.

Making the appropriate substitutions,

$$(C_{vCO2}*Q + F_{ICO2}*VLDOT) - (C_{aCO2}*Q + MU*F_{ECO2}*VLDOT) =$$
$$(CDOT_{aCO2}*VBL + FDOT_{ACO2}*VL + F_{ACO2}*VLDOT) \qquad (5.5)$$

With MU = 0 $\quad t < TI \quad$ Within each breath

= 1 $\quad t > TI$

Within the blood, gas concentrations are expressed as liters per liter, STPD. Lung air and expired air are expressed as liters per liter, BTPS. To complete the model of gas exchange, gas concentrations in the blood must be related to concentrations in the lung.

This is accomplished by converting the concentrations to partial pressures which equilibrate across the membrane either STPD or BTPS. BTPS will be used.

To convert dissolved blood gas concentrations to partial pressures, use the carbon dioxide dissociation curve.(34)

$$C_{iCO2} = 0.01 * (14.9 - 1.4*SAT) * P_{iCO2}^{0.35}$$
$$= K1 * P_{iCO2}^{0.35} \quad (5.6)$$

Since derivatives are needed,

$$CDOT_{iCO2} = 0.35 * K1 * P_{iCO2}^{-0.65} * PDOT_{iCO2} \quad (5.7)$$

To convert lung and expired air concentrations use Dalton's Law,

$$P_i = F_i * P_{ATM}$$
$$F_i = P_i / P_{ATM} \quad (5.8)$$

The derivative

$$FDOT_i = PDOT_i / P_{ATM} \quad (5.9)$$

Here it is important to recognize the total pressure is based on dry air. Lung and expired air, which is saturated with water vapor, needs correction.

$$F_i = P_i / (P_{ATM} - 47.)$$
$$= P_i / CONV \quad (5.10)$$

The amount of expired carbon dioxide is a function of gas exchange rates, lung storage

volume, dead space, the size of the previous breath, and the amount of inspired air in the current breath. This makes estimation of the expired carbon dioxide difficult. For averaged, steady-state breathing, however, expired carbon dioxide concentrations reflect to alveoli concentrations. Therefore,

$$F_{BCO2} = F_{ACO2} = P_{ACO2}/CONV$$

After converting concentrations to partial pressures, the conservation of mass equation takes the form

$$.35 * K1 * P_{ACO2}^{0.65} * PDOT_{aCO2} =$$
$$Q*(C_{VCO2}-K1*P_{aCO2}) + VLDOT*(MU*P_{ACO2}/CONV-P_{ACO2}/CONV) - P_{ACO2}*VL/CONV \quad (5.11)$$

Assuming partial pressures equalize in the blood and lung air, $P_{aCO2} = P_{ACO2}$ and

$$PDOT_{aCO2} = Q * (C_{VCO2}-K1*P_{aCO2}^{0.35}) * CONV - VLDOT * P_{aCO2} * (1 - MU)$$
$$* 1 / (VL + .35 * K1 * VBL * CONV * P_{aCO2}^{-0.65} \quad (5.12)$$

With,

C_{VCO2} = Metabolic production of CO2 in liters/liters, BTPS
VL = Lung volume, liters, BTPS
VLDOT = Minute volume, liters/min, BTPS
VBL = Volume of blood in the lung, liters, BTPS
$P_{aCO2} = P_{ACO2}$

5.3 DEAD SPACE

Anatomical and alveolar dead space volumes received little attention as part of this

thesis research. The algorithms translate lung volume into the active alveoli volume. Active alveoli volume is what is exposed to gas exchange with the blood in the pulmonary capillaries. Equations for dead space were extracted from Sauders et al.(31)

Anatomical Dead Space $VD_{AN} = 0.175 \quad TV < 0.875$ (5.13)

$= 0.2 * TV \quad TV > 0.875$

Alveolar Dead Space $VD_{ALV} = 0.175$ (5.14)

5.4 VENTILATION

Ventilation is approximated as a sinusoidal phenomena. The lung volume is a function of tidal volume and breathing frequency, so

$$VL = TV/2 * SIN(2*PI*F*t) \quad (5.15)$$

The minute ventilation is the time rate of the lung volume.

$$VLDOT = 2*PI*F*TV/2 * COS(2*PI*F*t) \quad (5.16)$$

The model generates ventilation updates by deriving a new value of minute volume at the start of each breath. This minute volume must be split between tidal volume and frequency, see Section 4.4. The algorithm relating tidal volume, frequency, and ventilation is extracted from Saunders et al (31) and has the form

$$VL = TV * F$$

$$TV = 0.089 * VL \quad 0 < VL < 10.47 \quad (5.17)$$

$$TV = 0.288 * VL^{0.5} \quad VL > 10.47$$

5.5 MUSCLE COMPARTMENT MODEL

Metabolic production of carbon dioxide as a function of work load was derived from experimental data, see Chapter 6.0. The rates were left as a table function. Recognize that the values in the table have already been converted to BTPS.

The muscle compartment receives a continuous flow of arterial blood. Carbon dioxide produced in the muscle is absorbed by the passing blood. Because low work levels are used in this thesis research, all of the metabolic carbon dioxide is assumed to be carried away by the blood. Finally, the muscle compartment is assumed to have a constant volume. This means no storage of carbon dioxide takes place in the muscle compartment.

Therefore,

$$C_{vco2} = (Q * C_{aco2} + \text{METABOLIC CO2}) / Q \qquad (5.18)$$

The model filters the arterial blood before it reaches the muscle compartment. This simulates the mixing that takes place in the vasculature between the carotid body and the muscle. The filter is a first order lag with a break frequency of 20 seconds.

5.6 TIME DELAYS

Time delays are needed for the muscle blood to reach the lung, pulmonary blood to travel from the lung to the carotid body, and arterial blood to travel from the carotid body to the muscle compartment.

The time delays are determined by estimating the volume of blood in the path and

dividing that by the blood flow rate. Blood flow rates very with work load, so time delays vary with work load also. Time delay values were extracted from Grodin's et al (30),

$$\text{Muscle to Lung} = 3.128 / Q \quad (5.19)$$

$$\text{Muscle to Carotic Body} = 1.070 / Q \quad (5.20)$$

$$\text{Carotid Body to Muscle} = 0.735 / Q \quad (5.21)$$

5.7 CONTROLLER

The controller is based on the one proposed by Saunders.(30) The amount of air required for the next breath is a function of the maximum slope of the oscillations before it and the average of the carbon dioxide concentration.

$$VLDOT = SCV * PMAX + CC * (PMEAN - PSET) \quad (5.22)$$

These two terms have physiological meaning. The average of the carbon dioxide concentrations is fairly simplistic. To maintain an isocapnic response, the average carbon dioxide concentration must be held at 40 mmHG. When the average rises above the 40 mmHG, more air is needed by the body and ventilation is increased. The opposite is true when too much carbon dioxide has been blown off and the average falls below the 40 mmHG.

The effect of the carbon dioxide oscillation is more subtle. With an increase in work load, heart rate increases and therefore so does blood flow. This mechanism alone increases the maximum slope of the sinusoidal carbon dioxide oscillations. The controller attempts to keep ventilation in pace with the blood flow by using this "feedforward" response.

6. EXPERIMENTAL RESULTS

6.1 INTRODUCTION

Success of the model was evaluated by comparing its output with levels determined experimentally. To be successful, the model had to reasonably match minute ventilation and maintain arterial blood isocapnic. With minute ventilation defined as the volume flow rate of air in liters/min cycled through the lung and isocapnic defined as holding carbon dioxide arterial blood concentrations at a partial pressure of 40 mmHG.

An isocapnic response to exercise was not experimentally verified in the research for this thesis. The literature search showed carbon dioxide concentrations can drop below the nominal 40 mmHG during heavy work load demands.(40) However, at low work levels like those examined here, partial pressures of arterial carbon dioxide should hold at or just below 40 mmHG. Recognize that these carbon dioxide concentrations were an average over time. In reality, they oscillate in an almost sinusoidal fashion at a period determined by the breathing frequency.

Breathing patterns vary from person to person. The amount of carbon dioxide produced at a given work load, when respiration becomes anaerobic, the balance between tidal volume and frequency, and the size of each breath are functions of a person's age, weight, height, and fitness.

The intent of the testing for this thesis was to gather the parameters necessary to groom the model for one individual. This would give the model, and more specifically the controller, the best chance possible of mimicking actual ventilation responses to exercise.

Background data collected were age, height, weight, and general fitness. These established the distance between body compartments and allowed for estimation of time

delays. The data also allowed for the estimation of lung size. The test subject was a thirty year-old healthy male, was 180cm tall, and weighed 72kg.

The following data were experimentally derived: 1) the steady state production of carbon dioxide as a function of work load, 2) the steady-state relationship between tidal volume and ventilation, and 3) for use in comparing with the model, minute ventilation as a function of time and work protocol.

Carbon dioxide production rates in the working muscle were based on the assumption that during steady-state work loads, they equaled expired carbon dioxide rates. This was a fair assumption and required only the assurance that units matched. The relationship between tidal volume and ventilation was an important ingredient in the model. The model estimated the volume flow rate of air that must cycle through the lungs, the minute volume. Figuratively speaking, this air demand was translated to muscular signals which were manifested as changes in tidal volume and breathing frequency. How each of these increased in proportion to the additional air demands was the relationship that needed to be established. Tidal volume associated with each ventilation level and carbon dioxide production rates were derived for steady-state work levels of 0, 25, 50, 75, and 100 watts. The actual work protocol used to compare experimental and model output was designed to be a slow increase in work level to reduce the effects of the transient state as much as possible.

6.2 QUASI BREATH-BY-BREATH ANALYSIS

In response to a change in exercise level, the body goes through a transient before reaching its new steady-state level. Additionally, as described in section 4.2, algorithms representing respiratory action only hold true for the steady-state. The summation of these two facts means that although the model simulates respiratory action on a breath-

by-breath basis, experimentally derived functions internal to the model were generated only with steady-state data, and the model, therefore, may not predict transient behavior. For this reason, this thesis included only quasi breath-by-breath analysis of respiratory dynamics since the transient zones were omitted.

6.3 TEST APPARATUS

Most of the testing for this thesis was accomplished at the cardio-pulmonary testing center in the War Memorial Gymnasium here at Virginia Polytechnic Institute. Success in obtaining the necessary data was attributed largely to the support of Dr. W.G. Herbert of the health and physical education department and his staff. Access to the equipment was such that testing could be accomplished whenever the HPER department did not have scheduled classes. Tests were run in the time period from March to September 1988 on an Ergometrics exercise testing machine manufactured by S.M. Instruments.

In an attempt to harness the latest technology in exercise testing equipment, additional test data was obtained at the cardio-pulmonary research center at Wake Forest University. This testing accomplished with the support of Dr. W.G. Ribisol on a breath-by-breath analyzer manufactured by Medical Graphics Co. This testing was accomplished in May of 1988.

Breath-by-breath testing was attempted at the HPER lab here at VPI. Modifications to the Ergometrics unit were made to gather respiratory data within the breath. This proved only marginally successful as will be explained below.

6.3.1 ERGOMETRICS UNIT

This exercise testing machine provided expired gas concentrations on 15 second intervals.

The instrument specifications are in Appendix e. The 15 second intervals represented an average of each measured value over that period. Fifteen seconds was the fastest data could be gathered. This unit was not a breath-by-breath analyzer since the dynamics of individual breaths were lost in the average. The majority of test data was collected using this machine.

6.3.2 MODIFIED ERGONMETRICS

The software was the limiting parameter on the Ergometrics machine for the speed of gathering data. The carbon dioxide analyzer had the capability of tracking concentrations as fast as 0.02 seconds, but the software included with the unit could gather information at only 15 second intervals. To obtain a closer look at the respiratory dynamics, the Ergometrics machine was modified to capture breath-by-breath data. This consisted of changes in the system arrangement to allow for gas concentrations to be read at the mouth and use of data acquisition software that stored data at 0.02 second intervals the limit of the carbon dioxide analyzer. This arrangement proved marginally successful. The data acquisition software had been borrowed from a test program that required extremely fast data acquisition and as a result, its slowest configuration was 0.02 seconds. This equated to approximately 250 data points per breath and proved too much data to manage. Additionally, time delays for expired gases reaching the analyzers and reaching the pneumatac were different. Matching these wave forms could probably have been done successfully, but data storage limitations and other problems made this test set-up less than effective.

6.3.3 MEDICAL GRAPHICS UNIT

The exercise testing machine was manufactured from the ground up as a breath-by-

breath analyzer. It provided virtually every parameter concerning respiratory dynamics that can be evaluated. The intent of using this machine was to examine the structure of each breath as the test subject was exposed to an exercise transient. The breath-by-breath analyzer had an impressive software package the allowed for data to be examined in a multitude of ways. This cost of this unit on the open market was $70,000. This is typical for breath-by-breath analyzers.

Testing on the Medical Graphics machine also proved marginally successful. The machine provided respiratory data at the end of each breath. This made reconstruction of what occurred within the breath only an estimate. Also, respiratory patterns vary so much that breath-by-breath data had to be averaged to make any sense of what was occurring.

The unit was essentially a black box. No data reduction was possible if the software did not include what was desired. Data could not be downloaded in a format that could be interpreted by another computer. The software was a CTOS base. No method of transferring to an ASCII file was available.

According to Medical Graphics technical representatives, the unit does have the capability of creating within breath data, but modifications to the test set-up are required. A port in the back of the data processing unit can be tapped for a straight analogue signal that represents a continuous readout of each gas analyzer and the pnuematac.

This type of equipment represents a sizeable effort in development of both hardware and software yet its actual benefit was rather limited.

6.4 SUMMARY OF DATA COLLECTED

The breath-by-breath output gathered from the modified Ergometrics unit and the

Medical Graphics unit were discarded because their was just too much data to efficiently manage. To "see" what was happening in the data generated by these two machines, their outputs had to be averaged to remove the noise contained in the data. But, once an average was made, the information was the same as that obtained form the Ergometrics unit and its 15 second averaging.

The data kept and analyzed was the data from the Ergonmetrics unit. The standard protocol for this thesis consisted of a 0 to 100 watt ladder with 25 watt steps. Increments were made every 12 minutes to ensure steady-state output for each step had been reached. Each protocol was performed with the same test subject.

The length of the 0 to 100 watt incremental protocol brought to question whether the lower steps affected the ventilation rates at the 75 and 100 watt steps. For this reason, the individual 75 and 100 watt tests were run to prove steady- state values were being reached at the upper end of the incremental 0 to 100 watt protocol.

Fig. #19 shows the relationship between metabolic production of carbon dioxide and work. Fig. #20 shows the minute ventilation generated for the 0-100 watt incremental protocol. Fig. #21 shows the relationship between tidal volume vs ventilation. Figs. #23 and #24 show the ventilation profile for the 75 and 100 watt tests.

6.5 TEST RESULTS

The data gathered during the experimentation was compared with general results cited in literature and with Saunders.(30,31) The relationship between carbon dioxide production and work was not strictly linear. The published data and the curve proposed by Saunders indicated it probably should have been. The data was not altered, however, in hopes of more effectively reproducing the associated ventilation demand curve.

The line most closely approximating the tidal volume ventilation relationship was found to be TV = 0.375*VE + 0.4688. Fig. #22 is a comparison of the best fit line for the experimental data and the algorithm Saunders used.

Lastly the ventilation vs time curves represent raw data except for the removal of gross excursions that probably arose from coughs, sighs, or swallows.

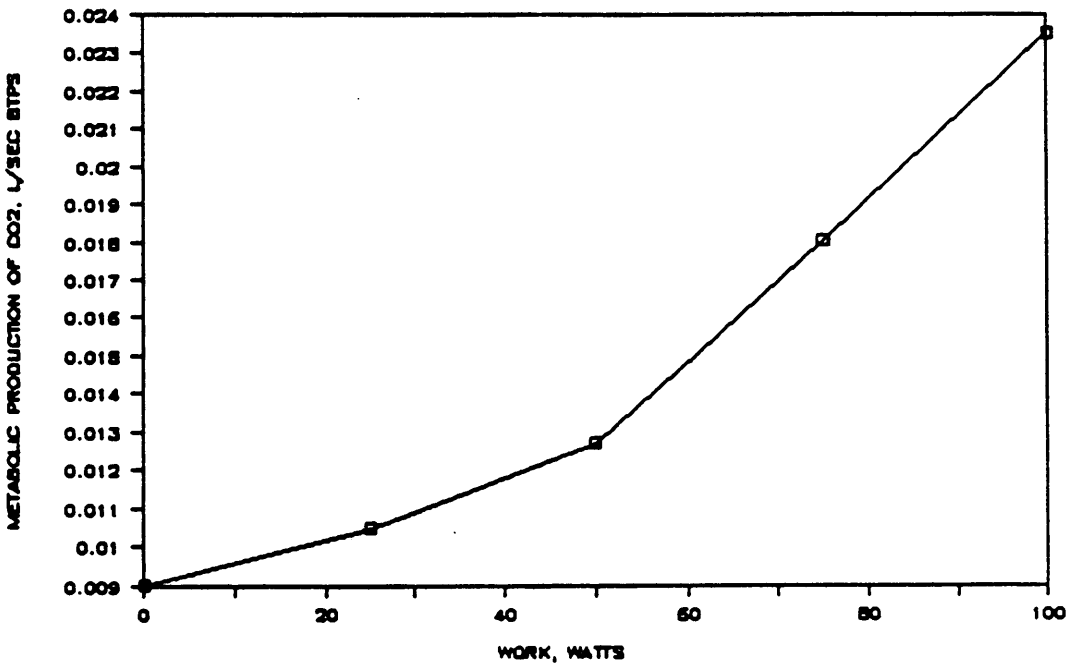


FIGURE 19, EXPERIMENTAL DATA SHOWING THE STEADY-STATE RELATIONSHIP BETWEEM METABOLIC CO2 IN THE AND WORK LEVEL

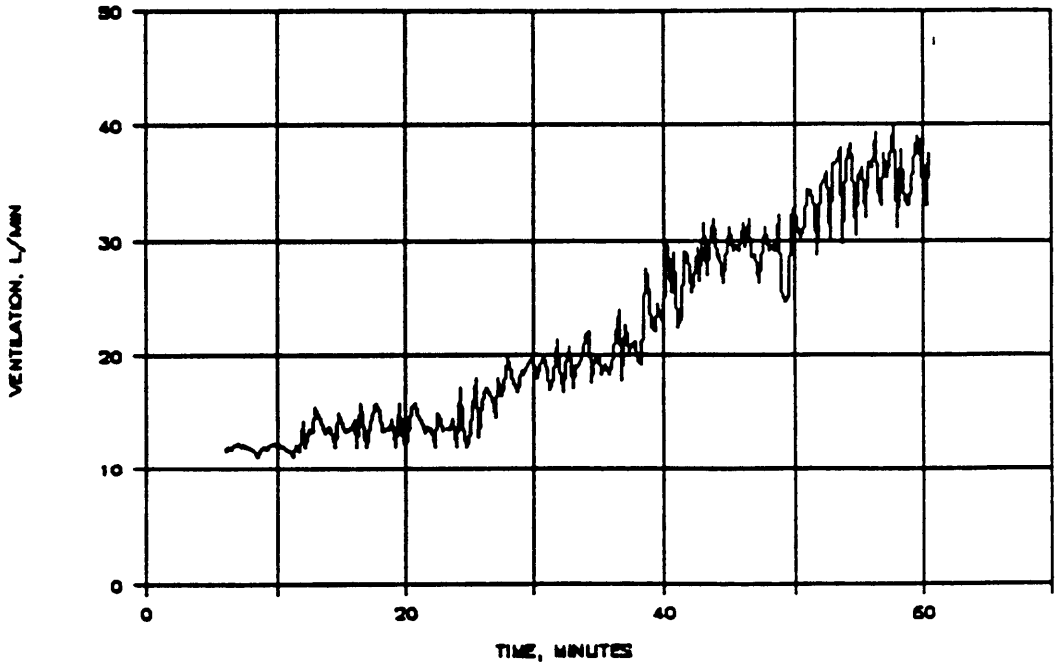


FIGURE 20, EXPERIMENTAL DATA OF A 0-100 WATT INCREMENTAL PROTOCOL WITH 25 WATT STEPS IMPOSED ON 12 MIN INTERVALS.

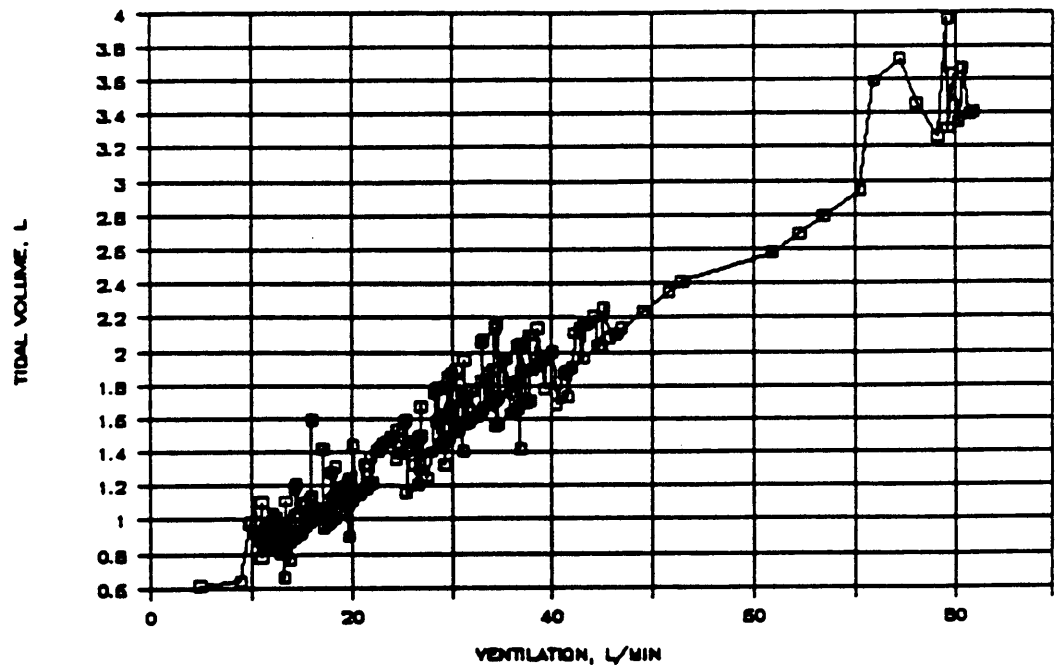


FIGURE 21, EXPERIMENTAL DATA SHOWING THE RELATIONSHIP BETWEEN TIDAL VOLUME AND VENTILATION

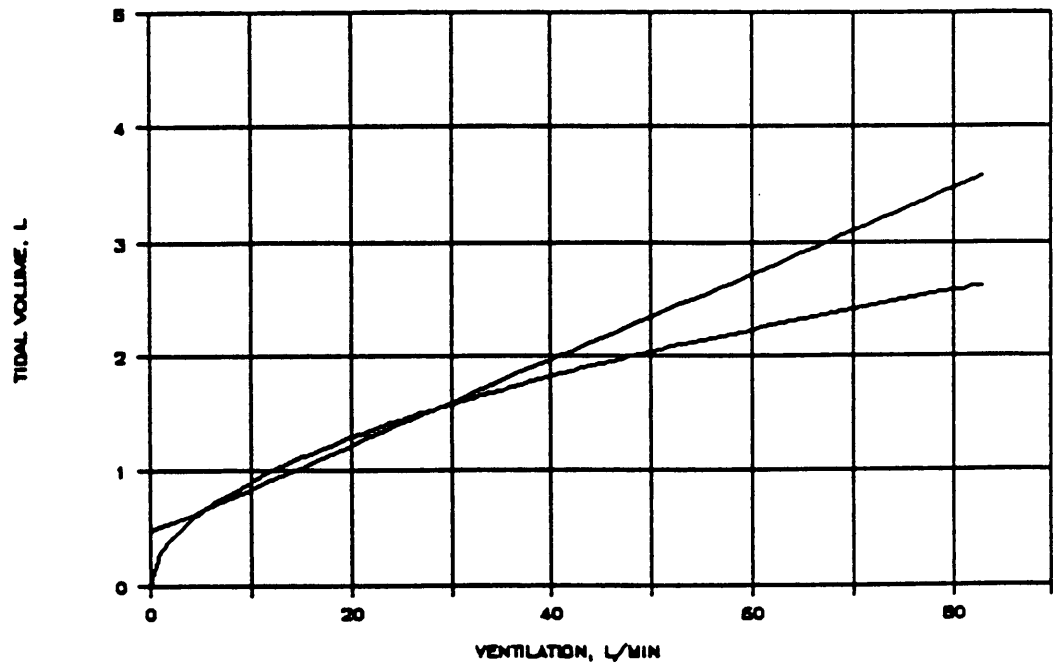


FIGURE 22, DERIVED RELATIONSHIP BETWEEN TIDAL VOLUME AND VENTILATION. THE LINE IS THE "BEST FIT" AS DETERMINED FROM EXPERIMENTATION. THE CURVE IS SAUNDER'S ESTIMATE.

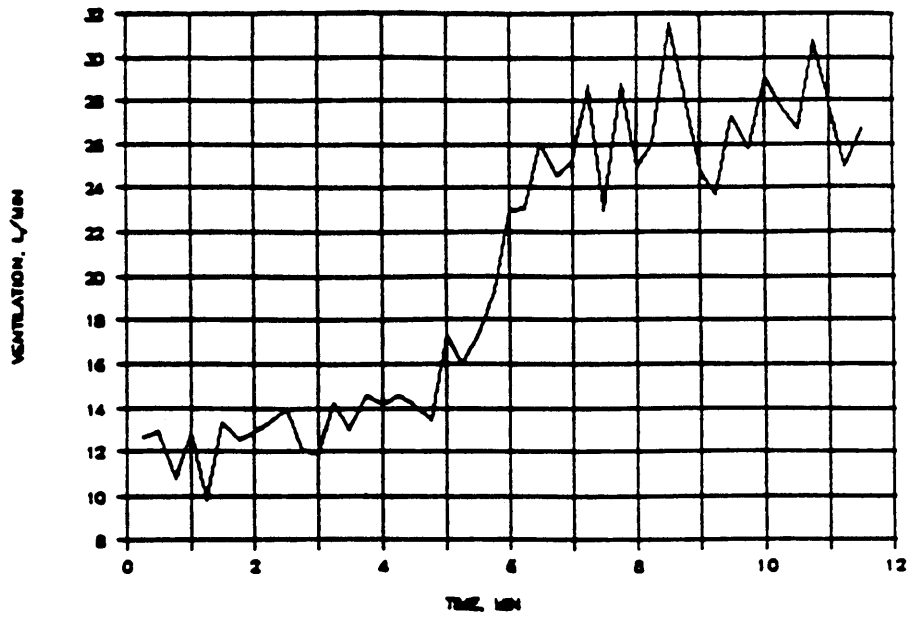


FIGURE 23, EXPERIMENTAL DATA SHOWING VENTILATION PROFILE OF A 0 TO 75 WATT STEP LOAD

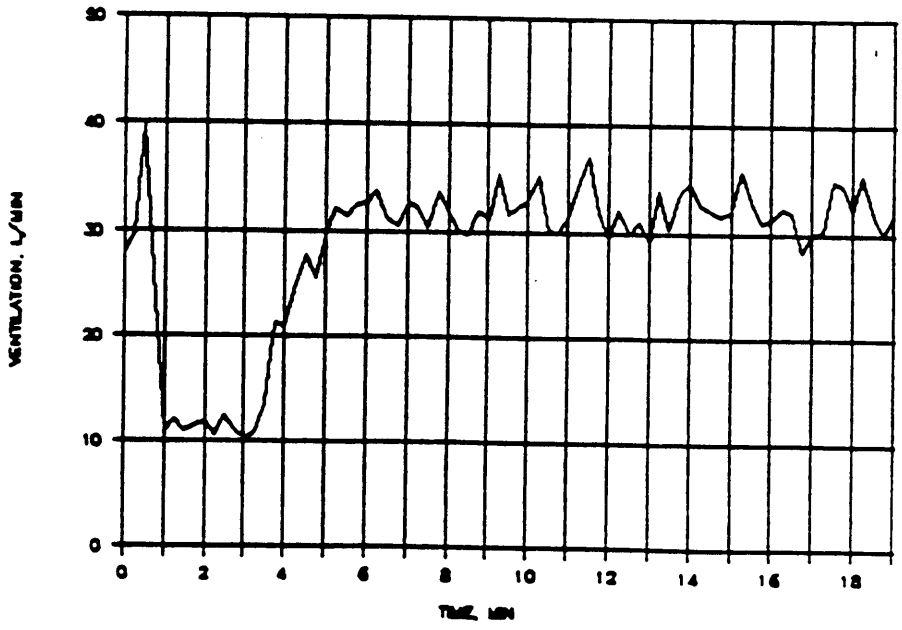


FIGURE 24, EXPERIMENTAL DATA SHOWING VENTILATION PROFILE OF A O TO 100 WATT STEP LOAD

7.0 DISCUSSION OF RESULTS

In his two papers published in 1980, Saunders described several equations that may serve as control laws for human respiration.(30,31) The first was a proportional control law using the work of Lloyd, Jukes, and Cunningham as a basis. The feedback variables in this equation were carbon dioxide and oxygen concentrations. He presented a second equation that used only derivative control. The feedback variable here was just arterial carbon dioxide concentrations. He presented a third equation that was a combination of the first two. The feedback variables were again the carbon dioxide and oxygen concentrations. This equation reproduced here is equation (5) in reference 30.

$$\text{Minute Ventilation} = f(CO_2,O_2) + f(\max dCO_2/dt) - 7.4 \qquad (7.1)$$

Ellis modified this controller by deleting the oxygen dependence in the proportional term and omitting the constant. The result was equation 5.22 in this thesis.

The intent of the research behind this thesis was to apply a go, no-go test on a control law using proportional and derivative control to answer the question: can it act as a partial state estimator and satisfactorily control respiration for different system disturbances?

Successful system control was based on how well model generated minute ventilation tracked experimental data while maintaining arterial blood isocapnic. To reemphasize the meaning of isocapnic, even though arterial carbon dioxide levels oscillate in conjunction with lung volume, the respiratory system maintains an average arterial carbon dioxide concentration of 40 mmHG. How well a controller maintains this regulation point was a measure of its ability to maintain isocapnic response.

The model of the respiratory control system was tailored for a specific test subject. Additionally, the model was groomed to eliminate items that, although were physiologically correct, contributed little to its performance. The idea was to build a simple, bare-bones model of the test subject and see how well the controller managed operation.

7.1 RESULTS FROM OTHER PUBLISHED MODELS.

To help gage the success of the model used for this thesis, the models cited in Chapter 4 were reviewed to determine how well they fit experimental data. The most obvious trait of all the models was their reliance on engineering rational. Each model's performance was based on what was expected to happen in accordance with the published literature rather than experimental results. This probably arose for two reasons. The first was the difficulty in obtaining data on blood chemistry with awake, exercising test subjects. The second was the ever-present difficulty in evaluating experimental results of respiratory data. As described in Section 4.3 and in Chapter 6, respiratory data moves randomly about mean values. These mean values vary greatly from individual to individual. Published respiratory data tends to be for the "average test subject."

Of the models cited in Chapter 4, Poon's and Khoo's models did not incorporate experimental data. Poon's focus was on presenting a controller that optimized the work needed for respiratory action against the demand the body had for air. Humoral concerns did not enter into his model. Khoo's interest was in periodic breathing. He was more concerned with the stability of the model then correct model output.

Grodin's first model estimated model parameters from experimental work done on cats. He evaluated model output based on what he considered normal expectations. This first model was developed in the early fifties. His work, which may seem trivial in relation to what is done today, was state-of-the-art then.

Grodin's work published in 1964 incorporated experimental data, but was vague on how the data was gathered and then reduced. The experimental data were shown as smooth curves which the model tracked "reasonably well."

In his model published in 1972, Milhorn used algorithms derived from literature to piece together a model. He too was not specific in how his experimental data was collected. His model results are also qualitatively expressed as having "a good fit."

Saunders' work which serves as the basis for this thesis gives the best evaluation of model results. He too was vague on what his raw experimental data looked like. How ever, he does describe model output in detail. His model using proportional and derivative control could reproduce expected results for ventilation and maintain arterial blood isocapnic for a one step protocol. Saunders expressed concern over minor overshoots in the model that produced ventilation data that he said did not appear in experimental results. It was unclear how he could interpret experimental data clearly enough to have confidence to state overshoots did not exist in actual data. His controller and model closely matched that of the experimental data he presented. His model was able to start, ramp to a steady-state ventilation level predicted by experimentation, and hold average carbon dioxide concentrations within 1.5 mmHG.

The unfortunate part of Saunder's work, and its true for others who have published respiratory models, was that he did not include an exercise protocol beyond one step. His work showed results from a step load of 0 to 50 or 0 to 100 watts. It was not stated whether the model would survive additional protocols and whether the control equation constants had to be modified to meet the different work loads.

By judicious selection of the parameters in the control equation, the controllers presented in Saunders papers or in this thesis could probably have been made to match the minute

ventilation for a given carbon dioxide production level while maintaining isocapnic response. Problems would have arisen when models were exposed to disturbances of several carbon dioxide loads.

Since this thesis was attempting to construct a controller that could mimic the respiratory control mechanism used by the body, it was important for the model to withstand any type of disturbance thrown at it.

7.2 DESIGN OF CONTROLLERS INVESTIGATED

After evaluating a number of different controllers for overall performance, three were chosen to receive additional examination. Overall performance was based on the controller's ability to respond to the protocol shown in Fig. #20, Section 6.4 which contains small work level steps and no off-transients. The three controllers chosen for further examination were labeled alpha, beta, and gamma. Table 1 shows the three controllers.

The alpha configuration contained just proportional and derivative control and was the controller used by Ellis during his research. The beta configuration was a proportional and derivative controller with a constant added and was similar to the controller proposed by Saunders, equation 7.1. The constant bears no physiological significance. Its effect was to stabilize the carbon dioxide concentrations in the blood. The gamma configuration was an attempt at a non-linear controller. Examination of the results of many simulation runs with the alpha and beta configurations indicated the relationship between the proportional and derivative components in the control equation needed to change with increasing work load. Coefficients could be chosen to make the model generate correct output at a certain work load at the expense of accuracy at other work loads. Blood flow rate was the only variable that changed with work load, affected the

TABLE 1. CONFIGURATION OF PROPORTIONAL AND DERIVATIVE CONTROLLERS INVESTIGATED

CONFIGURATION	CONTROL LAW
ALPHA	$A^*(MAX\ d\ P_{a,CO_2}/dT) + B^*(PMEAN - PSET)$
BETA	$A^*(MAX\ dP_{a,CO_2}/dT) + B^*(PMEAN - PSET) + CONSTANT$
GAMMA	$A^*(MAX\ dP_{a,CO_2}/dT)^*QDOT^{.5} + B^*(PMEAN - PSET)^*QDOT + CONSTANT$

PMEAN = Average arterial carbon dioxide concentrations

P_{a,CO_2} = Partial pressure of carbon dioxide at the carotid body

QDOT = Blood flow rate

PSET = Regulation set point for PMEAN

carbon dioxide signal at the carotid body, and was external to the respiratory control system. Being external to the respiratory control system made blood flow rate an independent variable. However, making ventilation a function of blood flow rate, tied respiratory control to the cardio-vascular system. While this compromises the independence of the respiratory controller, the relationship between cardiac output and pulmonary action is strong and appears justified, see Section 4.3.

Model performance was examined with different configurations of the non-linear controller. That is, just the proportional term was made a function of blood flow rate, then the derivative term then the constant term, and then the different permutations that can result from these. Having the proportional and derivative terms a function of blood flow rate proved the most responsive. This was the gamma configuration. Model output for each of the permutations was not included in this thesis for the sake of brevity.

Choosing the constants in the control equation that provided the best fit to experimental data was an extremely time consuming, heuristic process. Adjustments made to constants to improve minute ventilation compromised isocapnic constraints. The sensitivity of each of the three configurations of controllers made robustness of the controller design a question. However, from a sensitivity standpoint, none of the configurations was any more robust then the other.

One of the rules for evaluating the success of each controller in maintaining respiratory control, was the ability of the controller to hold an isocapnic response. Whether or not the model generated a 40 mmHG partial pressure of carbon dioxide was unimportant. The fact that average carbon dioxide concentrations hovered around one value was.

A strange occurrence that could only be explained as a quirk in the mathematics was that simply raising the set point (PSET) in the proportional term did not elevate the

average carbon dioxide concentrations accordingly. Adjusting the set point tended to disrupt the stability of the controllers. This instability was not viewed as a problem. The adjustment of constants in the control equation and the model's carbon dioxide set point could ostensibly produce an output that would generate correct minute ventilation and have an isocapnic response centered on 40 mmHG. The selection would be a long, trial-and-error process, but could be accomplished.

7.3 SUMMARY OF RESULTS

The alpha, beta, and gamma configurations were exposed to three additional protocols of varying complexity. This resulted in nine model generated outputs. The outputs were evaluated qualitatively and then quantitatively to determine which performed best. Fig. #25 shows the protocols applied. Fig. #26 through #34 show the results. Each figure showing model output includes minute ventilation and average arterial carbon dioxide concentrations (PMEAN). The figures also indicate the expected results. Expected ventilation levels were the steady-state minute ventilation rates experimentally derived, see Fig. #20.

Table 2 was a numerical listing of each model's performance compared to the expected values. The numbers in the table in the column for PMEAN indicated the difference between the highest and lowest average carbon dioxide concentrations measured at the carotid body over the length of the protocol. A small difference indicated a more isocapnic response which meant a better acting model.

The alpha configuration which contained only proportional and derivative control was the least effective in controlling respiratory action. The beta configuration maintained better performance in meeting the higher ventilation demands. The gamma configuration was able to respond to off-transients more effectively and was much better at maintaining an isocapnic response. The gamma configuration was also faster in achieving steady-state levels after a disturbance.

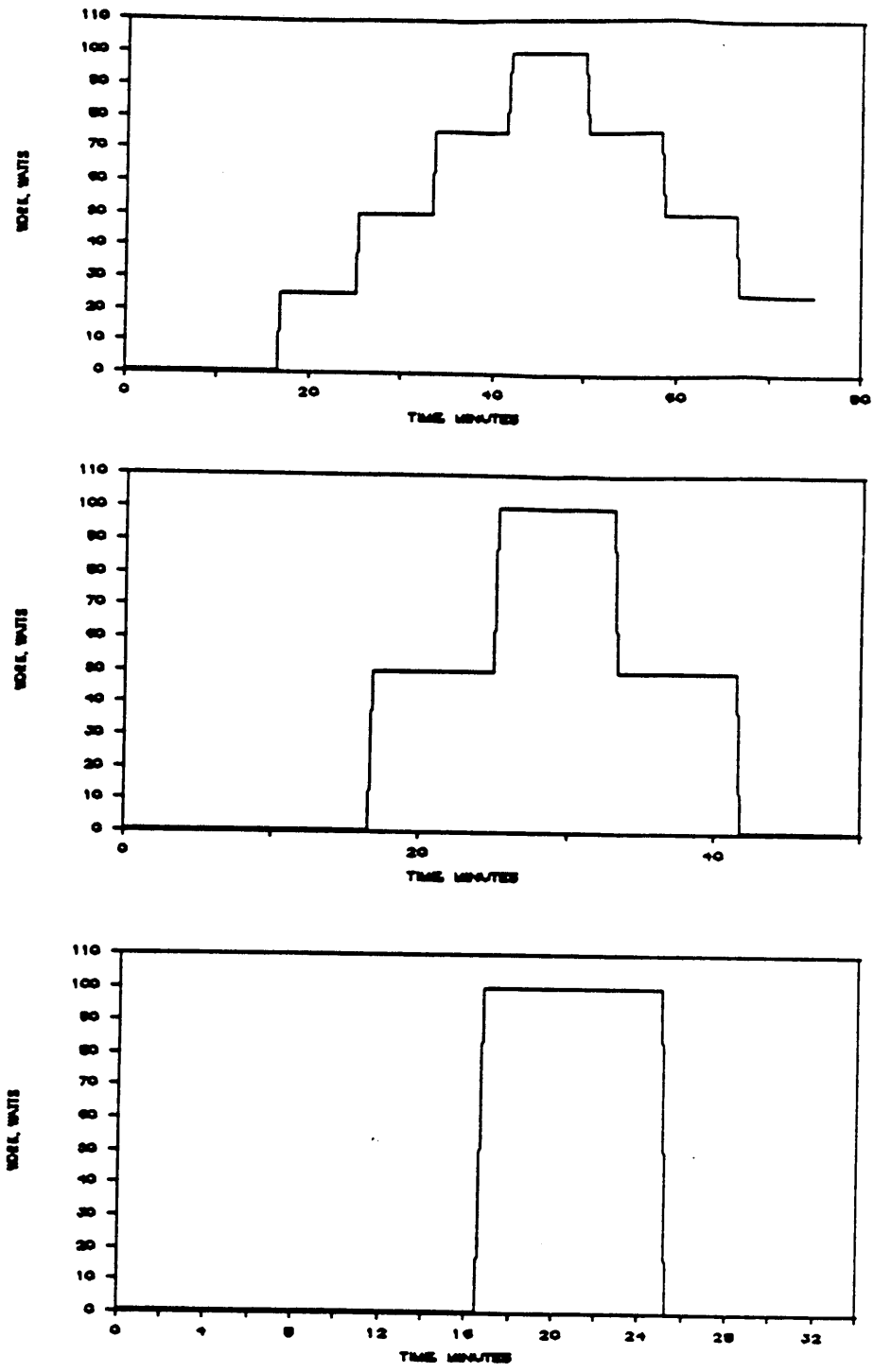


FIGURE 25, WORK PROTOCOLS APPLIED TO THE MODEL TO TEST THE PERFORMANCE OF EACH CONTROL LAW. TOP IS PROTOCOL 1. MIDDLE IS PROTOCOL 2. BOTTOM IS PROTOCOL 3.

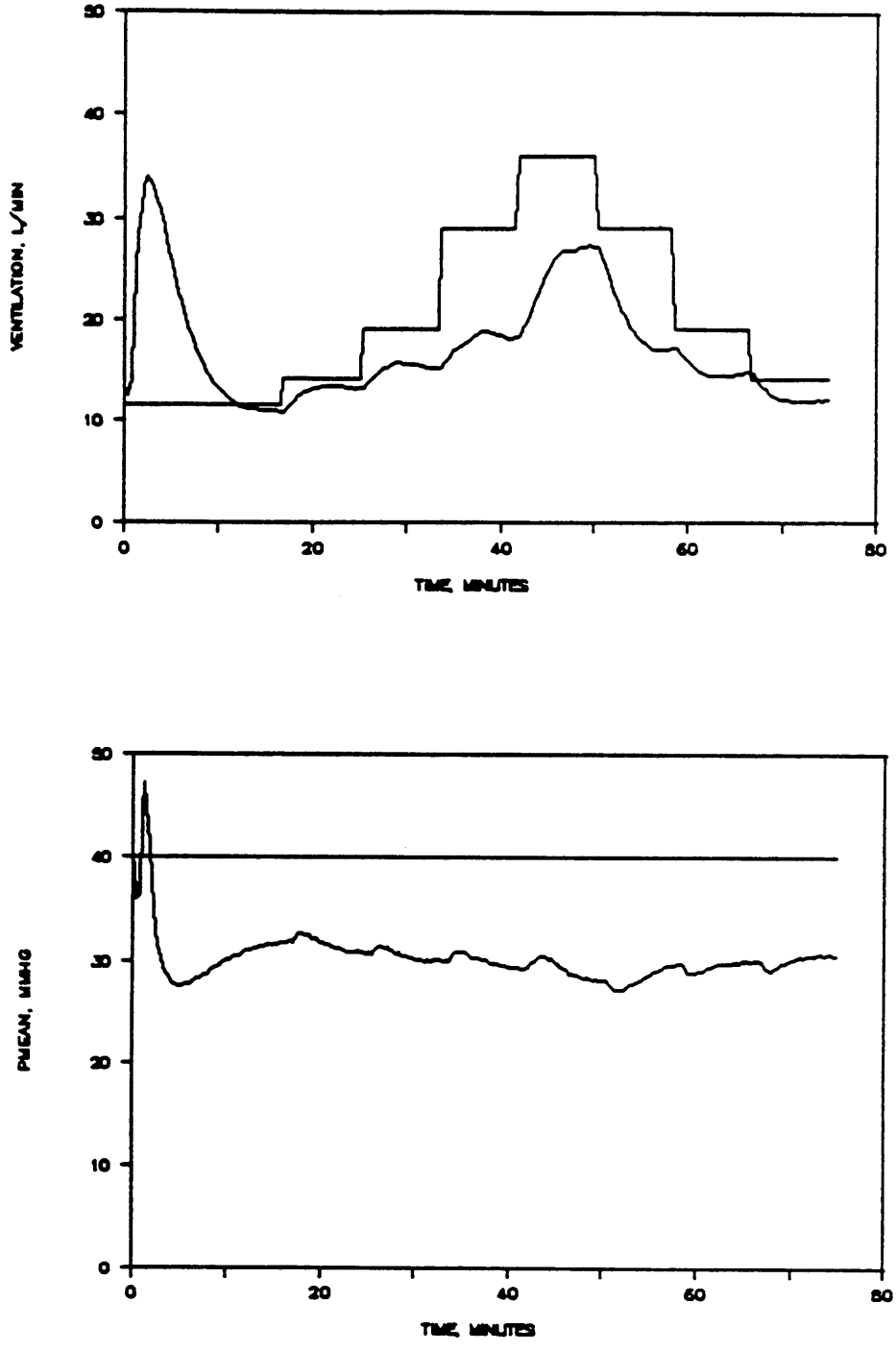


FIGURE 26, CONFIG ALPHA'S RESPONSE TO PROTOCOL 1. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

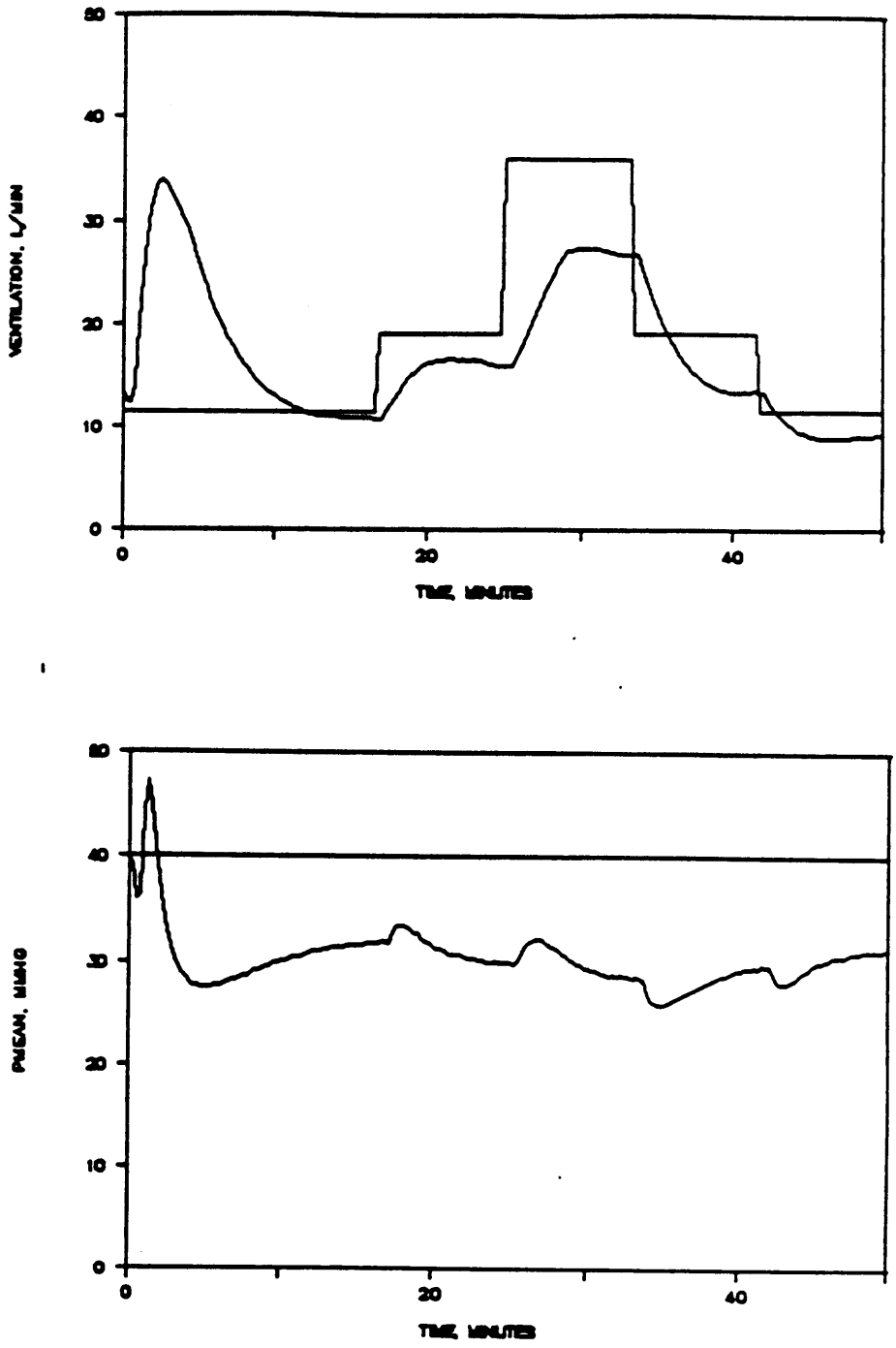


FIGURE 27, CONFIG ALPHA'S RESPONSE TO PROTOCOL 2. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

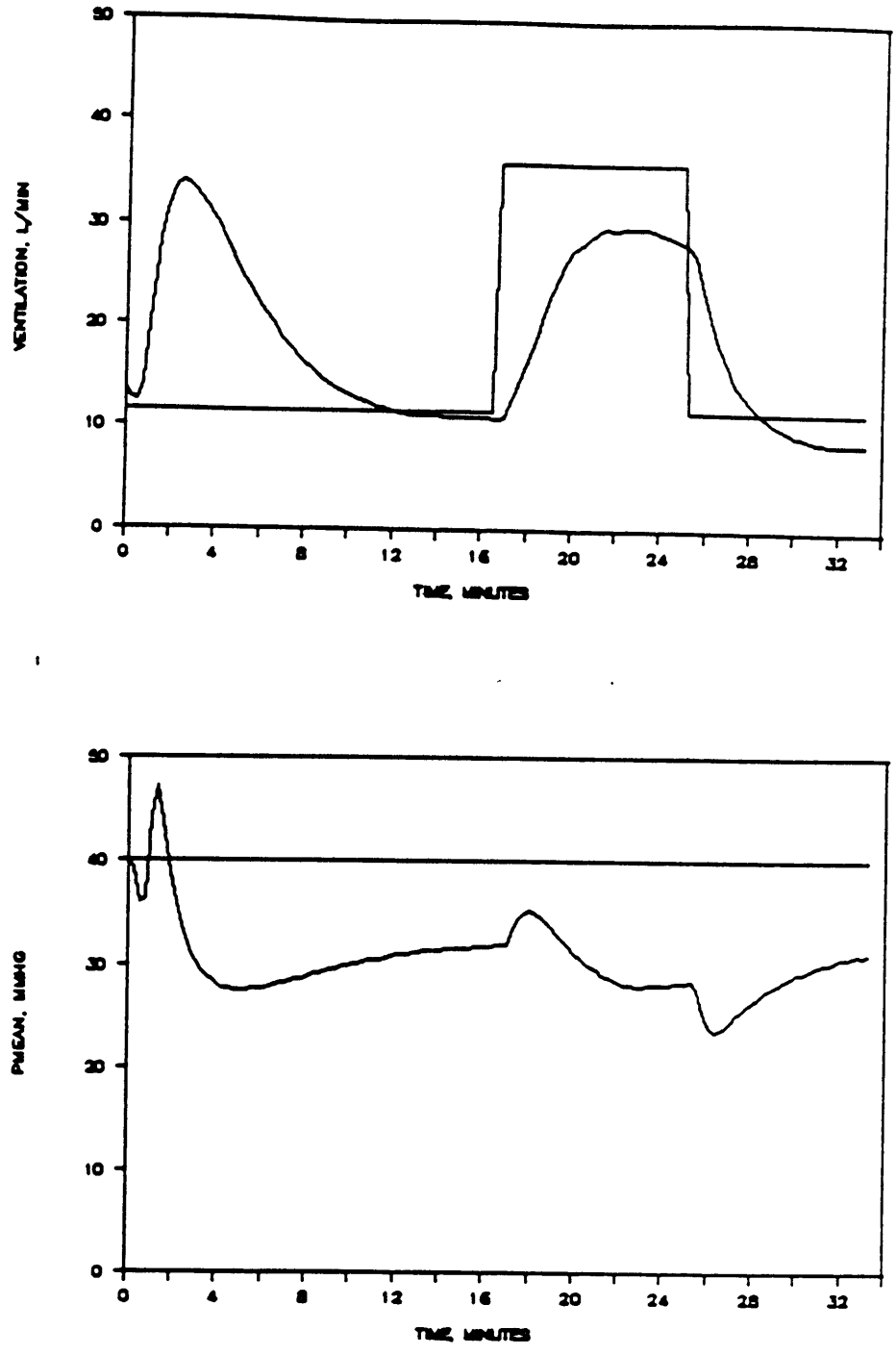


FIGURE 28, CONFIG ALPHA'S RESPONSE TO PROTOCOL 3. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

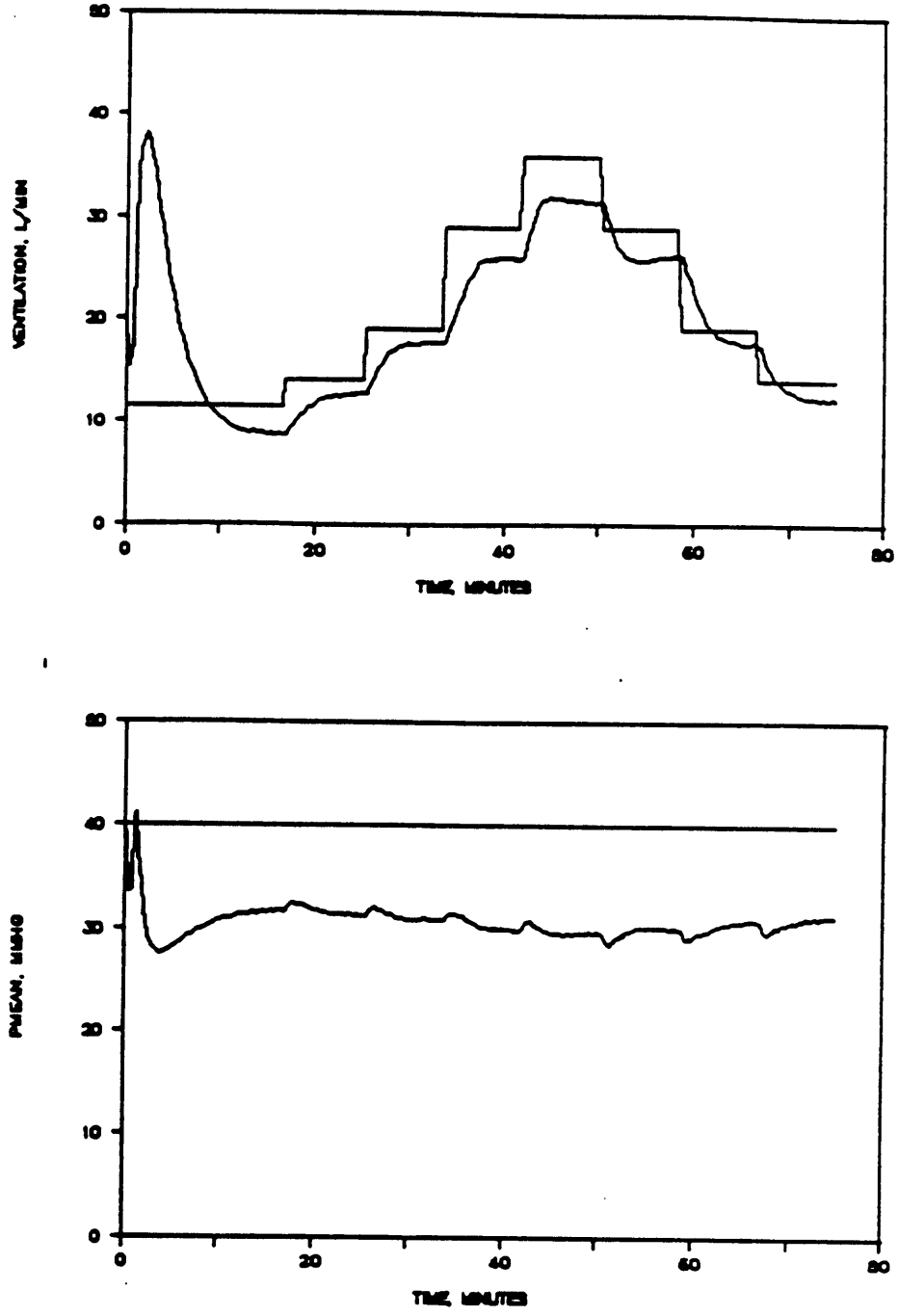


FIGURE 29, CONFIG BETA'S RESPONSE TO PROTOCOL 1. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

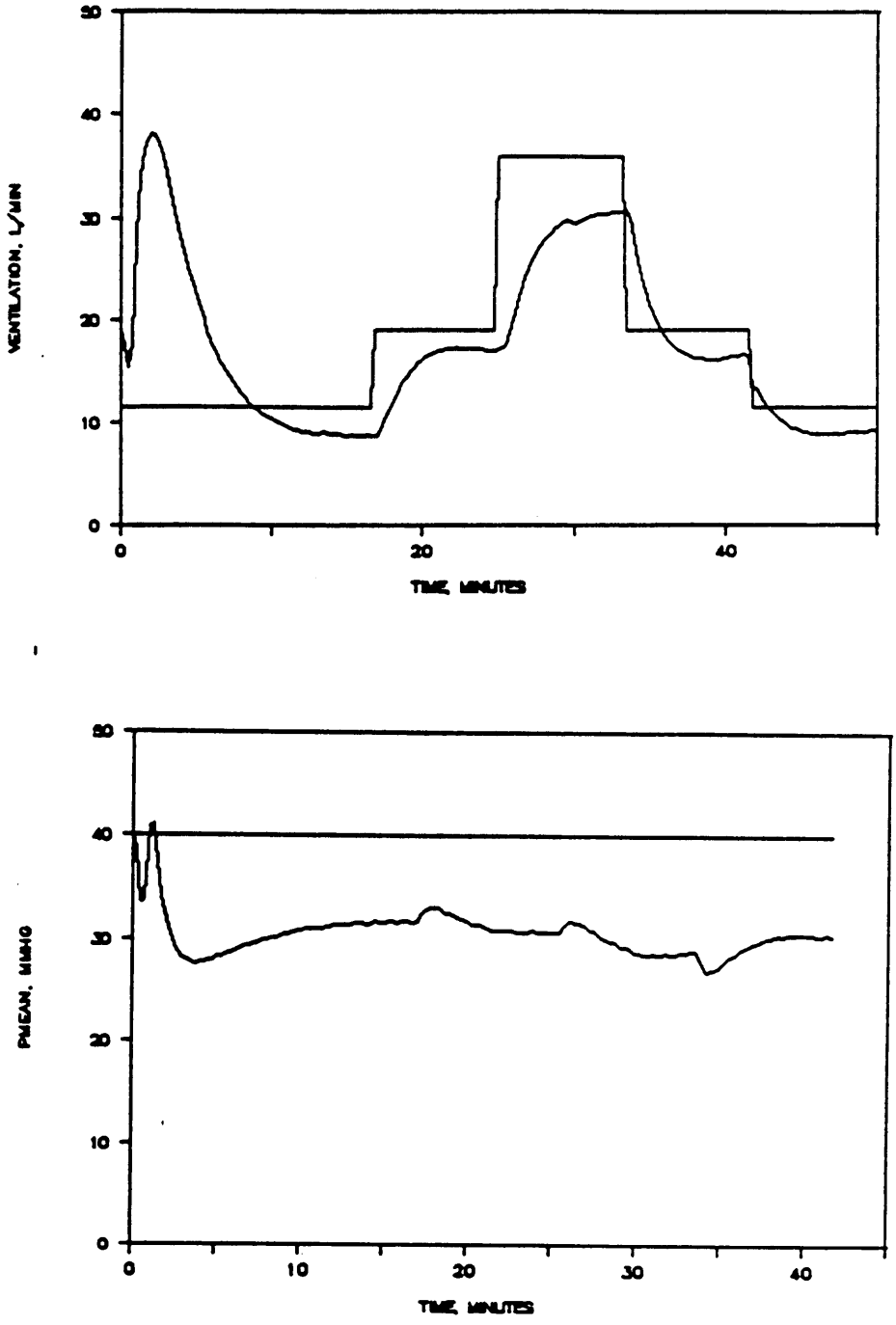


FIGURE 30, CONFIG BETA'S RESPONSE TO PROTOCOL 2. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

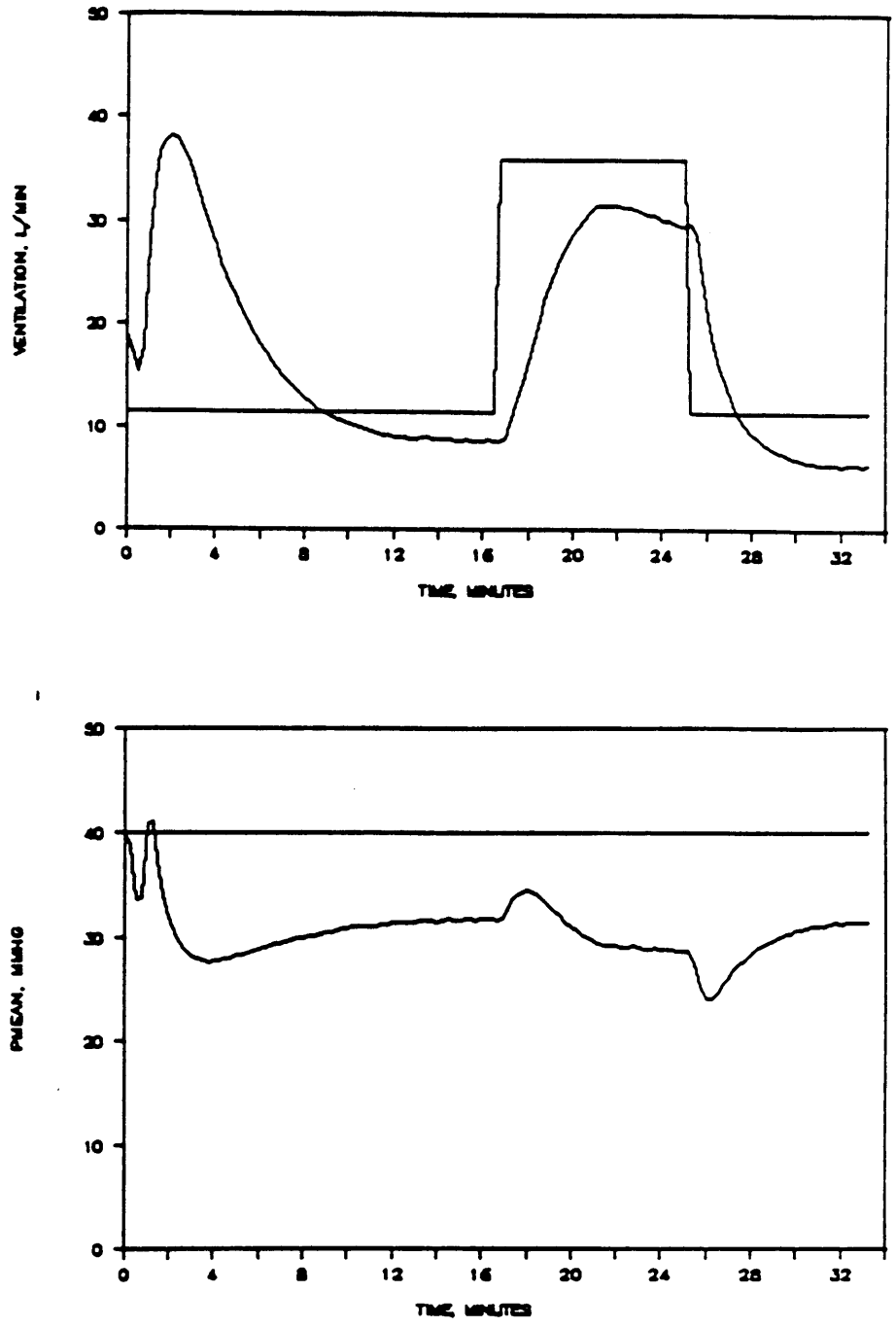


FIGURE 31, CONFIG BETA'S RESPONSE TO PROTOCOL 3. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

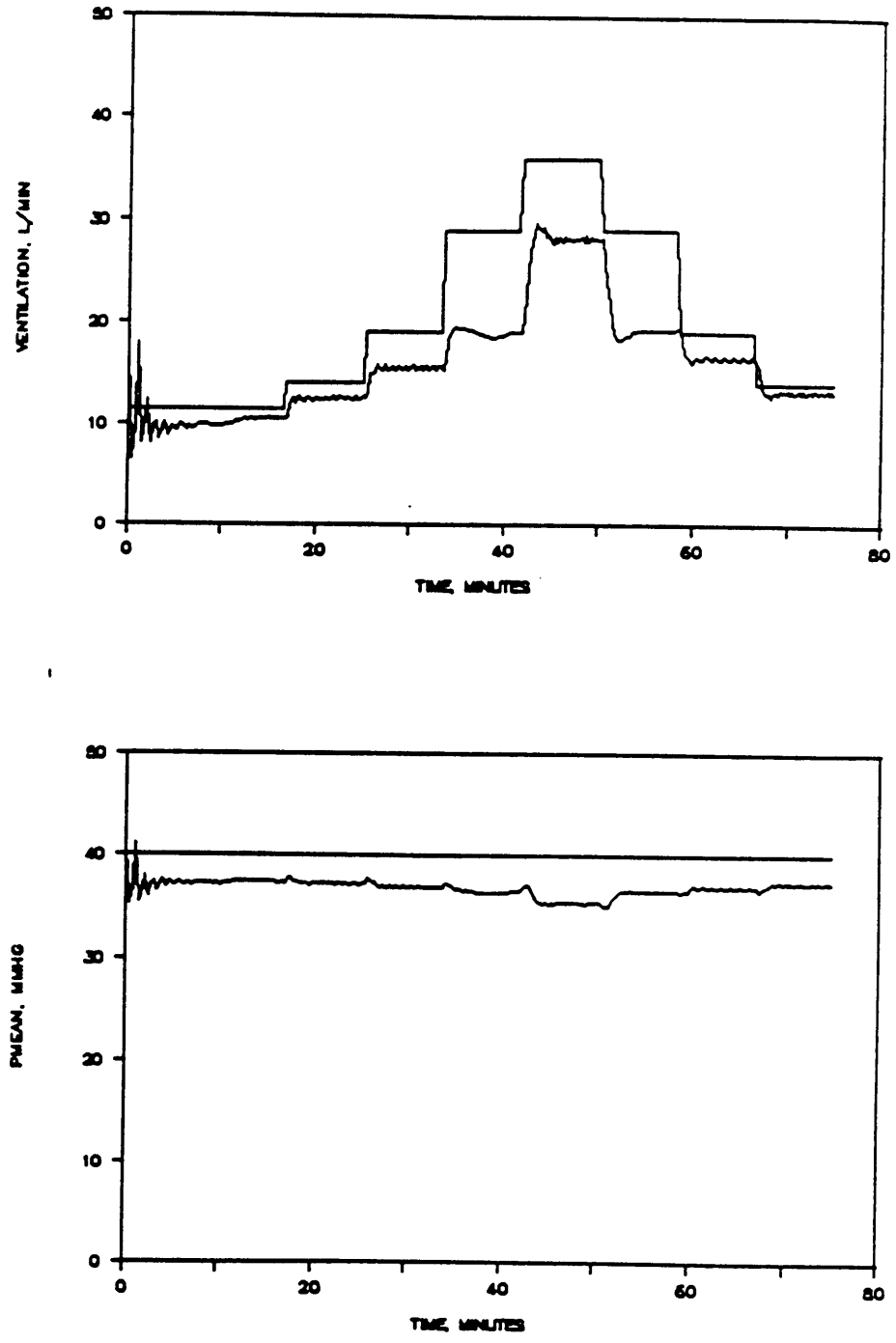


FIGURE 32, CONFIG GAMMA'S RESPONSE TO PROTOCOL 1. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

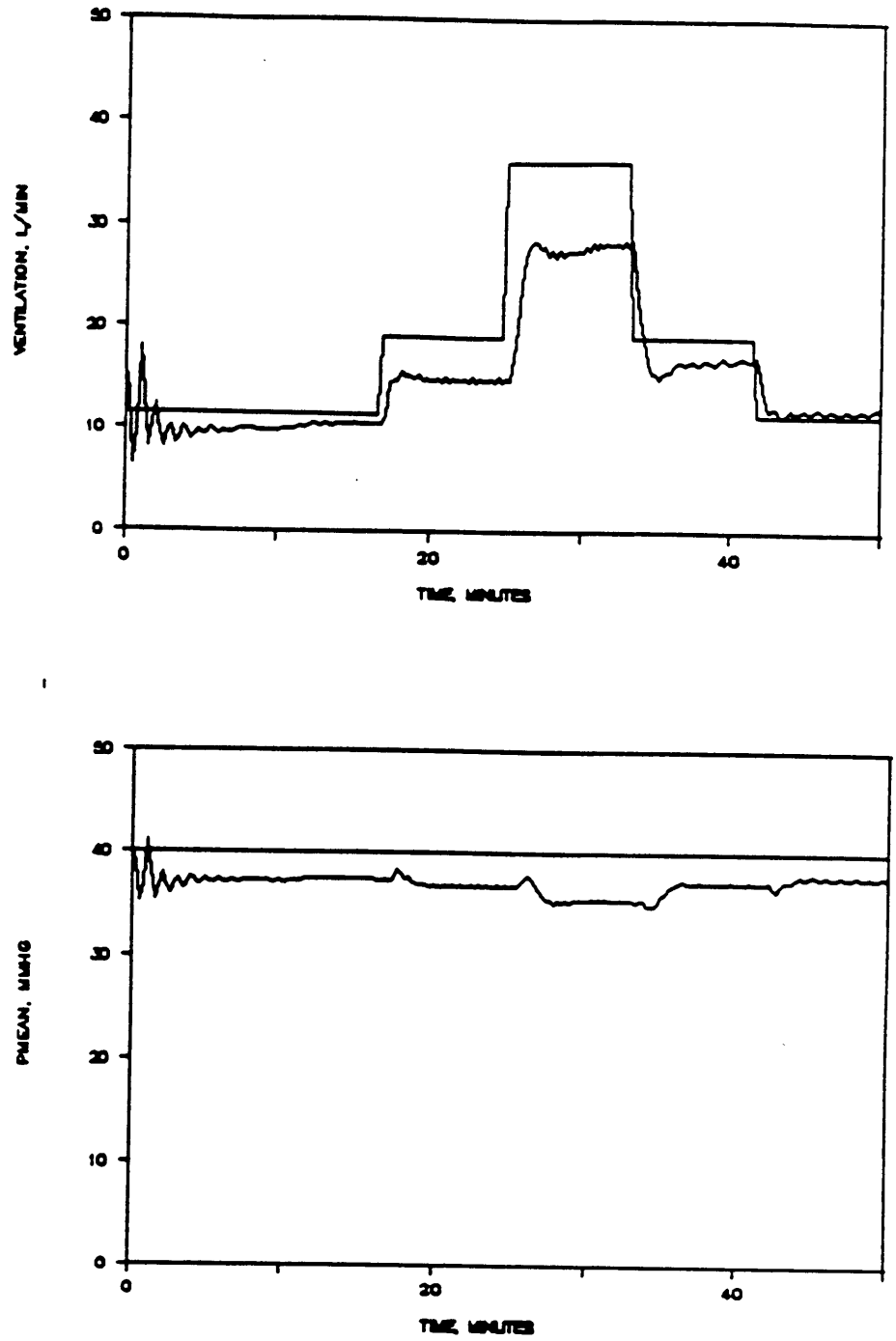


FIGURE 33, CONFIG GAMMA'S RESPONSE TO PROTOCOL 2. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

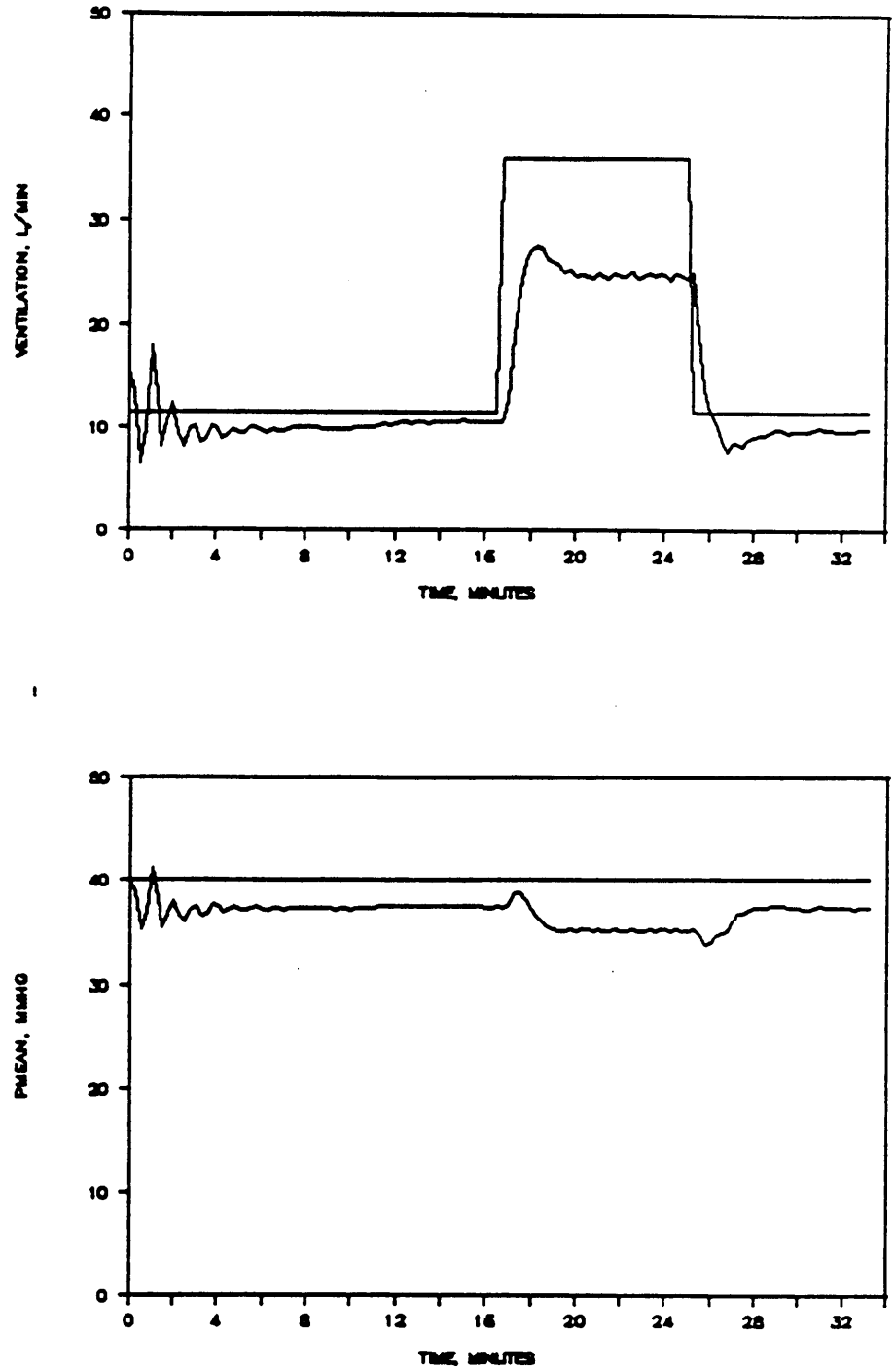


FIGURE 34, CONFIG GAMMA'S RESPONSE TO PROTOCOL 3. TOP IS THE MODEL GENERATED VENTILATION. BOTTOM IS ITS ABILITY TO MAINTAIN ISOCAPNIA. SOLID LINES REPRESENT EXPECTED VALUES

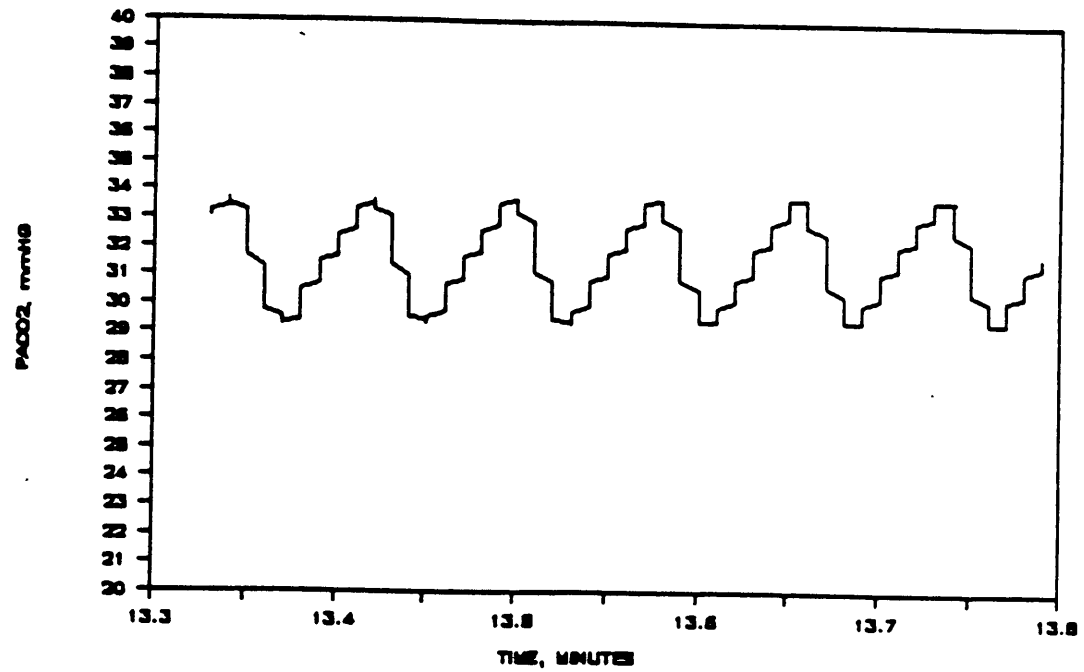
Based on reproducing experimental data, the gamma controller, out performed the other two. However, the gamma configuration had continuous oscillations throughout its operation. The marginally stable action was not viewed as critical. In many systems the continuous oscillations would be a problem, but as seen in Fig. #19, actual ventilation data is unsteady. The oscillations of the gamma controller would be lost if plotted with actual minute ventilation data.

One last item on controller dynamics, the protocols listed in Fig. #24 were used to evaluate performance. The expected results applied to determine the success of each controller were based on the experimental protocol in Fig. #19. The Fig. #19 protocol includes only on-transients and is a steady increase from 0 to 100 watts. Off-transient data, as revealed in the data collected at Wake Forest University which included an off-transient, does not return to the on-transient steady-state. The reason for this may have to do with the low work-load production of lactic acid and deserves additional research. However, what caused the elevated ventilation after an off-transient was not modeled. This means the model interprets the off-transient as a simple subtraction of a carbon dioxide load. Model generated ventilation for an off-transient should return to the steady-state values determined using Fig. #19. The fact that off-transient ventilation rates for the model data were in general higher then their on-transient counterparts was an indication of the models inability to pick-up the transient rather then a mirror of what happens experimentally.

7.4 TIME COURSE OF CO2 CONCENTRATIONS AS GENERATED BY THE MODEL

Figs. 35 and 36 portray the dynamics of carbon dioxide oscillations at key places in the model. Each of the figures represents the same span of time during which the model was exposed to a steady-state work load of 0 watts. Configuration Alpha was the

control law in use. Fig. 35 shows the oscillations of arterial carbon dioxide concentrations over five complete breaths and the result of passing the oscillations through a filter to yield an average value, PMEAN. Fig. 36 is the time rate of change of the oscillating carbon dioxide signal and the maximum value of this derivative over each cycle, PMAX. This maximum value should remain constant during steady-state modes.



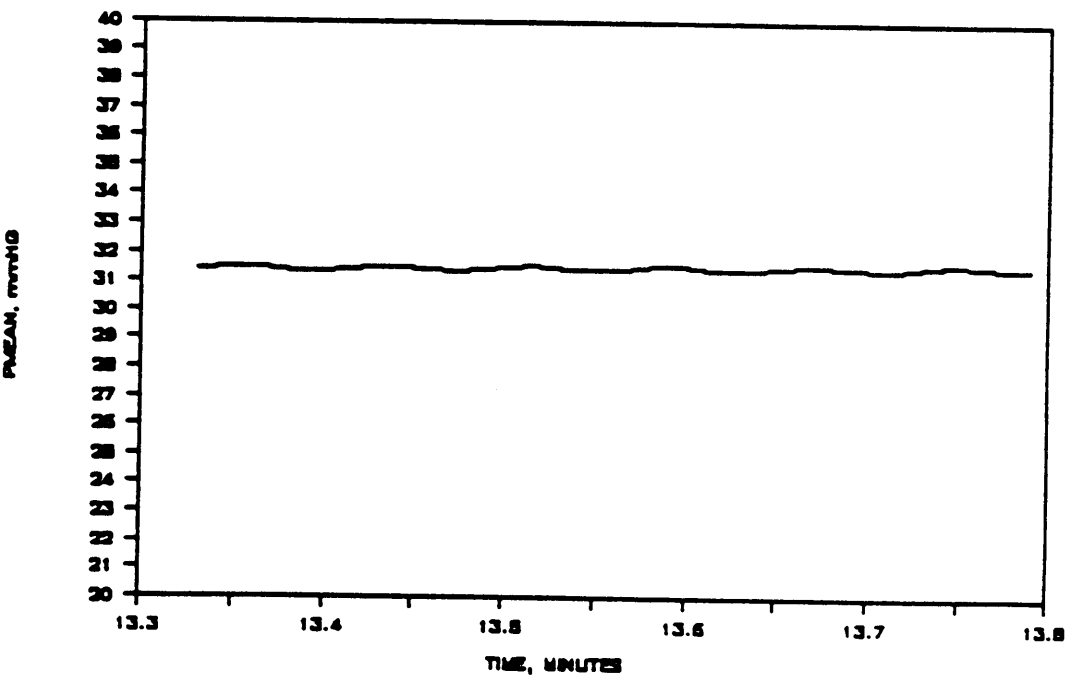
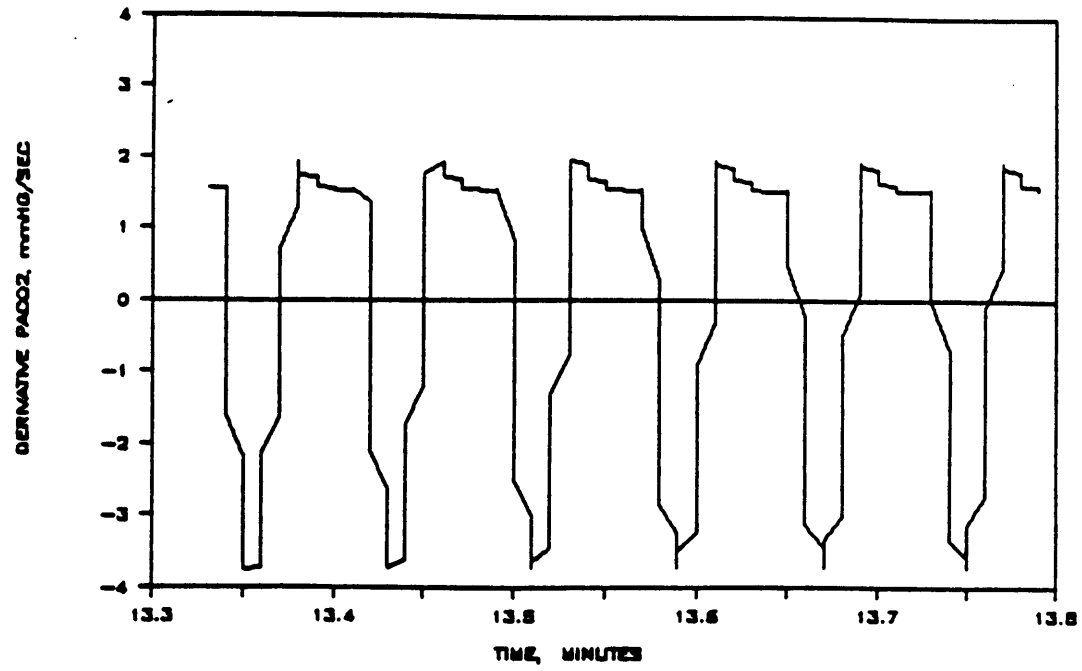


FIGURE 35, GENERAL FORM OF ARTERIAL CO2 OSCILLATIONS AND PMEAN



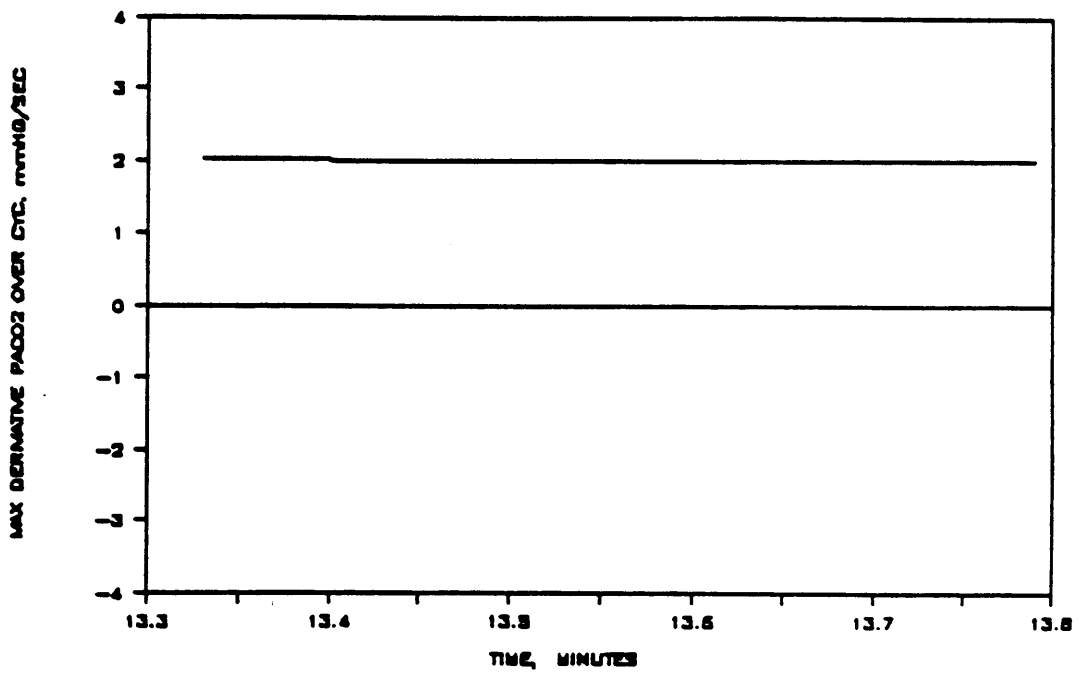


FIGURE 36, GENERAL FORM OF dCO2/dT AND PMAX

8.0 CONCLUSION

The intent of the research for this thesis was to determine if a controller using proportional and derivative control and arterial concentrations of carbon dioxide as feedback could satisfactorily regulate a model of the human respiratory system during exercise protocols that consist of several work loads. This thesis documents the first documented efforts to optimize a respiratory controller through the application of a multi-step test protocol.

Included was a discussion of the physiology pertinent to respiratory modeling. The major point of this discussion was that regulation of carbon dioxide and oxygen was critical for maintaining the proper supply of the energy storage compound, adensine triphosphate at the cellular level.

Work for this thesis began with a computer model generated by Ellis and modified by Villiger. Modification of the computer code was made by tailoring the model for one test subject by experimentally deriving algorithms for relating tidal volume to ventilation and carbon dioxide to work load. Additionally, the code was modified to improve organization and simplicity by eliminating variables when possible, changing the arrangement of the muscle compartment, and altering the way ramp inputs were applied to the model.

This thesis investigated the use of the latest respiratory equipment for providing experimental data. A state-of-the-art pulmonary testing machine was used to gather breath-by-breath data during an exercise protocol. The variations that were a part of normal respiratory function made the breath-by-breath data difficult to interpret. Averaging the data was mandatory. However, once the data was averaged it provided no more information then what was available using older equipment that provided data on 15 second intervals rather then every breath.

Finally, the intent of this thesis was satisfied by examining three versions of a proportional and derivative controller to determine if they could regulate lung action in response to a system disturbance. The investigation showed that judicious selection of constants on each of the controllers could yield model output that matched a specific step load, but that application of a multi-step load compromised model performance.

A controller with just proportional and derivative control failed to hold arterial blood isocapnic. A controller with proportional and derivative control and a constant added in generated satisfactory minute ventilation when compared to experimental data and had improved isocapnic response. A non-linear controller was examined with the proportional and derivative terms of the equation a function of blood flow rate. The addition of blood flow rate to the control equation subjugated the respiratory control system to the cardio-vascular system. This appeared justifiable considering the strong correlation between cardiac output and ventilation.

Even though the controllers failed to increase ventilation to match experimental results, it was judged that the last two configurations satisfactorily controlled ventilation. The non-linear controller proved the best of the three configurations because of its speed and ability to hold an isocapnic response.

A controller using proportional and derivative control with carbon dioxide concentrations as input does not incorporate all of the variables that have been identified as having a role in respiratory control, but it does act as a partial state estimator to satisfactorily control exercise hyperpnea at low work levels.

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APPENDIX A. GLOSSARY OF RELATED TERMS

Acetyl Coenzyme A - An acetic acid that plays a role in the Krebbs cycle. Pyruvic acid is converted to Acetyl Co A. The end of the Krebbs cycle is again Acetyl Co A.

ACSL - Advanced Simulation Language. A simulation language with a fortran IV base.

ADP - The low energy form of ATP. Adensine diphosphate.

Aerobic Glycolysis - The portion of the chemical process that extracts energy from glucose that takes place only with oxygen present. Starts with pyruvic acid and ends with formation of H2O.

Alveolar Dead Space - The portion of alveoli that can not exchange gases with the blood.

Alveoli - Small bubble-like sacs in the lungs. Capillaries in the alveoli walls absorb O2 and liberate CO2 to air in the sac.

Anaerobic Glycolysis - The portion of the chemical process that extracts energy from glucose that takes place with out oxygen. It ends with the formation of pyruvic acid.

Anatomical Dead Space - The trachea, bronchi, and other passage ways that do not have the capability of gas exchange with the blood.

Aortic Bodies - Small organs in the aorta that have been postulized as chemoreceptors.

ATP - The energy storage compound used by the body to power all biological processes. Adensine triphosphate.

Beta Oxidation Cycle - A chemical transformation process that begins with a fatty acid and ends with Acetyl Co A which then may enter the Krebbs cycle. Only way fats can enter catabolic process.

Bicarbonate - A compound formed with CO2 and H2O. It is part of the buffer system that maintains correct blood PH.

Bohr Effect - The reduction in O2 carrying capacity of hemoglobin during to the presence of CO2.

Breathing Frequency - Number of breathing cycles per minute.

Breath-by-breath - Experimentally it means gathering data for each individual breath. In modelling, it means updating tidal volume and breathing frequency each breath using current air demands.

BTPS - Body temperature and pressure, saturated. 37C, 747mmHG, and saturated air. Used when discussing ins/exp air volumes.

Carotid Body - A chemoreceptor located in the carotid artery in the neck. Research indicates correlation between CO2 concentration and nerve output from the carotid body.

Cardiodynamics - The theory that cardiac output establishes ventilation rates.

Catabolization - The breakdown of nutrients to yield bound energy.

Chemoreceptor - A sensor within the body that reads blood chemistry.

Control Law - A mathematical expression relating system out put to input.

Cretine Phosphate - An energy storage compound that serves as a quick source of energy for the conversion of ADP to ATP.

CSF - Cerebrol Spinal Fluid.

Dead Space - Portions of the respiratory system not exposed to gas exchange.

Derivative Control - A type of control based on the time rate of change of the state variable(s). $Y = K * (dX/dT)$

Diaphragm - Large concave, smooth muscle at the base of the chest cavity. Its action is the driving force behind lung inflation/deflation.

Dissociation Curve - Mathematical relationship determining the percentage of O2 and CO2 carried by hemoglobin verses the partial pressure of blood.

Electron Transport - The mechanism for extracting energy from hydrogen ions in the metabolic process. Water and CO2 are by products.

End-tidal Air - The last portion of the exhaled breath. It represents actual lung air concentrations at the end of a breath.

Expiratory Reserve Volume - ERV. The portion of lung air left at the end of a breath that could have been exhaled during a force exhalation.

FADH - Reduced FAD, flavin adenine dinucleotine. A coenzyme that is used to carry hydrogen ions towards electron transport zones.

Feed Back - A signal generated from system output that the controller uses to make adjustments to system operation based on the error between desired and actual output.

Feed Forward - A signal generated from a system input that the controller uses to make adjustments to system operation based on the anticipated error that would result in the output.

Functional Residual Capacity - FRC. The total amount of air left in the lung at the end of a forced exhalation.

Glucose - The most typical basic sugar. $C_6H_{12}O_6$

Glycolysis - The breakdown of glucose to yield energy for the production of ATP.

Haldane Effect - The reduction CO2 carrying capacity of hemoglobin due to the presence of O2.

Hemoglobin - An organic compound in the blood used for carrying oxygen and carbon dioxide.

Humoral - Pertaining to the blood. With respect to respiratory control, it is a signal that is generated in response to blood chemistry.

Hypercapnia - Abnormally high amounts of CO2 in the blood.

Hyperpnea - An increase in ventilation over resting conditions.

Hypocapnea - Abnormally low amounts of CO2 in the blood.

H+ - Hydrogen ions are a product of the breakdown of nutrients. Energy in hydrogen ions is captured by electron transport.

Intercostal Muscles - Muscles of the upper chest cavity that assist the diaphragm during heavy ventilation demands.

Isocapnea - Normal levels of CO2 in the blood.

Krebbs Cycle - Begins with pyruvic acid and yields 6 molecules of NADH and 2 molecules of FADH.

Lactic Acid - Formed when insufficient supplies of oxygen are present to allow aerobic glycolysis to take place. Pyruvic acid is shunted to lactic acid when pyruvic acid concentrations become too high.

Lung Blood Volume - The volume of blood in the lung capillaries at any one moment.

Minute Ventilation - The amount of air cycled through the lungs in one minute. Tidal Volume * Breathing Frequency = Minute Ventilation.

NADH - Reduced form of NAD, nicotinamide adenine dinucleotide. A coenzyme that serves to carry hydrogen ions towards electron transport zones.

Neural - Pertaining to brain function. With respect to respiratory control, it is a signal generated in the brain that directs lung dynamics.

Phosphorylization - Resysnthesis of ATP from ADP.

Proportional Control - A type of control based on the actual value of the state variable(s). $Y = K * (X - XSET)$

Pyruvic Acid - End product of anaerobic glycolysis. It is the starting point for the Krebbs Cycle.

Quasi Breath-by-breath - Modelling on a breath-by-breath basis were work loads are raised at rate slow enough to approximate steady-state conditions.

Residual Lung Volume - RV. The volume of lung air that is left at the end of a breath. FRC = ERV + RV.

Respiratory Quotient - The ratio of oxygen usage to carbon dioxide production.

STPD - Standard temperature and pressure, dry. 0C, 760mmHG, and dry air. Used when discussing blood chemistry.

Tidal Volume - The amount of air cycled through the lungs in one breath.

Vasculate - Blood vessels of the body.

Ventilation - Used interchangeably with minute ventilation.

APPENDIX B. ACSL PROGRAM CODE FOR RESPIRATORY MODEL

```
PROGRAM
INITIAL

CONSTANT  VBL=0.15,    PATM= 715.0,  FREQ=12.25, ...
          FICO2=0.0,   SAT=0.9,      WORK=0.5,   ...
          PIC=40.0

CONSTANT  TREF=0.0, PCIC=40.0, A=0.473, W=1.2

"      TIME DELAY CONSTANTS"

CONSTANT  DPIC=0.1, VIC=40.0, FIC=0.055, VOLSEG = 1.07

"      MUSCLE COMPARTMENT CONSTANTS"

CONSTANT  CMIC=0.550, CVCO2=0.55,  VM=24.0, ...
          CVIC=0.550, CAIC=0.550


"      CONTROLLER CONSTANTS"

CONSTANT  SCV=  24.1, CC=16.0, PSET=40.1
CONSTANT  WAG= -6.25

CONSTANT  TAU=30.0, IC=2.2

CONSTANT  PMIC=40.0, WCUT=20.0, PSLOPE=2.0, PMAX=2.0, ...
          PACBD=2.0, PACO2D=2.0, PACB=40.

"      DEFINE VARIABLES "

PI=ACOS(-1.0)
K1=(14.9-1.4*SAT)/100.0
CONV= PATM-47.

"      BLOOD FLOW RATES FOR VARIOUS METABOLIC WORK LOADS"

TABLE QD,1,5/0,25,50,75,100,0.12,0.14,0.1667,0.190,0.2167/

"      METABOLIC PRODUCTION RATES FOR VARIOUS WORK LOADS"

TABLE CO2,1,5/0,25,50,75,100,0.009,0.0105,.0127,0.018, ...
0.0235/

" SET INITIAL TIDAL VOLUME"
```

```
TV=2.0*A
CINTERVAL CINT=15.
NSTEPS NSTP= 150

CONSTANT TSTP= 4500.
END

DYNAMIC

IF(T.GT.1000) WORK=25.
IF(T.GT.1500) WORK=50.
IF(T.GT.2000) WORK=75.
IF(T.GT.2500) WORK=100.
IF(T.GT.3000) WORK=75.
AF(T.GT.3500) WORK=50.
IF(T.GT.4000) WORK=25.

IF(WORK.EQ.0.5 ) ALPHA=11.5     $" ALPHA REPRESENTS THE      "
IF(WORK.EQ. 25.) ALPHA=14.      $" STEADY-STATE VENTILATION  "
IF(WORK.EQ. 50.) ALPHA=19.      $" VALUES DERIVED FROM EXPER"
IF(WORK.EQ. 75.) ALPHA=29.      $" -MENTATION. APLHA IS USED"
IF(WORK.EQ.100.) ALPHA=36.      $" TO HELP COMPARE MODEL OUT"
                                $" PUT WITH EXP DATA         "
TIME = T/60.
WRITE(20,600) TIME,VAVED,WORK,PMEAN,ALPHA
600..FORMAT(5(1X,F7.2))

DERIVATIVE


PROCEDURAL(MRMCO2,QDOT=WORK)

MRM1  = CO2(WORK)
QD1   = QD(WORK)
MRMCO2 = REALPL(10,MRM1,.009)
QDOT = REALPL(10,QD1,.12)
END

"  DETERMINATION OF DEAD SPACE FROM TIDAL VOLUME"

PROCEDURAL(VD,VDALV=TV)
VD=0.175
IF(TV.GT.0.875)VD=0.2*TV
VDALV=VD-0.175
END
```

```
"  APPROXIMATION OF DEAD SPACE DERIVATIVE"
PROCEDURAL(VDALVD=VD)
VDALVD = (VD-VDOLD)/(CINT/NSTP)
VDOLD  = VD
END


"      LUNG MECHANICS "

PROCEDURAL(VL=A,W)
VL = VFRC + A*(1-COS(W*(T-TREF)))
VLDOT = A*W*COS(W*(T-TREF))
IF(W*(T-TREF).GT.2.0*PI)GO TO 50
GO TO 60
50..CONTINUE
TREF=T
60..CONTINUE
VADOT = VLDOT-VDALVD
VA = VL - VDALV
END


"      SET MU FOR INHALATION  OR  EXHALATION:   "
"            MU=0.0  VLDOT < OR = 0.0           "
"            MU=1.0  VLDOT > 0.0                "

MU=FCNSW(VLDOT,0.0,0.0,1.0)


"      GAS EXCHANGE EQUATIONS                "

PACO2D =(MU*VADOT*(FICO2-PACO2) + QDOT*CONV*(CVCO2 - ...
K1*PACO2**0.35)) / (CONV*K1*0.35*VBL*(PACO2**(-0.65)) + VA)

/(CONV*K1*0.35*VBL*(PACO2**(-0.65)) + VA)

PACO2 = INTEG(PACO2D,PIC)


"      TIME DELAY FROM LUNG TO CAROTIC BODY    "

TAU1 = VOLSEG/QDOT              $" NUMBER OF SECONDS DELAYED "
PACB  = INTEG(PACBD,PCIC)
PACBD = DELAY(PACO2D,DPIC,TAU1,10000)


"      DERIVATIVE CONTROL : MAX SLOPE OF PACBD"

PROCEDURAL(PMAX=PACBD,PSLOPE)
```

```
IF(PACBD.GT.PSLOPE)PSLOPE=PACBD
IF(PACBD.LT.0.0.AND.PSLOPE.NE.0.2)PMAX=PSLOPE
IF(PACBD.LT.0.0)PSLOPE=0.2
END

"      FIRST ORDER LAG TO FILTER MAX SLOPE VALUES      "

FPMAX = REALPL(TAU,PMAX,IC)


"      PROPORTIONAL CONTROL : MEAN VALUE OF PACB       "
"      FIRST-ORDER LAG TO OBTAIN PMEAN                 "

PMEAN = REALPL(WCUT,PACB,PMIC)


"      CONTROLLER EQUATION                             "

PROCEDURAL(VAVED=FPMAX,PMEAN)

X =  SCV * FPMAX * (QDOT**.8)       $"  THE ADDITION OF QDOT"
Y =  CC * (PMEAN - PSET) * QDOT     $"  MAKES THIS CONTROL- "
Z =  WAG                            $"  LER NON-LINEAR      "

VAVED  = X + Y + Z

TV = 0.0375*VAVED + 0.4688
A = TV/2                        $" UPDATING LUNG DYNAMICS FOR "
FREQ = VAVED/TV                 $" FOR THE NEXT BREATH BASED  "
W = 2.0*PI*FREQ/60.0            $" ON THE NEW VAVED           "
VFRC = 2.9-0.312*TV

END


"    CO2 CONCENTRATION AT THE CAROTID BODY    "

CACO2  = K1*PACB**0.35


"    TIME DELAY FROM CAROTID BODY TO MUSCLE"

TAUAM  = 0.735/QDOT             $"  NUMBER OF SECONDS DELAY  "
MIX1   = REALPL(WCUT,CACO2,.550)
CAMCO2 = DELAY(MIX1,CAIC,TAUAM,10000)

"    MUSCLE COMPARTMENT EQUATIONS"

CMCO2D = (MRMCO2 + QDOT*(CAMCO2-CMCO2))/VM
```

```
CMCO2   = INTEG(CMCO2D,CMIC)
CVMCO2 =(MRMCO2 + QDOT * CAMCO2)/QDOT

"     TIME DELAY FROM MUSCLE TO LUNG"

AUVM = 3.128/QDOT              $"  NUMBER OF SECONDS DELAY   "
MIX2   = REALPL(10,CVMCO2,CAIC)
CVCO2 = DELAY(MIX2,CVIC,TAUVM,10000)

END

TERMT (T.GE.TSTP)
END
TERMINAL
END
END
```

APPENDIX C. LISTING OF VARIABLES USED IN TCB ACSL

A - AMPLITUDE, LITERS
CAIC - DEFAULT VALUE OF CAMCO2 UNTIL TIME DELAY IS REACHED,mmHG
CAMCO2- CONC OF CO2 REACHING MUSCLE, L/L STPD
CC - GAIN FOR PROPORTIONAL PART OF CONTROL EQUATION
CINT - TIME OF COMMUNICATION INTERVAL
CMCO2 - METABLOLIC PRODUCTION RATE OF CO2 IN MUSCLE,
CMCO2D- DERIVATIVE, METABOLIC PRODUCTION RATE IN MUSCLE,
CMIC - INITIAL VALUE OF CMCO2 IN MUSCLE COMPARTMENT, L/L CMCO2(0)
CO2 - TABLE FUNCTION YIELDING CO2 PRODUCTION VS WORK
CONV - CONVERSION FACTOR, STPD TO BTPS
CVMCO2- CONC OF CO2 LEAVING MUSCLE,
DPIC - DEFAULT VALUE OF PACBD UNTIL TIME DELAY IS REACHED, mmHG
FICO2 - CONC OF INSPIRED CO2, DIMENSIONLESS
FPMAX - FILTERED PMAX, 1ST ORDER LAG BASED ON TAU = 30, mmHG
FREQ - FREQUENCY, BREATHS/MIN
IC - DEFAULT VALUE OF FPMAX UNTIL TIME DELAY IS REACHED
MRMCO2- METABOLIC PROD RATE OF CO2 IN MUSCLE.
MU - SWITCH, O OR 1. ADJUSTS EQUATION FOR INSP OR EXPIRATION
NSTP - CINT/NSTPS IS THE INTERGRATION STEP SIZE
PACBD - DERIVATIVE OF PACO2 AT CB, mmHG/SEC
PACO2 - PACO2 AT LUNG EXIT, mmHG
PACO2D - DERIVATIVE OF PACO2 AT LUNG EXIT, mmHG/SEC
PATM - AMBIENT PRESSURE, mmHG
PCIC - INITIAL VALUE OF PACB, mmHG. PACB(0)
PIC - INITIAL VALUE OF PACO2, mmHG. PACO2(0)
PMAX - MAXIMUM SLOPE OF THE SINUSOIDAL PACO2 OSCILLATIONS
PMEAN - FILTERED PCO2 AT CB, mmHG
PMIC - DEFAULT VALUE OF PMEAN UNTIL TIME DELAY IS REACHED, mmHG
PSET - NORMAL LEVEL OF CO2 IN BLOOD, mmHG
PSLOPE - TEMP VALUE, SLOPE OF PACB. EQUALS PMAX WHEN SLOPE NEG
QD - TABLE FUNCTION YIELDING BLOOD FLOW VS WORK
QDOT - BLOOD FLOW. BASED ON TABLE FUNCTION
SAT - CO2 DISSOCIATION CURVE CONSTANT,
SCV - GAIN FOR DERIVATIVE COMPONENT OF CONTROL EQUATION
TAU - TIME CONSTANT FOR FILTERING PMAX TO GET FPMAX, SEC
TAU1 - TIME DELAY FROM LUNG TO CB, SEC (VOLSEG/QDOTV)
TAUAM - TIME DELAY FROM CB TO MUSCLE, SEC
TAUVM - TIME DELAY FROM MUSCLE TO LUNG, SEC
TIMED - AMOUNT OF TIME TO BLOW OUT DEAD SPACE, SEC
TREF - TREF IS THE END POINT OF THE PREVIOUS BREATH, SEC
TSTP - ACSL STOPS WHEN T EXCEEDS TSTP
TV - TIDAL VOLUME, LITERS
VA - ALVEOLAR VOLUME, (LUNG VOLUME - DEAD SPACE), LITERS
VADOT - DERIVATIVE, ALVEOLAR VOLUME, LITERS/SEC
VAVED - MINUTE VOLUME, LITERS/SEC
VBL - VOLUME BLOOD IN LUNGS, LITERS
VD - VOLUME DEAD SPACE, LITERS
VDALV - VOLUME ALVEOLAR DEAD SPACE, LITERS
VL - VOLUME LUNG, LITERS
VLDOT - DERIVATIVE, LUNG VOLUME, LITERS/SEC
VM - VOLUME OF BLOOD IN MUSCLE COMPARTMENT, LITERS
VOLSEG - CONTANT USED TO CALC TAU1. VOL OF BLOOD LUNG TO CB, L
WCUT - TIME CONSTANT IN FIRST ORDER LAG TO FIND PMEAN
WORK - EXERCISE LEVEL, WATTS

APPENDIX D. TEST EQUIPMENT SPECIFICATIONS

ERGOMETRICS UNIT

MANUFACTURER: S/M Instruments, Doylestown, Pa.
TECH REP: 215-345-9232
MODEL: Ergometrics
CO2 ANALYZER: Amatek Thermox CD-3, P61-b, infrared
MAX SAMPLING RATE: 15 seconds, software limited
SOFTWARE: MSDOS base, supplied by S/M

MEDICAL GRAPHICS UNIT

MANUFACTURER: Medical Graphics Corp, 350 Oak Grove Parkway, St. Paul, Minnisota 55127
TECH REP: 800-328-9232
MODEL: Cardiopulmonary testing system 2001
CO2 ANALYZER: infrared absorbtion, supplied with unit
MAX SAMPLING RATE: 100 samples per second
SOFTWARE: CTOS base (no conversion to MSDOS available)

MODIFED ERGOMETRICS UNIT

MANUFACTURER: S/M Instruments, Doylestown, Pa.
TECH REP: 215-345-9232
MODEL: Ergometrics
CO2 ANALYZER: Amatek Thermox CD-3, P61-b, infrared absorb tion
MAX SAMPLING RATE: 100 samples per second
SOFTWARE: MSDOS base, created by Robert Winn, ME dept. VPI

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