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Dynamic sensitivity and Lyapunov stability analysis of the human respiratory control system

Barry Lee Johnson
Iowa State University

DYNAMIC SENSITIVITY AND LYAPUNOV STABILITY ANALYSIS OF THE HUMAN RESPIRATORY CONTROL SYSTEM

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Barry Lee Johnson

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Signature was redacted for privacy.

Head of Major Department

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Dean of Graduate College

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INTRODUCTION

Biomedical Engineering

The purpose of an introduction to any subject material is to prepare the reader for the subject content which follows the introduction. With this in mind, the introduction to this dissertation has been divided into two parts. Prior to discussion of the research objectives of this thesis, a short discussion of the academic area in which this investigation is being undertaken will be included. This will be followed by the second part of the introduction, which will be a formal outline of the motivations and the objectives of this investigation. It is felt that the reader will have a better appreciation of the problem under investigation if the general problem area is first discussed.

Engineering methods have been increasingly utilized in the disciplines of physiology and biology. The application of these methods has, in turn, within the last decade fostered a separate new discipline, biomedical engineering. Biomedical engineering is then that area of engineering which applies engineering methodology to problems of physiology and biology. Some of the current general areas of interest in biomedical engineering are as follows:

The mathematical modeling of physiological systems

Increasing interest is being shown in the mathematical modeling of physiological systems, because the derived mathematical models often provide additional insight into the physiological system being modeled, insight which is not always evident from strictly physiological considerations. Development of an adequate model of a physiological system often

permits the investigation of effects which would be difficult or undesirable to investigate in the laboratory. For example, use of an adequate model of the respiratory system would permit investigations involving a lethal exposure to a toxic gas, thereby avoiding the loss of experimental animals. Some other benefits gained from the modeling of physiological systems can be listed as follows: transient effects are more easily investigaged with a model than in vivo, system parameter influences are easier to study with a model than in vivo, and the effects of many different types of physiological system forcing functions (i.e., inputs) can be more readily investigated with a model. Implicit in this discussion of modeling is the assumption that the model equations can be solved by some means; in most cases a digital or an analog computer must be used to obtain the solution.

The application of engineering theory to physiological system analysis

In many instances engineering theory has been used as an aid to better understanding of a physiological process. Engineering control theory has been utilized frequently in this regard, since many physiological systems serve as regulatory control systems. Thus the application of engineering control theory, an engineering area having a well developed theory, to analysis of a physiological process often leads to a better understanding of that process. As an example, it is well known in control systems theory that the effect of a sufficiently large time delay in a system will be system instability. This system instability will be reflected as a nondecreasing oscillatory mode of the system. Guyton et al. (1) have shown that the respiratory system, which has many of the properties of a feedback control system, will exhibit instability when the arterial

circulation time delay is made sufficiently large. This physiological observation is then better understood when the stability theory of feedback control systems is considered.

Other examples of the application of engineering theory to physiological situations could be cited. For example, the application of the theory of electric transmission lines has been used as an aid to better understanding of the pressure characteristics of the arterial circulation system. See, for example, the paper by Fry (2).

The design of specialized equipment to meet physiological needs

Often the equipment required to satisfy a physiological or medical requirement is not available commercially. This lack of specialized equipment has provided the impetus for the development of many new instruments designed to meet specific physiological needs. Two examples will be given for which specialized equipment was engineered to meet a specific physiological need.

Carlson (3) has designed a neonatal respiratory augmenter to meet a specialized physiological requirement. The augmenter was engineered to provide mechanically assisted respiration for the treatment of the respiratory distress syndrome occurring in newborn infants. The engineering design of this instrument required careful consideration of the respiratory physiology of the neonate.

Clynes (4) has also engineered an instrument to meet a specific physiological need. In this case, a small digital computer was specifically designed to provide an arithmetic average of signals contaminated with noise. Under certain conditions the averaging process can effectively

improve the signal to noise ratio of the signal. This instrument has been used extensively as an aid in the study of certain types of electroencephalographic signals, particularly electroencephalographic evoked responses to various stimuli.

The application of computer techniques to problems of physiology

Much effort is presently being expended by many investigators in the application of computer techniques as an analysis aid for physiological problems. In addition to the routine application of the computer to the processing of volumnious amounts of physiological data, there are two other computer application areas that potentially have great importance in physiology and medicine.

The first of these two areas involves basically the problem of pattern recognition. That is, given the normal range of a physiological signal, e.g., an electrocardiogram; how can a machine be programmed to recognize the presence of an abnormal signal? An adequate solution to this problem will prove to be enormously valuable for routine clinical diagnosis. Advances in this area have been reported by Gustafson (5) who investigated the feasibility of digital computer recognition of the electrocardiogram.

A second area of computer application involves analysis of physiological data using statistical techniques. With the aid of a computer, data analysis using correlation techniques and spectral analysis methods for the interpretation of physiological data is becoming more common. An example of a rather complete statistical treatment of physiological data is given by Wooley (6), who computed autocorrelation functions, cross-correlation functions, and power spectral densities for electroencephalographic signals recorded from the hippocampus area of the brain.

The development of replacement artificial organs

An area of great importance in biomedical engineering is the development of replacement artificial organs for the human body. The ultimate goal is to develop artificial organs capable of replacing nonfunctioning organs of the human body. The development of artificial organs requires close design cooperation between the engineer and the physiologist. For example, if the artificial organ is to be implanted within the body; the device material selected must cause minimal tissue reaction. At the same time, however, the device material chosen will have to satisfy certain engineering considerations, e.g., distensibility, dielectric constant, etc.

There are presently three areas of artificial organ replacement which are receiving intense investigation. These are as follows: development of an artificial heart, development of an artificial kidney, and the development of prosthetic limbs.

The preceding discussion has listed five general areas of interest in biomedical engineering. A brief description of each area was given, and examples were cited of current research endeavors. The purpose of this discussion was to demonstrate some of the applications of engineering methodology to physiology. The motivation for such a discussion is the anticipation that the thesis problem under investigation may be of interest to both the engineer and the physiologist.

The research to be reported in this dissertation will utilize three of the five general areas previously discussed. The objectives of this study can be listed basically as follows.

1. Development of mathematical models for both the adult human respiratory system and the neonatal human respiratory system.

2. Analysis of these models using two new engineering systems analysis techniques, engineering dynamic sensitivity analysis and Lyapunov stability analysis.
3. Computer computation of the sensitivity of various parameters of the respiratory system models and the physiological implications of these calculations.

In summary, the objective of this study is to investigate the feasibility of obtaining, through use of new engineering systems analysis methods, additional information regarding the respiratory system of man.

The Objectives of this Research

It is anticipated that the research to be reported in this thesis may be of interest to both the physiologist and to the engineer, since this thesis basically dexcribes an engineering analysis of a given physiological system. Because of this dual interest, a brief description of how engineering methods can be utilized in physiological research has been given.

The purpose of the present discussion will be to discuss the overall research objectives of this thesis. In addition, the motivations which led to the consideration of the present thesis problem will be indicated.

The main objective of this study is to obtain through use of two new engineering analysis techniques additional invormation about a given physiological system, the human respiratory system. Both the respiratory systems of the adult and the neonate will be considered in order that comparisons between the two can be made.

The engineering analysis methods to be utilized in this thesis are known in the engineering literature as enginerring dynamic sensitivity

analysis (Tomovic, 7), and second, Lyapunov stability analysis. The theory of both methods is still being developed in the literature.

This these describes the first known application of dynamie sensitivity analysis to a physiological situation. For brevity, the term "engineering dynamic sensitivity analysis" will normally be shortened to "sensitivity analysis". It will be necessary at this point to briefly describe sensitivity analysis in order to put the objectives of this study in proper context.

Sensitivity analysis, as the term is used in the engineering literature, attempts to provide answers in an analytical method to questions of the following type. Suppose that a given system (electrical, mechanical, physiological, etc.) is described in terms of its component parameters. This system description can take one or both of two forms; a mathematical model description, or an actual physical model. For both cases the question arises, how much is the system performance changed as a result of a change in a system parameter? Do all the parameters of the system exert comparable effects on system performance, or is one parameter more critical than the others? Is there a range of values for a system parameter for which the system is more sensitive to a parameter change than when the parameter values lies outside the range? These are the types of questions which sensitivity analysis attempts to answer.

There are two ways in which sensitivity analysis can be applied to a physical situation. These two ways can be outlined as follows:

1. An analytical approach, which requires application of certain sensitivity equations to a mathematical model of the physical

process.

2. A measurement approach, which requires measurement of certain sensitivity coefficients of the entact physical process.

For the purposes of this study, only the first approach, the analytical approach, will be utilized. This approach will obviously require the development of appropriate mathematical models of the human respiratory system. One of the objectives of this study then is the development of the appropriate mathematical models of the human respiratory system, models which are amenable to sensitivity analysis.

It is appropriate then to briefly describe at this point those aspects of the respiratory system which will be required to further clarify the objectives of this study.

The human respiratory system has a primary responsibility in regulation of blood gas concentrations and body pH regulation. Close regulation of both of these quantities is required to maintain the metabolic balance of the body cells. The respiratory system achieves this regulation through a change in effective alveolar ventilation. Thus, when the human encounters an anoxic atmosphere, he immediately begins to hyperventilate in an effort to supply the body with more oxygen. Hyperventilation is also observed when an atmosphere containing carbon dioxide is inhaled and also when metabolic acidosis occurs for any reason.

The respiratory system exhibits then the properties of a feedback regulator, having effective alveolar ventilation as the dependent variable. The independent variables are the blood pH, carbon dioxide tension in the blood, and the oxygen tension in the blood. The pertinent anatomy and

physiology of the human respiratory system will be given in Part I of this thesis.

For the present, though, assume that it is known that an inhalation of carbon dioxide into the lungs will effect increases in alveolar ventilation and carbon dioxide tension in the arterial blood (there are, of course, additional effects). Then one aspect of the response of the respiratory system of an adult to a change in carbon dioxide inhalation is illustrated in Figure 1, which is taken from Defares (8). A careful examination of the carbon dioxide tension in the arterial blood $(P\ co_2)_a$ curve shows that the "on" and the "off" transients are asymmetric, in particular, the "off" transient exhibits a pronounced undershoot. How can this asymmetry be explained? As state by Defares (8), "We can only claim that we understand its mechanism (i.e., the mechanism responsible for the asymmetry) if we are able to predict the phenomenon on the basis of knowledge of the parameters and the initial conditions of the system. This requires a theoretical analysis of the system in terms of what is generally called a mathematical model."

Therefore, another objective of this study is to analytically determine, using sensitivity analysis, those parameters of the respiratory system which are the most important during the transient periods shown in Figure 1. How do the parameter sensitivities of the adult respiratory system compare with those of the neonatal respiratory system during the transient periods? To illustrate, one of the important parameters associated with both the adult and the neonatal respiratory systems is the cardiac output of the heart, since the heart serves to pump blood through the lungs. It is then desirable to know the sensitivity of the

adult and the neonatal respiratory systems to a change in cardiac output when both systems are operating under normal physiological conditions. Of course, other model parameter sensitivities will also be examined in addition to the cardiac output.

It has been mentioned previously that Guyton (1) has shown that the adult respiratory system will exhibit instability (persistent oscillations in the alveolar ventilation) for a sufficiently large arterial blood circulation time delay. The following question then arises, what are the sufficient conditions required to insure stability of the respiratory systems of the adult and the neonate? And further, which are the most important respiratory system parameters as the instability condition is approached? It will be an objective of this study to provide the stability information for these two physiological systems. This information is of interest in those clinical respiratory cases for which abnormal respiratory oscillations are observed. A combinational analysis using stability theory from nonlinear control systems, Lyapunov stability theory, together with sensitivity analysis will be used to obtain the desired stability information.

Finally, it will be an objective of this research to investigate the sensitivities of certain respiratory parameters for those parameter values which would indicate abnormal physiological conditions. This line of investigation is motivated by the following type of question. Assume a person has the disease emphysema, a lung disease which basically causes a decrease in total alveolar volume. Is such a person's respiratory system now more sensitive to a change in, e.g., cardiac output, than under normal

physiological conditions? Again, this type of question can be best answered through use of sensitivity analysis.

The preceding discussion has outlined the objectives of the present study. These objectives can be summarized then as follows:

1. Development of appropriate mathematical models of the respiratory systems of the adult and the neonate.
2. Determination of thos parameters which have the greatest effect on the respiratory systems' transient response.
3. Determination of sufficient conditions which will insure stability of the respiratory systems of the adult and the neonate.
4. Determination, using sensitivity analysis, of the sensitivity of the respiratory systems of the adult and the neonate for certain abnormal physiological conditions.

PART I. MATHEMATICAL MODELS OF THE RESPIRATORY SYSTEM

PERTINENT ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY SYSTEM

As was mentioned in the Introduction, the respiratory system of man is the physiological system which has been chosen for investigation in this thesis. It is the purpose of Part I of this thesis to develop the mathematical models of the respiratory system to be used in this study, since the ultimate purpose of this study is the analysis of these models using the methods of sensitivity analysis and Lyapunov stability analysis.

The development of the respiratory system models which follows is based upon knowledge of the physiology and anatomy of the respiratory sysbem. The present chapter will therefore discuss the pertinent anatomy and physiology of the human respiratory control system required for the development of the ensuing mathematical models.

The Mechanics of Respiration

The functional purpose of the respiratory effort can be described by consideration of the effects of two gases: oxygen and carbon dioxide. Each body cell requires oxygen as a vital constitutent of its energy-producing processes. And as a consequence of the cellular utilization of oxygen, there is a corresponding cellular production of carbon dioxide. The functional purpose of the respiratory effort is then to supply the cells of the body with adequte quantities of oxygen and, in addition, to remove the consequent carbon dioxide as this product is produced by the body cells.

The action of the respiratory system pertinent to the present discussion can best be understood by functional division of the respiratory system into three separate anatomical groups as follows:

1. The respiratory tree.
2. The circulatory system.
3. The cells of the body.

The respiratory tree is considered to be that part of the respiratory system which serves as the "exchange" unit between man and his atmosphere. The respiratory tree is considered to be composed of the following separate anatomical structures: the nasal passages, pharynx, glottis, trachea, and the lungs. The lungs, of course, are the basic gaseous exchange units for man. Each inspiratory effort brings a fresh supply of oxygen into the lungs to replace the oxygen which has been used in body metabolism. The inspiratory effort is the direct result of an increase in the volume of the chest, or thorax. As the volume of the thorax is increased through the action of the respiratory muscles of inspiration, the pressure of the gaseous mixture within the lungs decreases to a slightly negative value (relative to the atmospheric pressure). And as a consequence, a gaseous mixture from the atmosphere is forced into the lungs. During expiration exactly the opposite effects to those of inspiration occur; compression of the thoracic cage around the lungs compresses the lungs and forces air out of the lungs into the atmosphere. The rate and depth of the respiratory effort are controlled by the muscles of respiration (the most important of which is the diaphragm), and these muscles, in turn, are controlled by a respiratory center situated in the brain stem.

The functionally active units of the lungs are the alveoli, which are approximately spherical sacs having a diameter which varies from 75 to 300 microns. Each lung in an adult man contains approximately 150 million

alveoli. The alveolar wall is composed of a 1 to 4 micron thick membrane which is highly permeable to the passage of molecules of oxygen and carbon dioxide. The alveoli are anatomically situated as terminal sacs to the bronchioles, which are small passageways arising, in turn, from the two bronchi. The alveoli-bronchiole portion of the lung can conceptually be likened to a cluster of grapes. The point to be emphasized, though, is that it is at the alveolar level of the lung that the vital process of gaseous exchange occurs.

The circulatory system serves as the connecting link between the respiratory tree and the cells of the body. For it is the circulatory system that transports to the body cells blood which has been oxygenated in the lungs. In addition, carbon dioxide is transported from the body cells to the lungs where the CO_2 is experlled from the body. The role that the circulatory system plays in the overall respiratory process is shown schematically in Figure 2. The respiratory processes associated with Figure 2 are crucial to an understanding of the functioning of the respiratory system and therefore will be explained in more detail.

Each inspiratory movement seves to move a quantity of oxygen into the alveoli. Since this oxygen is still in the gaseous phase while in the alveoli, it exerts a partial pressure (or tension) which can be calculated from Dalton's law of partial pressure. Experimental measurements have shown the partial pressure of oxygen (denoted, by convention, as Po_2) in the alveoli to be equivalent to 103 millimeters of mercury (mm. Hg.). However, the systemic venous blood present in the pulmonary artery is deficient in 0_2 due to tissue oxygen utilization. The equivalent partial

pressure of O_2 in the pulmonary artery is approximately 40 mm. Hg. Hence, a partial pressure gradient exists. This pressure gradient effects diffusion of O_2 molecules from the alveoli into the pulmonary capillary blood. The O_2 molecules are held in reversible chemical combination with the hemoglobin molecule present in the erythrocytes of the blood. The reverse process occurs in the systemic capillaries. Here the systemic arterial blood has a Pco_2 of approximately 100 mm. Hg. at the arterial end of the systemic capillaries. Since the equivalent O_2 tension of the body cells is 40 mm. Hg., oxygen is releasted from the hemoglobin of the arterial blood to diffuse through the capillary wall into the body cells. The net effect is that an adequate supply of O_2 is made available for utilization by the body cells.

In a manner analogous to that of O_2 delivery to the cells, carbon dioxide is transported from the body cells to the lungs for expulsion. The systemic arterial blood has an equivalen Pco_2 of 40 mm. Hg. The Pco_2 in the body tissues (intracellular fluid), however, is 50 mm. Hg. CO_2 is thus forced from the body cells into the venous blood by the partial pressure gradient. The net effect is that systemic venous blood arrives at the pulmonary level having an effective Pco_2 of 46 mm. Hg. Since the Pco_2 in the alveolar air is only 40 mm. Hg., CO_2 diffuses through the pulmonary membrane (the membrane composed of the pulmonary capillary wall and the alveolar wall) into the alveoli. The respiratory cycle is completed when alveolar CO_2 is expelled from the lungs into the atmosphere.

It has been mentioned that oxygen is transported in the blood in chemical combination with hemoglobin; rather than in physical solution in

the blood plasma. The major portion of the carbon dioxide is also carried in chemical combination in the blood. The forms of combined CO_2 in the blood are carbonic acid (H_2CO_3), bicarbonate ion (HCO_3^-), and carbamino hemoglobin ($HHbCO_2$). The volume of CO_2 in the blood is expressed by the "CO_2 dissociation curve", which is shown in Figure 5.

Regulation of Respiration

Respiration normally takes place rhythmically and unconsciously. Under normal, resting conditions the respiratory effort is well regulated at a level which minimizes the mechanical work required to effect respiration. Since it is desired to mathematically describe this regulator action, those factors that influence respiration regulation must be discussed.

Respiration appears to be primarily regulated by three chemical agents: carbon dioxide tension, oxygen tension, and hydrogen ion concentration (pH). The anatomical sites at which these chemical factors have their effects are two in number. First, there appear to be diffuse areas in the brain stem (medulla and pons) responsible for the basic oscillatory pattern of normal breathing. The nerve impulses that activate the muscles of respiration arise in this area of the brain. These brain stem areas are collectively called "the respiration center" of the brain. There appear to be three functionally distinct areas of the respiratory center. These areas are as follows: the inspiratory area, the expiratory area, and the pneumotaxic area. Although the physiology of the respiratory center has not been fully elucidated, it is generally agreed that the basic respiratory rhythm is generated by the inspiratory and the expiratory areas of the respiratory center. The pneumotaxic area modifies the action, i.e., the

rate and depth of respiration, of the expiratory and inspiratory areas.

There is another important area of the body which contains specialized receptors that helps regulate respiration. This area is comprised of receptors found at the bifurcation of the common carotid arteries together with receptros located in the arch of the aorta. Two different types of receptros are present at these two sites. One type of receptor, called the chemoreceptor, is selectively responsive to the chemical composition of the blood perfusing them. The second type of receptor, called the pressoreceptor, is responsive to the pressure exerted by the arterial blood. Under normal blood pressure conditions the pressoreceptros have little effect on respiration, since the pressoreceptors are stimulated only when blood pressure changes to a value considerably different from the normal value. The chemoreceptors, in contrast, can greatly influence respiration under certain conditions. Both types of receptors have nerve fibers which pass to the brain where nerve impulses can modity the activity of the brain respiration center.

There are other factors which can have an effect on respiration regulation. One of these factors is the voluntary control the individual has over his respiratory pattern. However, longterm regulation of respiration is an involuntary process. For the purposes of this thesis no voluntary respiration effects are considered.

In addition to the chemoreceptors and the pressoreceptors previously discussed, there are other specialized body receptors that can affect respiration. Some of these receptros are situated, for example, in the hypothalamus of the brain (thermoreceptors), the lungs (pulmonary stretch

receptros), and the muscles and body tendons (primarily stretch receptors). The contributions these receptors make toward respiratory regulation is usually minor in comparison with other regulatory mechanisms.

In summary, the regulation of respiration is under the control, primarily, of specialized receptors situated in the brain and the aorta. These receptros are, in turn, influenced by the chemical composition of the blood perfusing these sites.

Respiratory Effects of Blood Gases

The chemical composition of the blood perfusing the receptors responsible for respiratory activity serves as the "signal" required for respiratory regulation. As has been mentioned previously, the blood gas tensions of carbon dioxide, oxygen, together with hydrogen ion concentration are the main determinants of respiratory activity. The magnitudes of the respiratory effects of these three are not equal, and in addition, the sites at which these concentrations have their effects differ.

The brain respiratory center serves as the primary area of respiratory regulation. Medullary respiratory centers are affected directly by changes in the blood gas tensions of carbon dioxide and hydrogen ion concentration. The respiratory center does not appear to be stimulated by a decrease in the oxygen tension of the blood. Thus oxygen tension does not carry the same weight in regulation of respiration as do pCO_2 and pH (9).

Haldane (10) discovered experimentally that an increase in the arterial Pco_2 increased the respiratory ventilation (i.e., the volume of air passed into and out of the lungs per minute). This same respiratory response is also observed when the arterial pH becomes slightly acidic.

However, the magnitudes of these two effects are different. As stated by Cherniack (9), "A rise in arterial carbon dioxide tension is the most outstanding of all the known chemical influences on ventilation." In addition, since an increase in Pco_2 in the arterial blood is also reflected as a decrease in pH, it has been difficult to separate the effects of pCO_2 increases and pH decreases. However, recent work by Hamilton and Brown (11) suggests the respiratory effects of Pco_2 and pH to be distinct mechanisms.

The aortic and carotid chemoreceptos are also influenced by gas tensions in the blood. These receptors are particularly sensitive to changes in the amount of dissolved oxygen in the plasma, a decrease in the arterial oxygen tenstion inducing an increase in ventilation. However, under normal conditions, the role of the peripheral chemoreceptors in the regulation of ventilation is suboridnate to that of the chemoreceptors in the medullary centers. The aortic and carotid chemoreceptros do not appear to be particularly sensitive to changes in Pco_2 and pH (9).

Summary of Regulation of Ventilation

In summary, ventilation is regulated by the body in an effor to maintain the blood pH at a constant level and, in addition, to minimize the mechanical work required for ventilation. Ventilation regulation is normally controlled by the blood gas tensions of carbon dioxide and oxygen, and hydrogen ion concentration. There are two sites in the body which possess specialized receptors that are sensitive to blood gas concentrations. These sites are the respiratory center of the brain and the aortic and carotid chemoreceptor complex. Present data suggest that the single

most important determinant of respiratory regulation is the carbon dioxide tension in the brain respiratory center. The respiratory models to be utilized in this thesis are based upon this premise.

It must be pointed out that the preceding discussion of respiration regulation has been drawn from the literature, and as such, the results reported were for the adult. However, it is also of interest in this study to investigate the respiratory regulation of the neonatal infant. A review of the literature shows that the regulation of respiration in the neonate has not been adequately investigaged. However, for the purposes of this study the contention of Cross (12) that "It is likely that normal adult physiological controls are functioning at birth." is accepted. That is, it is assumed that carbon dioxide tension in the brain respiratory center is the predominant regulator of ventilation for the neonate.

MATHEMATICAL MODELS OF CARBON DIOXIDE REGULATION OF RESPIRATION

It is the purpose of the present discussion to present the development of mathematical models appropriate to describe carbon dioxide regulation of ventilation in man. The respiratory models developed will subsequently be analyzed using the engineering analysis methods of dynamic sensitivity analysis and Lyapunov stability analysis. Mathematical models appropriate for both the adult and the neonatal infant will be developed.

The involuntary factors that effect respiratory regulation were given in the preceding chapter as blood Pco_2, Po_2, and pH. It was pointed out there that the tension of carbon dioxide in the arterial blood is the predominant factor regulating ventilation. Oxygen tension and pH of the arterial blood exert strong effects on ventilation only when the arterial Pco_2 is at or below its normal value. It has been experimentally established that an increase in arterial blood Pco_2 is always accompanied by an increase in ventilation. This increase in ventilation reflects an attempt by the body to maintain the tissue level of CO_2 constant. Increased ventilation then tends to lower body CO_2 tension. A response of this nature is characteristic of a proportional feedback control system. That is, part of the system output (tissue Pco_2) signal is used by the body to stabilize the tissue Pco_2 level against system disturbances (e.g., an inhalation of CO_2). The desired corrections needed to control tissue Pco_2 are made through changes in ventilation. Thus it has become common practice to consider the respiratory system as a feedback control system when studying respiratory regulation.

Review of Literature

Mathematical analyses of various aspects of respiration are numerous in the literature. Such analyses usually have the intended purpose of clarifying a physiological situation which is difficult to examine experimentally. The development of mathematical mdoels for the regulatory effect of carbon dioxide on ventilation falls in this category.

The first mathematical model of the regulatory action of carbon dioxide was offered by Grodins et al. (13). Their model of the regulatory action of carbon cioxide was derived by considering the body as being divided into three compartments: the lungs, the tissues, and an error sensing controller. The controller is that part of the respiratory control system that measures the system variable being regulated and makes the required corrections. Equations describing the regulatory action of CO_2 were derived by applying laws of mass continuity. The model derived by Grodins assumed all body tissues exterior to the lungs and the circulatory system to be lumped into a single compartment, the "body tissues" compartment. In addition, it was assumed that all circulation times (i.e., the time required for the blood to circulate throughout the body) were zero. From a physiological standpoint both assumptions are invalid. Nevertheless, Grodins' model was quite successful in predicting certain respiratory effects of an inhalation of CO_2.

Chilton and Stacy (14) developed a model that accurately accounted for the distribution of carbon dioxide in the lungs and its evolution from the pulmonary blood into the alveoli. They later developed a respiratory model which was concernted with the distribution of oxygen in the lungs

and its absoprtion into the arterial blood (15). Neither study, though, was explicitely concerned with the regulatory action of carbon dioxide or oxygen.

Defares et al. (16) extended Grodins' work by including two factors not included in the Grodins' model. First, circulation time was included in the Defares model. Second, Defares subdivided the "tissue" compartment of Grodins into two separate compartments; tissues external to the brain, and brain tissues. Ventilation was then controlled by the Pco_2 level in the brain tissues. In a series of later papers, Defares extended this work by including the regulatory effects of pH and oxygen tension (17, 18, 19).

Both Defares and Grodins made use of engineering control theory as an aid in analysis of the respiratory control system. However, even though the respiratory control system has been shown to be a nonlinear system by Grodins and Defares, no analysis using theory from nonlinear control systems has been attempted by previous investigators.

Important contributions to respiratory control system analysis have been made by Horgan and Lange (20, 21, 22). These investigators extended Defares' work by including a more accurate description of the circulation time delay effect. This was achieved by expressing the circulatory time delay as a transfer function (i.e., the ratio of the output of the delay device to the input). In addition, it was assumed that the algebraic expression of ventilation control was that given by Gray (23). That is, ventilation is controlled by the blood gas tensions in the arterial blood. This differs from the approach taken by Grodins and Defares, since they

both assumed that carbon dioxide control of ventilation was localized somewhere in the body tissues. Horgan and Lange have utilized their respiratory model to investigate those respiratory factors which could contribute to an abnormal breathing situation called Cheyne-Stokes breathing. This clinical abnormality is characterized by persistent oscillatory ventilation. However, no analytic treatment of respiratory oscillatory activity was attempted.

Additional improvements in the mathematical modelling of the respiratory system have been made by Milhorn and Guyton (24, 25, 26). The regulator model developed by them considered respiratory regulation by pH, Pco_2 and Po_2. The model so developed (24) differed from the Horgan-Lange model (20) in two respects. First, the representation of the circulation time delay differed. Horgan and Lange used a transfer function representation. Milhorn and Guyton utilize a time delay operator in their equations. Second, Milhorn and Guyton follow Grodins when they assume that carbon dioxide tension is regulated at the tissue level (i.e., the respiratory center in the brain). Horgan and Lange, in contrast, considered carbon dioxide tension in the arterial blood to be the regulating carbon dioxide tension.

Milhorn and Guyton also investigated the possible mechanism of Cheyne-Stokes respiration (25). Thier approach was to examine with an analog computer a respiratory model of Pco_2 control of ventilation. Again, like Horgan and Lange, no analytic analysis of persistent respiratory oscillations was attempted.

Other contributions to respiratory system modeling have been made by

Grodins et al. (27, 28) and Longobardo et al. (29, 30). A rather complete bibliography of mathematical modeling of the respiratory control system is found in reference 19.

The literature cited thusfar has been concerned entirely with the respiratory system of the adult. The mathematical modeling or respiratory regulation in the neonatal infant has received little attention in the literature. This can be attributed to the lack of physiological information regarding the infant's respiratory control system.

A MATHEMATICAL MODEL OF THE CARBON DIOXIDE RESPONSE OF THE RESPIRATORY SYSTEM

It is the purpose of the present discussion to develop mathematical models for the carbon dioxide response of the respiratory system. It is desired to analyze these models using the engineering methods of sensitivity analysis and Lyapunov stability analysis. In order to achieve this aim, a compromise has to be made between the complexity of the model and the complexity of the engineering analysis of the models. This situation arises because the engineering methods to be employed are computationally difficult. The mathematical models developed must therefore meet two criteria: they must reasonably predict the regulatory action of the respiratory system and consistent with this, the models must be of minimum mathematical complexity. For this reason only the respiratory effects of carbon dioxide regulation will be considered. It was shown in the previous chapter that this is a reasonable physiological assumption.

The respiratory control system can be divided into four functional units as shown in Figure 3. These four units are as follows:

1. The lungs.
2. The circulatory system.
3. The body tissues.
4. The ventilation controller.

It is evident from consideration of Figure 3, together with the prior discussion, that there are several factors that complicate any attempt to mathematically model the respiratory system. Some of these factors are as follows:

1. The lung volumes are functions of time, since breathing is a cyclic process.
2. Only a fraction of the inspired air reaches the alveoli to participate in gas exchange. This is caused by the presence of dead space in the respiratory tree. The dead space areas of the respiratory tree are defined as being those areas that do not participate in gas exchange. The anatomical dead space areas are composed then by the nasal passages, trachea, bronci, and bronchioles. In addition, not all the alveoli participate in the gas exchange process, thus giving use to a physiological dead space.
3. The blood passes through the pulmonary circulatory system in a pulsatile flow, since the heart pumps the blood in such a manner.
4. The process of gas exchange in the alveoli requires a finite amount of time, since passage of blood through the lungs is not instantaneous. In addition, a finite amount of time is required for the gas molecules to diffuse through the pulmonary membrane.
5. Oxygen as well as carbon dioxide is exchanged across the pulmonary membrane. If the respiratory quotient, R.Q., (the ratio of CO_2 produced to O_2 consumed) is not unity, dry inspired and expired gas volumes will differ.
6. The rate of carbon dioxide production by the body tissues varies with the different types of tissues.

It must be pointed out, though, that these complicating factors are secondary in nature when considering the overall regulation of respiration. That is, breath-by-breath regulation of respiration is not of primary concern in this thesis, but rather, long term regulation (e.g., over a time interval of 20 minutes) is of primary interest.

It is common practice to divide any physiological system being mathematically modeled into functional compartments. Such a division is shown in Figure 3 for the respiratory control system. It is then required that mathematical relations among the compartments be established. These equations always take the form of continuity of mass equations whenever the system under consideration involves the movement of materials among compartments. As an example of this approach consider Figure 4, which shows a compartment of the body to which a solute S is delivered via fluid flow $F_1(t)$. The solute is removed from the compartment via fluid flow $F_o(t)$. Since in general the quantity of solute introduced into the compartment differs from the quantity removed from it, it is of concern to be able to express how the solute changes as a function of time within the compartment. This is effected by writing a mass continuity equation for solute S. Such an equation states the physical fact that the quantity of solute S entering the compartment must equal the quantity of S leaving plus any quantity change within the compartment. All quantities are referred to unit time. Thus if the quantity (e.g., liters) of solute S within the compartment is denoted by $Q_s(t)$; then the continuity law can be stated mathematically as follows:

$$\frac{dQ_s(t)}{dt} = \dot{Q}_i(t) - \dot{Q}_o(t) \qquad (1)$$

where $\dot{Q}_1(t)$ equals the rate (liters/unit time) at which solute S is delivered to the compartment. $\dot{Q}_o(t)$ equals the rate at which solute S is removed from the compartment. Equation 1 states that the change per unit time in the quantity of S in the compartment is equal to the rate at which S is delivered minus the rate at which S is removed from the compartment. An appreciation of Equation 1 is vital for understanding of the respiratory models which follow.

It is usually desirable to express the dependent variables of a model in terms of measurable quantities of the physical process. Thus, it would be desirable to express the time variations of solute S in Figure 4 in terms of solute concentrations. If it is known that the concentrations of S in the fluid being delivered to the compartment is $C_1(t)$ (liters of S per liter fluid), and since the input fluid flow is $F_1(t)$ then the rate at which S is delivered to the compartment is

$$\dot{Q}_1(t) - C_1(t)F_1(t) \quad \text{liters solute/unit time.} \tag{2}$$

In a similar manner, the rate at which solute S is removed from the compartment is given by

$$\dot{Q}_o(t) = C_o(t)F_o(t) \quad \text{liters solute/unit time.} \tag{3}$$

Thus, Equation 1 can be expressed as follows:

$$\frac{dQ_s(t)}{dt} = C_1(t)F_1(t) - C_o(t)F_o(t) \ . \tag{4}$$

The concentration os S within the compartment can be expressed by definition as

$$C_s(t) = Q_s(t)/V_c(t), \tag{5}$$

where $V_c(t)$ is the volume of the compartment in liters. If Equation 5 is substituted into Equation 4 the result is given by

$$V_c(t)\frac{dC_s(t)}{dt} + C_s(t)\frac{dV_c(t)}{dt} = C_1(t)F_1(t) - C_o(t)F_o(t). \qquad (6)$$

If it is assumed that the compartment has constant volume, and in addition, that the fluid flows $F_1(t)$ and $F_o(t)$ are equal, then Equation 6 reduces to

$$\frac{dC_s(t)}{dt} = \frac{F_i(t)}{V_c}[C_1(t) - C_o(t)]. \qquad (7)$$

Equation 7 thus describes the time variations of solute S within the compartment. Equation 7 can be solved for $C_s(t)$ when know relationships for $C_1(t)$, $C_o(t)$, and $F_1(t)$ are substituted.

The preceding discussion illustrated the use of compartments and development of continuity equations to arrive at a model of a physiological process. For example, the preceding discussion could apply to delivery via the blood of a drug to a specific area of the body, e.g., the brain. The principles illustrated by the one-compartment model discussion are basic to development of the respiratory system models.

Assumptions

In order to arrive at a reasonable model of the regulator action of the respiratory system, certain assumptions have to be made. These assumptions are as follows:

1. The respiratory control system is controlled only by the body tissue tension of carbon dioxide.

2. All voluntary respiratory effects are excluded from analysis, as well as breath-by-breath analysis of respiratory control.

3. The respiratory system can be divided into four functional divisions as shown in Figure 3.

4. The lungs contain zero dead space, and the volume of the alveolar compartment can be represented by an effective volume of constant value.

5. The cardiac output of the heart is not a function of time, and is not a function of any carbon dioxide tension.

6. All circulation times are finite, and the pulmonary circulation times are negligible in comparison to systemic circulation times.

7. Carbon dioxide dissociation curves are equal for arterial and venous blood and body tissues.

8. The respiratory quotient remains constant and equal to unity.

9. Arterial blood carbon dioxide tension remains equal to alveolar carbon dioxide tension at all time.

10. Venous blood carbon dioxide tension remains equal to tissue carbon dioxide tension at all time.

11. The effects of pulmonary blood shunting can be accounted for by assuming a single equivalent circulatory shunt.

12. Carbon dioxide encounters no resistance in diffusing through the pulmonary membrane.

Assumptions 1, 2, 4, 5, 7, 8, 9, 10, and 12 are assumptions made by Grodins et al. in their work (13). A discussion of the validity of these assumptions is given by Grodins. In general, there are physiological data to support all assumptions except Assumptions 1 and 3. Later investigators (16, 20) have considered the respiratory system as having an additional compartment, the brain compartment; which is an extention of Assumption 3. Assumption 1 has been questioned by several investigators (20, 29), who consider ventilation controlled by arterial blood Pco_2 rather than tissue

Pco_2. These refinements by later investigators to the Grodins respiratory model have not changed the basic validity of the Grodins model. For this reason, Assumptions 1 and 3 are maintained in this thesis. Assumptions 6 and 11 permit extensions of Grodins' model to a more realistic physiological situation.

The Model Equations

The alveolar compartment

Consideration of Figure 3 permits writing a carbon dioxide continuity equation for this compartment. The rate of change of the quantity of CO_2 in the alveolar volume is equated to the rate at which CO_2 is delivered minus the rate at which CO_2 is removed from the alveoli. Thus, it follows that the alveolar CO_2 continuity equation can be written as

$$\frac{dV_A(t)}{dt} = \bar{V}_A(t)C_1(t) - \bar{V}_A(t)C_A(t) + Q_A C_{vA}(t) - Q_A C_{Aa}(t) \qquad (8)$$

Table 1 lists all symbols used. All equations will be expressed in terms of carbon dioxide concentrations (i.e., volume percent), rather than carbon dioxide tensions (mm. Hg.). This consideration is made for mathematical convenience.

The respiratory ventilation is expressed in terms of an effective alveolar ventilation, $\bar{V}_A(t)$. The effective alveolar ventilation is the volume of air per minute required to produce the same gas exchange in a real lung as in the constant volume idealized lung compartment. $C_1(t)$ represents the CO_2 volume percent inhalation into the alveoli. This inhaled CO_2 concentration serves as the system driving function, and is used to assess the control action of the respiratory system. Such an

inhalation is used clinically also, to assess the control ability of the respiratory system (9).

The tissue compartment

A carbon dioxide continuity equation for the tissues compartment is derived from consideration of Figure 3, together with the previously listed assumptions. This equation is as follows:

$$\frac{dV_T(t)}{dt} = QC_{aT}(t) - QC_{Tv}(t) + M. \tag{9}$$

An equivalent metabolic production of carbon dioxide by the tissues is represented by M. Since the tissue metabolic rate of CO_2 production varies with tissue type, M represents an average value for all tissues.

The controller

It has been assumed that the tissue concentration level of CO_2 serves as the regulator of respirtation, i.e., ventilation. Thus as the tissue level of CO_2 increases, the ventilation also increases; thereby decreasing the body CO_2 levels. It is evident then that a feedback relation exists between alveolar ventilation and tissue CO_2 concentration. This control action is invested in the "respiratory controller" shown in Figure 3. It is assumed that the controller provides proportional feedback given by the following relation:

$$\overline{V}_A(t) = aC_T(t) - b \geq 0. \tag{10}$$

Reduction of unknown variables

The number of unknown CO_2 concentrations can be reduced to two by utilization of the previously listed assumptions. It has been assumed from Assumption 9 that arterial Pco_2 equals elveolar Pco_2 at all time.

The relation between the concentration (involume percent) of CO_2 in the arterial blood and its equivalent tension is expressed by the CO_2 dissociation curve (32). This curve is shown in Figure 5. It is assumed that this curve can be approximated over the range shown by a straight line approximation given by

$$C_{Aa} = k_1(pCO_2)_{Aa} = k_2 \ , \tag{11}$$

where k_1 and k_2 are constants and are the slope and intercept, respectively, of the linerized CO_2 dissociation curve. The partial pressure of CO_2 in the alveolar compartment can be calculated using Dalton's law of partial pressures as follows:

$$(Pco_2)_A = \bar{B}\, C_A \ , \tag{12}$$

where $\bar{B}$ represents the barometric pressure corrected for the presence of water vapor in the lungs. It follows from Assumption 9 then that

$$\bar{B}\, C_A(t) = \frac{1}{k_1}\left[C_{Aa}(t) - k_2\right] \ , \tag{13}$$

or in terms of arterial CO_2 concentration,

$$C_{Aa}(t) = k_1\, \bar{B}\, C_A(t) + k_2 \ . \tag{14}$$

Assumptions 7 and 10 permit the equating of venous blood CO_2 and tissue CO_2 concentrations. Thus, it follows that

$$C_{Tv}(t) = C_T(t) \ . \tag{15}$$

Assumptions 3 and 4 permit considering the alveolar and tissue compartments as compartments of constant volume. Thus it is possible to express Equations 8 and 9 in terms of CO_2 concentrations through use of the relations

$$v_A(t) = C_A(t)V_A \qquad \text{and} \qquad v_T(t) = C_T(t)V_T \ . \tag{16}$$

Substitution of Equations 14, 15, and 16 into Equations 8 and 9 yields the following set of equations:

$$V_A \frac{dC_A(t)}{dt} = \bar{V}_A(t) [C_1(t) - C_A(t)] + Q_A [C_{vA}(t) - k_1 \bar{B} C_A(t) - k_2] \quad (17)$$

and

$$V_T \frac{dC_T(t)}{dt} = Q [C_{aT}(t) - C_T(t)] + M . \quad (18)$$

It is required to now express the CO_2 concentrations $C_{vA}(t)$ and $C_{aT}(t)$ in terms of $C_A(t)$ and $C_T(t)$. From Assumption 6 (and Figure 3) it follows that venous-alveolar blood CO_2 concentration, $C_{vA}(t)$, is related to the venous-tissue CO_2 concentration, $C_{Tv}(t)$ by

$$C_{vA}(t) = C_{Tv}(t - T_v) = C_T(t - T_v), \quad (19)$$

where T_v represents venous circulation time. The arterial-tissue CO_2 concentration, $C_{aT}(t)$, is related to the CO_2 concentration in the pulmonary venous blood, $C_{pv}(t)$, as follows:

$$C_{aT}(t) = C_{pv}(t - T_a) , \quad (20)$$

where T_a represents arterial circulation time. However, $C_{pv}(t)$ consists of a mixture of two CO_2 concentrations, $C_{vA}(t)$ and $C_{Aa}(t)$, and it is desired to express both these concentrations in terms of alveolar and tissue concentrations. This is effected by accounting for the quantity of CO_2 per minute being returned to the left side of the heart as follows:

$$Q C_{pv}(t) = Q_s C_{vA}(t) + Q_A C_{Aa}(t) . \quad (21)$$

Continuity of blood flow (Figure 3) requires that

$$Q = Q_A + Q_s . \quad (22)$$

From Assumption 12 it follows that the fraction of blood being shunted

around the lungs can be expressed by the following relation:

$$Q_s = k\,Q\ , \tag{23}$$

where k represents the shunting fraction and varies form 0 to 1. Substitution of Equation 23 into Equation 22 yields for Q_A the following:

$$Q_A = (1 - k)\,Q\ . \tag{24}$$

Substitution of Equations 24, 23, 19, and 14 into Equation 21 yields

$$Q\,C_{pv}(t) = k\,Q\,C_T(t - T_v) + (1 - k)\,Q[k_1\bar{B}\,C_A(t) + k_2]\ , \tag{25}$$

and substitution of this equation into Equation 20 yields for $C_{aT}(t)$:

$$C_{aT}(t) = kC_T(t - T_v - T_a) + (1-k)[k_1\bar{B}\,C_A(t-T_a) + k_2]\ . \tag{26}$$

It is now assumed that the venous circulation time and the arterial circulation time are qual. This assumption is made for sake of mathematical simplicity, but is also reasonable from a physiological standpoint. Equation 26 can thus be written as

$$C_{aT}(t) = kC_T(t-2T) + (1-k)[k_1\bar{B}\,C_A(t-T) + k_2]\ . \tag{27}$$

Substitution of Equations 19 and 27 into Equations 17 and 18 yields two difference-differential equations in two unknowns, $C_A(t)$ and $C_T(t)$:

$$V_A\,\frac{dC_A(t)}{dt} = \bar{V}_A(t)[C_1(t) - C_A(t)] + (1-k)Q[C_T(t-T) - k_1\bar{B}C_A(t) - k_2] \tag{28}$$

$$V_T\,\frac{dC_T(t)}{dt} = kQC_T(t-2T) + (1-k)Qk_1\bar{B}C_A(t-T) + (1-k)Qk_2 - QC_T(t) + M. \tag{29}$$

It is not possible to apply the engineering methods of sensitivity analysis and Lyapunov stability analysis to Equations 28 and 29, since neither method is presently applicable to difference-differential equations.

However, this objection can be removed if all time delays are approximated by the first two terms of a Taylor's series as follows:

$$C_T(t-T) \approx C_T(t) - T\frac{dC_T(t)}{dt}\,, \quad C_A(t-T) \quad C_A(t) - T\,\frac{dC_A}{dt}$$
$$C_T(t-2T) \approx C_T(t) - 2T\,\frac{dC_T(t)}{dt}\,. \tag{30}$$

This approximation has the effect of representing, in engineering terminology, the circulation time as a first-order lag. This assumption is not physiologically justified, but physiological evidence is lacking as how to represent the circulation time delay effect. It will be shown, however, that the approximation used does account for certain respiratory effects reported in the physiological literature. Since respiratory control action is exerted only when ventilation is greater than zero (i.e., the feedback is present), it will be assumed that normally $V_A(t)$ is greater than zero. All digital computer solutions of the respiratory equations are programmed to provide a continuous check on this assumption. Therefore, when Equations 28 and 29 have substituted into them Equations 10 and 30, the result is as follows:

$$V_A\,\frac{dC_A(t)}{dt} + (1-k)QT\,\frac{dC_T(t)}{dt} = [b - (1-k)Qk_1\bar{B}]C_A(t)$$
$$+ [aC_I(t) + (1-k)Q]C_T(t) - aC_A(t)C_T(t) - bC_I(t)$$
$$- (1-k)Qk_2 \tag{31}$$

$$(1-k)Qk_1\bar{B}\,T\,\frac{dC_A(t)}{dt} + (V_T + 2kQT)\,\frac{dC_T(t)}{dt} = (1-k)Qk_1\bar{B}\,C_A(t)$$
$$- (1-k)QC_T(t) + (1-k)Qk_2 + M. \tag{32}$$

It is desirable to be able to express each of the independent variables, C_A and C_T, in the form of a single first-order differential equation. Therefore, if Equations 31 and 32 are algebraically solved simultaneously, using Cramer's rule, the result is a set of two nonlinear, first-order differential equations. This result is given by

$$\frac{dC_A(t)}{dt} = a_{11}C_A(t) + a_{12}C_T(t) - a_{13}C_A(t)C_T(t) + a_{14}C_1(t)C_T(t) - a_{15}C_1(t) - a_{16} \tag{33}$$

$$\frac{dC_T(t)}{dt} = a_{21}C_A(t) - a_{22}C_T(t)\ a_{23}C_A(t)C_T(t) - a_{24}C_1(t)C_T(t) + a_{25}C_1(t) + a_{26} \tag{34}$$

where the following definitions have been made:

$$a_{11} = \{(V_T + 2kQT)\ [b - (1-k)Qk_1\bar{B}] - (1-k)^2Q^2k_1\bar{B}T\}/D$$

$$a_{12} = (1 - k)\ Q[V_T + (1 + k)\ Q\ T]/D$$

$$a_{13} = a\ (V_T + 2\ k\ Q\ T)/D$$

$$a_{14} = a\ (V_T + 2\ k\ Q\ T)/D$$

$$a_{15} = b\ (V_T + 2\ k\ Q\ T)/D$$

$$a_{16} = (1 - k)Q[k_2V_T + (1 + k)k_2\ QT + MT]/D$$

$$a_{21} = \{(1 - k)k_1\bar{B}Q[V_A - T\ \{b - (1 - k)Qk_1\bar{B}\}]\}/D$$

$$a_{22} = \{(1 - k)Q[V_A + k_1\ \bar{B}\ T\ (1 - k)\ Q]\}/D$$

$$a_{23} = a\ (1 - k)\ Q\ T\ k_1\ \bar{B}/D$$

$$a_{24} = a\ (1 - k)\ Q\ T\ k_1\ \bar{B}/D$$

$$a_{25} = b\ (1 - k)\ Q\ T\ k_1\ \bar{B}/D$$

$$a_{26} = \{V_A[M + (1 - k)\ Q\ k_2] + (1 - k)^2\ Q^2k_2k_1\bar{B}\ T\}/D$$

$$D = V_A (V_T + 2 k Q T) - (1 - k)^2 Q^2 k_1 \bar{B} T^2$$

The simultaneous solution of Equations 33 and 34 then describes the respiratory system's response to an inhalation of CO_2. Since the equations are nonlinear in nature (due to the product terms of dependent variables), digital computer solutions will be obtained for the respiratory equations.

Open loop equations

Equations 33 and 34 describe CO_2 control of ventilation assuming that feedback control is present. The respiratory effects of open loop (i.e., no feedback between tissue CO_2 concentration and alveolar ventilation) operation are also of interest in this investigation. This is due to the fact that sensitivity analysis will be applied to both the open loop and the closed loop siturations. Such an investigation will shed light on the effects of feedback control on respiration.

The open-loop respiratory equations are derived from Equations 28, 29, and 30. It is assumed that alveolar ventilation, $\bar{V}_A(t)$, is a constant, since no feedback exists. The open-loop respiratory equations can then be investigated as the respiratory system is subjected to an inhalation of CO_2 from rest while ventilation is constant. The open-loop respiratory equations can be written as follows:

$$V_A \frac{dC_A(t)}{dt} + (1-k)QT \frac{dC_T(t)}{dt} = \bar{V}_A C_1(t) + (1-k)QC_T(t) - [\bar{V}_A + (1-k)Qk_1\bar{B}]\, C_A(t) - (1-k)Qk_2 \qquad (35)$$

$$(1-k)Qk_1\bar{B}T \frac{dC_A(t)}{dt} + [V_T + 2kQT] \frac{dC_T(t)}{dt} = (1-k)Qk_1\bar{B}C_A(t) - (1-k)QC_T(t) + (1-k)Qk_2 + M. \qquad (36)$$

Again, it is desirable to express Equations 35 and 36 as two first-order differential equations. This result is - using Cramer's rule - as follows:

$$\frac{dC_A(t)}{dt} = -b_{11}C_A(t) + b_{12}C_T(t) + b_{13}C_1(t) - b_{14} \tag{37}$$

$$\frac{dC_T(t)}{dt} = b_{21}C_A(t) - b_{22}C_T(t) - b_{23}C_1(t) + b_{24} \tag{38}$$

where the equations constants are given by

$$b_{11} = \{(V_T + 2kQT)\ [\bar{V}_A + (1-k)Qk_1\bar{B}] + (1-k)^2Q^2k_1\bar{B}T\}/D$$

$$b_{12} = (1-k)Q[V_T + (1+k)QT]/D$$

$$b_{13} = \bar{V}_A(V_t + 2kQT)/D$$

$$b_{14} = (1-k)Q[TM + k_2V_T + k_2QT + kk_2QT]/D$$

$$b_{21} = \{(1-k)Qk_1\bar{B}\ [V_A + T\bar{V}_A + T(1-k)Qk_1\bar{B}]\}/D$$

$$b_{22} = \{(1-k)Q\ [V_A + (1-k)Qk_1\bar{B}T]\}/D$$

$$b_{23} = k_1\bar{B}QT\bar{V}_A(1-k)/D$$

$$b_{24} = \{V_AM + (1-k)Qk_2V_A + (1-k)^2Q^2k_1k_2\bar{B}T\}/D$$

$$D = V_A(V_T + 2kQT) - (1-k)^2Q^2T^2k_1\bar{B}$$

It is to be noted that the open-loop respiratory equations are linear, first-order differential equations, whereas the closed-loop respiratory equations are nonlinear in nature. The solution of Equations 37 and 38, in response to an inhalation of CO_2, will provide insight into the control effectiveness of the respiratory system when this solution is compared to the closed-loop solution for the same CO_2 inhalation.

Calculation of steady state values

The preceding respiratory equations, both closed and open-loop, provide information regarding the transient phase of respiration regulation. The steady-state (i.e., the state that prevails after all transients have disappeared) nature of the respiratory control system is also of interest, since calculation of the steady-state values of alveolar and tissue CO_2 concentrations will be required for the Lyapunov stability analysis to follow. In addition, expressions for the steady-state CO_2 concentrations are of considerable importance themselves, since considerable insight into respiratory control can be gained from their analysis. The steady-state values can be calculated from the respiratory equations previously developed by equating to zero all derivatives with respect to time. The steady-state alveolar and tissue CO_2 concentrations will be denoted by $\bar{C}_A$ and $\bar{C}_T$, respectively.

The closed loop steady state CO_2 concentrations are found from Equations 31 and 32 by setting the following to zero:

$$\frac{dC_A(t)}{dt} = 0 \qquad \text{and} \qquad \frac{dC_T(t)}{dt} = 0$$

and solving the resultant algebraic equations. These equations are as follows:

$$[b - (1-k)Qk_1\bar{B}]\bar{C}_{Ac} + [aC_1 + (1-k)Q]\bar{C}_{Tc} - a\bar{C}_{Tc}\bar{C}_{Ac} - bC_1 - (1-k)Qk_2 = 0$$

$$(1-k)Qk_1\bar{B}\,\bar{C}_{Ac} - (1-k)Q\bar{C}_{Tc} + (1-k)Qk_2 + M = 0.$$

The solution of these equations for steady-state alveolar and tissue CO_2 concentrations $\bar{C}_{Ac}$ and $\bar{C}_{Tc}$, is given by

$$\bar{C}_{Tc} = \frac{G + \sqrt{G^2 - H}}{J} \tag{41}$$

$$\bar{C}_{Ac} = \frac{\bar{C}_{Tc}}{k_1 \bar{B}} - \frac{M + (1-k)Qk_2}{(1-k)Qk_1 \bar{B}} \tag{42}$$

where

$$G = aM + (1-k)Q(ak_2 + b + ak_1 \bar{B} C_1)$$

$$H = 4a(1-k)Q\{bM + (1-k)Q\, bk_2 + k_1 \bar{B}(bC_1 - M)]\}$$

$$J = 2a(1-k)Q.$$

It has been assumed in the derivation of Equations 41 and 42 that the inhaled CO_2 concentration, C_1, was constant. It should be pointed out that the derivation of Equation 41 required solving a quadratic equation in $\bar{C}_T$. The solution to such an equation always results in two roots. The second root of Equation 41 can be found by changing the plus sign that precedes the radical to a minus sign. However, this second root of Equation 41 will always result in a negative $\bar{C}_A$ when substituted into Equation 42. This situation is physically disallowed since $\bar{C}_A$ represents a CO_2 concentration.

The steady state CO_2 concentrations can be derived for the open-loop case in a manner similar to the derivations for the closed-loop respiratory equations. That is, all derivatives with respect to time in Equations 35 and 36 are set equal to zero and the resultant algebraic equations solved. The equations to be solved are as follows:

$$(1-k)Q\bar{C}_{To} - [\bar{V}_A + (1-k)Qk_1 \bar{B}]\bar{C}_{Ao} = (1-k)Qk_2 - \bar{V}_A C_1$$

$$-(1-k)Q\bar{C}_{To} + (1-k)Qk_1 \bar{B}\, \bar{C}_{Ao} = -(1-k)Qk_2 - M.$$

The solution of these equations for the open loop, steady state alveolar and tissue CO_2 concentrations is given by

$$\bar{C}_{To} = k_2 + k_1\bar{B}C_1 + \frac{k_1\bar{B}M}{\bar{V}_A} + \frac{M}{(1-k)Q} \tag{43}$$

$$C_{Ao} = C_1 + \frac{M}{\bar{V}_A} \quad . \tag{44}$$

It is noted that the steady state CO_2 concentrations (both open and closed loop) are not functions of tissue volume (V_T), alveolar volume (V_A), or circulation time (T). The effects of respiratory parameter variations on the steady state CO_2 concentrations can be examined when the appropriate parameter values have been substituted into the steady state equations. It is necessary first, though, to establish a set of normal values for the physiological parameters.

Establishment of 'normal' respiratory parameter values

In order to numerically solve any of the respiratory equations previously derived, parameter values must be substituted. Parameter values for hypothetical 'normal' individuals (both adult and infant) must be established prior to investigation of any abnormal respiratory effects. In this context, 'normal' will denote an individual whose respiratory parameters fit the mathematical model parameters derived for an individual in good health and at rest. The 'normal' respiratory parameter values to be utilized are both calculated and experimentally determined in nature. The experimentally determined values will be taken from the physiology literature. The calculated parameter values will be obtained from the steady state respiratory equations previously discussed. Since several

simplifications were employed to arrive at a mathematical model of respiratory control, certain respiratory parameters have to be calculated in order to make the model performance approximate data reported in the physiology literature.

The parameter values for normal individuals are listed in Table 2. The parameter values in Table 2 marked with an asterisk are calculated values. The normal parameter values for tissue metabolic rate of CO_2 production (M) and ventilation controller intercept (b) are the two respiratory parameters that are calculated. This implies, in turn, that the tissue CO_2 tension, as well as tissue CO_2 content (C_T), are calculated values, as shown in Table 2.

The normal value for the adult metabolic rate of CO_2 production (M) can be established in the following manner. It is assumed that a 70 kg. adult is at rest, at one atmosphere pressure (760 mm. Hg.), achieving normal ventilation, and experiencing no CO_2 disturbance. These conditions imply that the steady state, open loop respiratory equations apply, and further, that C_1 is zero. Thus, Equations 43 and 44 are applicable, and reduce by the listed assumptions to the following:

$$\bar{C}_{To} = k_2 + \frac{k_1 \bar{B} M}{\bar{V}_A} + \frac{M}{(1-k)Q} \tag{45}$$

$$C_{Ao} = \frac{M}{\bar{V}_A} \quad . \tag{46}$$

Equations 45 and 46 are extensions of analogous equations given by Grodins (13, 28). Using Equation 12 to express Equation 46 in terms of CO_2 tension, and then solving for tissue metabolic rate of CO_2 production (M) yields

$$M = \frac{\bar{V}_A \, (Pco_2)_A}{\bar{B}} \text{ liters/minute.} \qquad (47)$$

Guyton (32, p. 514) states the normal respiratory minute volume (commonly denoted by $\dot{V}_E$ in young males averages about 6 liters per minute. However, the effective alveolar ventilation, $\bar{V}_A$, will be a lesser value due to the dilution effect of respiratory dead space. Avery et al. (31) state that the ratio of $\bar{V}_A$ to $\dot{V}_E$ is from 0.7 to 0.8. The 'normal' value of effective alveolar ventilation is thus chosen to be 5.0 liters per minute. Guyton (32, p. 544) also states that the normal alveolar Pco_2 is 40 mm. Hg. Since it has been assumed that the individual is at one atmosphere of pressure, it follows then that

$$M_{adult} = \frac{(5 \text{ liters/min.})(40 \text{ mm. Hg.})}{(760\text{-}47 \text{ mm. Hg.})} = .2805 \text{ lit./min.}$$

where the barometric pressure has been corrected for the partial pressure of water vapor in the lungs. This value compares favorably with the value used by Grodins (13), and Milhorn (24), who used Grodins' value in his study. The Grodins' value for metabolic rate of CO_2 production was 0.263 liters per minute. However, this value was calculated by Grodins without correcting for the effect of water vapor partial pressure in the lungs.

The calculation of the metabolic CO_2 production for the infant proceeds in a manner analogous to that of the adult. However, the establiahment of 'normal' parameters for the neonatal infant are somewhat hypothetical, since 'normal' values vary widely among healthy infants. In addition, certain infant respiratory parameters are age dependent, due primarily to the gradual closing of the ductus arteriosus and the foramen ovale. These two circulatory shunts are normally both fully closed at

about 7 weeks of age. The blood gas concentrations are dependent on the degree of pulmonary blood shunted around the lungs. Carlson (3) reported that the alveolar CO_2 tension averaged 32 mm. Hg. during the first few days of life. The 'normal' value of alveolar ventilation, $\overline{V}_A$, is assumed to be 0.6 liter per minute, which represents an average of data presented in Reference 31. It follows then from Equation 47 that the metabolic rate of CO_2 production for the 'normal' infant is calculated to be

$$M_{infant} = \frac{(0.6 \text{ liter/minute})(32 \text{ mm. Hg.})}{713 \text{ mm. Hg.}} = 0.0269 \text{ liters/min.}$$

This value is somewhat larger than that given by Avery et al. (31) who use a value of 0.018 liters per minute, assuming a 3 kg. infant.

The fraction of blood shunted around the lungs is an important respiratory parameter, even for the adult. In the newborn, the major shunting of blood around the lungs (Figure 3) is via the forament ovale and the ductus arteriosus. This shunting, which is a necessary aspect of fetal life, can average 25% in healthy newborns (3), and may approach 70% in respiratory distressed infants (3). Accordingly, a shunting fraction (k) of 25% will be considered normal for the infant. Cherniack et al. (9, p. 48) state that in the adult a shunting effect equivalent to 2.5% is normal. The shunting in the adult is caused by passage of blood from the right to the left side of the heart via the thebesian and the bronchial veins. In addition, certain disease states cause the pulmonary blood to come into contact with nonfunctioning alveoli, which can be considered an effect analogous to pulmonary blood shunting.

The normal value of the cardiac output, Q, for the adult (70 kg. young male at rest) is given by Guyton (32) as 6.0 liters per minute. The

normal value for infant cardiac output is assumed to be 0.3 liter per minute, the value cited by Cross (12).

The normal value for the controller slope, 'a', is obtained from Avery et al. (31). Data taken from this study that are pertinent to the present study are shown in Figure 7. This plot shows minute ventilation, $\bar{V}_A$, as a function of alveolar Pco_2 for both the adult and the infant. Associated with each plot is a slope relating change in minute ventilation to a change in alveolar Pco_2. It follows from Figure 7 that

$$\frac{d\,\bar{V}_A}{d(Pco_2)_A} = 2.24 \text{ liters/min/mm Hg for the adult}$$

and

$$\frac{d\,\bar{V}_A}{d(Pco_2)_A} = 0.0962 \text{ liter/min/mm Hg for the infant.}$$

Using these values, it is possible to calculate the controller slope 'a' as follows. Since the CO_2 controller equation (Equation 10) is given by

$$\bar{V}_A = aC_T - b,$$

then it follows that

$$a = \frac{d\,\bar{V}_A}{d\,C_T} \quad . \tag{48}$$

Application of the chain rule of differentiation yields

$$a = \frac{d\,\bar{V}_A}{d\,C_T} = \frac{d\,V_A}{d(Pco_2)_A}\,\frac{d(Pco_2)_A}{d\,C_T} \tag{49}$$

The first term of Equation 49 has been obtained from Figure 7. The second term can be obtained through use of Assumptions 7 and 9, i.e.,

$$C_T = k_1(Pco_2)_A + k_2 \ ,$$

from which it follows that

$$\frac{d(Pco_2)_A}{d\,C_T} = \frac{1}{k_1} \quad . \tag{50}$$

The normal value for the controller slope for the adult is thus calculated to be

$$a = 2.24/.005 = 448 \text{ liters/minute},$$

and for the infant the controller slope is calculated to be

$$a = .0962/.0044 = 21.8 \text{ liters/minute}.$$

There remains now only the calculation of the controller set point, 'b', to complete the parameter specifications for normal individuals. The procedure required to specify 'b' assumes an individual under normal, resting conditions. The value of 'b' required to effect normal minute ventilation is then calculated. Specifically, if Equation 43 is solved for $\bar{V}_A$ as a function of $\bar{C}_{To}$, the result is

$$V_A[\bar{C}_{To} - k_2 - M/(1-k)Q] = k_1\bar{B}M \quad . \tag{51}$$

If Equation 10 is solved for $\bar{C}_T$ and substituted into Equation 51, the controller set point 'b' can be expressed in terms of known parameters as follows:

$$b = ak_2 - \bar{V}_A + \frac{aM}{(1-k)Q} + \frac{ak_1\bar{B}M}{\bar{V}_A} \quad . \tag{52}$$

Using Equation 52, the normal set point for the adult is calculated to be

$$b = 231.52 \text{ liters/minute},$$

and for the infant,

$$b = 8.99 \text{ liters/minute}.$$

A complete list of all normal respiratory parameter values is given in Table 2.

Calculation of equilibrium minute ventilation

It is instructive to examine the effects of individual parameter changes on steady state alveolar ventilation. That is, alveolar ventilation, $\overline{V}_A$, is computed as a function of each of the respiratory parameters, assuming only one parameter varies each time, while all other parameters are held constant. Figure 8 is a plot of steady state minute ventilation for the adult as a function of the respiratory parameters k_2, M, a, k, $\overline{B}$, Q, and CO_2 inhalation level (C_1). Figure 9 is a similar plot for the infant's minute ventilation. Each curve shown in Figures 8 and 9 was arrived at by solving Equation 41 for $\overline{C}_{Tc}$ using the normal parameter values listed in Table 2. This value of $\overline{C}_{Tc}$ was then substituted into Equation 10 to arrive at $\overline{V}_A$.

Examination of Figure 8 shows that decreased cardiac output, and increases in controller slope, cardiac output shunting, CO_2 dissociation curve intercept, barometric pressure, or CO_2 inhalation level will increase the minute ventilation. These effects are all in agreement with physiological observations with one exception. Figures 8 and 9 indicate that decreased barometric pressure effects decreased minute ventilation, which is contrary to experimental observations. The failure of the model to predict increased minute ventilation with decreased barometric pressure is explained by the fact that oxygen control of respiration was not included in the model. In the normal indifidual it is the chemoreceptor action in response to low blood Po_2 that causes increased ventilation at

low barometric pressures. It is to be noted from Figures 8 and 9 that increases in the controller slope 'a' have the greatest effect on ventilation. It is also interesting to note that the degree of cardiac shunting, k, has little effect on steady state minute ventilation in the adult.

Several interesting comparisons can be made between curves from Figures 8 and 9. First, it is noted that the infant's response to CO_2 inhalations is less than that for the adult. For example, an inhalation of 8% CO_2 causes the minute ventilation to increase to a value 10 times the normal value for the adult. However, a 8% inhalation level for the infant causes an increase in ventilation to a value of only 6 times the normal level. The implication, then, is that the infant's CO_2 control system is more efficient than the adult's system, since the percentage increase in ventilation is lower for the infant. It will be shown in the next section when transient effects are considered that this implication is incorrect.

Comparisons between corresponding curves of Figures 8 and 9 for controller slope (a), cardiac output (Q), and cardiac shunting fraction (k) reveal that changes in these three parameters have greater effects in the infant than for the adult. Thus a 50% increase from normal in infant controller slope results in a 160% increase in minute ventilation; whereas the same increase in the adult causes only a 40% increase in minute ventilation. Reduction of cardiac output to one-third normal results in a 450% increase in minute ventilation for the infant, but only an 80% increase in $\overline{V}_A$ for the adult. An increase in cardiac output shunting fraction to 50%, which is twice normal for the infant, results in an

increase of 100% in minute ventilation. The same percentage increase in the adult effects only a 1% increase in ventilation.

Percentage changes in metabolic rate of CO_2 production (M) and CO_2 dissociation curve intercept (k_2) appear to effect the identical corresponding changes in ventilation in the adult and the infant. That is, a 50% increase in M from the normal value effects a 50% increase in $\overline{V}_A$ for both the adult and the infant. Similarly, a 50% increase in k_2 will cause a 100% change in $\overline{V}_A$ for both infant and adult.

The results that have been discussed in this section have all been taken from Figures 8 and 9. With the one exception of the effects of barometric pressure, the data of Figure 8 agree qualitatively with results found in Guyton (32). No such comparison of results can be made for Figure 9, since information regarding the respiratory chemostat for the infant is lacking. The implication, though, is that the infant's respiratory control system is more sensitive to parameter variations in the steady state than is the adult system.

Calculation of transient minute ventilation

The value of the respiratory model under discussion lies in its ability to predict transient phenomenon, in addition to steady state effects. Figure 10 shows the effects of three different CO_2 inhalation levels on the minute ventilation of a normal adult. The three curves of Figure 10 were obtained by simultaneous solution of Equations 33 and 34 for $C_T(t)$ and substitution of these values into the ventilation controller equation (Equation 10) to give $\overline{V}_A(t)$. Each curve has been computed assuming a step function (Figure 1) inhalation of CO_2 commencing at time zero

and terminating at 20 minutes. It has been assumed that at time zero the individual is exhibiting normal minute ventilation. The ventilation responses shown plotted in Figure 10 were obtained by solving the respiratory equations on an IBM 1130 digital computer. A numerical solution routine based upon both the Runge-Kutta method and the Milne method for the numerical solution of differential equations was utilized (33). Both methods are discussed by Hildebrand (34). The numerical solution routine employed used the Runge-Kutta method to solve for the first three solution points, following which the numerical method was switched to the Milne method. The Runge-Kutta method was used because of its self-starting nature of solution. The Milne method was utilized because less computer time is required to obtain a solution than with the Runge-Kutta method. The integration interval, h, used was 0.05 minute. It was found that changing the integration interval to 0.01 minute changed the solution values for $C_A(t)$ and $C_T(t)$ (from Equations 33 and 34) at the sixth decimal place; and hence a 'h' of 0.05 was used in order to decrease the computer solution time.

The transient changes of adult minute ventilation in response to three separate CO_2 inhalation levels of 2, 5, and 7% are shown in Figure 10. Similar curves were first obtained by Grodins et al. (13), who showed that the computed curves for $\bar{V}_A$ were in good agreement with averaged clinical results. The outstanding characteristic of the ventilation curves of Figure 10 is their asymmetry, i.e., the 'on' portion of the $\bar{V}_A$ response differs from the 'off' portion. This asymmetry is a direct consequence of the nonlinearity of the CO_2 control system. It is to be noted that 10

minutes are sufficient to allow the minute ventilation to return to the steady state level following termination of the CO_2 inhalation.

Transient changes in adult alveolar CO_2 tension are shown in Figure 20. These curves were obtained by solution of the respiratory equations for $C_A(t)$ and multiplication of these values by $\overline{B}$ to yield alveolar Pco_2. Again, these curves are similar to corresponding curves first obtained by Grodins. The salient features of these curves are the 'overshoot' by the alveolar Pco_2 for low inhalation levels and the pronounced 'undershoot' of the steady state Pco_2. Both effects have been shown to be physilogically correct. However, the amount of undershoot shown in Figure 20 exceeds that which is experimentally observed - for the higher CO_2 inhalation levels the predicted undershoot may be 50% greater than that observed. Defares (16) corrected this situation by adding another compartment, the brain compartment, to the Grodins model. The price paid for this correction, though, was increased complexity of the model.

Figure 15 and 21 show plots of minute ventilation and alveolar Pco_2 respectively, as functions of CO_2 inhalation levels. Similar curves are not available in the literature. Cross (12) has recorded the change in minute volume in response to a 2% CO_2 inhalation for an infant, and comparison of this result with the 2% curve of Figure 15 shows good agreement. Comparison of the adult minute ventilation responses (Figure 10) to those of the infant (Figure 15) shows that the 'turn on' response (i.e., $\overline{V}_A$ from 0 - 20 minutes) to be the same for both the adult and the infant. However, the 'turn off' ventilation response (commencing at t = 20 minutes) of the infant differs considerably from that of the adult. In general, the time

required for the infant's minute ventilation to return to the steady state level is approximately twice the time required by the adult for the same inhalation level. This implies that the infant's CO_2 control system is less efficient at reducing excess CO_2 concentrations than is the adult system.

Comparison of Figures 20 and 21 shows differences between adult and infant alveolar Pco_2 for the same CO_2 inhalation level. First, it appears that the 'overshoot' of the Pco_2 curves associated with the 2 and 5% C_1 levels are sustained for a longer time in the infant's response curves. Also, the time required for the alveolar Pco_2 to recover from the undershoot following the C_1 termination is greater for the infant than for the adult. Finally, the percentage by which alveolar Pco_2 undershoots the steady state level is somewhat greater for the infant than for the adult. For example, a 7% CO_2 inhalation causes the adult alveolar Pco_2 to undershoot the steady state value of 40 mm. Hg. by approximately 40%, but the same C_1 causes an infant Pco_2 undershoot of 50%.

One of the benefits derived from using a mathematical model of a physiological system is the availability of studying individual parameter effects. The effects on minute ventilation of changing certain respiratory parameters of the adult are shown in Figures 11 through 14. All curves were computed assuming a 5% inhalation of CO_2. Figure 11 show the effects on minute ventilation as a result of changes in cardiac output. Thus, e.g., decreased cardiac output will increase the time that is required for $\overline{V}_A$ to approach an equilibrium. It was assumed in the computation of the curves of Figure 11 that circulation delay time varied inversely with

cardiac output. Figure 12 shows the effect of changes in CO_2 controller slope. The controller set point was adjusted to maintain $\overline{V}_A$ at its normal steady state level. Examination of Figure 12 shows that increased controller slope results in decreased time required for $\overline{V}_A$ to reach equilibrium. Figure 13 shows the effects of increased cardiac shunting and also, an increase in the CO_2 dissociation curve intercept. Examination of Figure 13 shows that the increase of cardiac shunting to a value 10 times normal does not substantially affect the minute ventilation. However, an increase in k_2 (to a value typical of reduced blood) results in increased time required to each equilibrium. The effects of an increased circulation time to 5 times normal (without a corresponding change in cardiac output) and also, a alveolar volume decreased to one-half normal are shown in Figure 14. It is noted that neither change affects the minute ventilation greatly.

The effects on minute ventilation of individual parameter changes in the infant's CO_2 control system are shown in Figures 16 through 19. The most interesting comparisons are those between comparable adult and infant CO_2 responses. Comparison of Figures 12 and 17 shows that an increase in controller slop to twice normal for the infant results in an increase in the 'turn on' time constant of $\overline{V}_A$, but effects a decrease in the adult's 'turn on' time constant. The general trend of an increased (with respect to the adult) 'turn off' time constant for the infant minute ventilation remains when individual parameter changes are considered. Other comparisons between adult and infant transient minute ventilations show that the effects of individual parameter variations follow the same trends as

parameter variations in the steady state. For example, comparison of Figures 13 and 18 reveals that the effects of increased cardiac shunting are much greater in the infant than in the adult.

The present chapter has given the development of a mathematical model of the CO_2 control system of the adult and the infant. Solution of the mathematical model equations for various combinations of respiratory parameters was given. There remains the problem of analyzing the effects of respiratory system parameter variations, using a precise definition of parameter sensitivity. This problem will be resoved in Part II of this thesis.

PART II. ENGINEERING DYNAMIC SENSITIVITY ANALYSIS

A REVIEW OF THE LITERATURE AND MATHEMATICAL THEORY

The objectives of this thesis have been outlined in the Introduction. It was pointed out there that the two engineering analysis tools to be utilized in this study are known in the literature as dynamic sensitivity analysis and Lyapunov stability analysis (35, 36). Of the two methods, dynamic sensitivity analysis is the more recent to the literature (37). For this reason, Part II of this thesis will be a discussion of the theory and the application of engineering dynamic sensitivity analysis. Lyapunov stability analysis will be discussed in Part III.

Mathematical models of the respiratory control systems of the adult and the neonate were developed in Part II. The actual application of sensitivity analysis to respiratory control system analysis will comprise Part II of this thesis. The present chapter will review the literature of engineering sensitivity analysis and, in addition, present the necessary mathematical theory of the method.

Modern engineering analysis methods rely heavily on the establishment of mathematical models of the process under analysis (38). For example, a feedback control system - which might typically be composed of electronic amplifiers, potentiometers, electric motors, etc. - can be mathematically described by application of the laws of physics to the individual system components; taking into account, of course, the various component interconnections. However, any design based upon such a mathematical model must take into account the fact that system components are never exact, but have tolerances about the nominal value. The question of system sensitivity then arises; i.e., how much will the system performance be changed as a

result of parameter variations? (39, 40, 41, 42)

The mathematical definition of sensitivity, as the term was used to analyze electrical circuits, was given originally by Bode (43), although the reciprocal of Bode's original definition is now preferred in the literature. The classical definition of sensitivity was based on the percentage change of the overall transmission T(s)* (the transfer function relating the system output to the input) of a process with a given percentage change in a single variable element λ. The reciprocal of Bode's original definition is given by

$$S_{\lambda}^{T} = \frac{d \ln T(s)}{d \ln \lambda} \tag{53}$$

where S_{λ}^{T} denotes the sensitivity of T(s) with respect to λ. The physical significance of Equation 53 is more apparent if Equation 53 is rewritten as

$$S_{\lambda}^{T} = \frac{d\, T(s)/T(s)}{d\, \lambda/\lambda} \quad . \tag{54}$$

It is important to note that the definition given above applies only to linear, time-invariant, single-input, single-output systems. Also, Equation 53 specifies that incremental parameter variations are considered. For large parameter variations the sensitivity function may be defined as

$$S_{\lambda}^{T} = \frac{\Delta T(s)}{T(s)} \frac{\lambda}{\Delta \lambda} \tag{55}$$

where $\Delta T(s)$ is the change in T(s) due to a change $\Delta\lambda$ in λ, and λ and T(s) represent the unchanged or nominal values.

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*T(s) indicates that the transmission T is a function of the complex frequency operator 's'.

One of the difficulties encountered by the application of Equation 53 is that time information is lost; i.e., S_{λ}^{T} is a function of frequency, not time. Nevertheless, some system design techniques based upon the use of Equation 53 can be found in the literature. For example, Horowitz and Truxal (41) have utilized sensitivity analyses in the synthesis of linear, time-invariant feedback control systems. Hoffman (40) has indicated the use of sensitivity considerations in the analysis of the stability of linear feedback control systems.

Horowitz (35) extended the use of Equation 53 to the case of multivariable, linear, time-invariant systems. In this instance the system transfer function, T(s), became a matrix of transfer functions.

Cruz and Perkins (39, 42) introduced a new approach to the problem of system sensitivity to parameter variations. The problem that was of concern was the determination of feedback structures that would insure that open loop system variations due to parameter changes would be decreased. Cruz and Perkins defined a sensitivity matrix, which related the effects of parameter variations in the open loop configuration to cosed loop effects, that was the basis of their solution to the feedback structure problem. Utilization of this sensitivity matrix, together with a performance index based on the integrated square of the error, was proposed as a design procedure.

The previously referenced literature on sensitivity analysis has two common shortcomings. First, sensitivity as a function of time is not easily obtained from use of the classical sensitivity definition. Second, classical sensitivity analysis cannot be applied to nonlinear system. To overcome these difficulties, a new approach, called dynamic sensitivity

analysis, has been introduced into the engineering literature.

Dynamic sensitivity analysis involves basically an investigation of the partial derivatives of the system's dependent variables with respect to the system parameters. The pertinent partial derivatives are obtained from the solution of corresponding sensitivity differential equations. To explain the sensitivity method, it will be sufficient to use the following mathematical model of a dynamic system:

$$F(\ddot{x}, \dot{x}, x, t, q_o) = 0 \tag{56}$$

where x is the system's dependent variable, $\dot{x}$ is the first derivative with respect to time, t is time, $\ddot{x}$ is the second derivative of x with respect to time, and q_o represents the nominal values of some system parameter q. The solution of Equation 56 will be written as

$$x = x(t, q_o) \tag{57}$$

where it has been indicated that the dependent variable x is a function of time and parameter q. If parameter q_o is changed by an amount Δq, and if it is assumed that this change does not change the order of the system's equation, then the system description becomes

$$F(\ddot{x}, \dot{x}, x, t, q_o + \Delta q) = 0 \tag{58}$$

The solution to the perturbated system, Equation 58, can be expressed as

$$x = x(t, q_o + \Delta q) \ . \tag{59}$$

It then follows that an indication of the effect that a change in parameter q has on the system (Equation 56) can be expressed by the fraction

$$\frac{x(t, q_o + \Delta q) - x(t, q_o)}{\Delta q} \tag{60}$$

If Equation 60 has a limiting value as Δq approaches zero, then it follows that

$$\lim_{\Delta q \to 0} \frac{x(t, q_o + \Delta q) - x(t, q_o)}{\Delta q} = \frac{\partial x(t, q_o)}{\partial q} = u(t, q_o). \qquad (61)$$

The function $u(t, q_o)$ in Equation 61 is called the 'sensitivity coefficient' of the dynamic system by Tomovic (7, 37), and it plays a significant role in dynamic system analysis.

Equation 61 provides the basic definition of the sensitivity coefficients of a dynamic system. Tomovic (7) considers three separate types of sensitivity coefficients: static sensitivity coefficients, dynamic sensitivity coefficients, and parametric sensitivity coefficients. If the dynamic system is in a steady state, that is, is time invariant, then the sensitivity coefficient becomes a function only of the parameter q_o, and is denoted by $u_s = u(q_o)$. For example, electrical circuits in a steady state are described by ordinary, and not by differential equations. For non-steady state conditions, Equation 61 applies, which Tomovic calls the dynamic sensitivity coefficient $u_t(t, q_o)$. It is apparent that the dynamic sensitivity coefficient contains both time and parameter information. The fact that the sensitivity coefficient u_t depends also on the value of the parameter q_o represents an additional difficulty in the sensitivity analysis of dynamic systems. The inherent assumption in the computation of u_t is that the basic parameter values of a given dynamic system have been fixed, and parameter tolerances near this nominal value are of concern. At times this assumption is not valid, because of the presence of parameters that may change within quite broad limits. The synthesis of adaptive control system provides such an example. In addition, the sensitivity considerations may require the consideration of several system parameters that may have quite large tolerances. This

situation of having several parameters that can have quite large tolerances requires the use of parameter sensitivity coefficients, $u(t, q_o, q_1, q_2, \ldots q_m) = u_q$. The dynamic sensitivity coefficient u_t is currently being utilized in the literature as an aid in the synthesis and analysis of dynamic systems. The use of parametric sensitivity coefficients u_q has not been wide spread, due to lack of acceptable methods for computation of u_q. This thesis will utilize only the dynamic sensitivity coefficient u_t in the sensitivity analysis of the respiratory control system.

There are two possible methods of obtaining the dynamic sensitivity coefficients for a given system. First, it is possible to measure the sensitivity coefficients, u_t, using the actual dynamic system, or a physical model of it. Measurement techniques to achieve this end have been given by Tomovic (7). The alternative approach is based on the use of a mathematical model of the dynamic system under consideration. The dynamic sensitivity coefficients are then obtained from the model equations. Assuming that the dynamic system under consideration can be expressed by Equation 56, then the definition of the dynamic sensitivity coefficients, Equation 61, requires taking the partial derivatives of all dependent variables with respect to a parameter q_o. Thus, it follows from Equation 56 that

$$\frac{\partial F}{\partial \ddot{x}} \frac{\partial \ddot{x}}{\partial q_o} + \frac{\partial F}{\partial \dot{x}} \frac{\partial \dot{x}}{\partial q_o} + \frac{\partial F}{\partial x} \frac{\partial x}{\partial q_o} + \frac{\partial F}{\partial q_o} = 0. \tag{62}$$

It is possible to interchange the order of differentiation indicated in two of the terms of Equation 61, and express them as follows:

$$\frac{\partial \ddot{x}}{\partial q_o} = \frac{\partial^2}{\partial t^2} \frac{\partial x}{\partial q_o} \qquad \text{and} \quad \frac{\partial \dot{x}}{\partial q_o} = \frac{\partial}{\partial t} \frac{\partial x}{\partial q_o} \quad . \tag{63}$$

Consideration of Equations 63 and 61 gives then

$$\frac{\partial \ddot{x}}{\partial q_o} = \ddot{u}(t, q_o) \qquad \text{and} \qquad \frac{\partial \dot{x}}{\partial q_o} = \dot{u}(t, q_o) \ . \tag{64}$$

Substitution of Equation 64 into Equation 62 yields the 'sensitivity differential equation' in u_t:

$$\frac{\partial F}{\partial \ddot{x}} \ddot{u} + \frac{\partial F}{\partial \dot{x}} \dot{u} + \frac{\partial F}{\partial x} u = - \frac{F}{q_o} \ . \tag{65}$$

The solution of Equation 65 requires the solution of the model equations (Equation 56), since these solutions for the dependent variables of the model are coupled into the sensitivity differential equation as driving functions. In practice, the model equations and the sensitivity equations are solved as a simultaneous set of differential equations. As an example of the method, consider a dynamic system described by the inhomogeneous linear equation

$$\ddot{x} + \mu \dot{x} + \lambda x = f(t) \tag{66}$$

where μ and λ are constants of the system. The sensitivity differential equation for the parameter μ can be established as

$$\ddot{u} + \mu \dot{u} + \lambda u = - \dot{x} \tag{67}$$

where the following definition has been made:

$$u(t,\mu) = \frac{\partial x(t,\mu)}{\partial \mu} \ .$$

The sensitivity differential equation for the parameter λ can be established as being

$$\ddot{v} + \mu \dot{v} + \lambda v = - x \tag{68}$$

where the following definition holds:

$$v = \frac{\partial x(t,\lambda)}{\partial \lambda}$$

Comparison of Equations 67 and 68 shows differences only in the right-hand side of the equations, i.e., the driving function. A solution of a sensitivity equation requires then that the solution of the model equations for the dependent variables appear as driving functions in the sensitivity equations. It is also apparent that the model equations (e.g., Equation 66) and the sensitivity equations will have the same characteristic equation if the model equations are linear in nature.

A solution of the sensitivity differential equations requires the establishment of appropriate initial conditions. The initial conditions for the sensitivity equations are established by using the basic definition (Equation 61) of the sensitivity coefficients.

The previous development of the sensitivity coefficients is based on mathematical foundations established by Miller and Murray (45), who investigated the effects of analog computer parameter errors on the computer solutions of differential equations. However, the use of sensitivity coefficients as an analysis tool in dynamic systems is due primarily to Meissinger (38). Tomovic (7, 37) has made several important contributions to the application of sensitivity coefficients to the analysis of dynamic systems, primarily in the application of sensitivity coefficients to nonlinear feedback control systems. Chang (36) reports the use of sensitivity coefficients to determine the amount of overshoot and damping of linear control systems as a function of component parameter inaccuracies.

The discussion has indicated the theory of dynamic sensitivity analysis as it has been developed in the literature. Attention has been

focused on the sensitivity coefficients and the obtaining of these coefficients from the sensitivity differential equation. The discussion utilized a model of a second order system (Equation 56), but the conclusions reached are valid for any order system.

It should be emphasized that the discussion of this chapter has not been restricted to only linear systems; but applies to both linear and nonlinear systems. In addition, both constant coefficients and time-varying coefficients are allowed in the system describing equations. The only condition inherent in the development of the sensitivity equations (Equation 65, for example) is that the solutions of the model differential equations must depend analytically on the model parameters.

SOME APPLICATIONS OF DYNAMIC SENSITIVITY ANALYSIS

The preceding discussion reviewed the literature of dynamic sensitivity analysis and presented the mathematical theory of the method. It will be the purpose of the present discussion to outline and illustrate some of the uses of the dynamic sensitivity coefficients in the analysis of dynamic systems.

An important application of the dynamic sensitivity coefficients is the analysis of the effects on system performace of errors in component parameters. That is, determination of the influence of parameter tolerances on the behavior of the dynamic system can be based on a knowledge of the sensitivity coefficients. The mathematical formulation of the problem can be given as follows. Assume that the solution of the system's describing equation, $x\ (t,\ q_o)$, is known where this solution has been obtained assuming nominal or 'design center' parameter values. An error in one of the system parameters will effect a different system solution, $x(t,\ q_o + \Delta q)$. Assuming that the solutions to the system's equations depend analytically on the parameters, and that the difference Δx is small, then the function $x(t,\ q_o + \Delta q)$ can be expanded in a Taylor's series as follows:

$$x(tq,_o + \Delta q) = x(t,q_o) + \frac{\partial x}{\partial q_o} \Delta q + \frac{1}{2!} \frac{\partial^2 x}{\partial q_o^2} (\Delta q)^2 + \cdots \qquad (69)$$

If it is assumed that the parameter tolerances are small, then Equation 69 can be terminated at the linear term; that is

$$x(t,q_o + \Delta q) = x(t,q_o) + \frac{\partial x}{\partial q_o} \Delta q \qquad (70)$$

The error due to neglecting higher order terms in Equation 69 is discussed by Tomovic (7) and can be determined analytically.

Equation 70 places in evidence the use of dynamic sensitivity coefficients in the error analysis of dynamic systems, since the term $\partial x/\partial q_o$ is by definition the dynamic sensitivity coefficient.

Two points are raised from consideration of Equation 70. The first point relates to the difference $\Delta x = x(t, q_o + \Delta q) - x(t, q_o)$. Since the solution of the system equation plus the sensitivity differential equations generally requires a computer solution, it would seem reasonable to calculate Δx directly. That is, solve for both $x(t, q_o)$ and $x(t, q_o + \Delta q)$ and subtract the two solutions to obtain Δx. However, for small values of Δq the difference Δx will also be small, and the machine results unreliable. But by using the sensitivity coefficients, Δx can be calculated using the full scale of the machine.

The second point relating to the use of Equation 70 relates to the effect of having several parameters that have tolerances. Equation 70 implies a linearization process, and as such, the principle of superposition is valid. By applying this principle, the simultaneous influence of several parameters on the performance of the dynamic system can be calculated by the following:

$$x(t,\Delta q_1,\cdots,\Delta q_m) = x(t, q_1,\cdots,q_m) \sum_{i=1}^{m} \frac{\partial x}{\partial q_i} (\Delta q_i) , \qquad (71)$$

which amounts to computing a 'worst case' design. If it is know that the parameter errors follow a Gaussian distribution, then the average values and standard deviations; a_1 and d_1, respectively, will be known usually.

Due to the linear nature of Equation 70, the average value a_x and the standard deviation d_x of the solutions of the dynamic system can be obtained by superposition as being as follows:

$$a_k = k_a \sum_{i=1}^{m} u(t,q_o)a_i \qquad \text{and} \qquad d_x^2 = k_d \sum_{i=1}^{m} u(t,q_o)^2 d_i$$

where k_a and k_d are scale factors.

As an example of the use of sensitivity coefficients in the error analysis of a dynamic system, the error analysis of a simple RC circuit, shown in Figure 22, will be illustrated. It is desired to ascertain the effects of resistance and capacitance errors on the step function response of the circuit. That is, how do comparable errors in R and C affect the system response $e_o(t)$, and which component exerts the greater influence? The system response, $e_o(t)$, can be obtained from the system equation, which is given by

$$RC\,\dot{e}_o(t) + e_o(t) = e_1(t) \qquad e_o(0) = 0. \tag{72}$$

Assuming an unit voltage step function input, $e_1(t)$, the output voltage can be shown to be as follows:

$$e_o(t) = 1 - \varepsilon^{-t/RC} \quad . \tag{73}$$

The sensitivity differential equation for the resistor R can be established from Equation 72 by taking the partial derivatives with respect to R of Equation 72:

$$\frac{\partial}{\partial R}(RC\,\dot{e}_o) + \frac{\partial}{\partial R} e_o = \frac{\partial}{\partial R} e_i(t) \tag{74}$$

from which the resistance sensitivity equation for R follows:

$$RC\,\dot{u}(t) + u(t) = -C\,\dot{e}_o(t) \qquad , \qquad u(0) = 0 \tag{75}$$

where the following definition has been made:

$$u(t,R) = \frac{\partial\, e_o(t,R)}{\partial R}$$

Solution of Equation 75, which requires using the derivative of Equation 73, results in the sensitivity coefficient for R:

$$u(t,\,R) = -\frac{t}{R^2C}\,\varepsilon^{-\frac{t}{RC}} \tag{76}$$

In order to make a meaningful comparison of results, it will be arbitrarily assumed that 1% tolerances in R and C are of interest. Thus, the error Δe_o due to a 1% error in R can be obtained by using Equations 76 and 70, from which it follows that the output error is

$$\Delta e_o(t,R) = -\,0.01\;t\;\varepsilon^{-t/RC}/RC\ . \tag{77}$$

The dynamic sensitivity coefficient with respect to the capacitor can be established in a manner similar to that for the resistor. The sensitivity coefficient for the capacitor is then given by

$$\nu(t.C) = -\,t\;\varepsilon^{-t/RC}/RC^2 \quad , \tag{78}$$

and a 1% error in C will effect an output error $\Delta e_o(t,\,C)$ of

$$\Delta e_o(t,\,C) = -\,0.01\;t\;\varepsilon^{-t/RC}/RC \tag{79}$$

Comparison of Equations 77 and 79 shows that comparable errors in R and C will effect the same error in the output voltage.

Another area of dynamic systems analysis in which sensitivity coefficients are utilized involves the question of system stability (7, 38).

Stability will be considered in the Lyapunov sense (33). That is, if the system is perturbated to a point away from an equilibrium state, does the system return to the equilibrium state? Thus, three possibilities exist: the system returns to the original equilibrium state (possibly in a damped oscillatory manner); the system establishes a new equilibrium state distinct from the original equilibrium; and third, the system diverges in an ever increasing manner. A system that returns to the original equilibrium state is termed asymptotically stable. A system that achieves a new equilibrium (or exhibits persistent oscillations about the original equilibrium point) is termed conditionally stable. A system that diverges is called an unstable system. An inherent assumption is that the system's motion in response to a perturbation is observed over infinite time. Obviously when computer investigations of stability are undertaken by solving the system equations directly, the requirement of an infinite time observation has to be violated. For those cases in which stability (or instability) is evident, the problem of a finite observation of the system's motion is of no consequence. However, situations arise in which the damping time constant of the system's oscillatory motion is quite large, and as a consequence it is difficult to distinguish this case from the case of pure oscillatory, that is, no damping, motion. The case of slowly diverging oscillations in an unstable system are also difficult to distinguish when compared to oscillations of constant amplitude. In these instances the use of sensitivity equations can serve to clarify the situation. For example, consider the linear, $n^{th.}$ order differential equation with constant coefficients given by

$$\sum_{i=0}^{n} a_i p^i x(t) = f(t) \ , \ p^i x(o) = C_i \ , \ i=0,1,\cdots,n-1 \tag{80}$$

where the differential operator $p^i = d^i/dt^i$ has been utilized. The solution of Equation 80 can be written as

$$s(t) = \sum_{i=1}^{n} A_i x_i(t) + X(t) \tag{81}$$

where the homogeneous solution of Equation 80 has been denoted by $X(t)$, and the solutions $x_i(t)$ will have the form

$$x_i(t) = \varepsilon^{(r+js)t} \tag{82}$$

where r and s are the real and imaginary partos of the roots of the characteristic equation of Equation 80. The sensitivity equation for an arbitrary parameter a_k can be established as being

$$\sum_{i=0}^{n} a_i p^i u(t) = -p^k x(t) \ , \ \frac{\partial x}{\partial a_k} = u(t) \tag{83}$$

which reduces to the following, using Equation 82:

$$\sum_{i=0}^{n} a_i p^i u(t) = -p^k [\sum_{i=1}^{n} A_i x_i(t) + X(t)] \ . \tag{84}$$

Equation 84 can be utilized to examine the stability of linear systems with constant coefficients. It is to be noted that the homogeneous parts of Equations 80 and 84 have the same characteristic equation. At the same time, the solutions of the homogeneous part of Equation 80 are introduced, via the differential operator p^k, as independent terms into the sensitivity equation, Equation 84. As a result, if some roots of Equation 80 have real parts equal to zero, indicating that undamped oscillations will appear in the solution of Equation 80; then the sensitivity equation will exhibit

oscillations of ever increasing amplitudes. Thus, in those cases for which decisions must be made between stable systems having oscillations possessing long time constants and on the other hand, conditionally stable systems having persistent oscillations; the sensitivity equations can be used to provide the differentiation. As an example of this approach, consider the second order linear differential euqation given by

$$\ddot{x}(t) + a\,\dot{x}(t) + b\,x(t) = 0 \qquad \dot{x}(0) = 1,\ x(0) = 0 \tag{85}$$

where 'a' and 'b' are constants. The solution for x(t) can be written for the underdamped case as

$$x(t) = \frac{\varepsilon^{-\alpha t}}{\beta} \sin\beta t \tag{86}$$

where the constants are defined by

$$\alpha = a/2 \qquad \text{and} \qquad \alpha^2 + \beta^2 = b.$$

The sensitivity equation for parameter 'b' can be shown to be

$$\ddot{u}(t) + a\,\dot{u}(t) + b\,u(t) = -\,x(t) \qquad \dot{u}(0) = u(0) = 0 \tag{87}$$

where the sensitivity coefficient is given by

$$u(t, b) = \frac{\partial\, x\,(t, b)}{\partial b} \quad .$$

If Equation 86 is substituted into Equation 87 and a solution effected, the result is given by

$$u(t, b) = -\,\frac{\varepsilon^{-\alpha t}}{2\,\beta^3}\,(\sin\beta t - \beta t\,\cos\beta t). \tag{88}$$

Examination of Equation 88 shows that when the system's oscillatory motion (Equation 86) is damped (i.e., $\alpha > 0$), the sensitivity coefficient u(t) is also damped. But when the system motion has zero damping ($\alpha = 0$), the sensitivity coefficient u(t) will exhibit an increasing amplitude with time.

Thus the sensitivity equation can be utilized to differentiate between stable systems having large time constant damped oscillations and conditionally stable systems having zero damping.

The previous discussion has indicated the usefulness of a sensitivity analysis in the investigation of linear system stability. It was shown that in certain cases it is possible to draw conclusions about the character of the original system's stability from the solutions of the sensitivity equation considered in a finite, not infinite, time interval. In principle the use of sensitivity coefficients in the stability analysis of nonlinear systems presents the same problem as with linear systems. Here again it is desirable to study the connection between the system's behavior and its sensitivity equations and then establish whether or not in a finite time interval it is easier to determine the stability of the original system on the basis of sensitivity coefficients. At present the relations desired are not available in the literature. Nevertheless, it is possible to demonstrate through use of an example that the sensitivity equations can indicate stability trends in nonlinear systems.

It would seem reasonable that as instability is approached in a dynamic system, the sensitivity coefficients should increase in magnitude, that is, the system should become more sensitive to parameter perturbations as instability is approached. This point was explored for the control system shown in Figure 23. The control system has been drawn using state variable notation (33). By proper selection of feedback element $g(x_1)$ the system can be linear or nonlinear in nature. Both types of systems will be illustrated in order that comparisons can be made. Two points of interest

will be the following: changes in which system parameter affects the system output most, and do the sensitivity coefficients indicate any trends in system stability?

The system equations for the control system of Figure 23 are as follows:

$$\dot{x}_1(t) = x_2(t)$$
$$\dot{x}_2(t) = - g(x_1) - a\, x_2(t)$$

and the initial conditions will be chosen to be

$$x_1(0) = 1 \qquad \text{and} \qquad x_2(0) = 0.$$

If the feedback element is chosen to be $g(x_1)$ b x_1, then the system becomes a linear system having constant coefficients, and the linear system equations are given by

$$\dot{x}_1(t) = x_2(t)$$
$$\dot{x}_2(t) = - b\, x_1(t) - a\, x_2(t) \; . \tag{90}$$

This set of equations can be reduced to a single second order differential equation:

$$\ddot{v}(t) + a\, \dot{v}(t) + b\, v(t) = 0. \tag{91}$$

A necessary and sufficient condition that Equation 91 be asymptotically stable is that both the parameters 'a' and 'b' be greater than zero (47). Thus, as 'a' and 'b' approach zero, the system will approach instability. This condition can be explored via the sensitivity coefficients. The sensitivity coefficients can be obtained from the following sensitivity differential equations:

$$
\begin{aligned}
\dot{x}_3(t) &= x_4(t) \\
\dot{x}_4(t) &= -\,b\,x_3(t) - a\,x_4^{(t)} - x_2(t) \\
\dot{x}_5(t) &= x_6(t) \\
\dot{x}_6(t) &= -\,b\,x_5(t) - a\,x_6(t) - x_1(t) \\
x_3(0) &= x_4(0) = x_5(0) = x_6(0) = 0
\end{aligned}
\qquad (92)
$$

where the sensitivity coefficients are defined by the following:

$$x_3 = \frac{\partial x_1}{\partial a} \quad , \quad x_4 = \frac{\partial x_2}{\partial a} \quad , \quad x_5 = \frac{\partial x_1}{\partial b} \quad , \quad x_6 = \frac{\partial x_2}{\partial b} \quad .$$

Equations 90 and 92 were solved simultaneously on an IBM 1130 digital computer for two separate sets of values for the system parameters: a = 2, b = 4 was one set, and a = .2, b = .4 was the other set. The sensitivity curves for the system's output (x_1), assuming 1% variations in 'a' and 'b' are shown in Figures 24 and 25. Equal percentage variations in 'a' and 'b' were chosen in order that meaningful comparisons could be made. The symbol $S_{a=2}^{x_1}$ denotes, for example, the sensitivity of the system's output (computed with a = 2 and b = 4) with respect to a 1% variation in parameter 'a' about the value 2. Examination of Figures 24 and 25 shows that for both sets of parameter values, parameter 'b' will have a greater effect on the system output than will parameter 'a'. And an error in 'b' had a greater effect, relative to an error in 'a', as the system damping was decreased. In addition, Figure 24 reveals that as 'a' and 'b' were decreased toward zero, the system moved in the direction of instability. That is, the sensitivity coefficients of Figure 25 are greater in magnitude than are those of Figure 24.

If the feedback element of Figure 23 is chosen to be $g(x_1) = b\,x_1^3$, the system becomes nonlinear, and the system equations are then

$$\dot{x}_1(t) = x_2(t)$$
$$\dot{x}_2(t) = - b\, x_1^3 - a\, x_2(t) \qquad (93)$$
$$x_1(0) = 1 \quad \text{and} \quad x_2(0) = 0$$

Derusso et al. (33) have shown the sufficient conditions to insure asymptotic stability for this particular nonlinear system to be

$$\begin{aligned} &(1)\ a > 0 \\ &(2)\ g(u)/u > 0\ ,\ u \neq 0\ . \end{aligned} \qquad (94)$$

Since $g(u) = b\, u^3$, the sufficient conditions for asymptotic stability reduce to:

$$a > 0 \qquad \text{and} \qquad b > 0\ .$$

The sensitivity equations for the nonlinear system can be shown to be as follows:

$$\dot{x}_3(t) = x_4(t)$$
$$\dot{x}_4(t) = - 3\, b\, x_1^2(t) x_3(t) - a\, x_4(t) - x_2(t)$$
$$\dot{x}_5(t) = x_6(t) \qquad (95)$$
$$\dot{x}_6(t) = - 3\, b\, x_1^2(t) x_5(t) - x_1^3(t) - a\, x_6(7)$$
$$x_3(0) = x_4(0) = x_5(0) = x_6(t) = 0$$

where the sensitivity coefficients are defined by

$$x_3 = \frac{\partial x_1}{\partial a}\ ,\quad x_4 = \frac{\partial x_2}{\partial a}\ ,\quad x_5 = \frac{\partial x_1}{\partial b}\ ,\quad x_6 = \frac{\partial x_2}{\partial b}\ .$$

As with the linear system, two separate sets of parameter values were investigated; a = 2, b = 4 and a = 0.2, b = 0.4. The sensitivity coefficients for the nonlinear system, assuming 1% variations again, are shown in Figures 26 and 27. Examination of Figures 26 and 27 shows that variations in parameter 'a' exert a greater effect on the system's output than do 'b'

variations. This effect is opposite to that for the linear system previously discussed. It is also apparent that the nonlinear system is overdamped for the parameter values a = 2 and b = 4 from examination of Figure 26, which contrasts with the underdamped linear system for the same set of parameter values. Figure 27 reveals that the system's motion has been moved in the direction of instability with decreased 'a' and 'b' values, since the sensitivity coefficients became greater in magnitude. It is apparent, then, that use of the sensitivity coefficients can shed insight into both stability and error analyses of certain types of nonlinear systems.

The present chapter has discussed some applications of the dynamic sensitivity coefficients in the analysis of dynamic systems. Other applications, such as in the synthesis of optimum control systems, can be found in the literature previously cited in this chapter.

PART III. A DYNAMIC SENSITIVITY ANALYSIS OF THE CO_2 RESPIRATORY CONTROL SYSTEM

THE DEVELOPMENT OF THE RESPIRATORY SENSITIVITY EQUATIONS

The basic objective of the present study is to provide a sensitivity analysis of the human CO_2 respiratory control system. A full appreciation of the regulator effectiveness of this system is not possible without an appreciation of the effects that changes in the component parameters will have on the system. Part II of this thesis has given the theory of dynamic sensitivity analysis. The present discussion will give the derivation of the appropriate sensitivity equations of the respiratory control system.

It is possible to derive sensitivity equations for each of the parameters of the respiratory control system. However, sensitivity equations will be derived only for those parameters that seem most subject to change under abnormal physiological states. To this end, sensitivity equations for nine of the respiratory parameters will be developed. These parameters are as follows: alveolar volume (V_A), cardiac output (Q), cardiac output shunting (k), circulation time delay (T), CO_2 controller slope (a), CO_2 controller set point (b), CO_2 dissociation curve intercept (k_2), metabolic rate of CO_2 production (M), and barometric pressure ($\bar{B}$). It is thus assumed that the tissue volume (V_T) and CO_2 dissociation curve slope (k_1) remain constant at their normal physiological values.

Sensitivity equations for both the open loop and the closed loop respiratory control systems will be derived.

The sensitivity equations for the closed loop respiratory system are best derived from Equations 31 and 32, which are repeated below:

$$V_A \dot{C}_A + (1 - k)QT \dot{C}_T = [b - (1 - k)Qk_1\bar{B}]C_A + [aC_1 + (1 - k)Q]C_T - aC_AC_T - bC_1 - (1 - k)Qk_2 \qquad (31)$$

$$(1 - k)Qk_1\bar{B}T\,\dot{C}_A + (V_T + 2kQT)\dot{C}_T = (1 - k)Qk_1\bar{B}\,C_A - (1 - k)Q\,C_T + (1 - k)Qk_2 + M \qquad (32)$$

The derivation of the sensitivity equations for the cardiac output will be illustrated first. The sensitivity equations for the remaining parameters follow the same derivation procedures.

Closed Loop Equations

Cardiac output sensitivity equations

The cardiac output sensitivity equations are derived from Equations 31 and 32 by taking the partial derivatives with respect to Q of each term. This result is

$$\frac{\partial}{\partial Q}(V_A\dot{C}_A) + \frac{\partial}{\partial Q}[(1-k)QT\,\dot{C}_T] = \frac{\partial}{\partial Q}\{[b-(1-k)Qk_1\bar{B}]C_A\} + \frac{\partial}{\partial Q}\{[a\,C_I + (1-k)Q]C_T\} - \frac{\partial}{\partial Q}(aC_AC_T) - \frac{\partial}{\partial Q}(bC_I) - \frac{\partial}{\partial Q}[(1-k)Qk_2] \qquad (96)$$

$$\frac{\partial}{\partial Q}[(1-k)Qk_1\bar{B}\,T\,\dot{C}_A] + \frac{\partial}{\partial Q}[(V_T + 2kQT)\dot{C}_T] = \frac{\partial}{\partial Q}[(1-k)Qk_1\bar{B}\,C_A] - \frac{\partial}{\partial Q}[(1-k)Q\,C_T] + \frac{\partial}{\partial Q}[(1-k)Q\,k_2] + \frac{\partial}{\partial Q}(M) \qquad (97)$$

If it is assumed that each parameter is independent of the other parameters, then Equations 96 and 97 reduce to the following

$$V_A\frac{\partial\dot{C}_A}{\partial Q} + (1-k)QT\frac{\partial\dot{C}_T}{\partial Q} = [b-(1-k)Qk_1\bar{B}]\frac{\partial C_A}{\partial Q} - (1-k)k_1\,\bar{B}\,C_A + a\,C_I\frac{\partial C_T}{\partial Q} + (1-k)Q\frac{\partial C_T}{\partial Q} + (1-k)C_T - aC_T\frac{\partial C_A}{\partial Q} - aC_A\frac{\partial C_T}{\partial Q} - (1-k)k_2 - (1-k)T\,\dot{C}_T \qquad (98)$$

$$(1-k)Qk_1\bar{B}\,T\frac{\partial \dot{C}_A}{\partial Q} + (V_T + 2kQT)\frac{\partial \dot{C}_T}{\partial Q} = (1-k)Qk_1\bar{B}\frac{\partial C_A}{\partial Q} + (1-k)k_1\bar{B}\,C_A - (1-k)Q\frac{\partial C_T}{\partial Q} \tag{99}$$

$$- (1-k)C_T + (1-k)k_2 - (1-k)k_1\bar{B}T\frac{\partial \dot{C}_A}{\partial Q} - 2k\,T\frac{\partial \dot{C}_T}{\partial Q}$$

Let the following definitions of the sensitivity coefficients be made

$$u_Q(t,Q) = \frac{\partial C_A(t,Q)}{\partial Q} \qquad \text{and} \qquad v_Q(t,Q) = \frac{\partial C_T(t,Q)}{\partial Q} \tag{100}$$

Using these definitions, together with the properties of the sensitivity coefficients (Equation 63), the cardiac output sensitivity differential equations follow from Equations 98 and 99:

$$V_A\dot{u}_Q + (1-k)QT\dot{v}_Q = [b-k_1\bar{B}(1-k)Q]u_Q - aC_Tu_Q + (1-k)Qv_Q + aC_1v_Q - aC_Av_Q \tag{101}$$

$$- (1-k)k_1\bar{B}C_A - aC_Av_Q - (1-k)T\dot{C}_T + (1-k)C_T - (1-k)k_2$$

$$(1-k)k_1\bar{B}TQ\dot{u}_Q + (V_T + 2kQT)\dot{v}_Q = (1-k)Qk_1\bar{B}u_Q - (1-k)Qv_Q - (1-k)C_T - 2kT\dot{C}_T \tag{102}$$

$$- (1-k)k_1\bar{B}T\dot{C}_A + (1-k)k_1\bar{B}C_A + (1-k)k_2$$

It is desirable to solve Equations 101 and 102 explicitely for u_Q and v_Q. Using Cramer's rule, this result is

$$\dot{u}_Q(t) = a_{11}u_Q + a_{12}v_Q - a_{13}C_Tu_Q - a_{13}C_Av_Q + a_{13}C_Iv_Q - d_{11}C_A + d_{12}C_T \tag{103}$$

$$+ d_{13}\dot{C}_A - d_{14}\dot{C}_T - d_{15}$$

$$\dot{v}_Q(t) = a_{21}u_Q - a_{22}v_Q + a_{23}C_Tu_Q + a_{23}C_Av_Q - a_{23}C_Iv_Q + d_{21}C_A - d_{22}C_T \tag{104}$$

$$-d_{23}\dot{C}_A + d_{24}\dot{C}_T + d_{25}$$

where the 'a' coefficients are those given in Chapter 5 for the model

Equations 33 and 34. The 'd' coefficients are defined as follows:

$$d_{11} = (1-k)k_1\bar{B}[V_T + (1+k)QT]/D$$

$$d_{12} = (1-k)[V_T + (1+k)QT]/D$$

$$d_{13} = k_1\bar{B}(1-k)^2QT^2/D$$

$$d_{14} = (1-k)V_TT/D$$

$$d_{15} = (1-k)k_2[V_T + (1+k)QT]/D$$

$$d_{21} = (1-k)k_1\bar{B}[V_A + (1-k)Qk_1\bar{B}T]/D$$

$$d_{22} = (1-k)[V_A + (1-k)Qk_1\bar{B}T]/D$$

$$d_{23} = (1-k)k_1\bar{B}TV_A/D$$

$$d_{24} = [k_1\bar{B}(1-k)^2QT^2 - 2kTV_A]/D$$

$$d_{25} = (1-k)k_2[V_A + (1-k)Qk_1\bar{B}T]/D \ .$$

Equations 103 and 104 represent the sensitivity differential equations for the cardiac output. It is to be noted that these equations are linear differential equations (with time varying coefficients), whereas the respiratory equations are nonlinear. Also, it is to be noted that both the system's dependent variables (C_A and C_T) and these variables' time derivatives appear in the sensitivity equations. To effect solutions of the sensitivity equations, initial conditions have to first be established. It will be assumed for all the results to be reported in this thesis, that the initial conditions are identical to the steady state conditions with zero inhalation of CO_2. Thus $C_T(0)$ and $C_A(0)$ are found from Equations 41 and 42 assuming that $C_1 = 0$, and using those values listed in Table 1 for normal parameter values. The initial conditions for $u_Q(0)$ and $v_Q(0)$ can be obtained from Equations 41 and 42 (with $C_1 = 0$) using the basic definition of the sensitivity coefficients. Equations 41 and 42 are listed

below (with $C_1 = 0$):

$$\bar{C}_T = \frac{G + \sqrt{G^2 - H}}{J} \tag{41a}$$

$$\bar{C}_A = \frac{\bar{C}_T}{k_1 \bar{B}} - \frac{M + (1-k)Qk_2}{(1-k)Qk_1\bar{B})} \tag{42a}$$

where $G = aM + (1-k)Q(ak_2 + b)$

$H = 4a(1-k)Q\{bM + (1-k)Q[bk_2 - k_1\bar{B}M]\}$

$J = 2a(1-k)Q$.

The initial conditions for $u_Q(0)$ and $v_Q(0)$ are found from Equations 41a and 42a as follows:

$$v_Q(0) = \frac{\partial \bar{C}_T}{\partial Q} = \frac{J \frac{\partial}{\partial Q}[G + \sqrt{G^2 - H}] - [G - \sqrt{G^2 - H}]\frac{\partial J}{\partial Q}}{J^2} \tag{104a}$$

$$u_Q(0) = \frac{\partial \bar{C}_A}{\partial Q} = \frac{1}{k_1\bar{B}}\frac{\partial \bar{C}_T}{\partial Q} - \frac{Q(1-k)k_2 - [M + (1-k)Qk_2]}{(1-k)Q^2 k_1\bar{B}} \tag{105}$$

Now it is true that

$$\frac{\partial}{\partial Q}[G + \sqrt{G^2 - H}] = \frac{\partial G}{\partial Q} + \frac{1}{2}[G^2 - H]^{-\frac{1}{2}}[2G\frac{\partial G}{\partial Q} - \frac{\partial H}{\partial Q}] \tag{106}$$

and that

$$\frac{\partial G}{\partial Q} = (1-k)(ak_2 + b) \tag{107}$$

$$\frac{\partial H}{\partial Q} = 4a(1-k)bM + 8a(1-k)^2Q(bk_2 - k_1\bar{B}M) \tag{108}$$

$$\frac{\partial J}{\partial Q} = 2a(1-k) . \tag{109}$$

Substitution of normal respiratory parameter values from Table 1 into Equations 104a-109 provides the desired initial values for $v_Q(0)$ and $u_Q(0)$.

Simultaneous solution of the respiratory equations, Equations 33 and 34, and the sensitivity equations, Equations 103 and 104, using the initial values $\bar{C}_A$, $\bar{C}_T$, $u_Q(0)$, and $v_Q(0)$, is required in order to obtain $u_Q(t)$ and $v_Q(t)$. In order to compare sensitivity results for various parameter combinations, an error analysis approach will be taken. Specifically, all sensitivity results will be reported in terms of the error effected by a one percent increase in the parameter under consideration at a particular point in parametric space. In addition, since the basic function of the respiratory control system is to regulate the tissue CO_2 concentration at a constant level, then the sensitivity of $C_T(t)$ will be the variable of concern. Thus, for example, the sensitivity results for $C_T(t)$ with respect to Q at the normal value of Q(Q = 6 lit/min) will be reported as follows:

$$S_Q^{C_T} = 6 = \Delta C_{TQ} = (.01)(6)v_Q(t) \ . \qquad (110)$$

The remaining sensitivity equations can be established in a like manner to that of the cardiac output sensitivity equations.

Alveolar volume sensitivity equations

The sensitivity differential equations for the alveolar volume can be shown to be as follows:

$$\dot{u}_{V_A}(t) = a_{11}u_{V_A} + a_{12}v_{V_A} - a_{13}C_T u_{V_A} - a_{13}C_A v_{V_A} + a_{13}C_1 v_{V_A} - c_{11}\dot{C}_A \qquad (111)$$

$$\dot{v}_{V_A}(t) = a_{21}u_{V_A} - a_{22}v_{V_A} + a_{23}C_T u_{V_A} + a_{23}C_A v_{V_A} - a_{23}C_1 v_{V_A} + c_{21}\dot{C}_A \qquad (112)$$

where $c_{11} = (V_T + 2kQT)/D$

$c_{21} = (1-k)Qk_1\bar{B}T/D$.

The initial conditions are

$$u_{V_A}(0) = 0 \qquad \text{and} \qquad v_{V_A}(0) = 0,$$

since $\bar{C}_T$ and $\bar{C}_A$ are independent of V_A.

Cardiac output shunting sensitivity equations

The sensitivity differential equations for the cardiac output shunting are

$$\dot{u}_k(t) = a_{11}u_k + a_{12}v_k - a_{13}C_Tu_k - a_{13}C_Av_k + a_{13}C_Iv_k + e_{11}C_A - e_{12}C_T - e_{13}\dot{C}_A + e_{14}\dot{C}_T + e_{15} \tag{113}$$

$$\dot{v}_k(t) = a_{21}u_k - a_{22}v_k + a_{23}C_Tu_k + a_{23}C_Av_k - a_{23}C_Iv_k - e_{21}C_A - e_{22}C_T + e_{22}C_T + e_{23}\dot{C}_A - e_{24}\dot{C}_T - e_{25} \tag{114}$$

where the following definitions hold:

$$e_{11} = k_1\bar{B}Q[V_T + (1+k)QT]/D$$

$$e_{12} = Q[V_T + (1+k)Q]/D$$

$$e_{13} = k_1\bar{B}(1-k)Q^2T^2/D$$

$$e_{14} = QT(V_T + 2QT)/D$$

$$e_{15} = k_2Q[V_T + (1+k)QT]/D$$

$$e_{21} = k_1\bar{B}Q[V_A + (1-k)Qk_1\bar{B}T]/D$$

$$e_{22} = Q[V_A + k_1\bar{B}(1-k)QT]/D$$

$$e_{23} = k_1\bar{B}QT\ V_A/D$$

$$e_{24} = QT[2V_A + (1-k)Qk_1\bar{B}T]/D$$

$$e_{25} = k_2Q[V_A + (1-k)Qk_1\bar{B}T]/D$$

The initial conditions for $u_k(t)$ and $v_k(t)$ are obtained from the following:

$$v_k(0) = \frac{\partial \bar{C}_T}{\partial k} = \frac{J\{\frac{\partial G}{\partial k} + \frac{1}{2}[G^2 - H]^{-\frac{1}{2}}[2G\frac{\partial G}{\partial k} - \frac{\partial H}{\partial k}]\} - [G + \sqrt{G^2 - H}]\frac{\partial J}{\partial k}}{J^2}$$

$$u_k(0) = \frac{\partial \bar{C}_A}{\partial k} = \frac{1}{k_1 \bar{B}}\frac{\partial \bar{C}_T}{\partial k} + \frac{M}{(1-k)^2 Q k_1 \bar{B}}$$

where

$$\frac{\partial G}{\partial k} = -Q(ak_2 + b)$$

$$\frac{\partial H}{\partial k} = -4aQbM - 8a(1-k)Q^2(bk_2 - k_1\bar{B}M)$$

$$\frac{\partial J}{\partial k} = -2aQ \quad .$$

Circulation time delay sensitivity equations

The sensitivity differential equations for the circulation time delay are as follows:

$$\dot{u}_T(t) = a_{11}u_T + a_{12}v_T - a_{13}C_T u_T - a_{13}C_A v_T + a_{13}C_I v_T + f_{11}\dot{C}_A - f_{12}\dot{C}_T \quad (115)$$

$$\dot{v}_T(t) = a_{21}u_T - a_{22}v_T + a_{23}C_T u_T + a_{23}C_A v_T - a_{25}C_I v_T - f_{21}\dot{C}_A + f_{22}\dot{C}_T \quad (116)$$

where
$$f_{11} = k_1\bar{B}T\,(1-k)^2Q^2/D$$
$$f_{12} = (1-k)QV_T/D$$
$$f_{21} = k_1\bar{B}V_A(1-k)Q/D$$
$$f_{22} = Q[(1-k)^2Qk_1\bar{B}T - 2kV_A]/D$$

The initial conditions for $u_T(0)$ and $v_T(0)$ are zero, since $\bar{C}_T$ and $\bar{C}_A$ are indenpent of T.

CO_2 controller slope sensitivity equations

The controller slope sensitivity equations are as follows:

$$\dot{u}_a(t) = a_{11}u_a + a_{12}v_a - a_{13}C_T u_a - a_{13}C_A v_a + a_{13}C_I v_a + g_{11}C_I C_T - g_{11}C_A C_T \quad (117)$$

$$\dot{v}_a(t) = a_{21}u_a - a_{22}v_a + a_{23}C_T u_a + a_{23}C_A v_a - a_{23}C_I v_a - g_{21}C_I C_T + g_{21}C_A C_T \quad (118)$$

where $g_{11} = (V_T + 2kQT)/D$ and $g_{21} = (1-k)Qk_1\bar{B}T/D$

The initial conditions for $u_a(t)$ and $v_a(t)$ can be calculated from

$$v_a(0) = \frac{\partial \bar{C}_T}{\partial a} = \frac{J\{\frac{\partial G}{\partial a} + \frac{1}{2}(G^2-u)^{-\frac{1}{2}}(2G\frac{\partial G}{\partial a} - \frac{\partial H}{\partial a})\} - [G + \sqrt{G^2 - H}]\frac{\partial J}{\partial a}}{J^2}$$

$$u_a(0) = \frac{\partial \bar{C}_A}{\partial a} = \frac{1}{k_1\bar{B}}\frac{\partial \bar{C}_T}{\partial a}$$

where

$$\frac{\partial G}{\partial a} = M + (1-k)Qk_2$$

$$\frac{\partial H}{\partial a} = 4(1-k)Q[bM + (1-k)Q(bk_2 - k_1\bar{B}M)]$$

$$\frac{\partial J}{\partial a} = 2(1-k)Q$$

CO_2 controller set point sensitivity equations

The controller set point sensitivity equations can be shown to be:

$$\dot{u}_b(t) = a_{11}u_b + a_{12}v_b - a_{13}C_T u_b - a_{13}C_A v_b + a_{13}C_I v_b + a_{13}C_I v_b + h_{11}C_A - h_{11}C_I \quad (119)$$

$$\dot{v}_b(t) = a_{21}u_b - a_{22}v_b + a_{23}C_T u_b + a_{23}C_A v_b - a_{23}C_I v_b - h_{21}C_A + h_{21}C_I \quad (120)$$

where $h_{11} = (V_T + 2kQT)/D$ and $h_{21} = (1-k)Qk_1\bar{B}T/D$.

The initial conditions for $u_b(t)$ and $v_b(t)$ are obtained from

$$v_b(0) = \frac{\partial \bar{C}_T}{\partial b} = \frac{\frac{\partial G}{\partial b} + \frac{1}{2}(G^2 - u)^{-\frac{1}{2}}(2G\frac{\partial G}{\partial b} - \frac{\partial H}{\partial b})}{J}$$

$$u_b(0) = \frac{\partial \bar{C}_A}{\partial b} = \frac{1}{k_1 \bar{B}} \frac{\partial \bar{C}_T}{\partial b}$$

where

$$\frac{\partial G}{\partial b} = (1-k)Q$$

$$\frac{\partial H}{\partial b} = 4\ a(1-k)QM + 4(1-k)^2Q^2ak_2$$

CO_2 dissociation curve intercept sensitivity equations

The CO_2 dissociation curve intercept sensitivity equations are as follows:

$$\dot{u}_{k_2}(t) = a_{11}u_{k_2} + a_{12}v_{k_2} - a_{13}C_T u_{k_2} - a_{13}C_A v_{k_2} + a_{13}C_I v_{k_2} - k_{11} \qquad (119a)$$

$$\dot{v}_{k_2}(t) = a_{21}u_{k_2} - a_{22}v_{k_2} + a_{23}C_T u_{k_2} + a_{23}C_A v_{k_2} - a_{23}C_I v_{k_2} + k_{21} \qquad (120a)$$

where

$$k_{11} = (1-k)\ Q[V_T + (1+k)QT]/D$$

$$k_{21} = (1-k)Q[V_A + (1-k)Qk_1\bar{B}T]/D$$

The initial conditions are calculated from the following:

$$v_{k_2}(0) = \frac{\partial \bar{C}_T}{\partial k_2} = \frac{\frac{\partial G}{\partial k_2} + \frac{1}{2}(G^2 - H)^{-\frac{1}{2}}(2G\frac{\partial G}{\partial k_2} - \frac{\partial H}{\partial k_2})}{J}$$

$$u_{k_2}(0) = \frac{\partial \bar{C}_A}{\partial k_2} = \frac{1}{k_1 \bar{B}} \frac{\partial \bar{C}_T}{\partial k_2} - \frac{1}{k_1 \bar{B}}$$

where

$$\frac{\partial G}{\partial k_2} = a(1-k)Q$$

$$\frac{\partial H}{\partial k_2} = 4a(1-k)^2Q^2b$$

Metabolic rate fo CO_2 production sensitivity equations

The sensitivity equations for M are as follows:

$$\dot{u}_M(t) = a_{11}u_M + a_{12}v_M - a_{13}C_Tu_M - a_{13}C_Av_M + a_{13}C_Iv_M - m_{11} \quad (121)$$

$$\dot{v}_M(t) = a_{21}u_M - a_{22}v_M + a_{23}C_Tu_M + a_{23}C_Av_M - a_{23}C_Iv_M + m_{21} \quad (122)$$

where $m_{11} = (1-k)QT/D$ and $m_{21} = V_A/D$.

The initial conditions for $u_M(t)$ and $v_M(t)$ are calculated from

$$v_M(0) = \frac{\partial \bar{C}_T}{\partial M} = \frac{\frac{\partial G}{\partial M} + \frac{1}{2}(G^2 - H)^{-\frac{1}{2}}(2G\frac{\partial G}{\partial M} - \frac{\partial H}{\partial M}}{J}$$

$$u_M(0) = \frac{\partial \bar{C}_A}{\partial M} = \frac{1}{k_1\bar{B}}\frac{\partial \bar{C}_T}{\partial M} - \frac{1}{(1-k)Q\,k_1\,\bar{B}}$$

where

$$\frac{\partial G}{\partial M} = a$$

$$\frac{\partial H}{\partial M} = 4a(1-k)Qb - 4a(1-k)^2Q^2k_1\bar{B}.$$

Barometric pressure sensitivity equations

The barometric pressure sensitivity equations can be shown to be

$$\dot{u}_{\bar{B}}(t) = a_{11}u_{\bar{B}} + a_{12}v_{\bar{B}} - a_{13}C_Tu_{\bar{B}} - a_{13}C_Av_{\bar{B}} + a_{13}C_Iv_{\bar{B}} + n_{11}\dot{C}_A - n_{12}C_A \quad (123)$$

$$\dot{v}_{\bar{B}}(t) = a_{21}u_{\bar{B}} - a_{22}v_{\bar{B}} + a_{23}C_Tu_{\bar{B}} + a_{23}C_Av_{\bar{B}} - a_{23}C_Iv_{\bar{B}} - n_{21}\dot{C}_A + n_{22}C_A \quad (124)$$

where

$$n_{11} = (1-k)^2Q^2T^2k_1/D$$

$$n_{12} = (1-k)k_1Q[V_T + (1+k)QT]/D$$

$$n_{21} = (1-k)Qk_1TV_A/D$$

$$n_{22} = (1-k)Qk_1[V_A + (1-k)Qk_1\bar{B}T]/D$$

The initial conditions for $u_B(t)$ and $v_B(t)$ can be calculated from

$$v_B(0) = \frac{\partial \bar{C}_T}{\partial \bar{B}} = \frac{2(G^2 - H)^{-\frac{1}{2}} a(1-k)^2Q^2k_1M}{J}$$

$$u_B(0) = \frac{\partial \bar{C}_A}{\partial \bar{B}} = \frac{1}{k_1\bar{B}} \frac{\partial \bar{C}_T}{\partial \bar{B}} - \frac{\bar{C}_T}{k_1\bar{B}^2} + \frac{M + (1-k)Qk_2}{(1-k)Q\ k_1\ \bar{B}^2}$$

where $\bar{C}_T$ is calculated from Equation 41a.

A discussion of the solutions of the closed loop sensitivity equations will be given in the next chapter.

Open Loop Sensitivity Equations

By employment of a sensitivity analysis of the open loop respiratory control system, a measure of the respiratory benefits to be gained from feedback can be gained. Sensitivity equations for seven of the respiratory parameters will be given. These seven parameters are as follows: alveolar volume (V_A), cardiac output (Q), cardiac shunting (k), circulation time delay (T), CO_2 dissociation curve intercept (k_2), metabolic rate of CO_2 production (M), and barometric pressure ($\bar{B}$). Since open loop considerations do not include the CO_2 controller constants 'a' and 'b', sensitivity equations for these two parameters cannot be developed. The derivation procedures for the open loop equations are the same procedures that were illustrated for the cardiac output sensitivity equations for the closed loop system. The sensitivity equations for the open loop situation are

derived from the open loop respiratory control equations, Equations 35 and 36.

Cardiac output sensitivity equations

The cardiac output sensitivity equations can be shown to be as follows:

$$\dot{u}_Q(t) = - b_{11}u_Q + b_{12}v_Q - \frac{b_{12}k_1\bar{B}}{Q} C_A + \frac{b_{12}}{Q} C_T - \frac{(1-k)TV_T}{D} \dot{C}_T$$

$$+ \frac{(1-k)T\, b_{23}}{\bar{V}_A} \dot{C}_A - \frac{b_{12}\, k_2}{Q} \qquad (125)$$

$$\dot{v}_Q(t) = b_{21}u_Q - b_{22}v_Q + \frac{k_1\bar{B}\, b_{22}}{Q} C_A - \frac{b_{22}}{Q} C_T - \frac{b_{23}V_A}{Q\,\bar{V}_A} \dot{C}_A$$

$$+ T\left[\frac{k_1\bar{B}QT(1-k)^2 - 2kV_A}{D}\right] \dot{C}_T + \frac{b_{22}k_2}{Q} \qquad (126)$$

where the 'b' constant and 'D' are defined by Equations 37 and 38. The steady state minute ventilation is represented by $\bar{V}_A$, which is assumed constant at its normal resting value (Table 1). The initial conditions for $u_Q(t)$ and $v_Q(t)$ are obtained from the steady state open loop equations, Equations 43 and 44. The initial conditions for $u_Q(t)$ and $v_Q(t)$ are as follows:

$$v_Q(0) = \frac{\partial \bar{C}_{To}}{\partial Q} = - \frac{M}{(1-k)Q^2}$$

and

$$u_Q(0) = \frac{\partial \bar{C}_{Ao}}{\partial Q} = 0.$$

Alveolar volume sensitivity equations

The alveolar volume sensitivity equations can be shown to be the follwoing:

$$\dot{u}_{V_A}(t) = - b_{11} u_{V_A} + b_{12} v_{V_A} - \frac{b_{13}}{\bar{V}_A} \dot{C}_A \tag{127}$$

$$\dot{v}_{V_A}(t) = b_{21} u_{V_A} - b_{22} v_{V_A} + \frac{b_{23}}{\bar{V}_A} \dot{C}_A \tag{128}$$

The initial conditions are both zero, since Equations 43 and 44 are independent of V_A.

Cardiac output shunting sensitivity equations

The cardiac output shunting sensitivity equations can be shown to be as follows:

$$\dot{u}_k(t) = - b_{11} u_k + b_{12} v_k + \xi_{11} C_A - \xi_{12} C_T - \xi_{13} \dot{C}_A + \xi_{14} \dot{C}_T + \xi_{15} \tag{129}$$

$$\dot{v}_k(t) = b_{21} u_k - b_{22} v_k - \xi_{21} C_A + \xi_{22} C_T + \xi_{23} \dot{C}_A - \xi_{24} \dot{C}_T - \xi_{25} \tag{130}$$

where the constants are defined by

$$\xi_{11} = \frac{k_1 \bar{B} b_{12}}{(1-k)} \qquad \xi_{21} = \frac{b_{12} k_1 \bar{B}}{(1-k)}$$

$$\xi_{12} = \frac{b_{12}}{(1-k)} \qquad \xi_{22} = \frac{b_{12}}{(1-k)}$$

$$\xi_{13} = \frac{Q\ T\ b_{23}}{\bar{V}_A} \qquad \xi_{23} = \frac{V_A\ b_{23}}{\bar{V}_A}$$

$$\xi_{14} = \frac{Q\ T(V_T + 2QT)}{D} \qquad \xi_{24} = \frac{QT[2V_A + (1-k)k_1 \bar{B} QT]}{D}$$

$$\xi_{15} = \frac{k_2\ b_{12}}{(1-k)} \qquad \xi_{25} = \frac{k_2\ b_{12}}{(1-k)}$$

The initial conditions for $u_k(t)$ and $v_k(t)$ are calculated from the following:

$$u_k(0) = \frac{\partial \bar{C}_{Ao}}{\partial k} = 0$$

$$v_k(0) = \frac{\partial \bar{C}_{To}}{\partial k} = \frac{k\,M}{(1-k)^2\,Q}$$

Circulation time delay sensitivity equations

The circulation time delay sensitivity equations can be shown to be the following:

$$\dot{u}_T(t) = - b_{11}u_T + b_{12}v_T + n_{11}\dot{C}_A - n_{12}\dot{C}_T \tag{131}$$

$$\dot{v}_T(t) = b_{21}u_T - b_{22}v_T - n_{21}\dot{C}_A + n_{22}\,\dot{C}_T \tag{132}$$

where the constants are defined by the following:

$$n_{11} = \frac{(1-k)Q\,b_{23}}{\bar{V}_A} \qquad n_{21} = \frac{V_A\,b_{23}}{T\,\bar{V}_A}$$

$$n_{12} = \frac{(1-k)Q\,V_T}{D} \qquad n_{22} = \frac{(1-k)^2Q^2k_1\bar{B}T - 2kQV_A}{D}$$

The initial conditions $u_T(0)$ and $v_T(0)$ are both zero.

Metabolic rate of CO_2 production sensitivity equations

The sensitivity equations for M can be shown to be

$$u_M(t) = - b_{11}u_M + b_{12}\,v_M - \frac{(1-k)\,Q\,T}{D} \tag{133}$$

$$v_M(t) = b_{21}u_M - b_{22}v_M + \frac{V_A}{D}\ . \tag{134}$$

The initial conditions are calculated from the following:

$$u_M(0) = \frac{\partial \bar{C}_{Ao}}{\partial M} = \frac{1}{\bar{V}_A}$$

$$v_M(0) = \frac{\partial \bar{C}_{To}}{\partial M} = \frac{k_1 \bar{B}}{\bar{V}_A} + \frac{1}{(1-k)\, Q} \quad .$$

Barometric pressure sensitivity equations

The sensitivity equations for $\bar{B}$ are as follows:

$$\dot{u}_{\bar{B}}(t) = - b_{11} u_{\bar{B}} + b_{12} v_{\bar{B}} - k_1 b_{12} C_A + \frac{(1-k)QT\, b_{23}}{\bar{V}_A\, \bar{B}} \dot{C}_A \tag{135}$$

$$\dot{v}_{\bar{B}}(t) = b_{21} u_{\bar{B}} - b_{22} v_{\bar{B}} + b_{22} k_1 C_A - \frac{V_A\, b_{23}}{\bar{B}\, \bar{V}_A} \dot{C}_A \quad . \tag{136}$$

The initial conditions for $u_{\bar{B}}(t)$ and $v_{\bar{B}}(t)$ are calculated from

$$u_{\bar{B}} = \frac{\partial \bar{C}_{Ao}}{\partial \bar{B}} = 0$$

$$v_{\bar{B}}(0) = \frac{\partial C_{To}}{\partial \bar{B}} = \frac{k_1 M}{\bar{V}_A} \quad .$$

CO_2 dissociation curve intercept sensitivity equations

The sensitivity equations for the CO_2 dissociation curve intercept can be given as

$$\dot{u}_{k_2}(t) = - b_{11} u_{k_2} + b_{12} v_{k_2} - b_{12} \tag{137}$$

$$\dot{v}_{k_2}(t) = b_{21} u_{k_2} - b_{22} v_{k_2} + b_{22} \tag{138}$$

The initial conditions are found to be

$$u_{k_2}(0) = \frac{\partial \bar{C}_{Ao}}{\partial k_2} = 0 \qquad \text{and} \qquad v_{k_2}(0) = \frac{\partial \bar{C}_{To}}{\partial k_2} = 1 \ . \tag{138a}$$

These particular sensitivity equations are unique with respect to the others in that they are independent of the respiratory system's dependent variables, $C_A(t)$ and $C_T(t)$. It is possible to solve Equations 137 and 138 explicitely for the sensitivity coefficients. If the Laplace transform (46) of these equations is taken and the resultant simultaneous algebraic equations solved for the transformed variables $U_{k_2}(s)$ and $V_{k_2}(s)$, the results are

$$U_{k_2}(s) = \frac{u(0)\ s + v(0)b_{12} - b_{12} + b_{22}u(0)}{s^2 + (b_{11} + b_{22})s + (b_{11}b_{22} - b_{12}b_{21})} \tag{139}$$

$$V_{k_2}(s) = \frac{s[v(0)s + b_{11}v(0) + b_{22} + b_{21}u(0)] + b_{11}b_{22} - b_{12}b_{21}}{x[s^2 + (b_{11} + b_{22})s + (b_{11}b_{22} - b_{12}b_{21})]} \tag{140}$$

Substitution of the initial conditions, Equation 138a, into Equations 139 and 140 yields:

$$U_{k_2}(s) = 0$$

$$V_{k_2}(s) = 1/s$$

for which the inverse Laplace transforms are given by

$$u_{k_2}(t) = 0 \qquad \text{and} \qquad v_{k_2}(t) = u(t) \ ,$$

where $u(t)$ is the unit magnitude step function. It is thus observed that the sensitivity coefficients for k_2 are time invariant. The sensitivity of the open loop control system with respect to k_2 would be reported as

$$S_{k_2}^{C_T} = \Delta C_{Tk_2} = (.01)(.28)\, v_{k_2}(t) = 2800 \times 10^{-6} \qquad (141)$$

for the adult, assuming the normal value of k_2 listed in Table 1. Equation 141 indicates that a 1% increase in k_2 from the normal value will change the tissue conecntration of CO_2 by 2800×10^{-6} liters/liter.

This completes the development of the sensitivity equations for the CO_2 respiratory control system. The results of the solutions for these equations follow.

SOLUTIONS OF THE SENSITIVITY EQUATIONS FOR THE RESPIRATORY SYSTEM

The preceding discussion presented the derivation of the parameter sensitivity equations for the CO_2 respiratory control system. Equations for both the open loop and the closed loop respiratory control systems were derived. It was shown previously that the sensitivity equations are linear differential equations with time varying coefficients, specifically, $C_A(t)$ and $C_T(t)$. In addition, the control system's two dependent variables, $C_A(t)$ and $C_T(t)$, together with the derivatives with respect to time of these variables, and the CO_2 inhalation level, $C_1(t)$, all appear as driving functions in the sensitivity equations. It is apparent then that solution of a given set of sensitivity equations for u(t) and v(t) requires a simultaneous solution of the sensitivity equations and the respiratory model equations. All such solutions were made on an IBM 1130 digital computer using the combined Runge-Kutta and Milne numberical integration routine previously discussed.

All results to be reported were obtained by using steady state values of $C_A(t)$ and $C_T(t)$ (computed with $C_1(t) = 0$) as the initial values $C_A(0)$ and $C_T(0)$ of the respiratory control system equations, Equations 33 and 34. The initial conditions for the sensitivity equations were given in the preceding chapter.

It should be pointed out again at this point that the CO_2 respiratory control system serves the function of a regulator. That is, this system attempts to regulate the tissue concentration of CO_2 at a physiologically normal level and fee of wide fluctuations. Any regulator - whether technological or physiological in nature - to be effective must be designed

so that parameter changes will have minimal effect on system performance. Thus an increased sensitivity, S^{C_T}, to a change in a given parameter of the respiratory system will indicate a decrease in the regulator effectiveness of the control system. The sensitivity results to be reported should be interpreted with this in mind.

The sensitivity results to be reported can be divided into three groups:

1. An open loop control system study for the adult.
2. A closed loop control system study for both and adult and an infant, assuming normal parameter values, and varying the CO_2 inhalation level, $C_1(t)$.
3. A closed loop control system study for the adult and the infant assuming abnormal parameter values and a five percent inhalation of CO_2.

The Open Loop Study

The open loop sensitivity equations of Chapter 8 were solved for the adult control system, assuming normal values for the respiratory parameters. The sensitivity results are shown in Figure 28 and Table 3. It should be noted that all results have been state in terms of the change in $C_T(t)$ to be expected from a one percent change in a given parameter. The CO_2 inhalation level, $C_1(t)$, was chosen to be a step function having a magnitude representing a five percent inhalation of CO_2. The inhalation of CO_2 was commenced at time zero in Figure 28 and terminated at 20 minutes. A five percent inhalation of CO_2 was chosen because this is a common value used clinically to assess the state of the respiratory system in individuals who have certain types of respiratory impairment (9).

Figure 28 shows plots of the sensitivity data for two of the respiratory parameters, the circulation time delay (T) and the effective alveolar volume (V_A). It is to be noted that the effects of a change in T and V_A are opposite in sign and increase with time. The sensitivity of $C_T(t)$ with respect to a change in the circulation time delay is somewhat greater in magnitude at t = 20 minutes than for the alveolar volume sensitivity.

Table 3 contains sensitivity data for the respiratory parameters not shown in Figure 28. The initical values of S^{C_T} and the 20 minute values are sufficient to characterize the sensitivity data for the open loop system. It is apparent from the data in Table 3 that the open loop system is more sensitive to changes in M, k_2, and $\bar{B}$ at t = 0 than to changes in the other parameters. However, after 20 minutes the predominate parameter becomes the cardiac output. $S_Q^{C_T}$ at 20 minutes increased to - 11,910 x 10^{-6}, which represents a minimum of 5 times the sensitivity value for any other parameter. This result means that if the cardiac output were increased by one percent from normal, there would be a decrease in $C_T(t)$ of 0.119 liters/liter at 20 minutes in response to a five percent CO_2 inhalation, relative to the normal response.

Using the date from Table 3 it is possible to rank the parameters in order of their importance in determining the tissue CO_2 concentration, $C_T(t)$. This ranking, in order of decreasing influence, is as follows: Q, k_2, M, $\bar{B}$, k, T, and V_A; using the values of S^{C_T} at 20 minutes. If this ranking had been compiled on the basis of the initial values of Table 3, the ranking would be as follows: k_2, M, $\bar{B}$, Q, k, T, and V_A. It is apparent that the two rankings are different. A comparison of this nature

shows the value of a dynamic sensitivity approach, which contains time information, over a static (i.e., steady state) analysis.

The Closed Loop, Normal Parameters, Study

A second study was undertaken to determine the closed loop respiratory system's sensitivity coefficients using normal parameter values. The procedure involved simultaneous solution of the closed loop respiratory equations, Equations 33 and 34, and the closed loop sensitivity equations derived in chapter 8. The sensitivity coefficients were computed for both the adult and the infant control systems. In addition, the effects of changing the CO_2 inhalation level on the sensitivity coefficients was examined.

Sensitivity coefficients for the normal adult

The parameter sensitivites, S^{C_T}, for the normal adult are shown plotted in Figures 29 through 37. All data have been plotted for a 30 minute time interval. Examination of these figures reveals several interesting trends in parameter sensitivity.

Figure 29 shows that the sensitivity of $C_T(t)$ with respect to the alveolar volume diminishes with time after reaching a negative peak for the interval 0 - 20 minutes. At t = 20 minutes there is a sign reversal of the sensitivity data, indicating that $C_T(t)$ will be increased because of a one percent increase in V_A over the $C_T(t)$ computed with the normal alveolar volume. It is observed that the alveolar volume sensitivity increases in magnitude as the magnitude of $C_1(t)$ is increased, indicating that the control system's effectiveness with respect to changes in V_A decreases somewhat. Examination of the S^{C_T} curve for the interval 0 - 20

minutes of Figure 29 computed with $C_1(t) = 5\%$ shows a negative peak of magnitude 5×10^{-6}. For the same time interval, the maximum value of $S_{V_A}^{C_T}$ for the open loop system was -10.1×10^{-6}.

The cardiac output sensitivity data is shown in Figure 30. It is apparent that changes in Q will have a greater effect on $C_T(t)$ during the 'turn off' period (i.e., the time greater than 20 minutes) of $C_1(t)$ than for the 'turn on' period; and the greater the magnitude of $C_1(t)$, the greater in magnitude is the $S_Q^{C_T}$ peak. It is to be noted that for the time interval 3 to 12 minutes, a five percent CO_2 inhalation will cause $S_Q^{C_T}$ to be larger than for a seven percent inhalation. The maximum magnitude of $S_Q^{C_T}$, assuming $C_1 = 5\%$, for the 0 - 20 minute interval is approximately 175×10^{-6}. For this same interval the comparable open loop value was $11{,}190 \times 10^{-6}$. Again the benefits of closed loop control are apparent.

The sensitivity effect of cardiac output shunting are shown in Figure 31 for the adult. It is interesting to note that the $S_k^{C_T}$ curves appear to be mirror images of the $S_Q^{C_T}$ curves of Figure 30; that is, the wave forms are the same, but reversed in sign. Thus the remarks for the $S_Q^{C_T}$ data pertain also to the $S_k^{C_T}$ data. The maximum magnitude of the 5% $S_k^{C_T}$ curve of Figure 31 for the interval 0 - 20 minutes is 4×10^{-6}, whereas the comparable open loop value was 152×10^{-6}. Again the benefits of closed loop control are apparent.

The circulation time delay sensitivity data is shown in Figure 32. The $S_T^{C_T}$ curves show a biphasic characteristic similar to that of the alveolar volume sensitivity data. The effect of a change in T diminishes with time, but becomes rather large during the 'turn off' period. The

maximum magnitude of the 5% $S_T^{C_T}$ closed loop curve for the interval 0 - 20 minutes is 1500 x 10^{-6}, but only 18 x 10^{-6} in the open loop system; which indicates a decreased respiratory effectiveness due to closing the feedback loop.

The sensitivities of the parameters of the brain CO_2 controller, 'a' and 'b', are shown in Figures 33 and 34. It is to be noted that the $S_a^{C_T}$ data and the $S_b^{C_T}$ data are approximately equal in magnitude but opposite in sigh (which would be expected from the form of Equation 10). It is also quite interesting to note that by increasing the $C_1(t)$ magnitude, the $S_a^{C_T}$ and $S_b^{C_T}$ sensitivities will be reduced. It is also important to note that any CO_2 inhalation will reduce the sensitivities with respect to 'a' and 'b'. The importance of this observation will be discussed in the next chapter when the stability of the respiratory system is discussed.

The sensitivity data for the metabolic rate of CO_2 production, CO_2 dissociation curve intercept, and barometric pressure are shown in Figures 35, 36, and 37, respectively. In general, all three sets of data have the same curve shape. The data indicates that changes in $\bar{B}$ and k_2 exert approximately 3 times the effect on tissue CO_2 concentration that a change in M will effect. Comparisons of the maximum values for the 0 - 20 minute interval for a 5% CO_2 inhalation are as follows: $S_M^{C_T}$ = 425 x 10^{-6}, $S_{k_2}^{C_T}$ = 1100 x 10^{-6}, and $S_B^{C_T}$ = 900 x 10^{-6}. The comparable values for the open loop system are 2479 x 10^{-6}, 2800 x 10^{-6}, and 2279 x 10^{-6}, respectively. It is apparent that closed loop operation greatly reduces the sensitivity of the respiratory control system to variations in M, k_2, and $\bar{B}$.

A ranking of the respiratory parameters in order of their importance

in determining the tissue CO_2 concentration can be made based on the maximum magnitude of the sensitivity data for the 30 minute interval, assuming that $C_1 = 5\%$. This ranking is as follows for the adult closed loop control system:

Parameter	Maximum Sensitivity Value, x 10^{-6}
a	5000
b	5000
T	2000
k_2	1100
$\overline{B}$	900
M	425
Q	200
V_A	8
k	5

It is apparent that the dominant parameters of the adult respiratory system are the CO_2 controller constants and the circulation time delay. This observation will be shown to have great significance when stability considerations are considered in the next chapter.

Sensitivity coefficients for the normal infant

The parameter sensitivities S^{C_T} for the normal infant are shown plotted in Figures 38 through 46. In general, the infant sensitivity data shows the same curve shapes as corresponding adult sensitivity data. The most pronounced difference between the infant sensitivity curves and the adult sensitivity curves is the lengthening of the time constants of most infant sensitivity curves. For example, the $S_{V_A}^{C_T}$ curve of Figure 38

computed with C_1 = 5% shows a value of -5×10^{-6} at 20 minutes. However, the corresponding adult sensitivity curve of Figure 29 shows a sensitivity value of zero.

Interesting comparisons between the parameter sensitivities of the adult and the infant CO_2 control systems can be made if the infant parameter sensitivities are ranked in order of their importance in determining the tissue CO_2 concentration. As with the adult sensitivity data, the infant parameter sensitivities will be ranked according to their maximum magnitudes for the interval 0 - 30 minutes and with C_1 = 5%. From Figures 38 - 46 this ranking would be as follows:

Parameter	Maximum Sensitivity Value, $\times 10^{-6}$
a	2000
b	1750
$\overline{B}$	1100
k_2	1000
M	1000
Q	700
k	250
V_A	35
T	13

A comparison of this ranking with the adult sensitivity ranking reveals several interesting facts. First, the most pronounced difference between the two systems is the apparent lack of sensitivity of the normal infant's control system to changes in the circulation time delay. The infant control system appears to be more sensitive to changes in cardiac

output, cardiac output shunting, metabolic rate of CO_2 production, and alveolar volume than does the adult system. However, the sensitivities of the infant's respiratory CO_2 controller parameters, 'a' and 'b', are less than half the adult values. The remaining respiratory parameters, k_2 and $\bar{B}$, appear to have sensitivity values approximately equal for the adult and the infant.

It has been reported in the literature (26) that the two respiratory parameters that are the main determinants of respiratory system instability (i.e., persistent oscillations in the minute ventilation) are 'a' and 'T'. The sensitivity data would indicate then that the infant's respiratory system is more stable than is the adult's system, since $S_a^{C_T}$ and $S_T^{C_T}$ for the infant are less in magnitude than the comparable adult values. This prediction, based at this point on a sensitivity analysis prediction, will be verified in the next chapter, which will deal with a Lyapunov stability analysis of the respiratory system.

The Closed Loop, Abnormal Parameters, Study

The development of the parameter sensitivity equations given in chapter 8 emphasized that the sensitivity with respect to a given parameter is a function of all the parameters of the respiratory system. The sensitivity data discussed thus far in this chapter were computed for normal respiratory parameter values. It is reasonable then to also investigate how the parameter sensitivities change when compute using 'abnormal' parameter values. In this context, an 'abnormal' parameter value is a value that differs from the 'normal' value listed in Table 1, though in most instances the 'abnormal' values used in this study would be

characteristic of certain abnormal physiological states.

Adult sensitivity data

Parameter sensitivity data for the adult CO_2 control system were computed for ten abnormal parameter values. Each set of sensitivity data, e.g., $S_Q^{C_T}$ was computed assuming that all the respiratory parameters were normal except one, which then assumed an 'abnormal' value. The abnormal values chosen for the adult were as follows (normal values are shown in parenthesis): V_A = 1.5 liters (3), Q = 2 lit/min (6), Q = 18 lit/min (6), T = 0.8 minute (0.16), k = 0.25 (0.025), a = 224 lit/min (448), $\overline{a}$ = 896 lit/min (448), k_2 = 0.32 mm Hg^{-1} (0.28, $\overline{B}$ = 350 mm Hg (713), and $\overline{B}$ = 1400 mm Hg (713). In order to conform to physiological fact, the circulation time delay was varied inversely with the cardiac output for the two instances of abnormal cardiac output. Also, when the CO_2 controller slope was set to its two abnormal values, the set point 'b' was recalculated (via Equation 52) to maintain the steady state minute ventilation at its normal, resting value).

The sensitivity data for the adult CO_2 control system are given in Tables 4 through 12. Each table gives parameter sensitivity data for ten selected times during the thirty minute interval for which all data were computed. It is possible to put the data of Tables 4 - 12 into a better perspective if maximum values only are considered. For each parameter sensitivity curve computed with normal parameters, there existed a point of maximum (in magnitude) sensitivity. Examination of the data in Tables 4 - 12 shows that in most instances computation of a given sensitivity curve assuming an abnormal parameter value resulted in a new value for the

maximum sensitivity. The ratio of this new maximum value to the 'normal' maximum value can then be taken as an index of the change in sensitivity that the abnormal parameter value effected. Following this procedure, the data contained in Tables 4 - 12 were reduced to that of Table 22. Only the $S_a^{C_T}$ and $S_b^{C_T}$ data of Table 22 were not based on the ratio of maximum values, but in these two cases the ratio of the 20 minutes abnormal value to the 20 minute normal value was used as an index of change, since these values at 20 minutes seemed more representative of change.

Examination of Table 22 shows the following general trends. First, a decrease of V_A to half its normal value causes a decrease in V_A and T sensitivity and has no effect on the other parameter sensitivities. A decrease in cardiac output to one - third normal will effect an increase in all parameter sensitivities except 'a' and 'b', which show a decrease. An increase in Q to three times normal has a tendency to decrease the sensitivities of all parameters, except the controller parameters, which show a slight increase in sensitivity. An increase in the circulation time delay to five times normal effected a five times normal increase in the time delay sensitivity, but had little effect on the remaining parameter sensitivities. In fact, the greatest change in sensitivity found in Table 22 was for $S_T^{C_T}$ evaluated with T equal to five times normal. The importance of this observation will be evident in the next chapter, which deals with respiratory stability. An increase in k to ten times normal, a decrease in 'a' to one-half normal, and an increase in 'a' to twice normal, respectively has little effect on system sensitivity. An increase in k_2 to a value typical of reduced blood showed a general trend of increasing

slightly the parameter sensitivities, though $S_a^{C_T}$ and $S_b^{C_T}$ are decreased. The effects of 'abnormal' barometric pressures show a trend of decreased parameter sensitivity as $\bar{B}$ is decreased, and an increased sensitivity when $\bar{B}$ is increased.

Infant sensitivity data

Parameter sensitivity data for the infant control system were also computed for ten abnormal parameter values. The abnormal values chosen for the infant parameters were as follows (with normal values in parenthesis): V_A = 0.4 liters (0.8), Q = 0.1 lit/min (0.3), Q = 0.9 lit/min (0.3), T = 0.4 minute (0.08), k - 0.5 (0.25), a = 10.9 lit/min (21.8), a = 45.6 lit/min (21.8) k_2 = 0.25 mm Hg^{-1} (0.18), $\bar{B}$ = 350 mm Hg (713), and $\bar{B}$ = 1400 mm Hg (713). The same computational procedures used for the adult were also used for the infant sensitivity data. The sensitivity data for the infant control system, computed assuming abnormal parameter values, are given in Tables 13 - 21, and summarized in Table 23.

Examination of Table 23 shows that the infant sensitivity data computed for abnormal parameter values follow the same trends noted for the adult data of Table 22 with one exception. An increase in cardiac shunting to twice normal increased the sensitivity with respect to 'k' to five times normal for the infant. The corresponding adult sensitivity was not nearly as great, only 1.8 times normal.

Summary of all sensitivity data

The present chapter has illustrated the use of dynamic sensitivity analysis to gain insight into the human CO_2 respiratory control system. It has been shown that one of the benefits from closed loop operation of

the CO_2 control system, relative to open loop operation, is a decreased sensitivity to parameter variations (with the exception of the circulation time delay T).

A sensitivity analysis of the normal adult and the normal infant control systems showed that the parameters 'a', 'b', and T exert the greatest influence on the determination of the tissue CO_2 concentration. In addition, it was concluded that the sensitivities of these three important parameters were greater for the adult than for the infant.

A sensitivity analysis of the CO_2 control system, using certain abnormal parameter values, showed essentially that both the adult and the infant control systems' parameter sensitivities are not greatly affected through use of the 'abnormal' parameter values previously cited. The greatest changes in parameter sensitivites were obtained for low cardiac output and increased circulation time delay.

It will be shown in the next chapter how the sensitivity data discussed in the present chapter can be used to indicate respiratory control system instability, a problem of clinical importance.

LYAPUNOV STABILITY ANALYSIS OF THE CO_2 RESPIRATORY CONTROL SYSTEM

It was mentioned in the Introduction of this thesis that one of the theses objectives was to present a stability analysis of the respiratory control system. In addition, it was shown in Part II that the sensitivity coefficients can provide stability information in certain instances. It will be the purpose of the present discussion to give a Lyapunov stability analysis of the human CO_2 respiratory control system and, in addition, compare these results with those predicted by the sensitivity analysis.

The theory of engineering control systems places great emphasis on an adequate understanding of system instability. The stability theory of linear control systems is well established in the literature (46). However, the stability theory of nonlinear control systems is still being developed. At present the only analytic theory of stability applicable to nonlinear control systems is the theory developed by the Russian mathematician, Lyapunov. Two excellent references on Lyapunov stability analysis are those provided by Derusso et al. (33) and Pontryagin (47).

The concept of the stability of nonlinear systems differs somewhat from the stability concept of a linear system. First, the stability of a linear system is a property of the system itself (i.e., its characteristic equation) and is not influenced by the input signals. And a linear system is stable or unstable in all of the state space (i.e., the space composed of those dependent variables that describe the system's motion). In contrast, the stability of a nonlinear system must be restricted to an infinitesimal region about each of the singular points in state space (i.e., the points in state space where the derivatives with respect to

time of the state variables are zero). In addition, the stability of a nonlinear system will be influenced by the input signal.

The concept of stability can be mathematically defined in the following manner. Let the system be described by the following vector - valued equation:

$$\dot{\underline{x}}(t) = \underline{f}(\underline{x}, t) \qquad \text{with} \qquad \underline{f}(\underline{0}, t) = \underline{0} \ , \tag{142}$$

where the vector $\underline{x}$ has as its components the system's state variables. It is also to be noted that the origin (i.e., $\underline{x} = \underline{0}$) in state space is an equilibrium point (i.e., $\dot{\underline{x}} = \underline{0}$). If the system is perturbated away from an equilibrium (Figure 47) there are three possible occurrences: the system's motion may return to the equilibrium point, the motion may increase in amplitude with time and move away from the equilibrium, or the motion may oscillate about the equilibrium. These concepts can be precisely defined as follows: an equilibrium point of Equation 142 is stable if, given any $\varepsilon > 0$, there exists a $\delta(\varepsilon, t_o) > 0$ such that $||\underline{x}_o|| < \delta$ implies $||\underline{x}(t; \underline{x}_o, t_o)|| < \varepsilon$ for all $t \geq t_o$; where $\underline{x}(t; \underline{x}_o, t_o)$ denotes the response of the system at time t to a sudden perturbation $\underline{x}_o = \underline{x}(t_o)$. The Euclidian length of the vector $\underline{x}$ is denoted by $||\underline{x}||$. Stated in words, a bound ε on the perturbated response is first specified. If a bound δ on the size of the perturbation $\underline{x}_o$ can be found such that the perturbated response $\underline{x}(t; \underline{x}_o, t_o)$ due to any $\underline{x}_o$ within the bound δ always remains within its bound ε, then the equilibrium is said to be stable. The equilibrium is unstable if it is not stable. The equilibrium, defined at the origin, is asymptotically stable if, in addition to the equilibrium being stable, there exists a $\delta_o(\varepsilon, t_o) > 0$ such that, if $||\underline{x}_o|| < \delta_o$, the

solution $\underline{x}(t; \underline{x}_o, t_o)$ approaches $\underline{0}$ as t approaches infinity.

The application of Lyapunov stability theory often requires the establishment of a Lyapunov function for the system. This function is commonly denoted by $V(\underline{x})$ and is a continuous scalar function of the state variables $\underline{x}$. Depending on the properties of $V(\underline{x})$ and its time derivative, instability or various forms of stability of the equilibrium can be proved. The form of the Lyapunov function will depend on the particular system under consideration. However, there now exists in the literature theorems which guarantee the existence of a Lyapunov function for a given system, even though $V(\underline{x})$ itself may not be known. The stability analysis to be presented in this thesis will be based on such a theorem.

The stability theorem alluded to has been given by Pontryagin (47, Theorem 19) as follows: "If all eigenvalues of the matrix $A = (a^i_j)$, where $(a^i_j) = \frac{\partial f^i(\underline{x}_o)}{\partial x_j}$ have negative real parts, then the equilibrium state $\underline{x}_o$ of the system (Equation 142) is asymptotically stable." Two points need to be emphasized with regard to use of this theorem. First, the theorem applies only for an autonomous system (i.e., a system having no driving functions). Second, the equilibrium of the system is considered to be at the origin in state space. Thus, in some instances the system's equilibrium may have to be mathematically shifted to the origin.

The stability of the respiratory control system is of considerable clinical importance, since clinical situations arise in which the resting minute ventilation is not constant (5 lit/min for the adult), but rather, displays cyclic oscillations having a period of approximately 1 minute.

These oscillations can be considered indicative of respiratory control system instability. The most common occurrence of such ventilation is called Cheyne - Stokes breathing (32). Ventilation oscillations are also normally observed in infants. These particular oscillations gradually disappear as the infant matures. However, Cheyne - Stokes breathing persists in the adult. Little is known of the cause of such oscillations, and hence, treatment effects are lacking. A common treatment of such breathing is to give inhalations of CO_2. Recent work reported in the literature by Milhorn and Guyton (25) and others (29, 30), based on computer solutions of various models of the respiratory control system, have shed light on possible mechanisms that could effect Cheyne - Stokes breathing. However, no analytic study using mathematical stability theory has been reported in the literature.

The closed loop respiratory equations, Equations 33 and 34, can be investigated for instability if they are manipulated into a form which meets the requirements of Pontryagin's stability theorem. First, the system's input, $C_1(t)$, must be set equal to zero. The following equations result then from Equations 33 and 34:

$$\dot{C}_A(t) = a_{11}C_A(t) + a_{12}C_T(t) - a_{13}C_A(t)C_T(t) - a_{16} \qquad (143)$$

$$\dot{C}_T(t) = a_{21}C_A(t) - a_{22}C_T(t) + a_{23}C_A(t)C_T(t) + a_{26} \qquad (144)$$

where the 'a' coefficients have been defined previously in Equations 33 and 34. However, the origin of Equations 143 and 144 is not an equilibrium point. The equilibrium of Equations 143 and 144 is given by the steady state values, $\bar{C}_A$ and $\bar{C}_T$, derived in chapter 5, with C_1 equal to zero. Specifically, let the equilibrium value of $C_A(t)$ be denoted by $\bar{C}_A$, where

$\bar{C}_A$ is calculated from Equation 42 with C_1 set equal to zero, and let the equilibrium value of $C_T(t)$ be denoted by $\bar{C}_T$, where $\bar{C}_T$ is computed from Equation 41 with C_1 set to zero. Define two new dependent variables as follows:

$$\rho_A(t) = C_A(t) - \bar{C}_A \tag{145}$$

$$\rho_T(t) = C_T(t) - \bar{C}_T \ . \tag{146}$$

These two new variables will thus have their equilibrium at the origin. Substitution of Equations 145 and 146 into Equations 143 and 144 results in the following:

$$\dot{\rho}_A(t) = (a_{11}-a_{13}\bar{C}_T)\rho_A(t) + (a_{12}-a_{13}\bar{C}_A)\rho_T - a_{13}\rho_A(t)\rho_T(t) + a_{11}\bar{C}_A + a_{12}\bar{C}_T - a_{13}\bar{C}_A\bar{C}_T - a_{16} \tag{147}$$

$$\dot{\rho}_T(t) = (a_{21} + a_{23}\bar{C}_T)\rho_A - (a_{22}-a_{23}\bar{C}_A)\rho_T(t) + a_{23}\rho_A(t)\rho_T(t) + a_{21}\bar{C}_A - a_{22}\bar{C}_T + a_{23}\bar{C}_A\bar{C}_T + a_{26} \tag{148}$$

Since it is now known that the origin is an equilibrium point (i.e., when $\rho_A = \rho_T = 0$; then $\dot{\rho}_A = \dot{\rho}_T = 0$); hence the constant terms in Equations 147 and 148 have to equal zero. It then follows that the equations to be investigated for instability are as follows:

$$\dot{\rho}_A(t) = (a_{11}-a_{13}\bar{C}_T)\rho_A(t) + (a_{12}-a_{13}\bar{C}_A)\rho_T(t) - a_{13}\rho_A(t)\rho_T(t) \tag{149}$$

$$\dot{\rho}_T(t) = (a_{21}+a_{23}\bar{C}_T)\rho_A(t) - (a_{22}-a_{23}\bar{C}_A)\rho_T(t) + a_{23}\rho_A(t)\rho_T(t) \tag{150}$$

If the vector $\rho_{\_}$ is defined as the column vector

$$\rho_{\_} = \begin{pmatrix} \rho_A \\ \rho_T \end{pmatrix}$$

then Equations 147 and 148 can be written as follows in vector notation:

$$\dot{\rho}_{\_}(t) = \underline{f}(\rho_{\_}, t) \qquad \text{with} \qquad \underline{f}(\underline{0}, t) = 0$$

where the vector function $\underline{f}$ is defined as

$$\underline{f}(\rho_{\_}, t) = \begin{bmatrix} (a_{11} - a_{13}\bar{C}_T) - a_{13}\rho_T(t) & (a_{12} - a_{13}\bar{C}_A) \\ (a_{21} + a_{23}\bar{C}_T) & -(a_{22} - a_{23}\bar{C}_A) + a_{23}\rho_A(t) \end{bmatrix} \rho_{\_}(t) \tag{151}$$

The stability matrix A defined in Pontryagin's theorem is obtained then from Equation 151 as:

$$A = \left.\frac{\partial \underline{f}}{\partial \rho^i}\right|_{\rho_{\_} = 0} = \begin{bmatrix} a_{11} - a_{13}\bar{C}_T & a_{12} - a_{13}\bar{C}_A \\ a_{21} + a_{23}\bar{C}_T & a_{23}\bar{C}_A - a_{22} \end{bmatrix} . \tag{152}$$

Application of the stability theorem requires an investigation of the eigenvalues of matrix A. The eigenvalues of any square matrix A are defined as the values λ that satisfy the following algebraic equation

$$\det[\lambda I - A] = [0] \tag{153}$$

where "det" denotes the determinant of the quantity in brackets, and I is a unit matrix of dimension equal to the dimension of A. Thus, the eigenvalues of Equation 152 are found as follows:

$$\det\left\{\begin{bmatrix} \lambda & 0 \\ 0 & \lambda \end{bmatrix} - \begin{bmatrix} a_{11} - a_{13}\bar{C}_T & a_{12} - a_{13}\bar{C}_A \\ a_{21} + a_{23}\bar{C}_T & a_{23}\bar{C}_A - a_{22} \end{bmatrix}\right\} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix} ,$$

which reduces to the following

$$\det\begin{bmatrix} \lambda - a_{11} + a_{13}\bar{C}_T & -a_{12} + a_{13}\bar{C}_A \\ -a_{21} - a_{23}\bar{C}_T & \lambda + a_{22} - a_{23}\bar{C}_A \end{bmatrix} = 0$$

Taking the indicated determinant in Equation 154 yields the following algebraic equation for λ:

$$\lambda^2 + [a_{22}-a_{23}\bar{C}_A - a_{11}+a_{13}\bar{C}_T]\lambda + (a_{21}+a_{23}\bar{C}_T)(a_{13}\bar{C}_A-a_{12}) + (a_{22}-a_{23}\bar{C}_A)(a_{13}\bar{C}_T-a_{11}) = 0 \qquad (154)$$

The roots of Equation 154 are found from use of the quadratic formula to be

$$\lambda_{1,2} = \frac{M \pm \sqrt{M^2 - 4N}}{2} \qquad (155)$$

where $M = a_{11} + a_{23}\bar{C}_A - a_{22} - a_{13}\bar{C}_T$

$$N = (a_{21}+a_{23}\bar{C}_T)(a_{13}\bar{C}_A-a_{12}) + (a_{22}-a_{23}\bar{C}_A)(a_{13}\bar{C}_T-a_{11}) .$$

Pontryagin's stability theorem states then that if both the roots of Equation 155 have negative real parts, Equations 149 and 150 will be asymptotically stable.

The investigation of the stability of the respiratory control system was based on an investigation of the roots of Equation 155. Two initial determinations were made to ascertain the effects of increased circulation time and also, an increased controller slope on respiratory stability, since the respiratory system was shown in the previous chapter to be affected most by changes in these two parameters. Equation 155 was programmed on an IBM 1130 digital computer. It was found that an increase in the circulation time delay of 1.0 minute was sufficient to effect respiratory instability. This value was obtained by assuming that all the respiratory parameters had normal values, except T, which was incremented in value until an eigenvalue having a positive real part appeared. Milhorn *et al.* (25, 26) reported in

a study on an analog computer solution of similar equations that a circulation time of 3 minutes was required to effect instability. The difference in the two results is attributed to the use of the Taylor series approximation to the time delay operator. The results, though, show that an increased circulation time by itself can cause respiratory instability.

Equation 155 was also investigated to ascertain the increase in the controller slope 'a' required to effect instability. For this case the controller set point 'b' was recomputed for each 'a' value used in Equation 155 in order to maintain the resting ventilation normal. The alternative is to increase 'a' without regard to 'b', which will result always in unrealistic values for the ventilation. The value of 'a' was increased, assuming that all the remaining parameter values were normal, until an eigenvalue having a positive real part appeared. The value of 'a' required for the adult was found to be 5835 liters/minute, or 13 times normal. Using this value predicted by the stability analysis, the original respiratory equations, Equations 33 and 34, were solved in the digital computer. The results are shown in Figure 48, which shows well - defined cyclic oscillations having a period of approximately one minute, a typical value for Cheyne - Stokes breathing. The ventilation oscillations of Figure 48 appear to be damping out with time. This is because the value of 'a' used in the solution of the respiratory equations had been set to 5800, not the critical value of 5835, through oversight.

A similar study was carried out for the infant control system. It was found that the circulation time delay required to cause instability was 3.5 minutes, or about 43 times the normal value. The controller slope

required to cause instability was computed to be 1100 liters/minute, or 51 times normal. It is apparent then that the infant's CO_2 control system is more difficult to drive into instability than is the adult CO_2 control system. This observation was predicted previously on the basis of the sensitivity analysis.

The results of a more complete stability analysis for the adult are shown in Figure 49. The effects on stability of individual parameters are shown plotted. These curves were obtained by setting, for example, Q to some value. All the remaining parameter values were assumed normal. For this situation a resting ventilation $\overline{V}_A$ was computed. The controller slope 'a' was then incremented (and 'b' was computed for each 'a' to maintain the $\overline{V}_A$ previously calculated) until Equation 155 indicated instability. This procedure reduced all the data to a common basis for comparison. Examination of Figure 49 shows that increases in k_2, V_T, $\overline{B}$, k, M, and k_1 tend to make the system more stable. Conversely, increases in Q and T tended to make the system unstable. Changes in V_A had little effect on respiratory stability, which was predicted by the sensitivity analysis. Also, changes in cardiac shunting were relatively important in determining system instability. The general trend indicated by the results of Figure 49 is that any factor that tends to decrease the tissue CO_2 level will move the respiratory system in the direction of instability. To reverse this situation it is apparent that one should raise the tissue CO_2 level by some means. To temporarily relive Cheyne - Stokes breathing inhalations of CO_2 are often administered.

Similar data for the infant CO_2 control system are shown in Figure

50. The general trend of decreased CO_2 tissue levels driving the system in the direction of instability also holds for the infant control system. However, examination of Figure 50 shows that the infant control system appears to be inherently more stable than the adult control system. This is probably due to the fact that the infant control system is more heavily damped than is the adult system.

The factors that can drive the respiratory system toward instability are additive in their effects. This means that while the circulation time delay is a most important factor in determining instability, its effects can be increased or decreased by changes in the other parameters. Figure 51 shows the effect on T that changes in the cardiac output for the adult will have. It is apparent that n increased cardiac output will decrease the value of T required for instability to occur. And the data of Figure 52 show that the required time delay to cause instability will be reduced even more when Q is abnormally large and also, $\overline{B}$ has decreased.

The conclusions drawn from the data presented in this section can be summarized as follows. Although respiratory system stability is a complicated function involving <u>all</u> the parameters of the respiratory system, increased circulation delay time (due usually to an enlarged left ventricle of the heart) and increased sensitivity of the brain CO_2 controller to changes in tissue CO_2 levels appear to be the main determinants of respiratory system instability. Either parameter by itself can cause instability. In general, any factor that tended to decrease the tissue CO_2 level drove the respiratory system in the direction of instability. It is concluded that the infant CO_2 control system is inherently more stable than is the

adult system.

While the data cited in this section obviously can not offer a complete explanation of why abnormal periodic breathing occurs, it is felt that such an analysis does lead to a better appreciation of possible contributing factors.

CONCLUSIONS AND SUMMARY

Engineering and mathematical methods are being increasingly utilized in the biological sciences as an aid to better understanding of biological systems. It was the purpose of this thesis to investigate the regulator effectiveness of the physiological system which regulates respiration by use of engineering sensitivity analysis. The major effort expended in this thesis was in providing a parameter sensitivity analysis of the CO_2 control system. In order to make comparisons between the sensitivity of an adult CO_2 control system and an infant control system, a mathematical model was derived for both systems.

Transient changes in tissue CO_2 concentrations C_T were computed for both the adult and the infant in response to an inhalation of CO_2, which was applied at $t = 0$ and terminated at $t = 20$ minutes. It was found that the infant control system is not as efficient at removing excess CO_2 from the body as is the adult's system. It is postulated from the sensitivity analysis data that this "inefficiency" of CO_2 removal is probably due to a decreased sensitivity of the brain tissue CO_2 controller to changes in CO_2 content.

An engineering dynamic sensitivity analysis was effected for the mathematical model equations in three separate studies. A dynamic sensitivity analysis is to be preferred over a steady state (or static) sensitivity analysis, since this study showed that peak magnitudes of sensitivity exist that would not be detected using a steady state approach.

The parameter sensitivities of the adult open loop CO_2 control system were computed. The effects on the tissue CO_2 concentration as a consequence

of individual 1% changes from normal in the cardiac output, cardiac output shunting, CO_2 dissociation curve intercept, circulation time delay, alveolar volume, metabolic rate of CO_2 production, and barometric pressure were computed. All results were computed using dynamic sensitivity coefficients. These results were compared with analogous sensitivity data for the adult closed loop CO_2 control system. Comparison indicates that the closed loop CO_2 control system is considerably less affected by respiratory system parameter changes than is the open loop system, which indicates one of the benefits of feedback.

A second sensitivity study compared the parameter sensitivities, based on normal parameter values, of the closed loop $C)_2$ control systems of the adult and the infant. It was found that the parameters that are of the greatest importance in the determination of the adult's tissue CO_2 concentration are those parameters associated with the brain controller (a and b) and the circulation time delay (T). It was also found that changes from normal in the cardiac shunting fraction and the alveolar volume (V_A) had little effect on the tissue CO_2 concentration. The parameter sensitivities of the infant were found to differ somewhat from the adult sensitivities. The parameters associated with the infant's controller (a and b) were found to have the greatest effect on tissue CO_2 concentration, but had half the effect that these same parameters had in the adult control system. The major difference between the two systems is the relative unimportance of the circulation time delay in the normal infant.

A third study computed adult and infant sensitivity data assuming

physiologically abnormal parameter values. The major finding was that an increased circulation time delay will become a dominant factor in the determination of tissue CO_2 concentration.

It was shown that the dynamic sensitivity coefficients can indicate control system stability trends in certain instances. Accordingly a stability analysis of the respiratory control system was effected using Lyapunov stability analysis. It was found that the stability of the respiratory control system involves a complex interrelationship of all the model parameters. In general, though, the two parameters that appear to be most important are the circulation time delay and the slope (a) of the CO_2 controller. It was found that the infant control system is inherently more stable than is the adult control system, though both systems are quite stable for normal values of the respiratory parameters. Finally, it was found that any parameter change that tended to decrease tissue CO_2 content moved the respiratory system in the direction of instability.

Sensitivity analysis appears to have at least two important area of application in physiological research. First, sensitivity analysis can indicate quantitative error information prior to the performance of an experiment. That is, it is desirous to have an idea of the effects on measured quantities that changes in parameters will have during the course of the experiment. This is, of course, contingent on having an acceptable mathematical model of the process under study.

A second area of application would be in the area of measurements. For example, assume that it is estimated that a parameter will change

during the course of an experiment. And assume that the effects of this parameter change will be reflected as a change in some system dependent variable. Sensitivity analysis can be used to predict the change in the dependent variable to be expected, and thus provide an estimate of the measurement requirements.

The limitations of this work are centered about the mathematical model employed and the parameter values chosen. It is probably true that any model of a physiological system will depart from physical reality to a degree. It is felt, though, that the model employed in this thesis is reasonable in that it predicts many experimentally observed respiratory occurrences.

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I dedicate this thesis to my wife, Billie, for her aid and patient understanding and who has made the whole effort worthwhile.

FIGURES

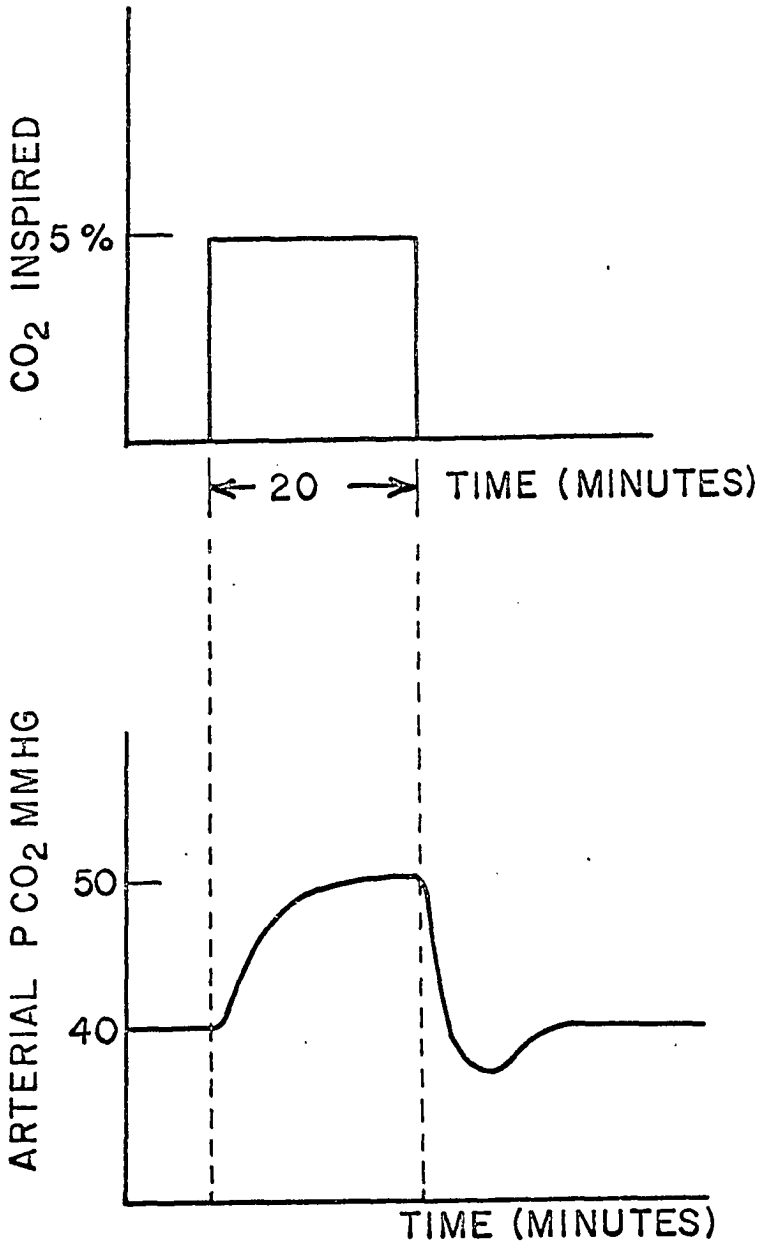


Figure 1. Effect of 5% inhalation of CO_2 on arterial CO_2 tension

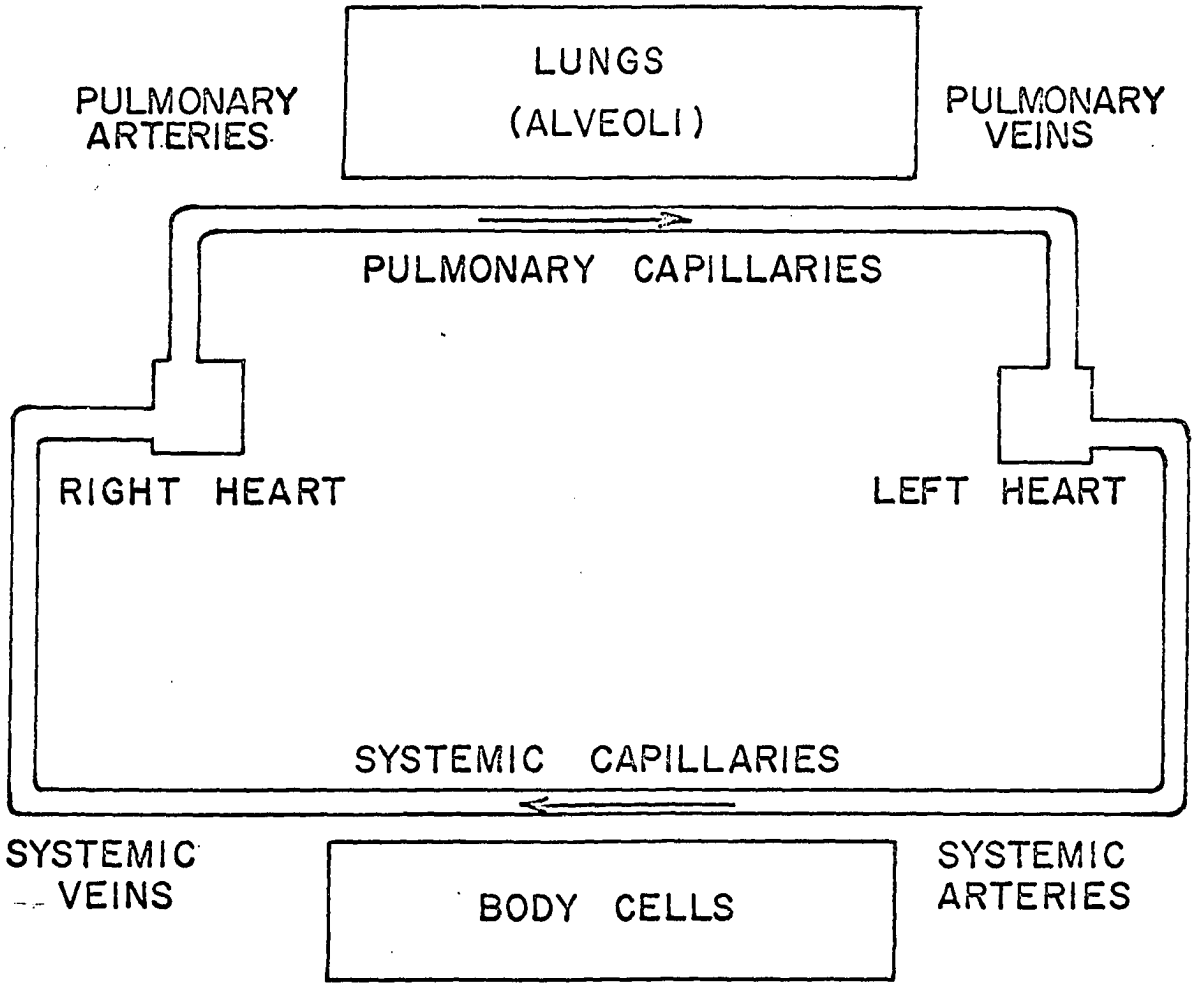


Figure 2. Schematic representation of the circulatory system's role in respiration

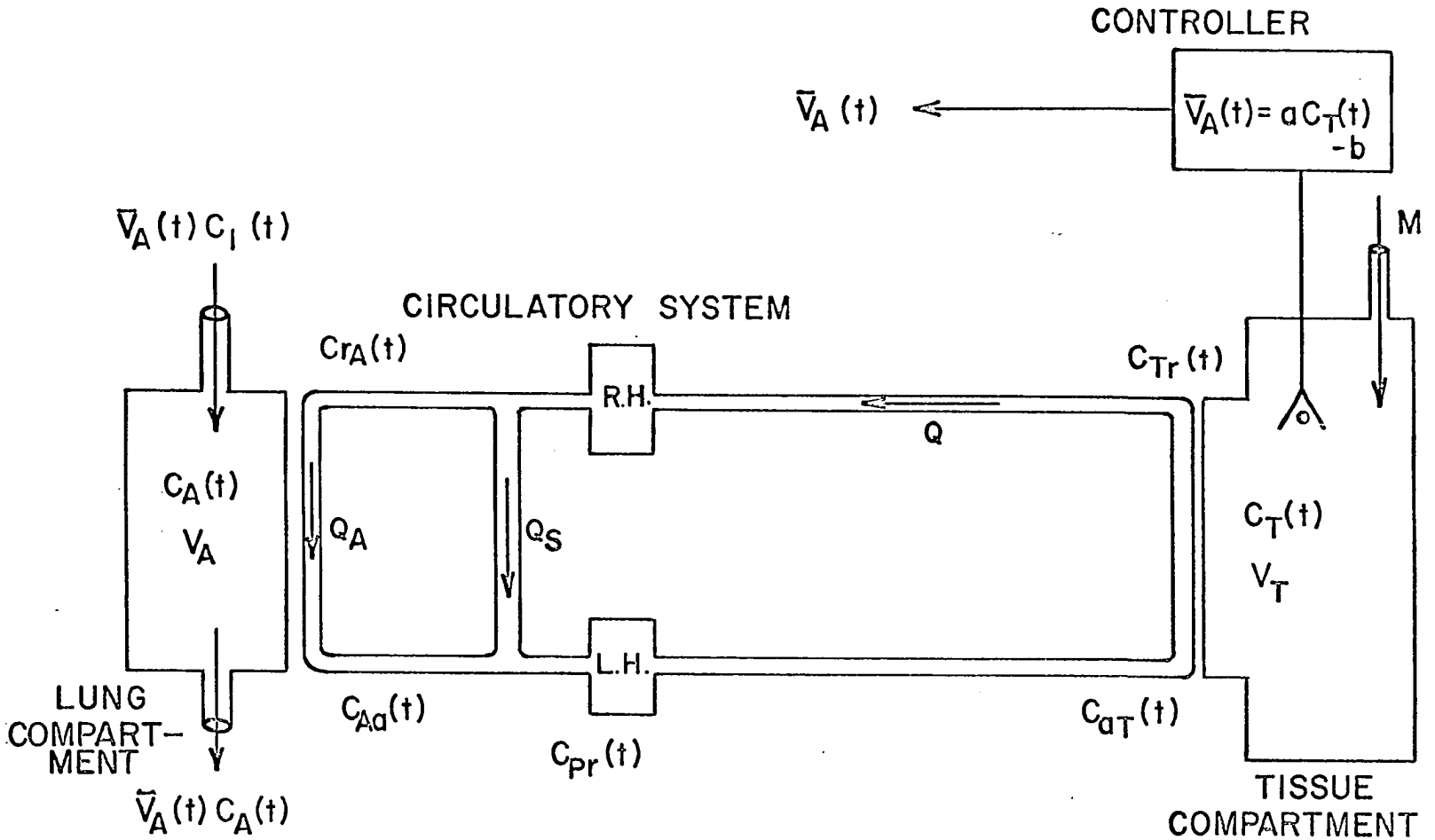
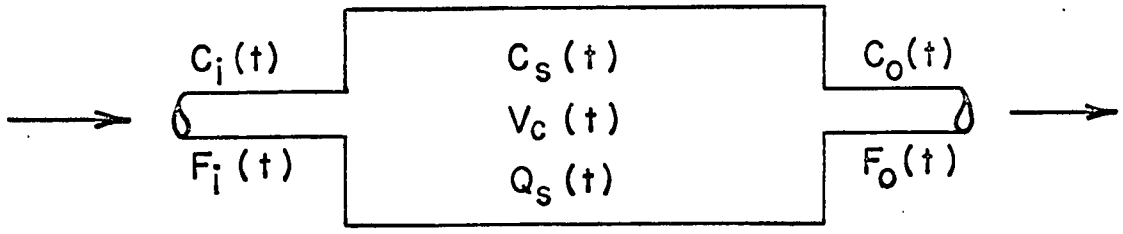


Figure 3. Compartmental model of the respiratory control system



$C_i(t)$ = CONC. OF SOLUTE "S" IN INFLOW
$C_o(t)$ = CONC. OF SOLUTE "S" IN OUTFLOW
$C_s(t)$ = CONC. OF SOLUTE "S" IN THE COMPARTMENT
$F_i(t)$ = INPUT FLOW (LITERS/UNIT TIME)
$F_o(t)$ = OUTPUT FLOW (LITERS/UNIT TIME)
$V_c(t)$ = COMPARTMENT VOLUME (LITERS)
$Q_s(t)$ = COMPARTMENT VOLUME OF "S" (LITERS)

Figure 4. A one-compartment model

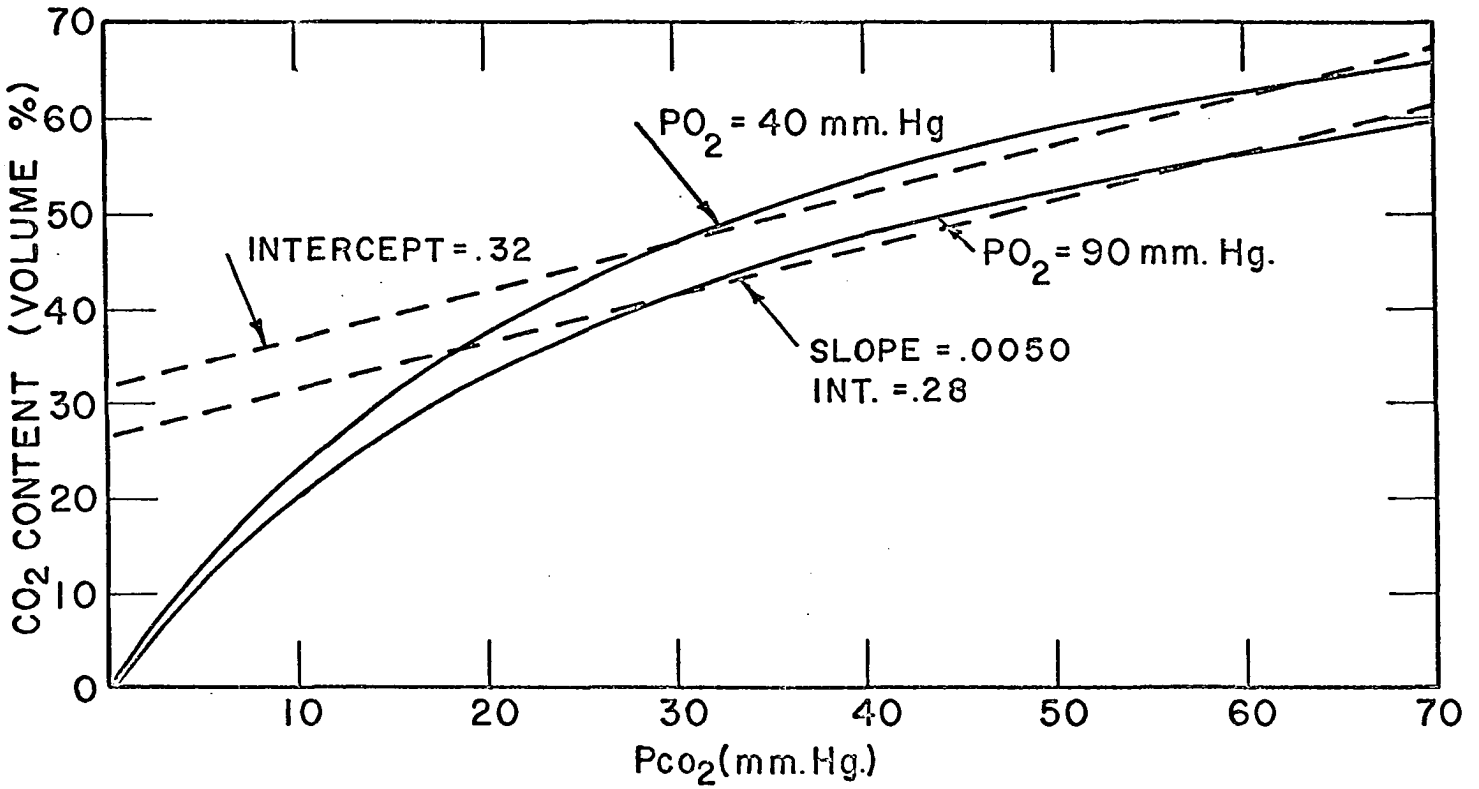


Figure 5. Adult CO_2 dissociation curve

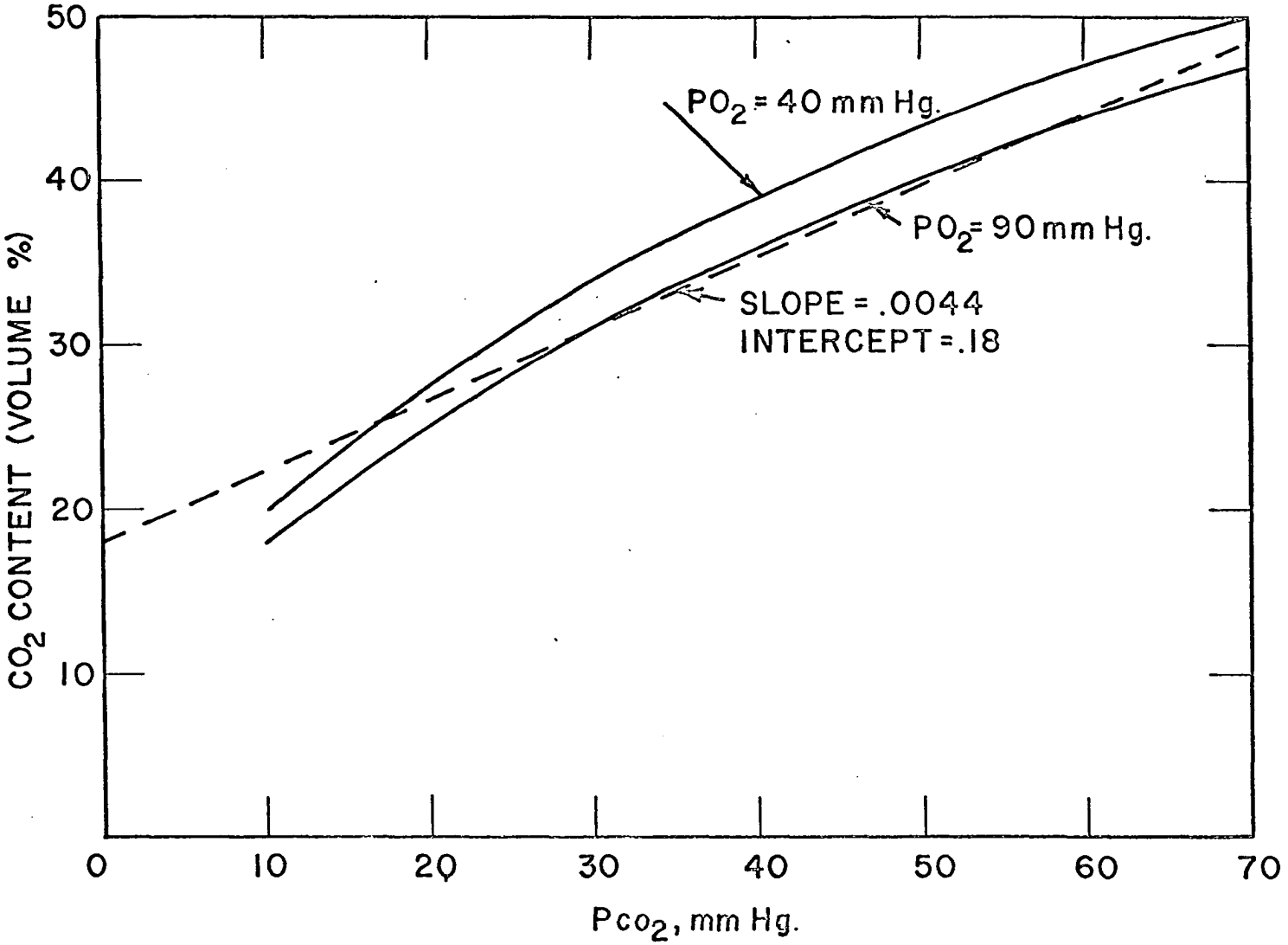


Figure 6. Neonatal blood CO_2 dissociation curves

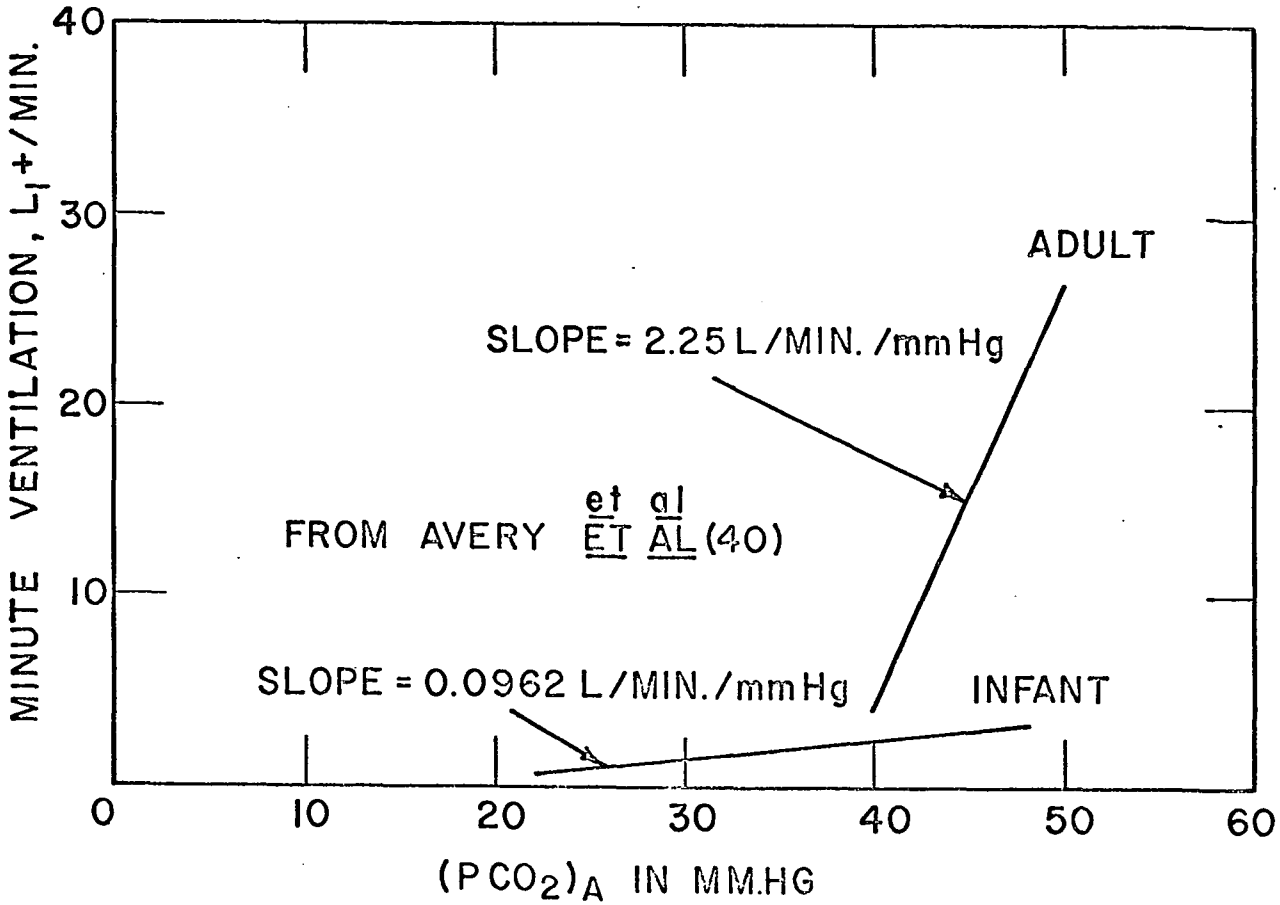


Figure 7. Steady state minute ventilation vs alveolar P_{CO_2}

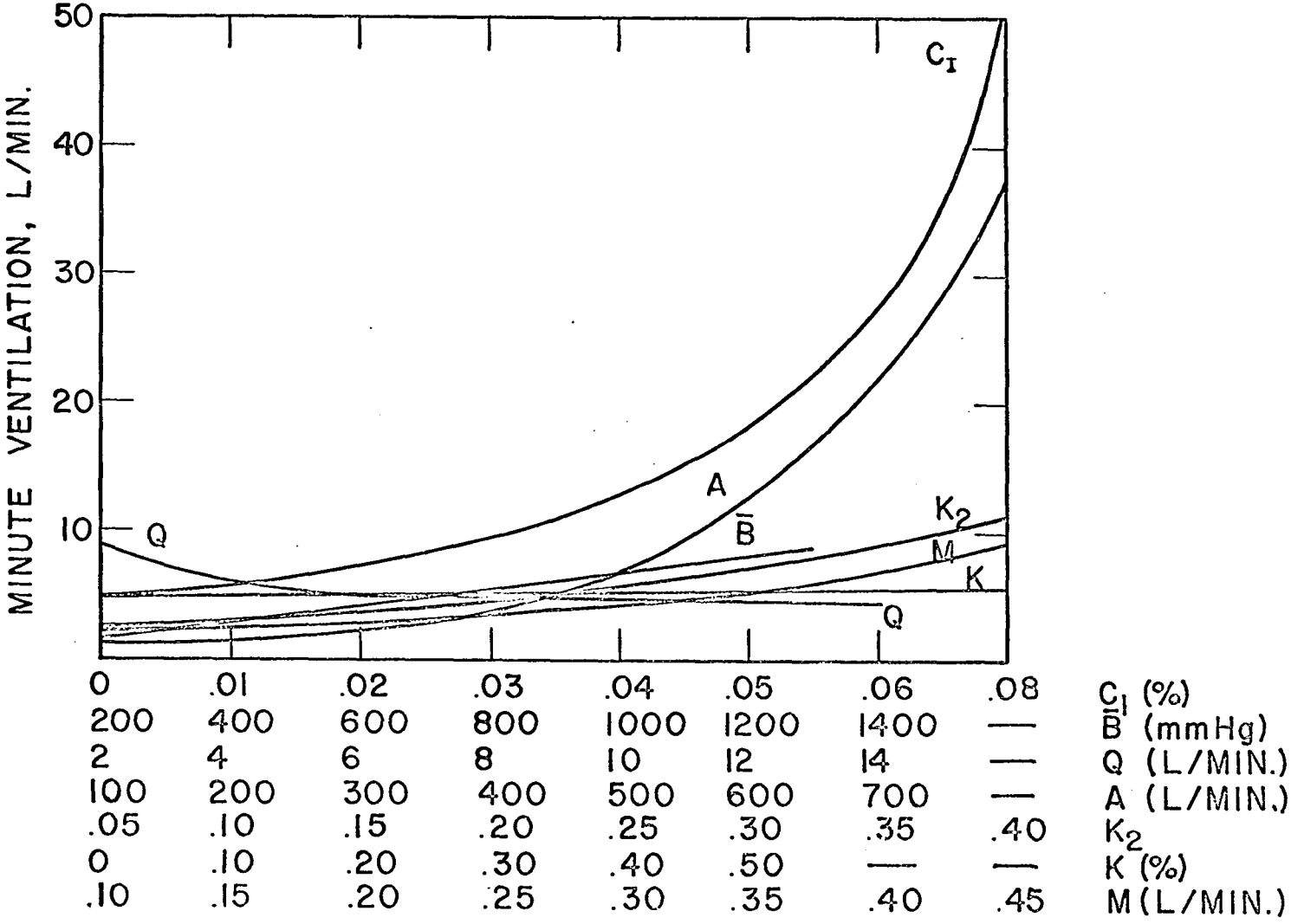
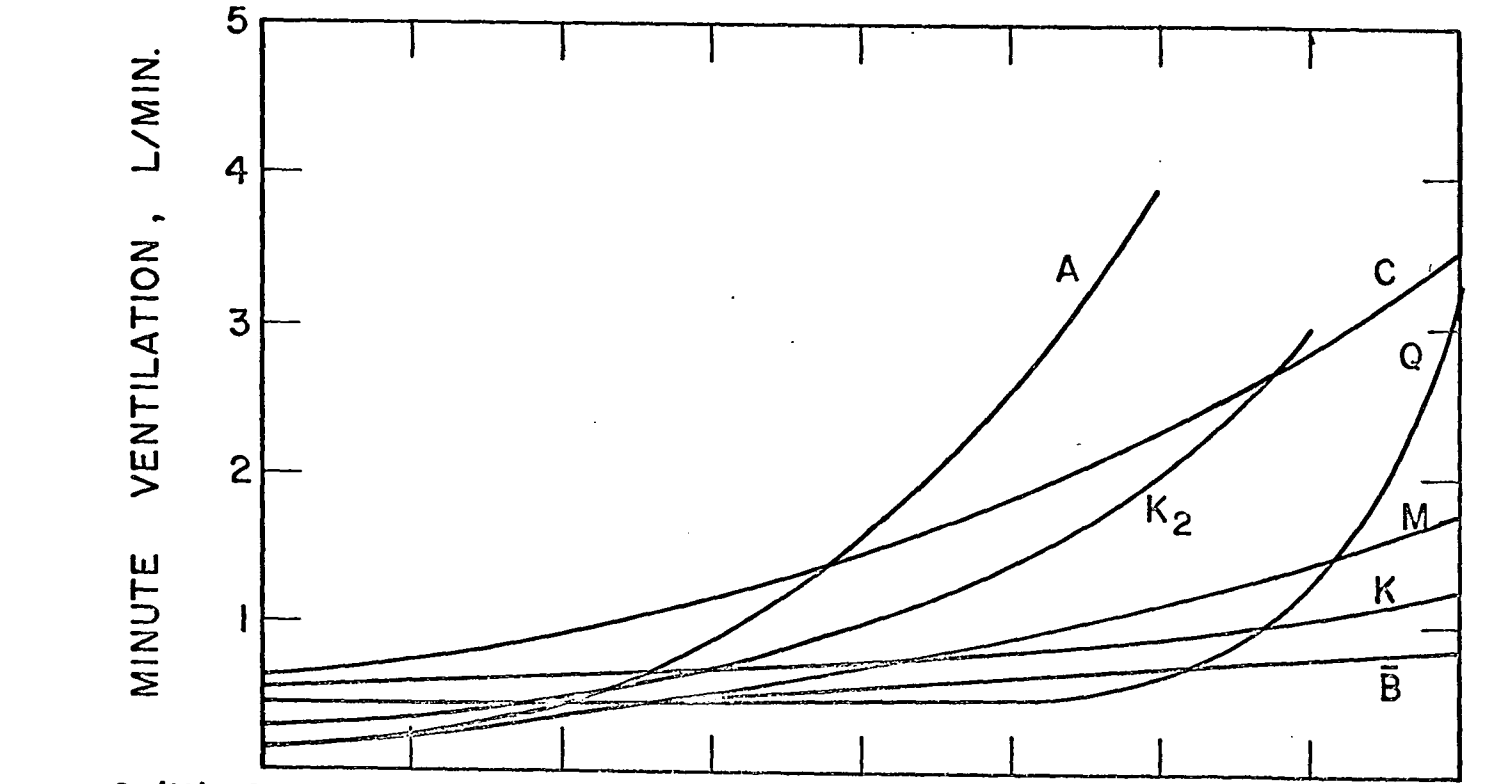


Figure 8. Adult steady state minute ventilation



C_I (%)	0	1	2	3	4	5	6	7	8
K (%)	20	—	30	—	40	—	50	—	60
Q (L/MIN)	.9	.8	.7	.6	.5	.4	.3	.2	.1
A (L/MIN)	10	—	20	—	30	—	40	—	50
K_2 ($mmHg^{-1}$)	.05	.10	.15	.20	.25	.30	.35	.40	—
M (L/MIN)	.010	—	.020	—	.030	—	.40	—	.050
$\bar{B}$ (mmHg)	300	400	500	600	700	800	900	1000	—

Figure 9. Infant steady state minute ventilation

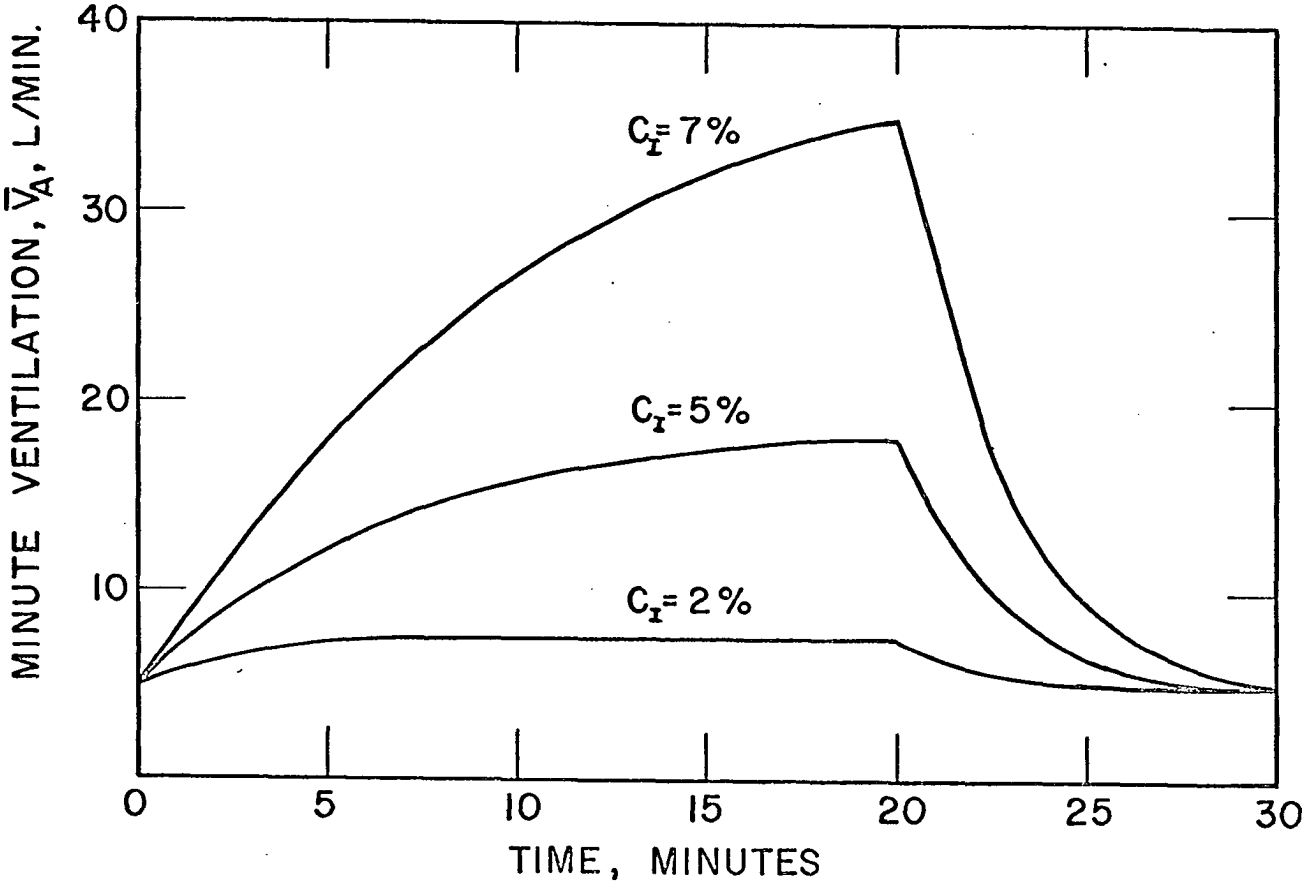


Figure 10. Ventilation response of the adult to CO_2 inhalations, normal parameters

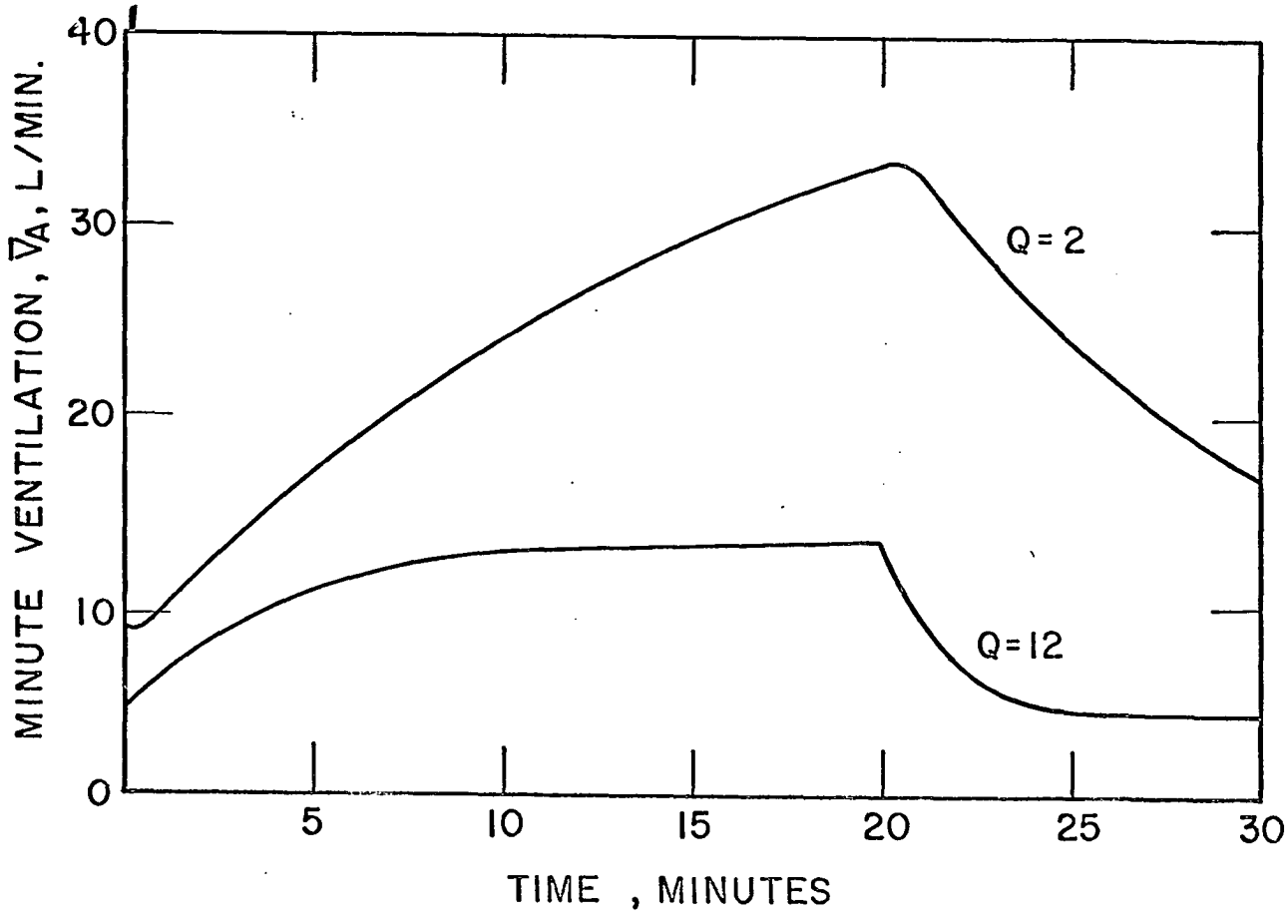


Figure 11. Adult minute ventilation vs cardiac output, C_I = 5%

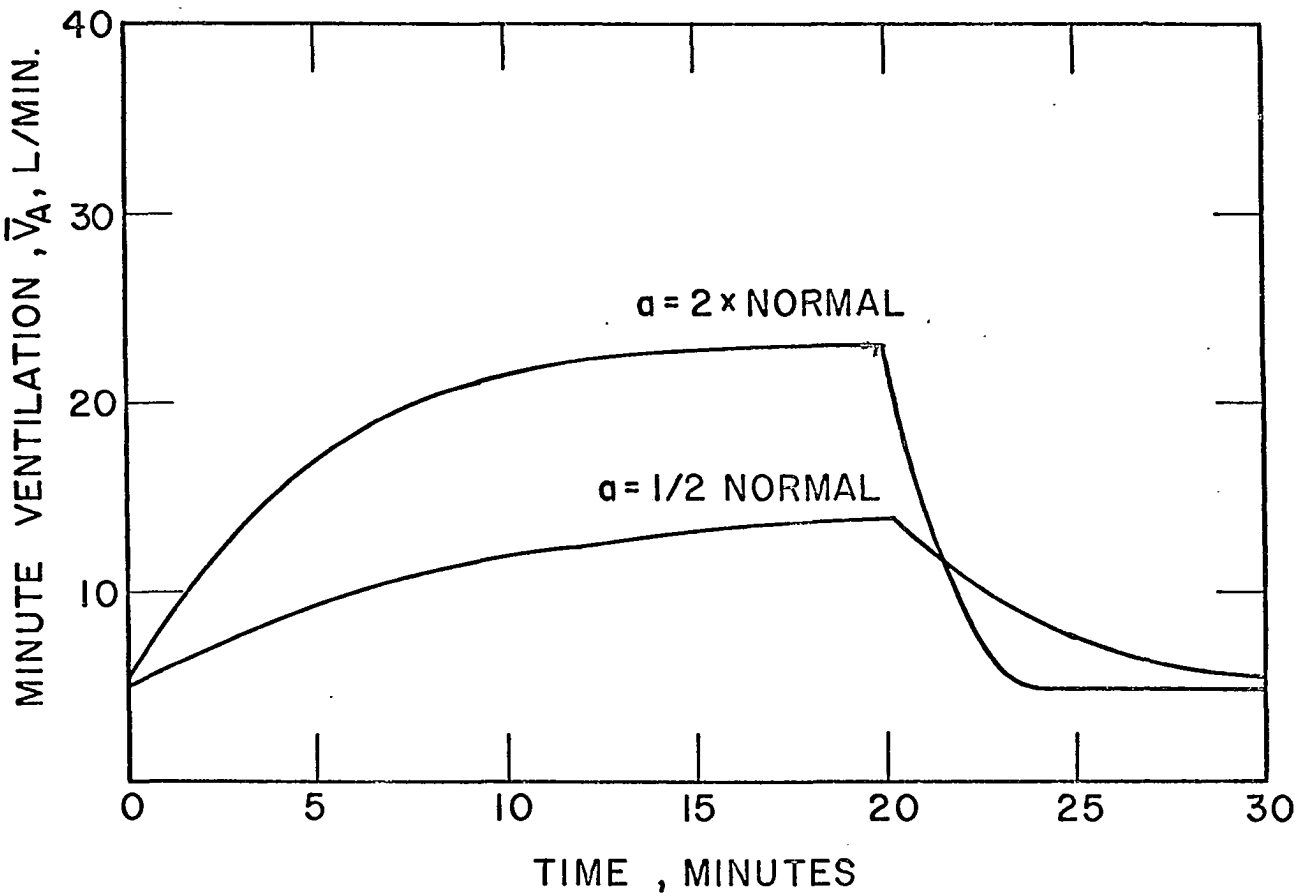


Figure 12. Adult minute ventilation vs CO_2 controller slope, C_I = 5%

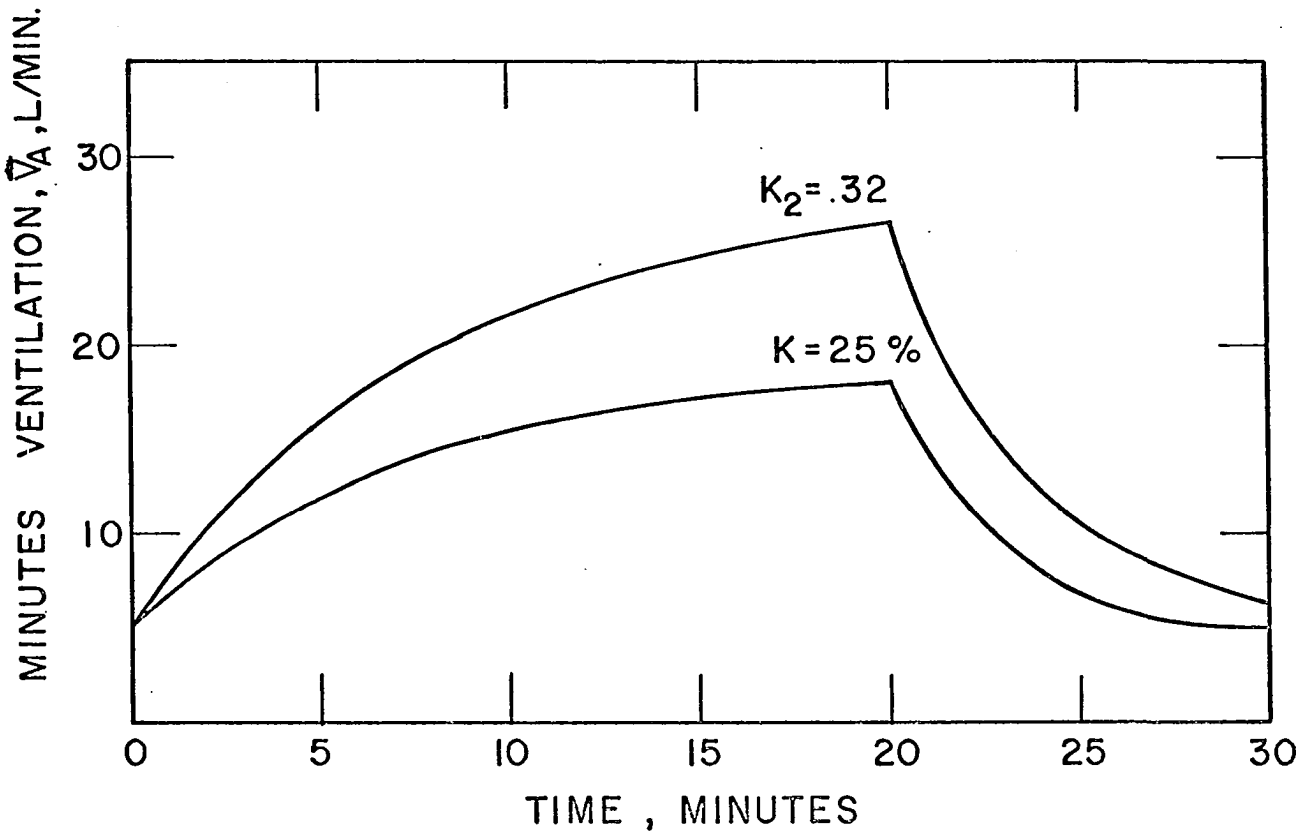


Figure 13. Adult minute ventilation vs cardiac shunting and CO_2 dissociation curve intercept, C_I = 5%

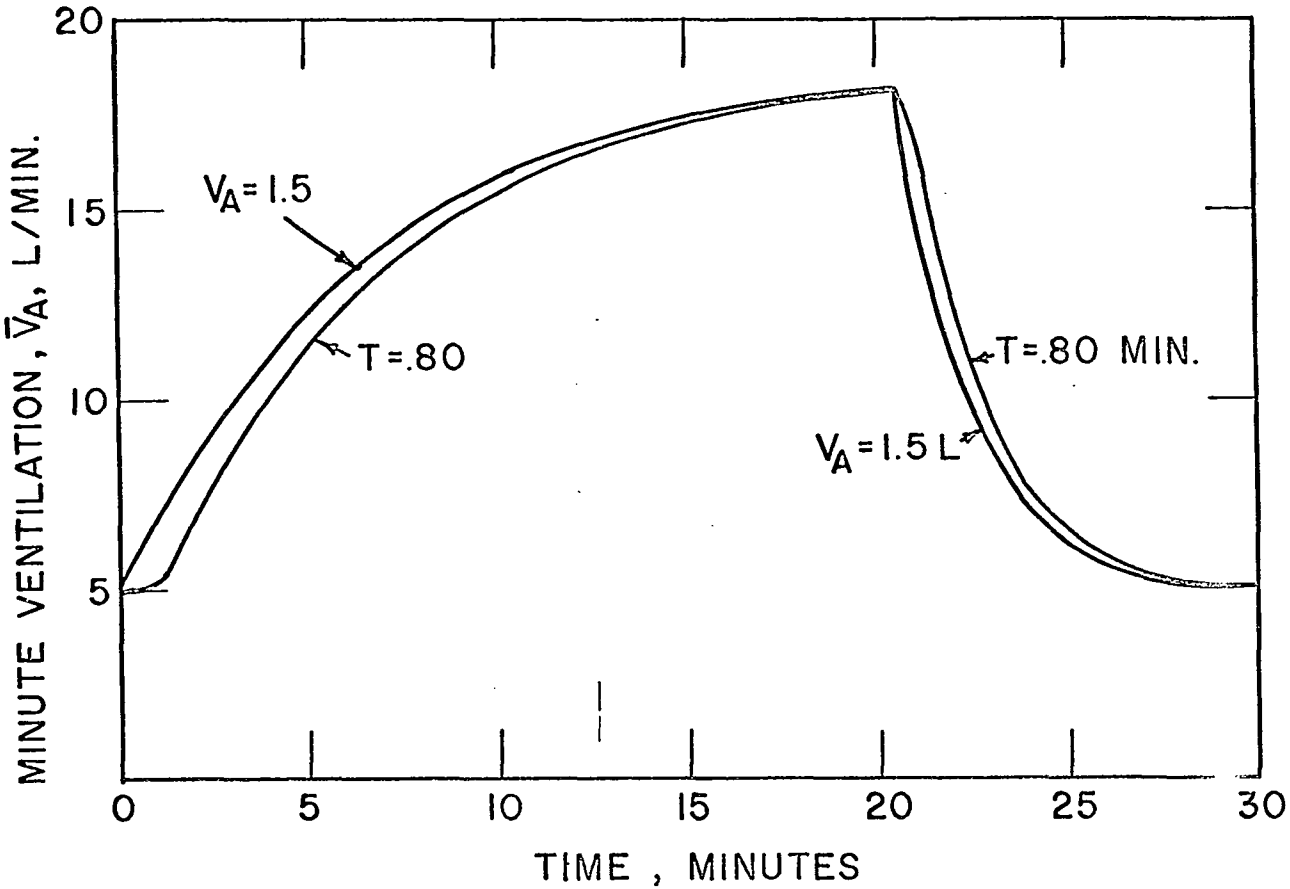


Figure 14. Adult minute ventilation vs alveolar volume and circulatory time delay, C_I = 5%

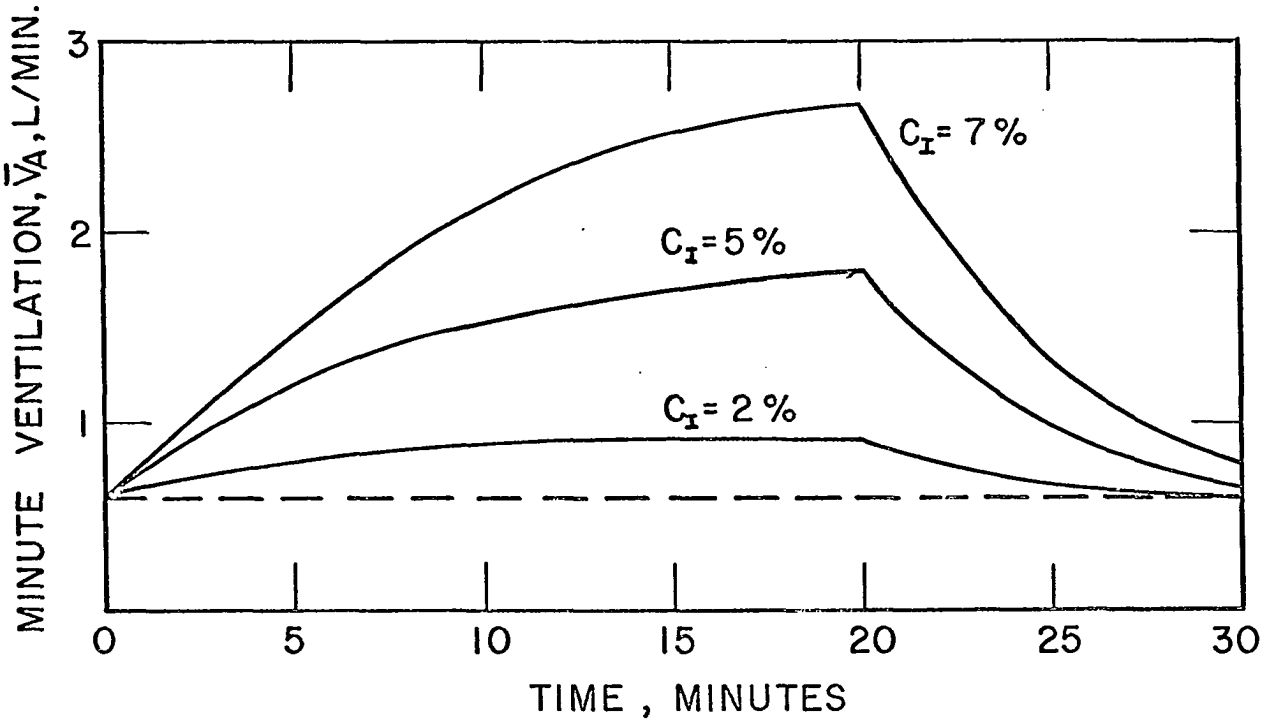


Figure 15. Ventilation response of the infant to CO_2 inhalations, normal parameters, C_I = 5%

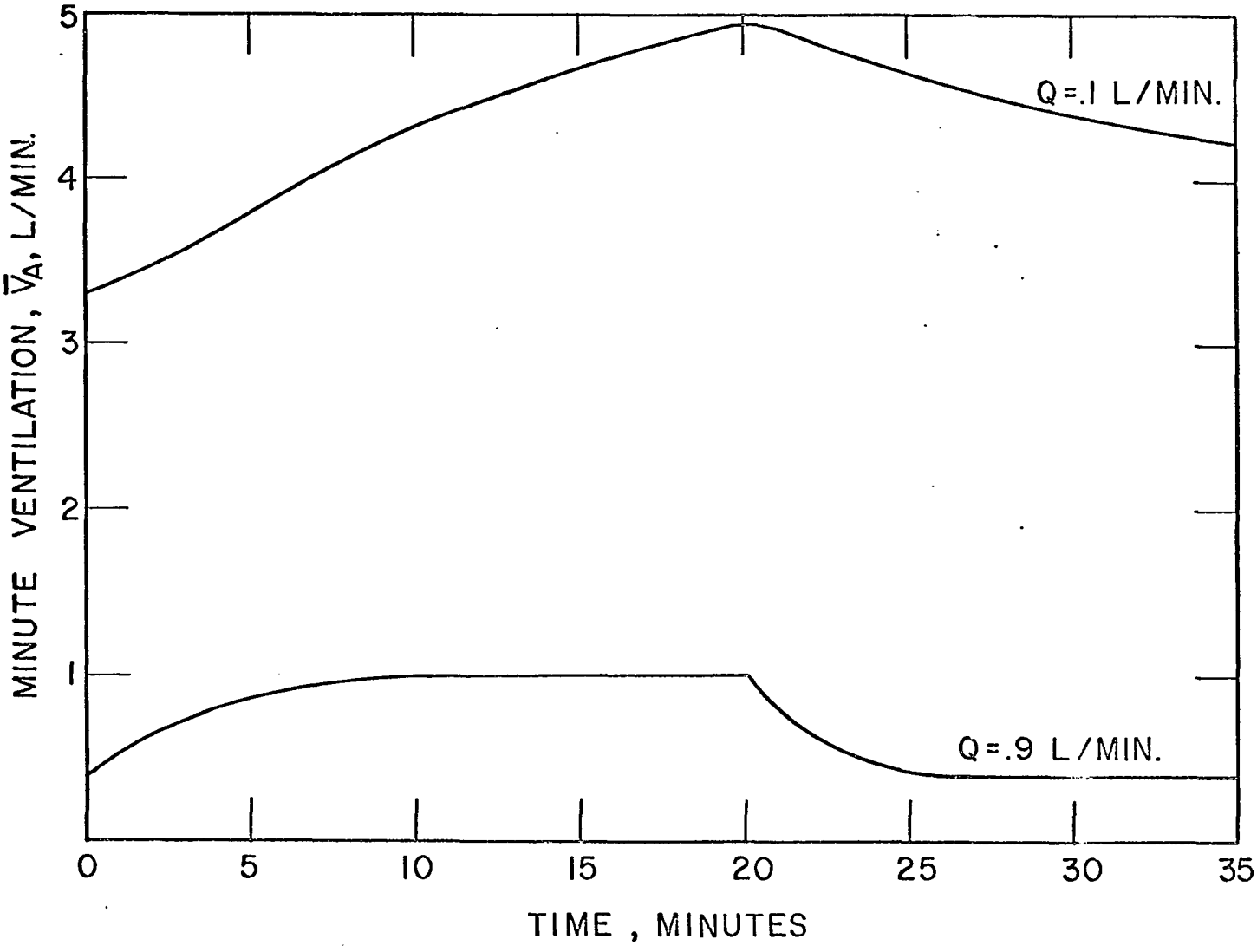


Figure 16. Infant minute ventilation vs cardiac output, C_I = 5%

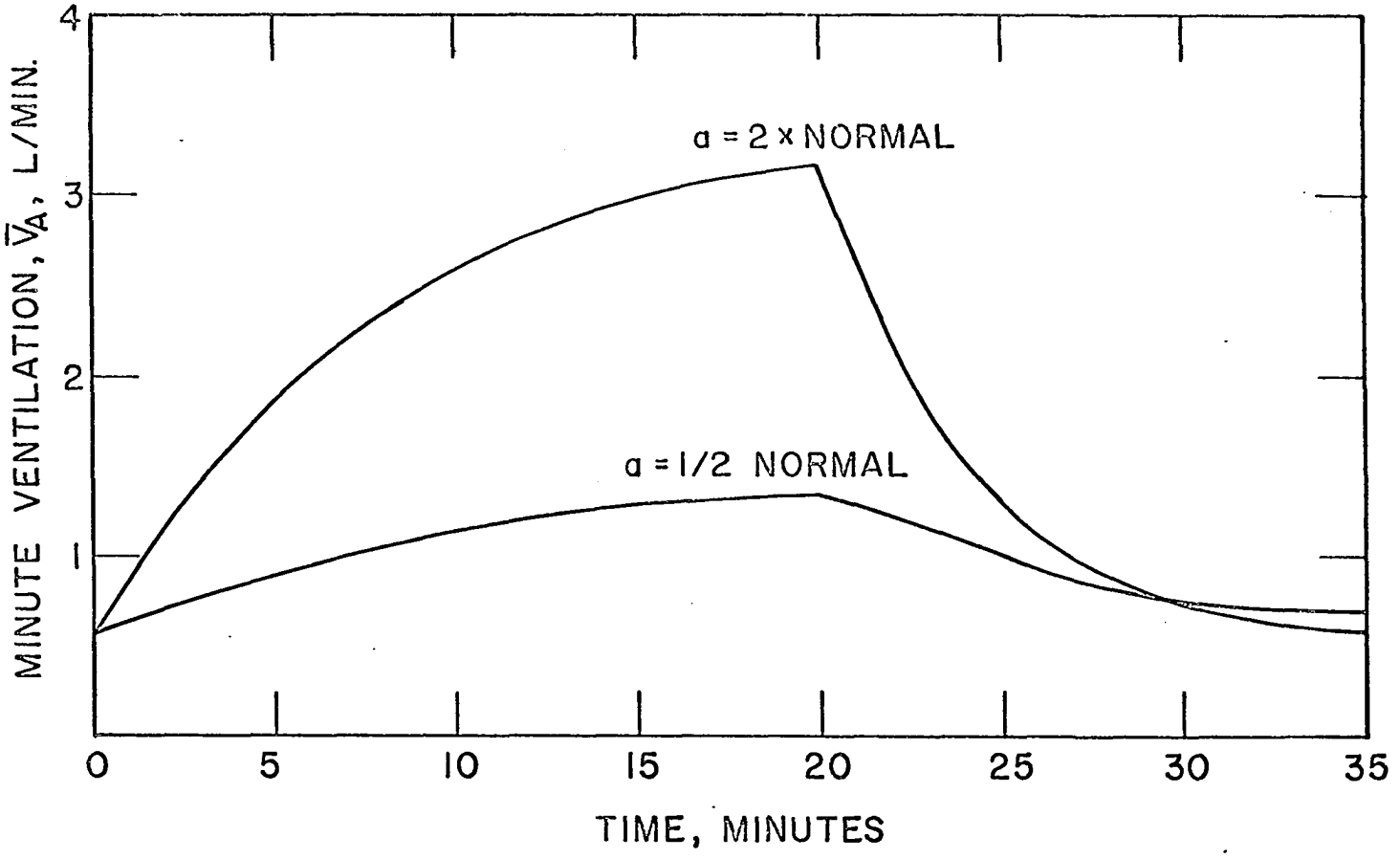


Figure 17. Infant minute ventilation vs CO_2 controller slope, C_I = 5%

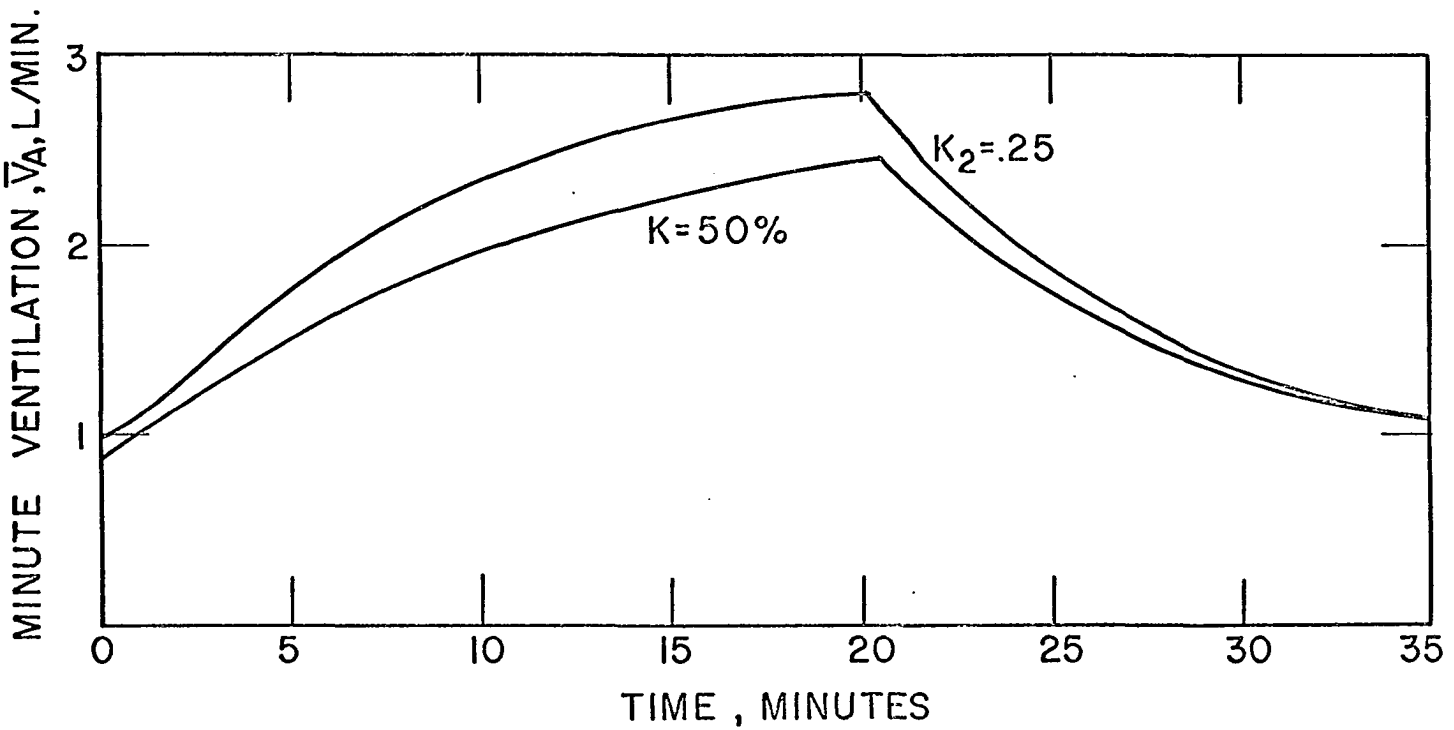


Figure 18. Infant minute ventilation vs cardiac shunting and CO_2 dissociation curve intercept, C_I = 5%

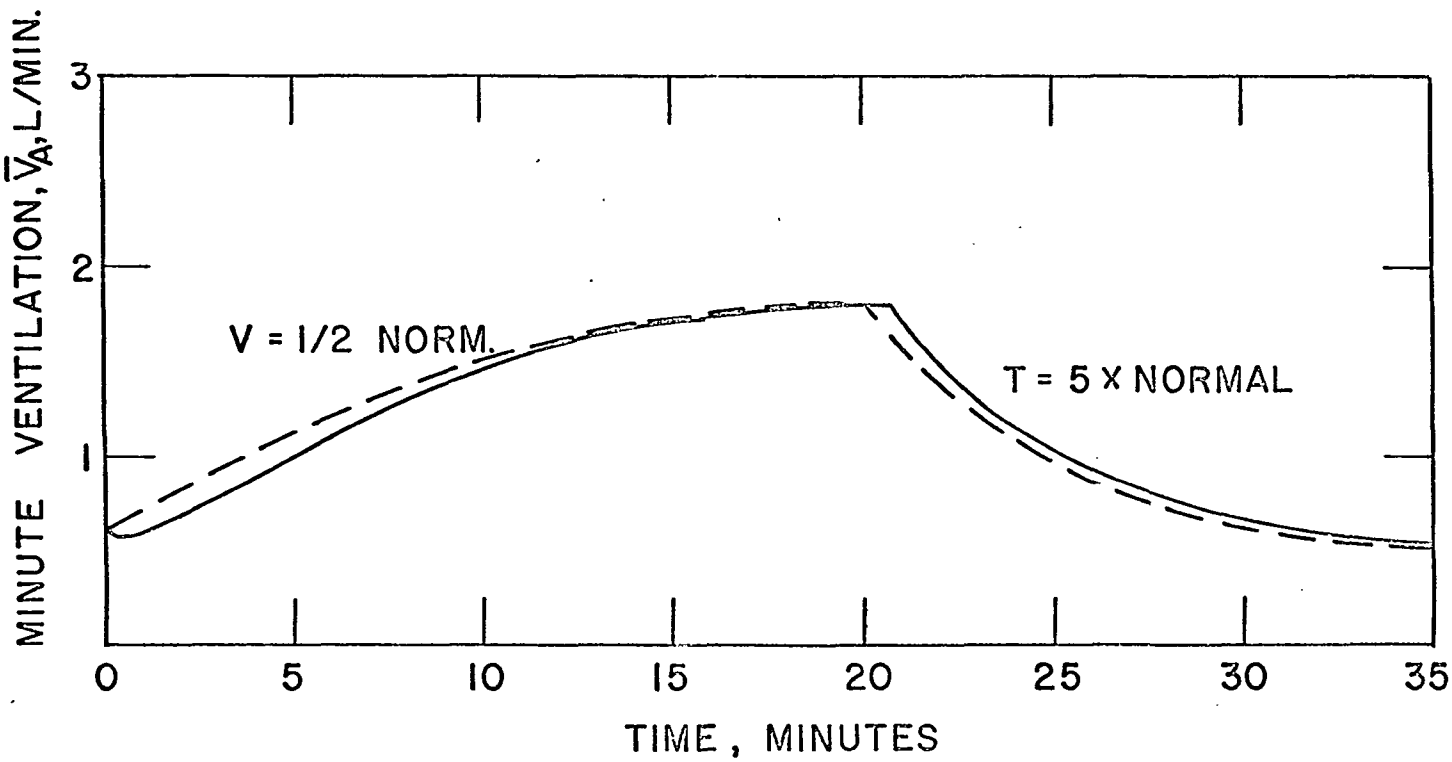


Figure 19. Infant minute ventilation vs alveolar volume and circulatory time delay, C_I = 5%

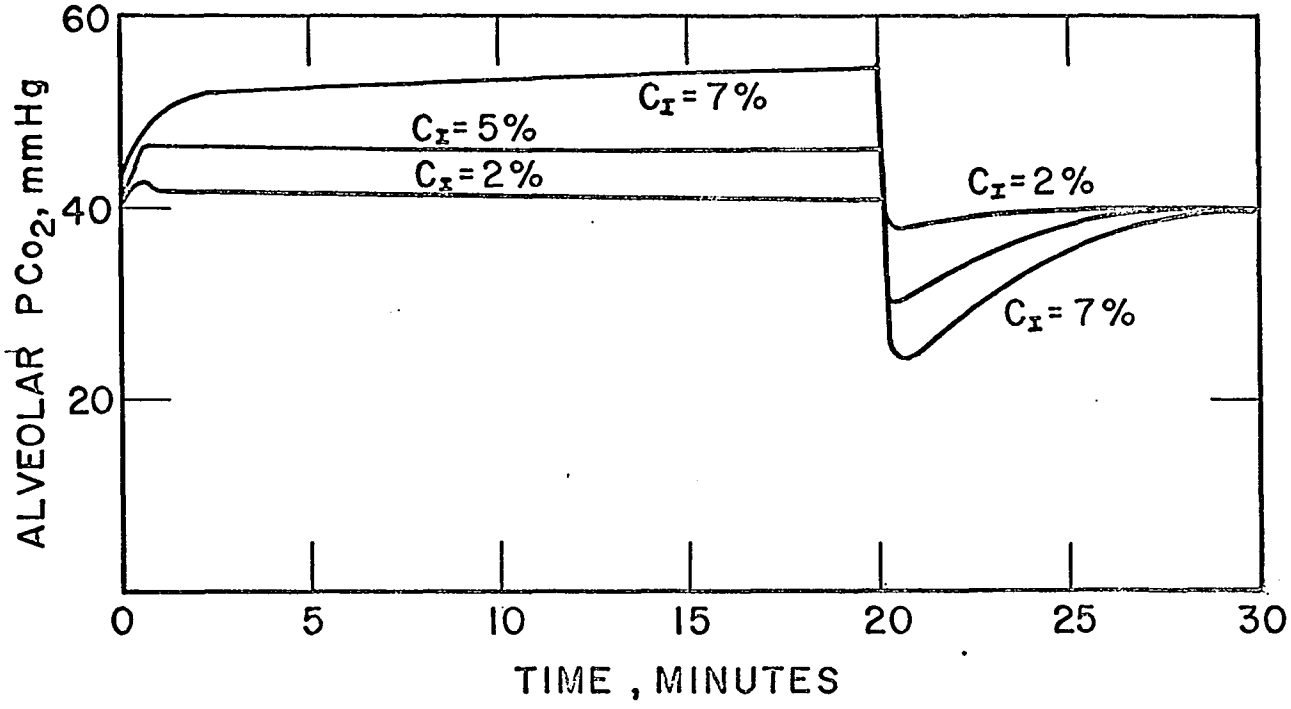


Figure 20. Adult alveolar P_{CO_2} in response to C_I

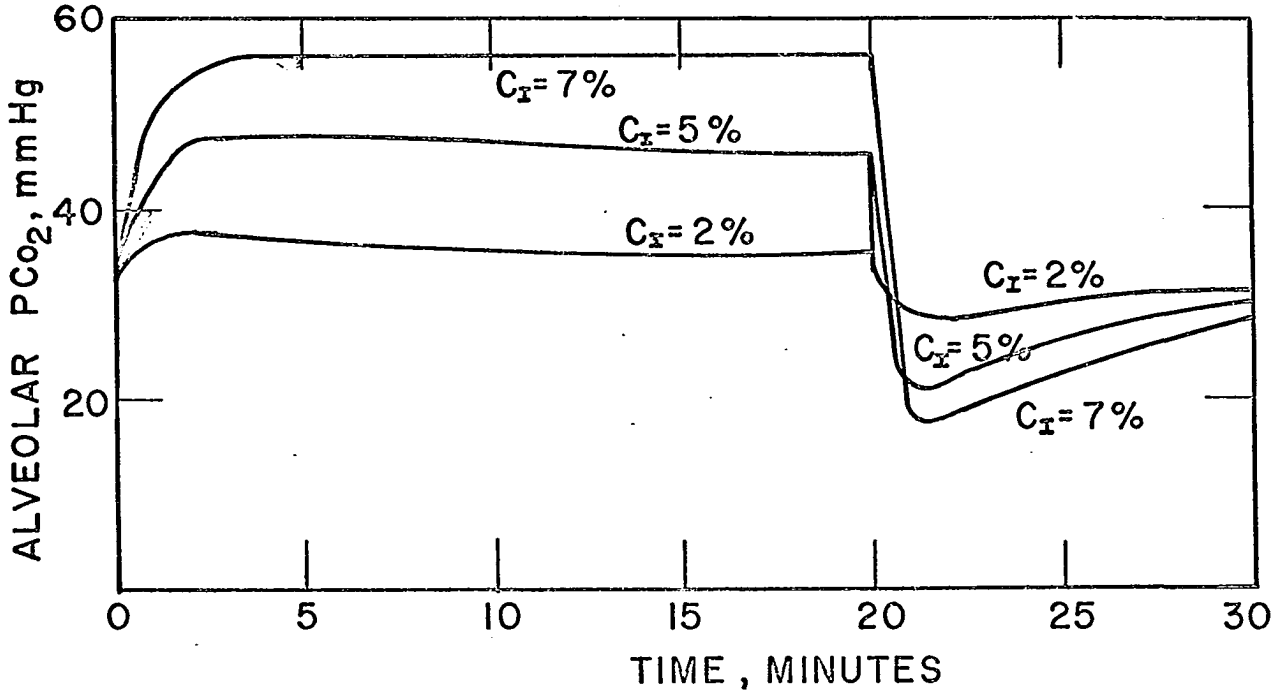
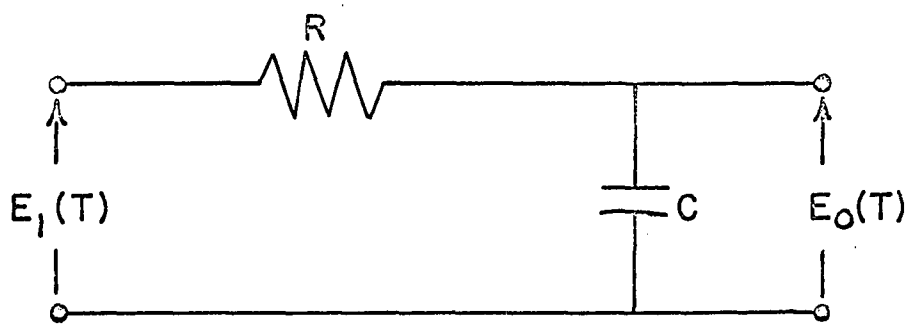


Figure 21. Infant alveolar P_{CO_2} in response to C_I

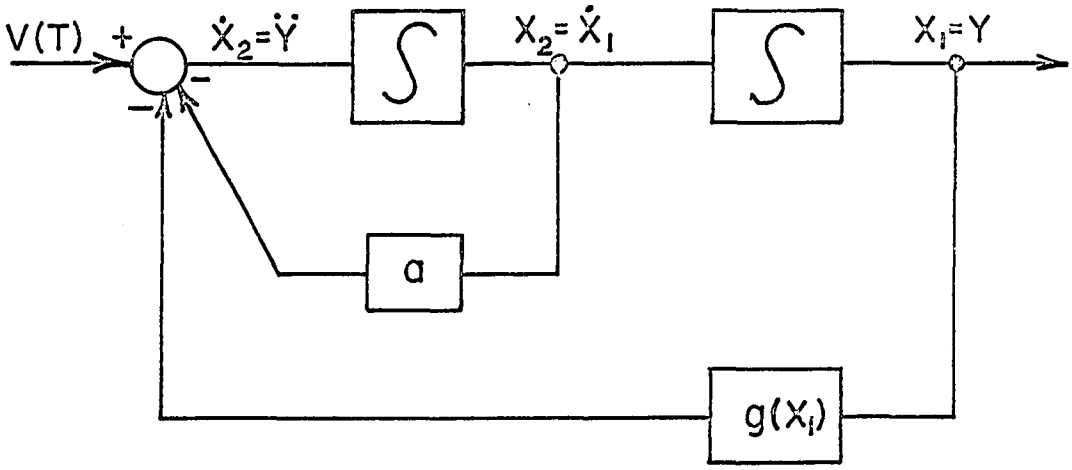


SYSTEM EQUATION : $RC\ \dot{E}_O(T) + E_O(T) = E_I(T)$

$E_I(T)$ = UNIT STEP FUNCTION

$E_O(T)$ AT T=0 IS ZERO

Figure 22. An RC circuit



SYSTEM EQUATIONS:

$$X_1(T) = X_2(T)$$

$$X_2(T) = -g(X_1) - a X_2(T)$$

$$v(T) = 0$$

Figure 23. A nonlinear control system

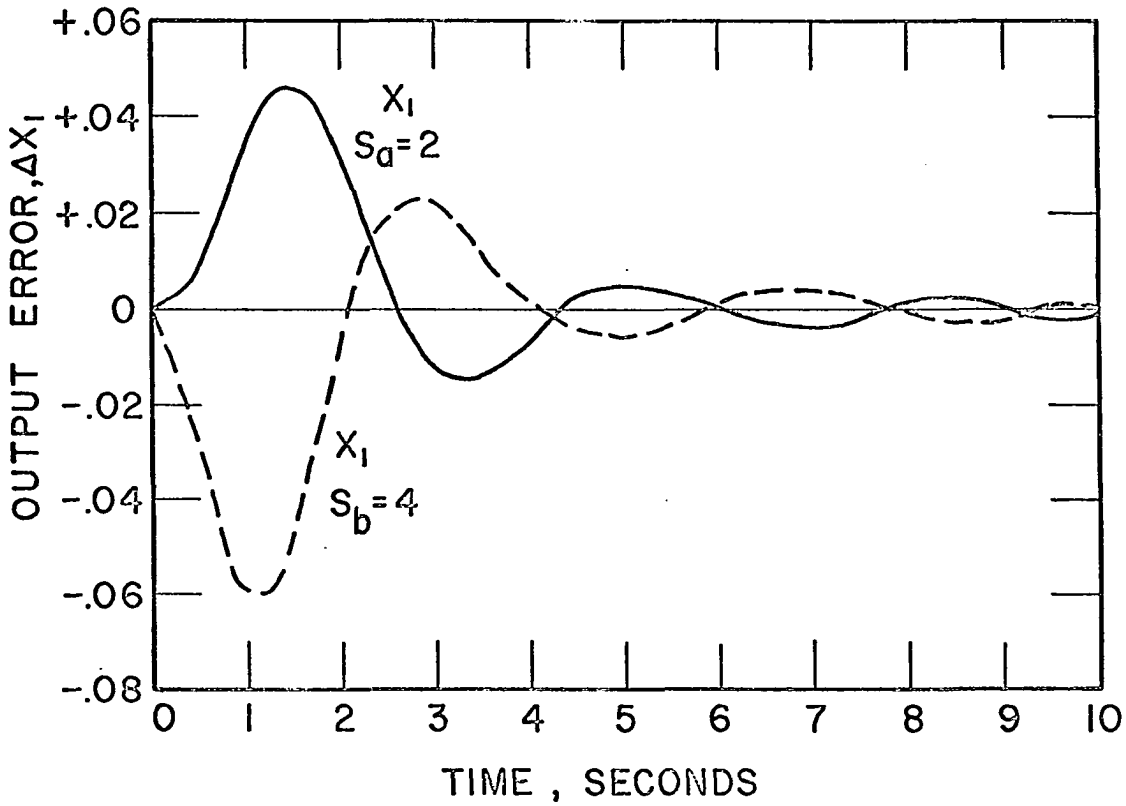


Figure 24. Linear control system sensitivity coefficients for a = 2, b = 4

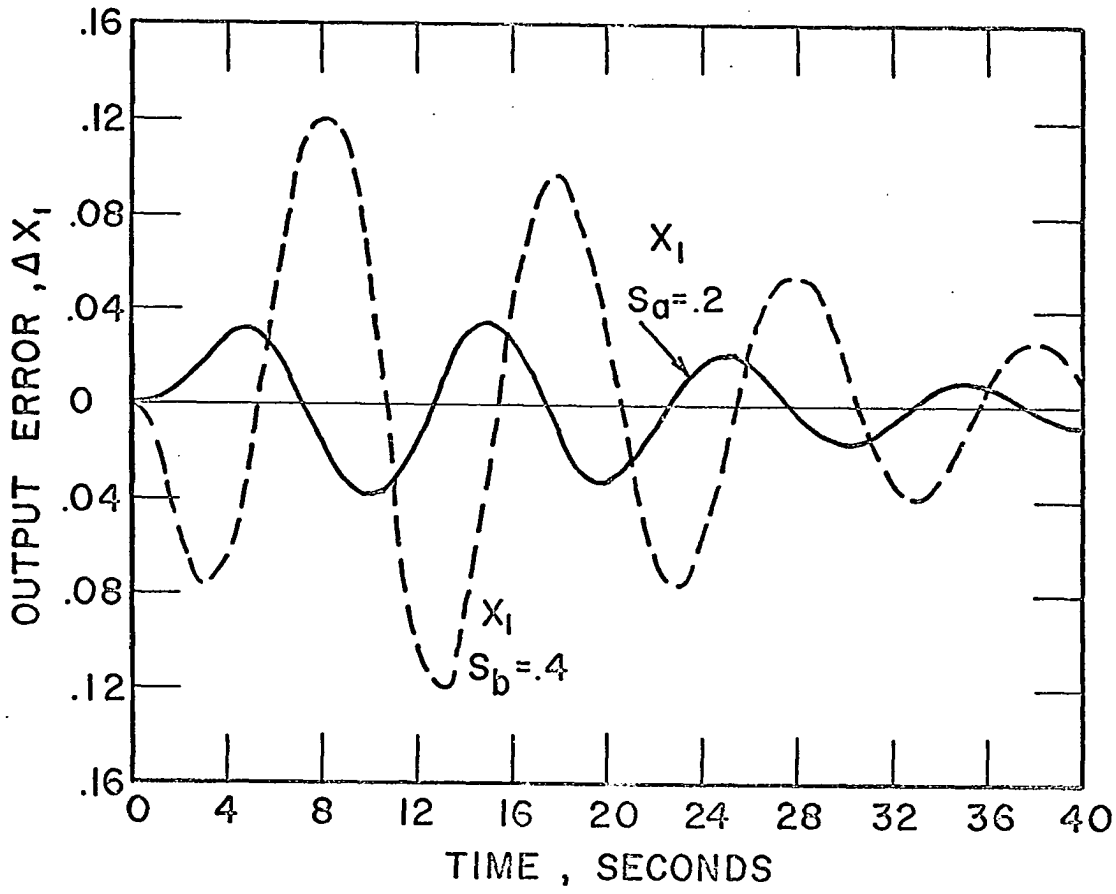


Figure 25. Linear control system sensitivity coefficients for a = .2, b = .4

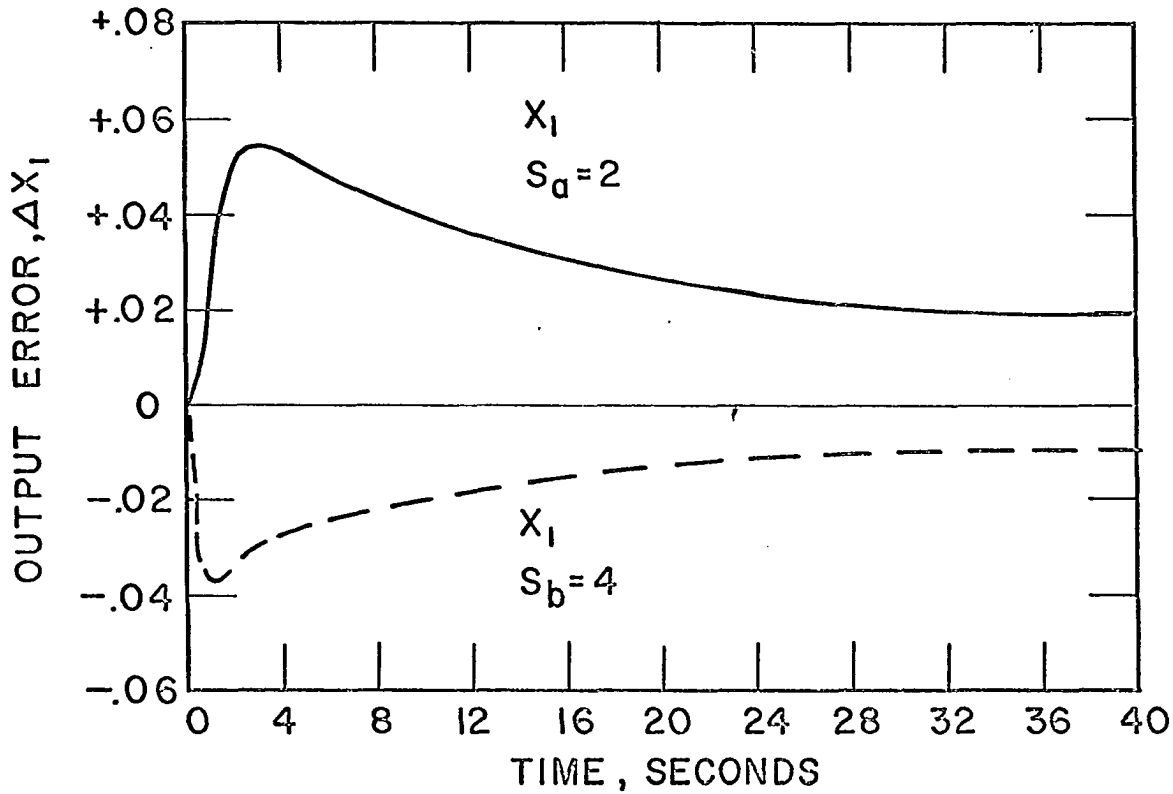


Figure 26. Nonlinear control system sensitivities for a = 2, b = 4

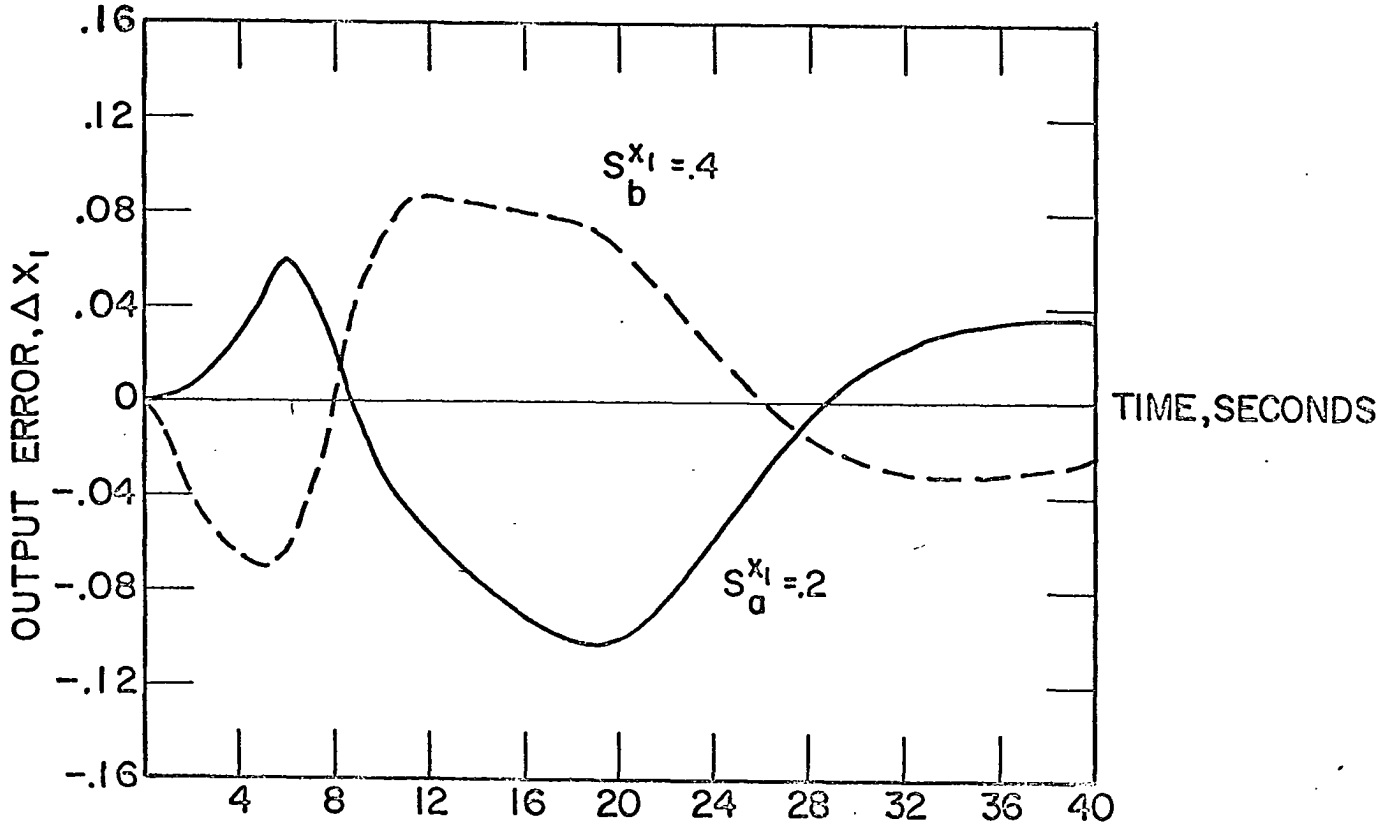


Figure 27. Nonlinear control system sensitivites for a = .2, b = .4

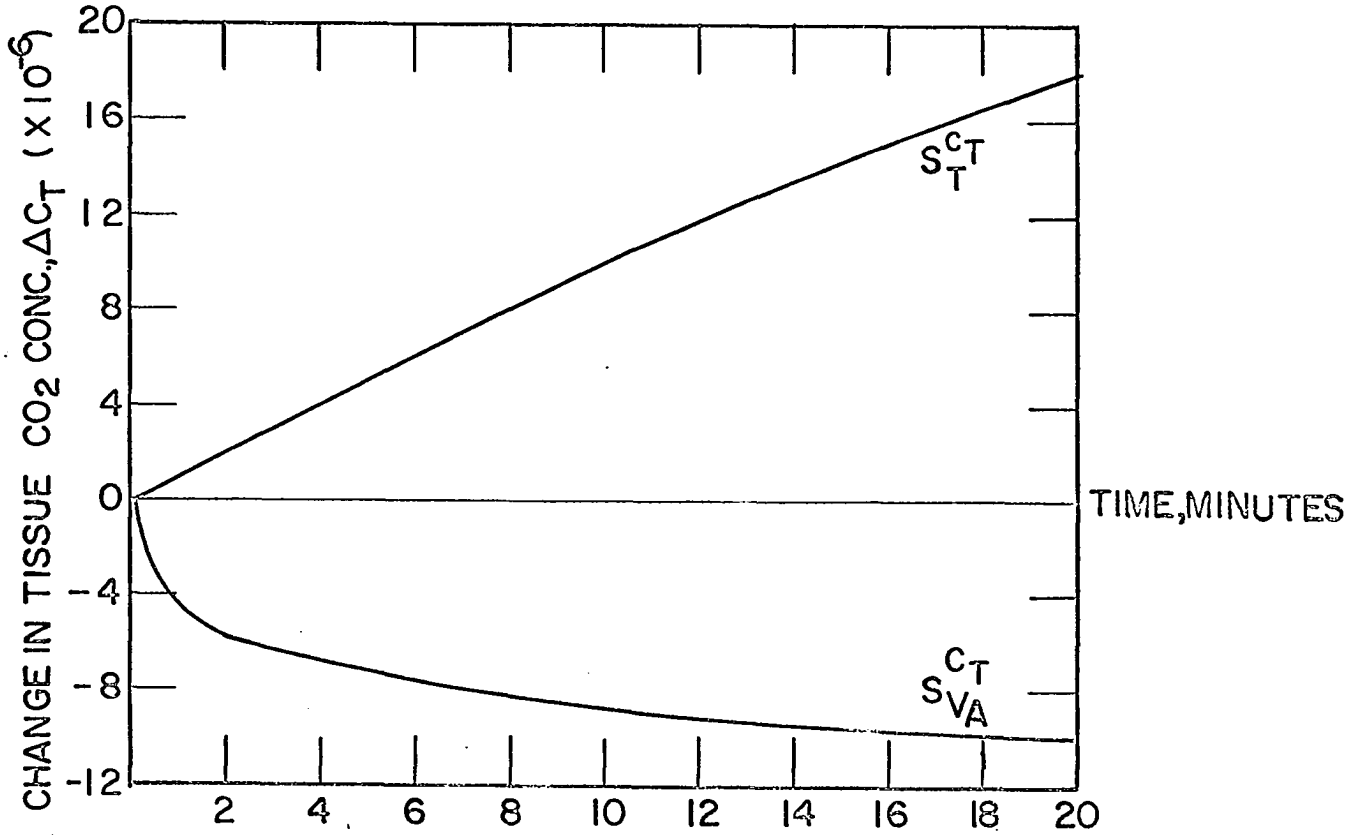


Figure 28. y_A and T sensitivity coefficients for open loop ventilation

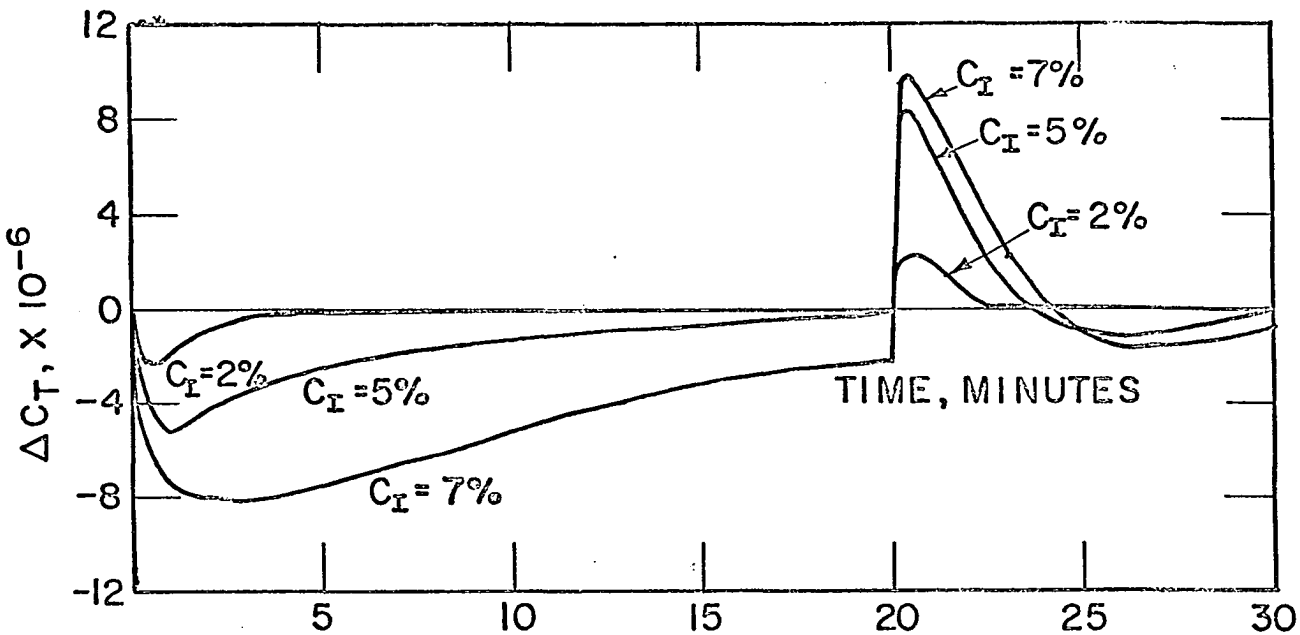


Figure 29. Alveolar volume sensitivity, $S_{V_A}^{C_T}$, as a function of CO_2 inhalation levels for the adult

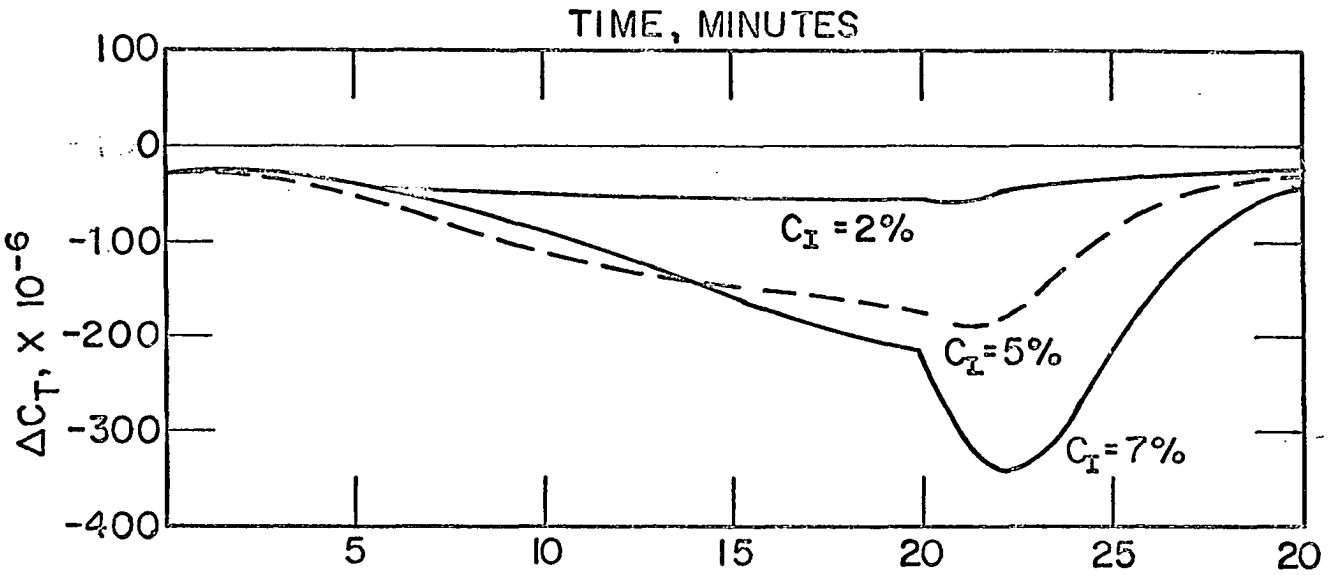


Figure 30. Cardiac output sensitivity, $S_Q^{C_T}$, as a function of CO_2 inhalation levels for the adult

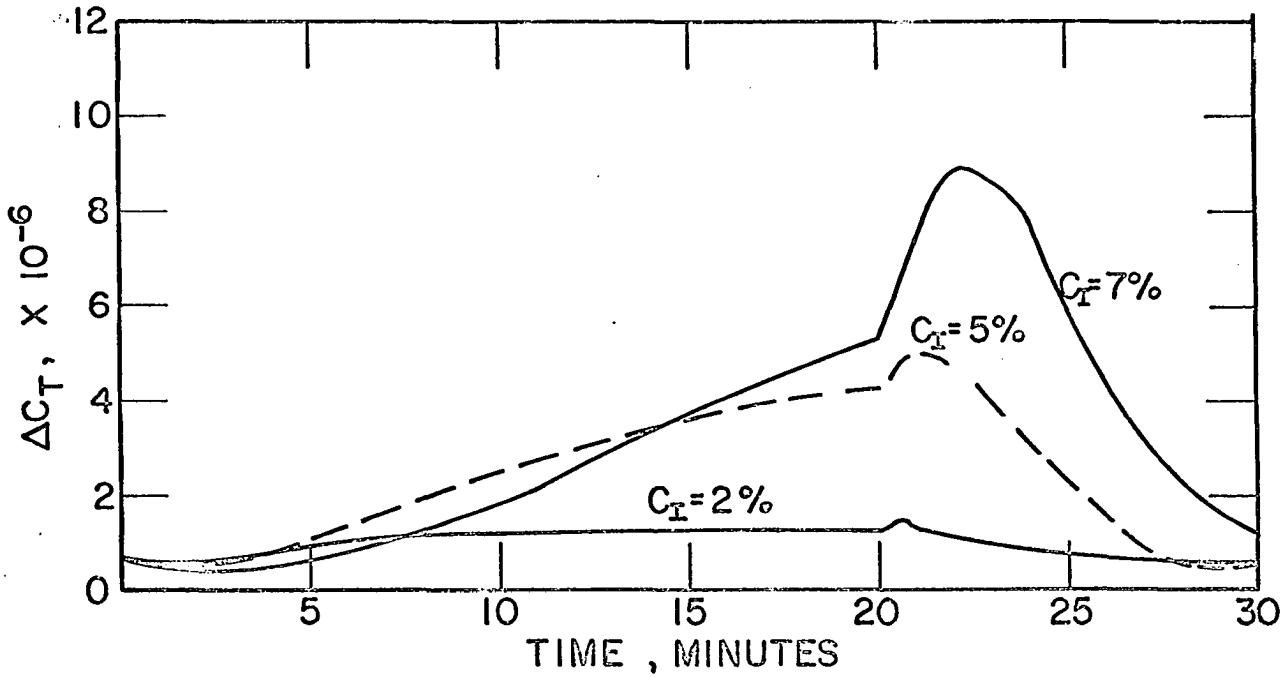


Figure 31. Cardiac shunting sensitivity, $S_k^{C_T}$, as a function of CO_2 inhalation levels for the adult

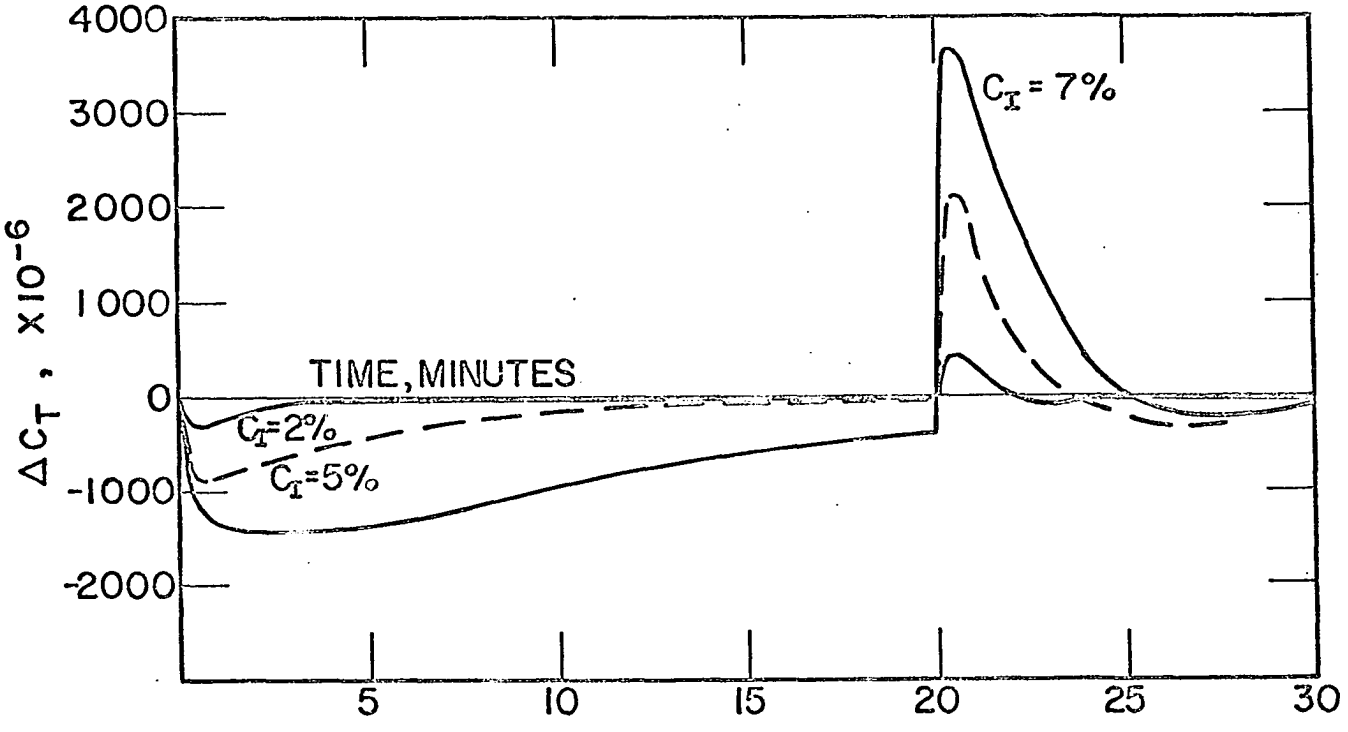


Figure 32. Circulation time delay sensitivity, $S_T^{C_T}$, as a function of CO_2 inhalation levels for the adult

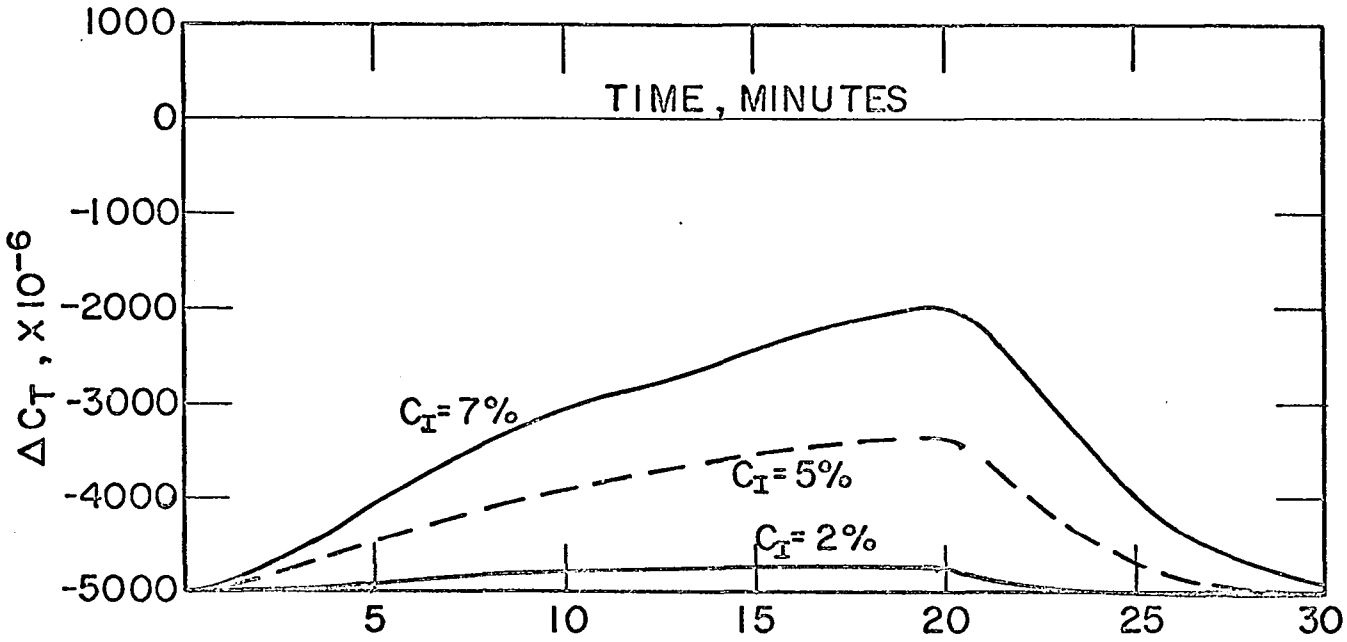


Figure 33. CO_2 controller slope sensitivity, $S_a^{C_T}$, as a function of CO_2 inhalation levels for the adult

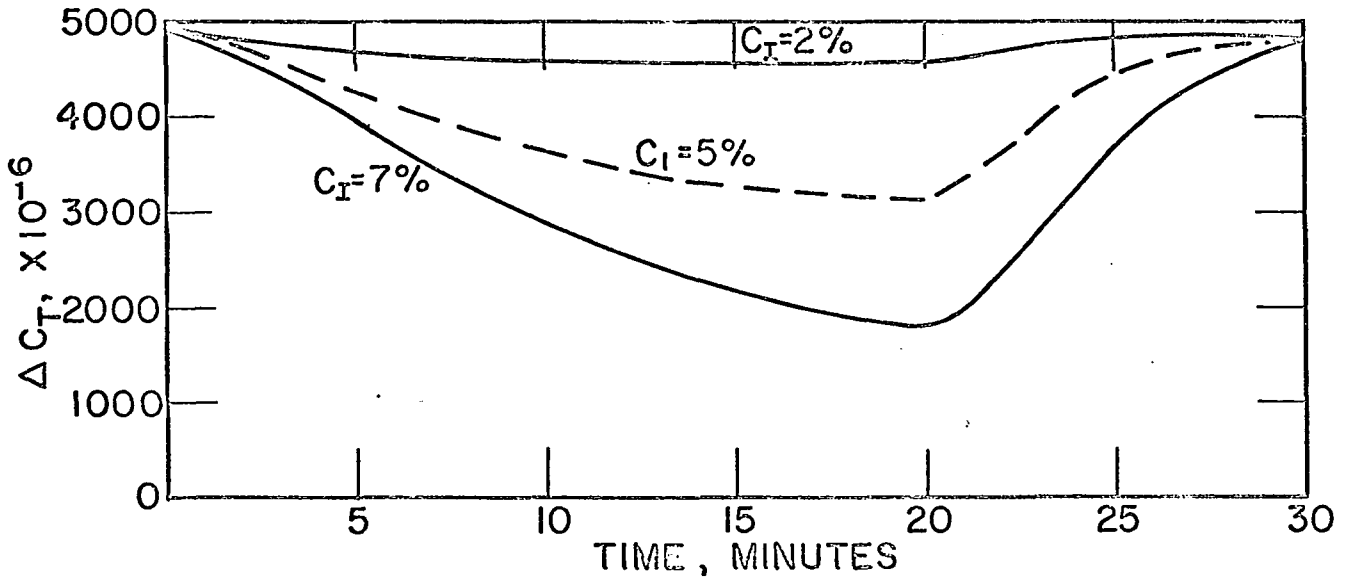


Figure 34. CO_2 controller set point sensitivity, $S_b^{C_T}$, as a function of CO_2 inhalation levels for the adult

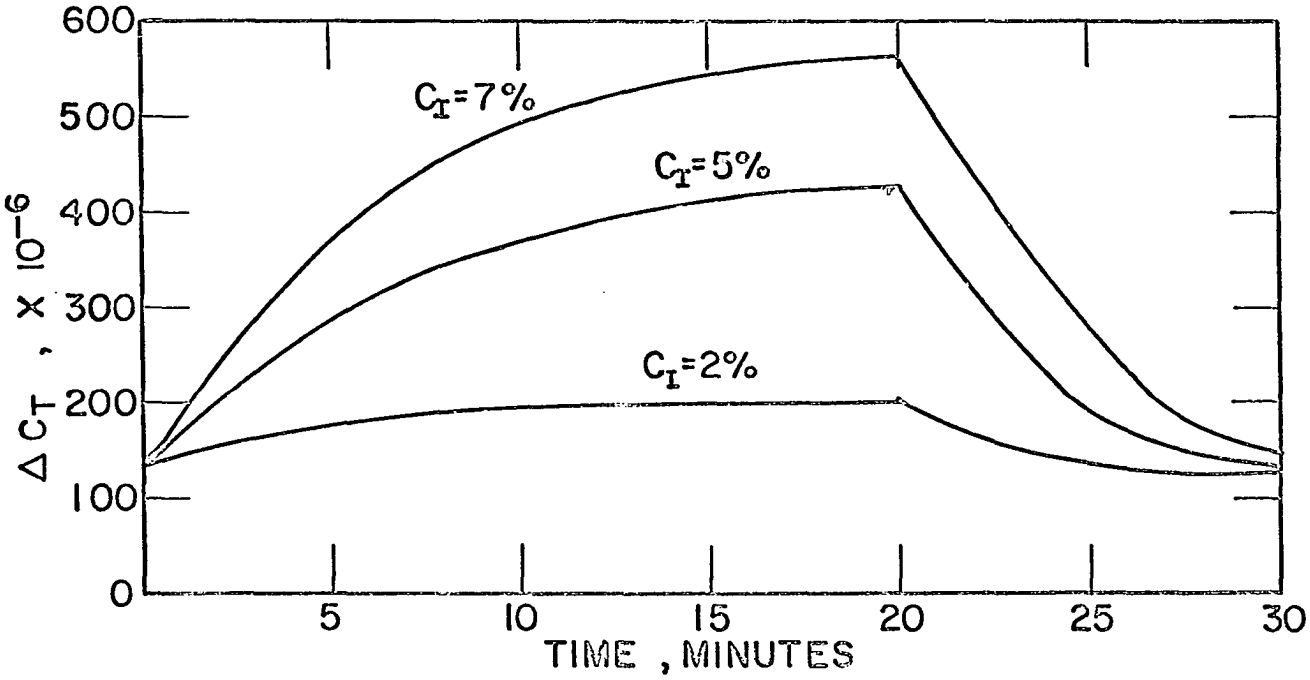


Figure 35. Metabolic rate of CO_2 production sensitivity, $S_M^{C_T}$, as a function of CO_2 inhalation levels

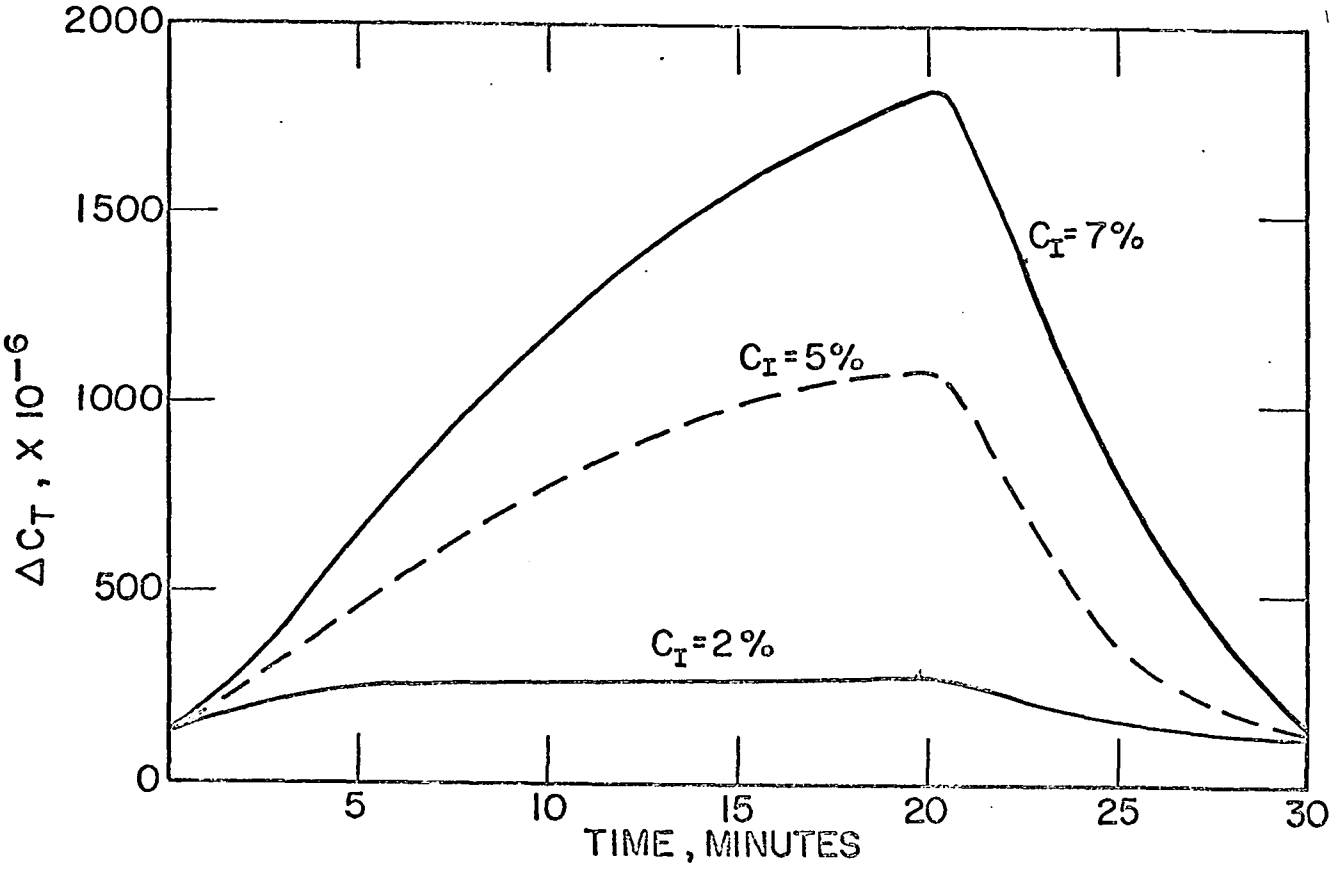


Figure 36. CO_2 dissociation curve intercept sensitivity, $S_{k_2}^{C_T}$, as a function of CO_2 inhalation levels for the adult

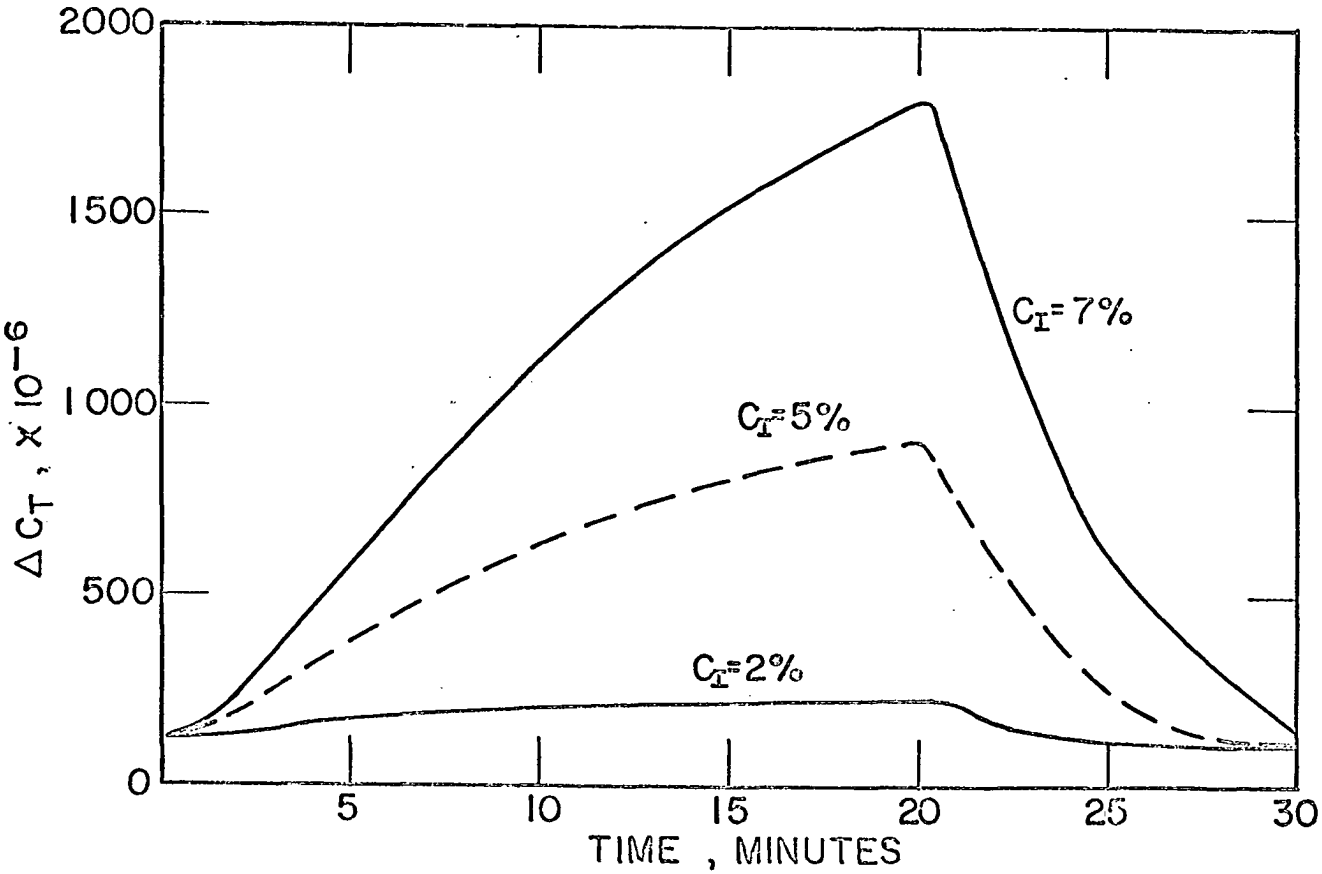


Figure 37. Barometric pressure sensitivity, $S_{\frac{C_T}{B}}$, as a function of CO_2 inhalation levels for the adult

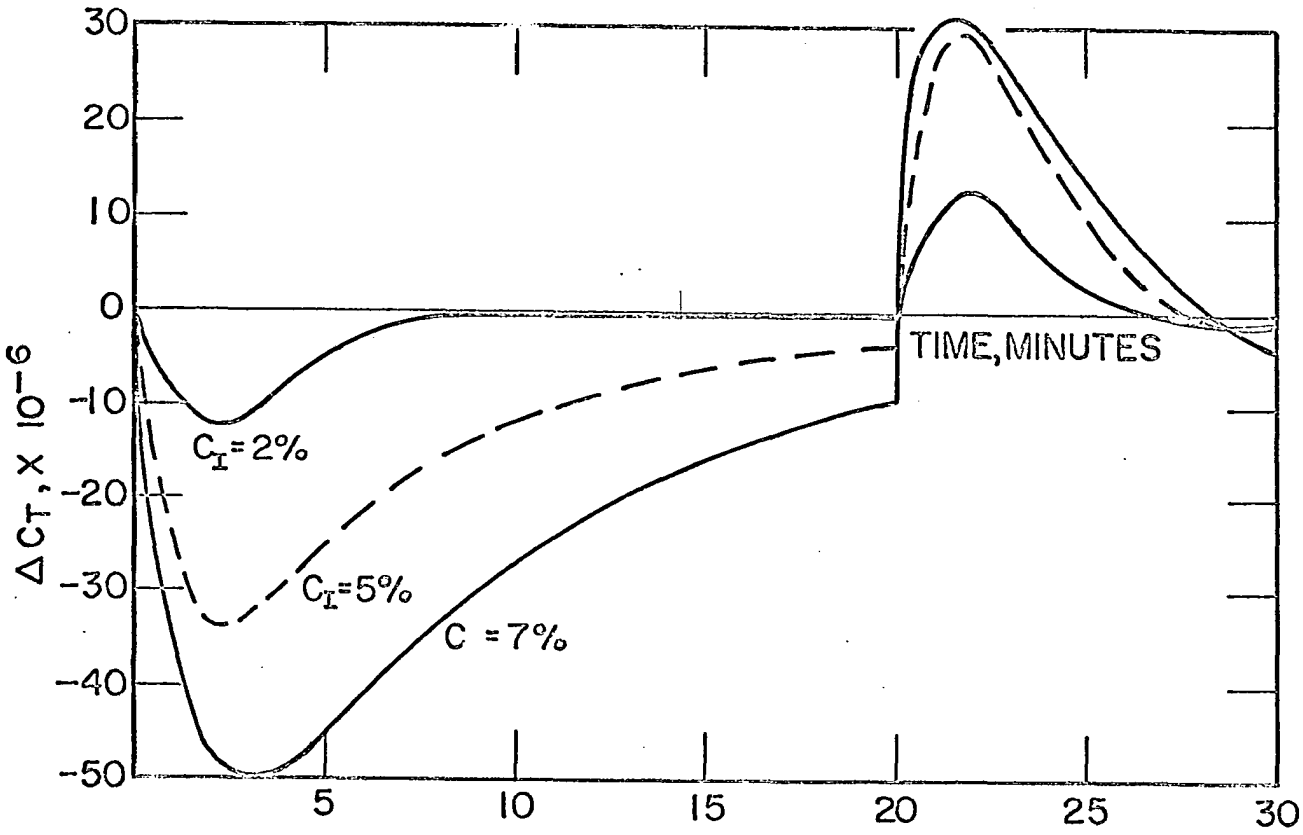


Figure 38. Alveolar volume sensitivity, $S_{V_A}^{C_T}$, as a function of CO_2 inhalation levels for the infant

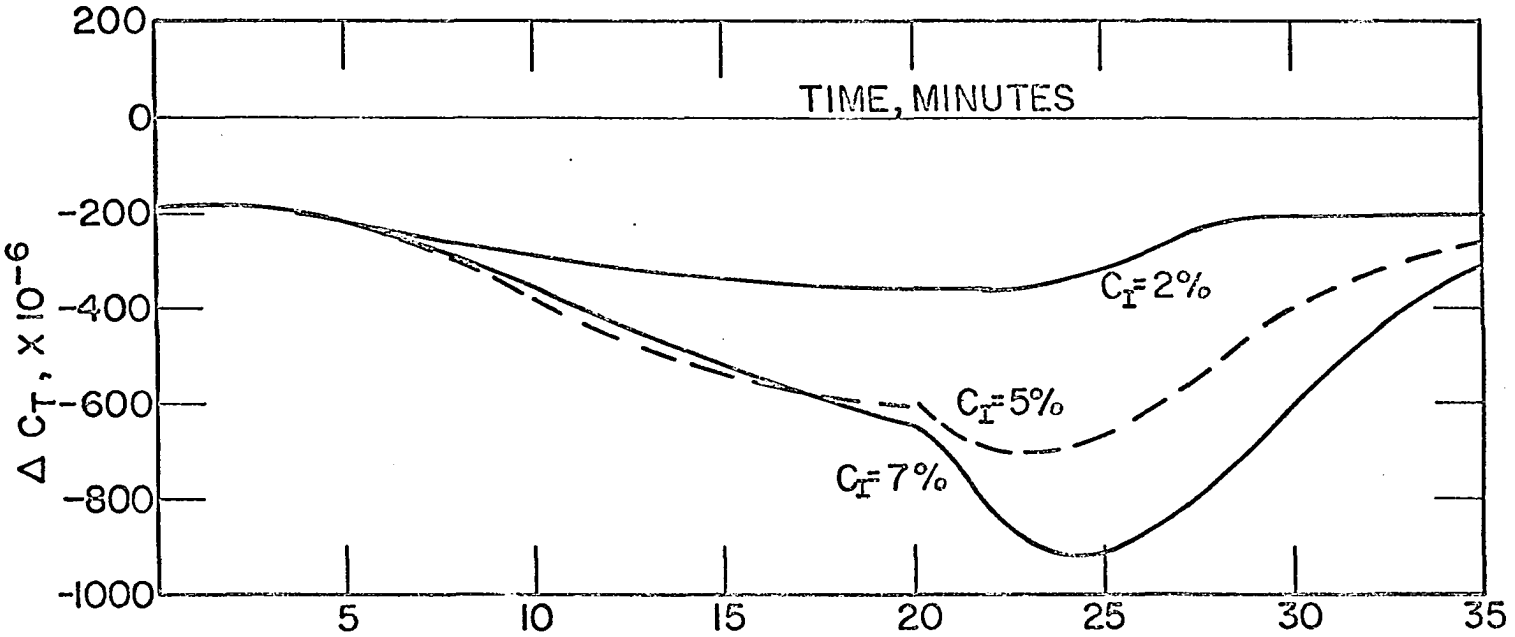


Figure 39. Cardiac output sensitivity, $S_Q^{C_T}$, as a function of CO_2 inhalation levels for the infant

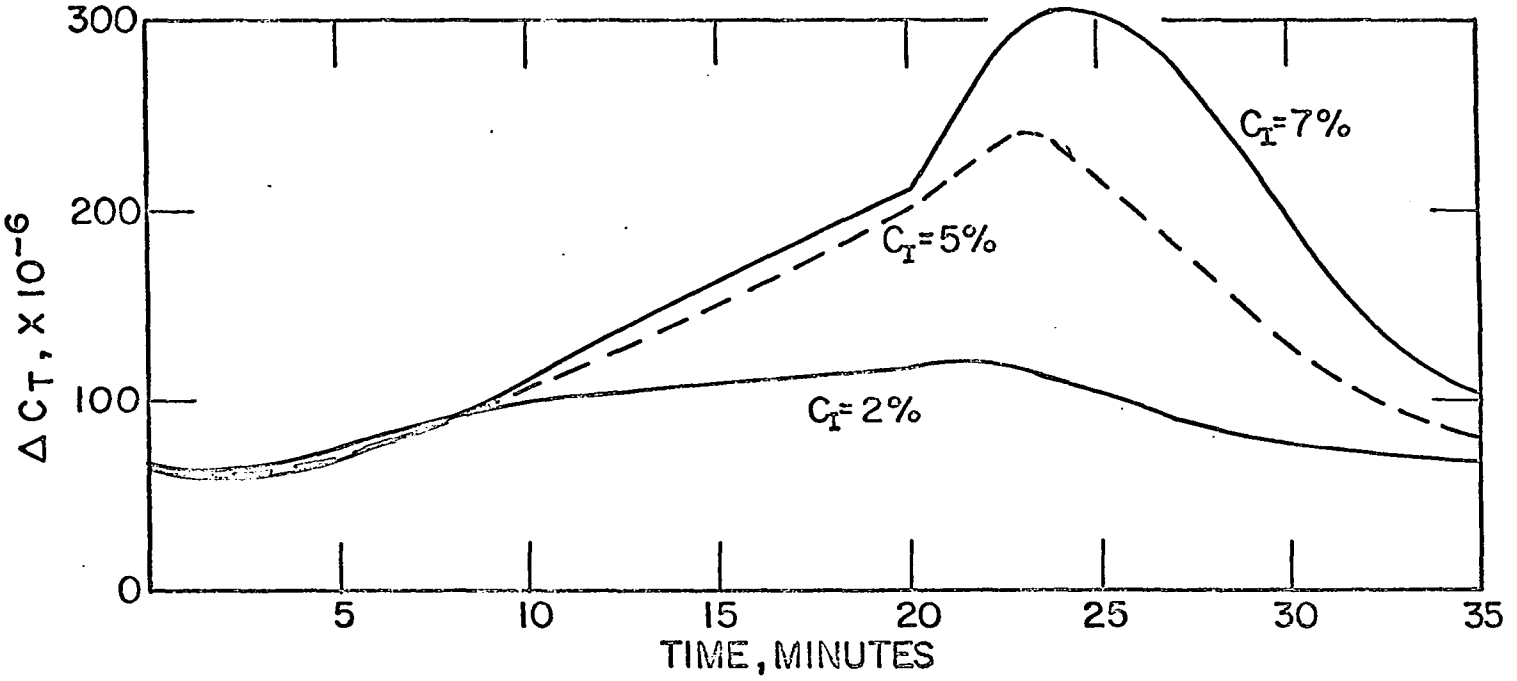


Figure 40. Cardiac output shunting sensitivity, $S_k^{C_T}$, as a function of CO_2 inhalation levels for the infant

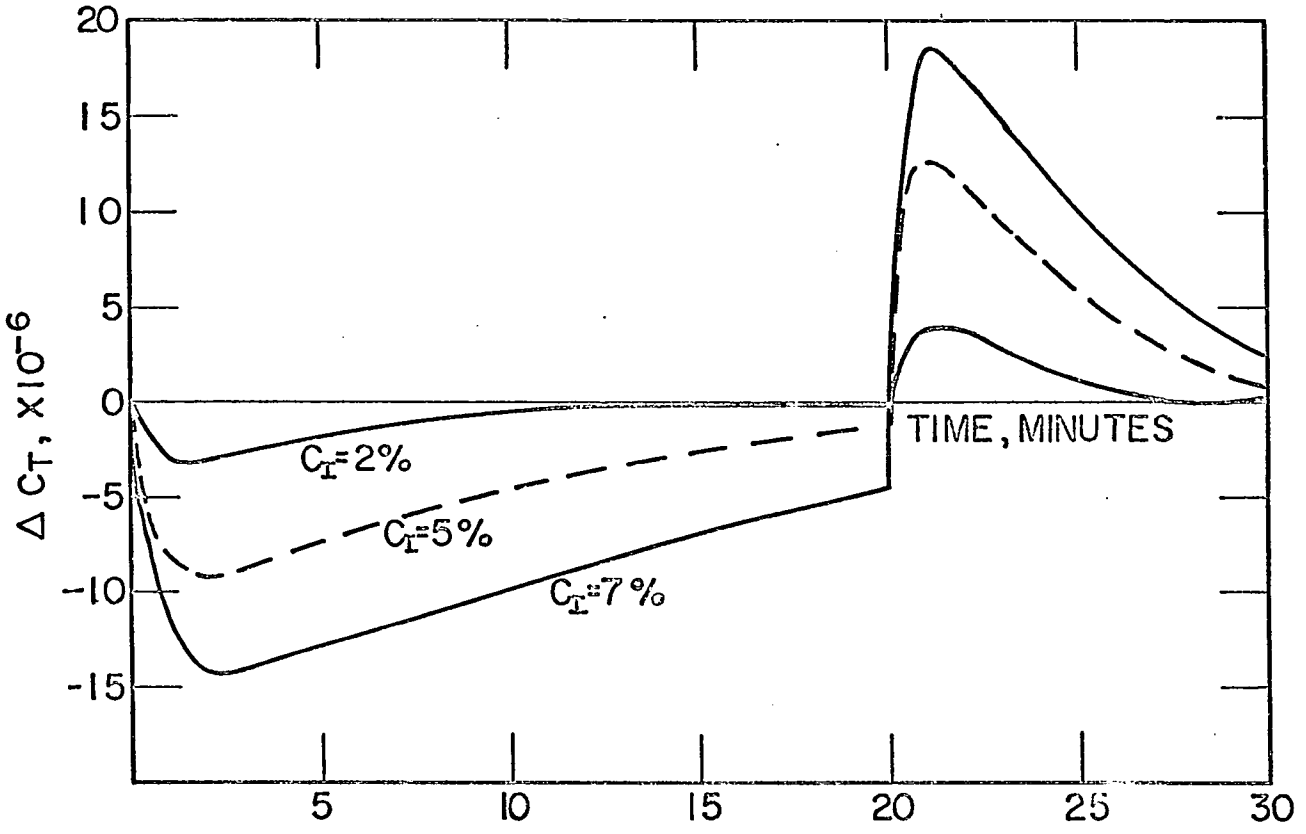


Figure 41. Circulation time delay sensitivity, $S_T^{C_T}$, as a function of CO_2 inhalation levels for the infant

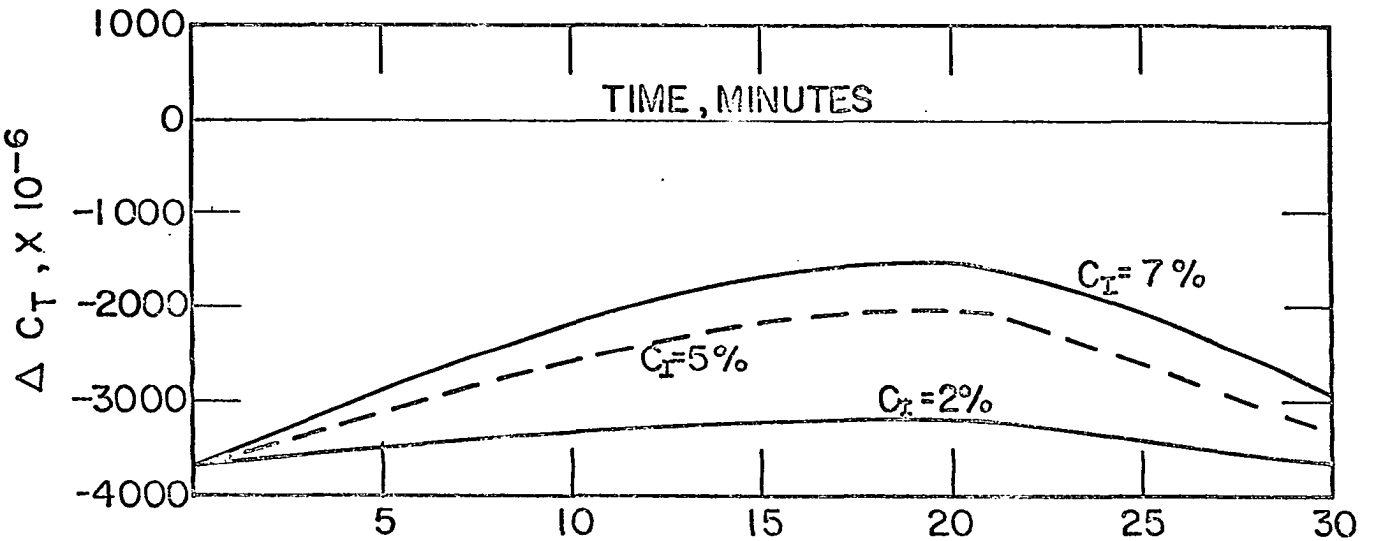


Figure 42. CO_2 controller slope sensitivity, $S_a^{C_T}$, as a function of CO_2 inhalation levels for the infant

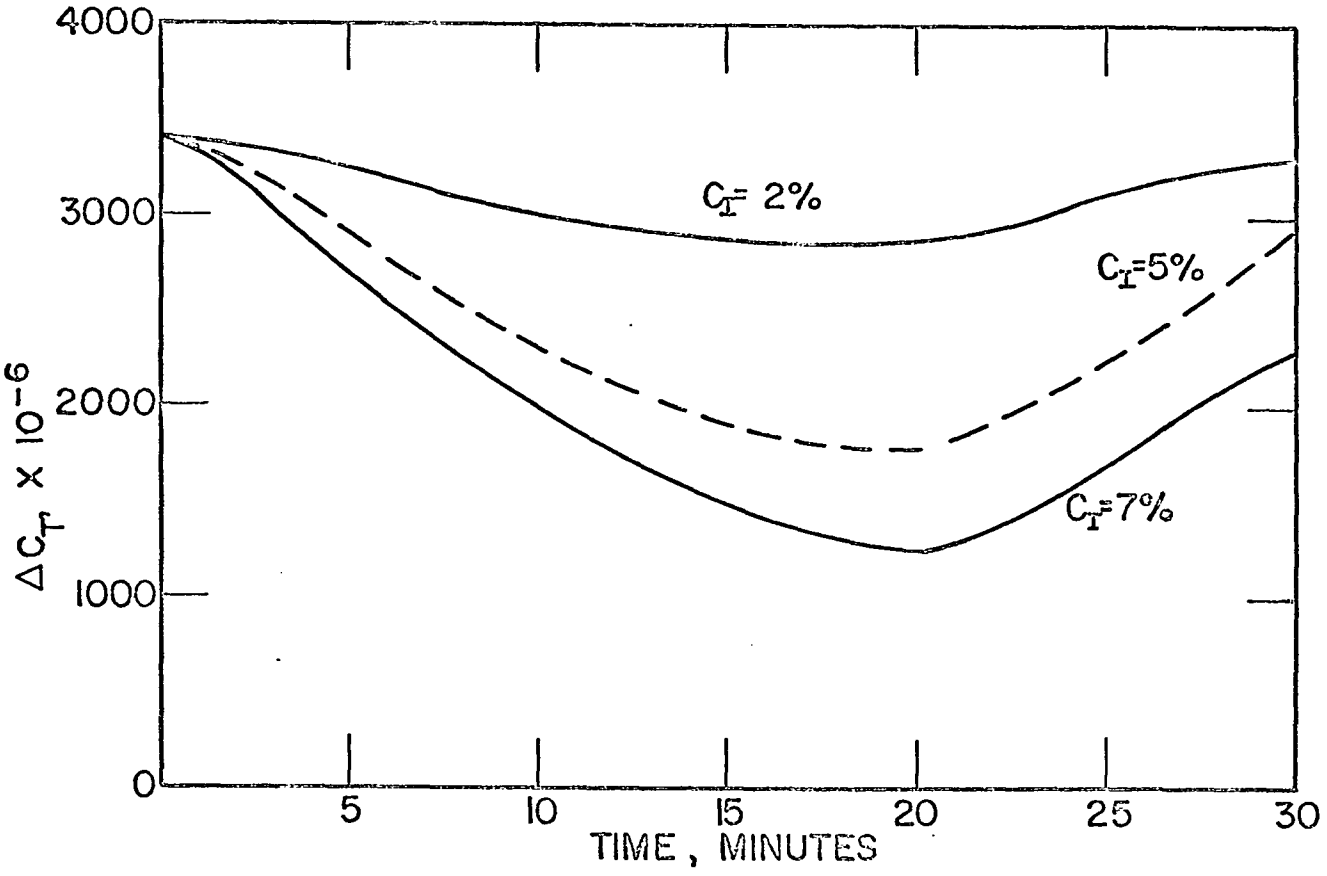


Figure 43. CO_2 controller set point sensitivity, $S_b^{C_T}$, as a function of CO_2 inhalation levels for the infant

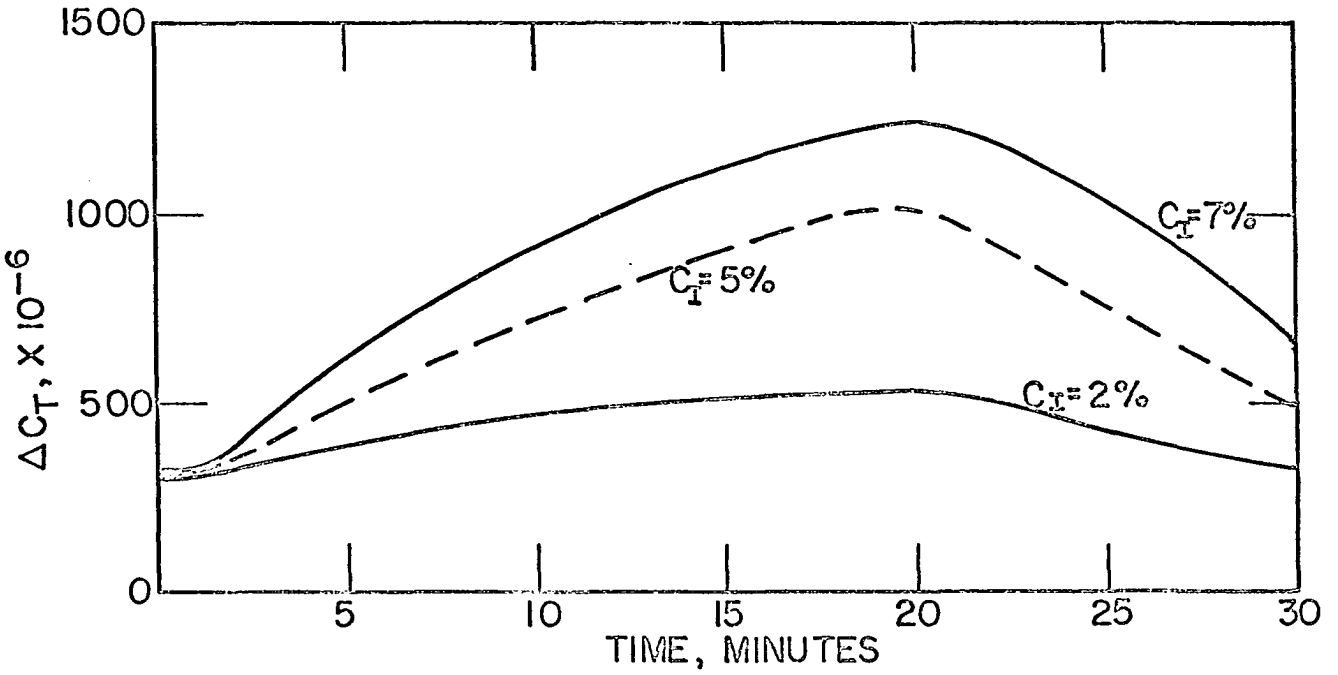


Figure 44. CO_2 dissociation curve intercept sensitivity, $S_{k_2}^{C_T}$, as a function of CO_2 inhalation levels for the infant

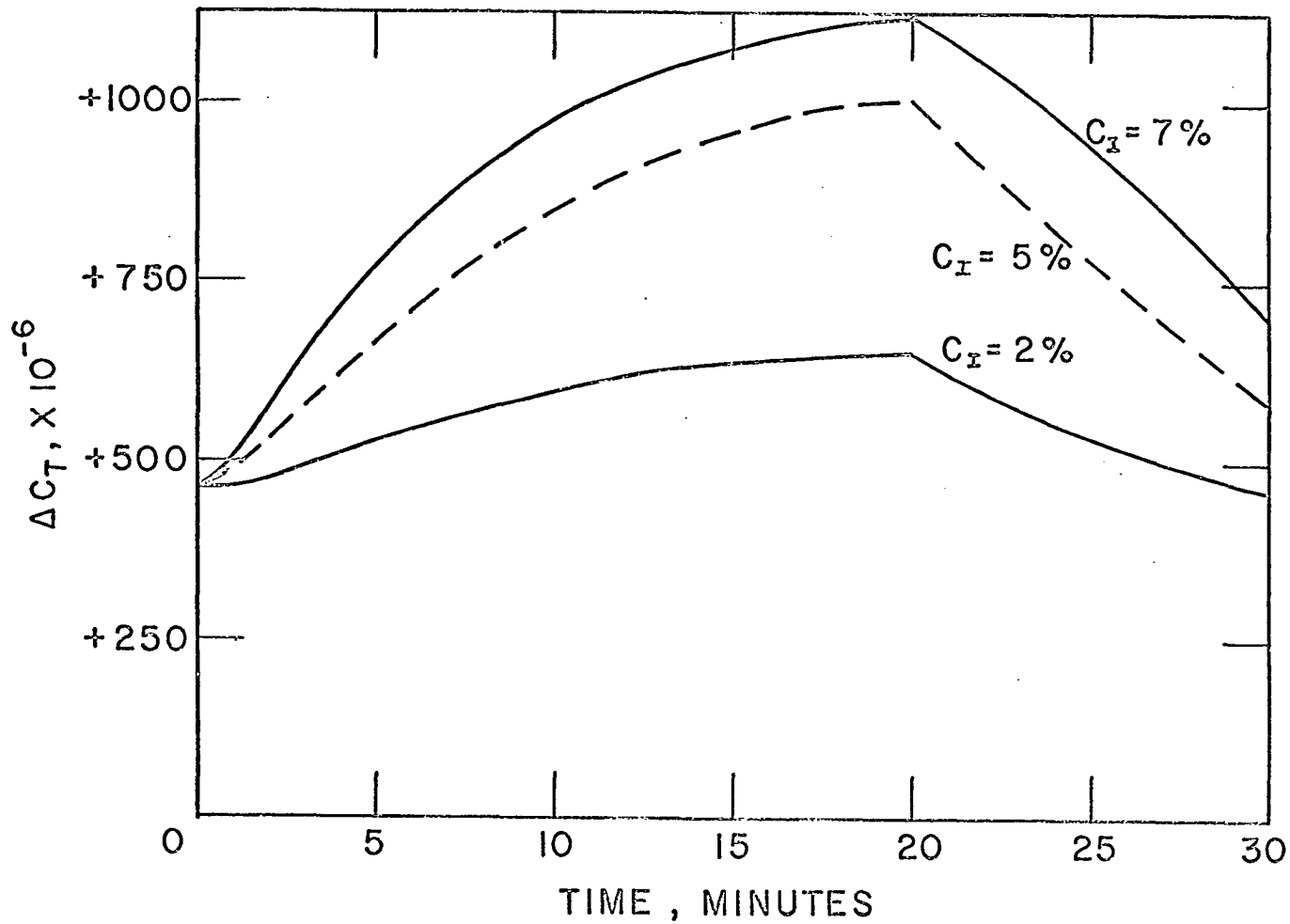


Figure 45. Metabolic rate of CO_2 production sensitivity, $S_M^{C_T}$, as a function of CO_2 inhalation levels for the infant

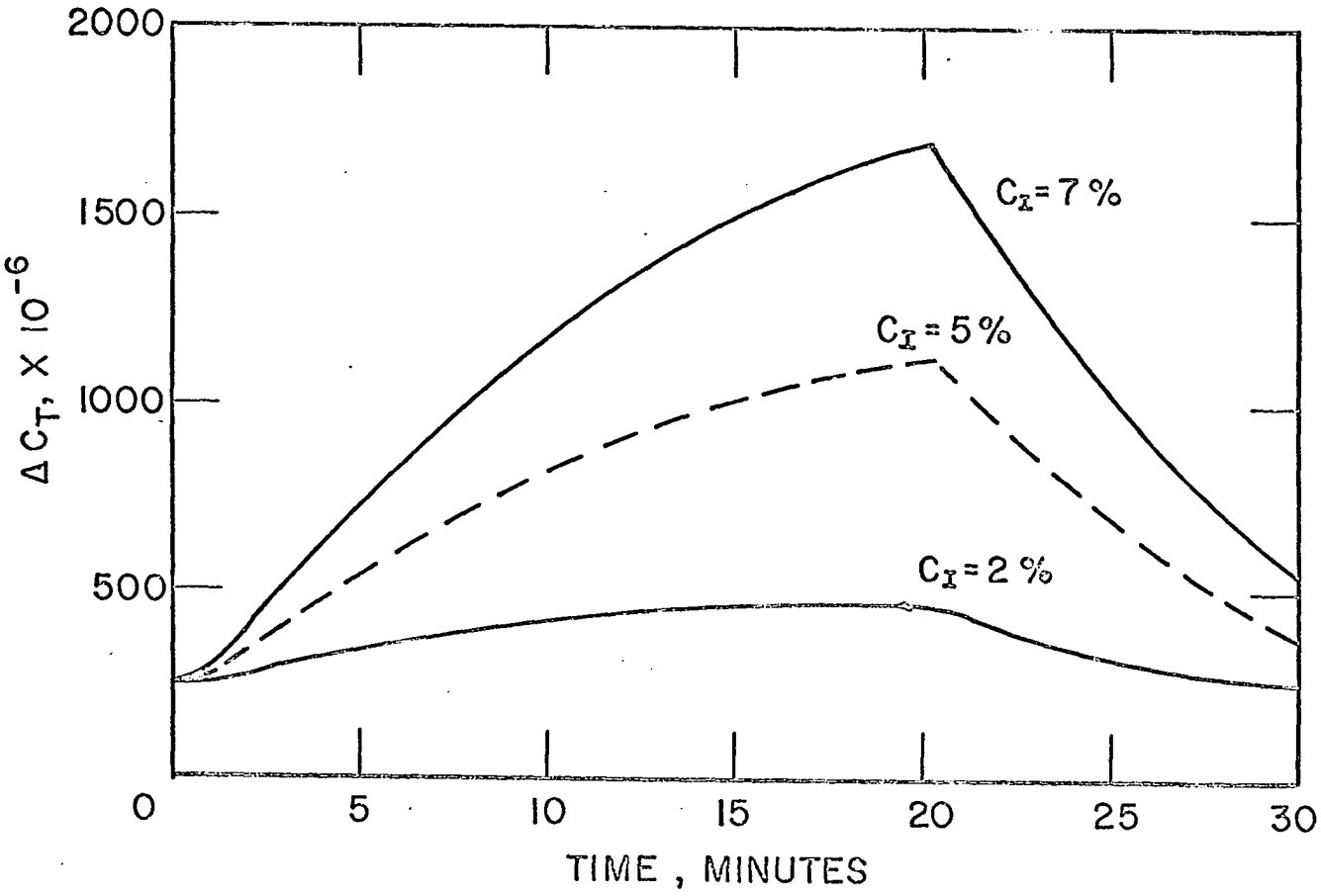


Figure 46. Barometric pressure sensitivity, $S_B^{C_T}$, as a function of CO_2 inhalation levels for the infant

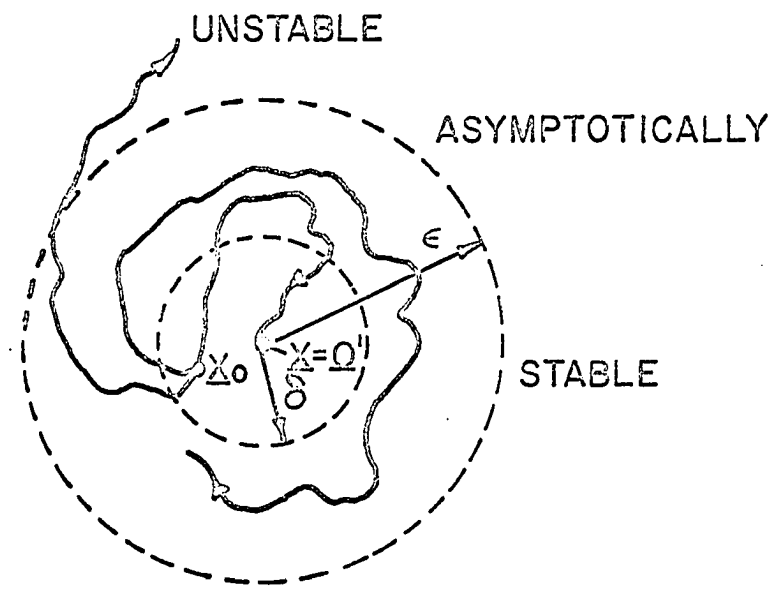


Figure 47. Stability in the Lyapunov sense

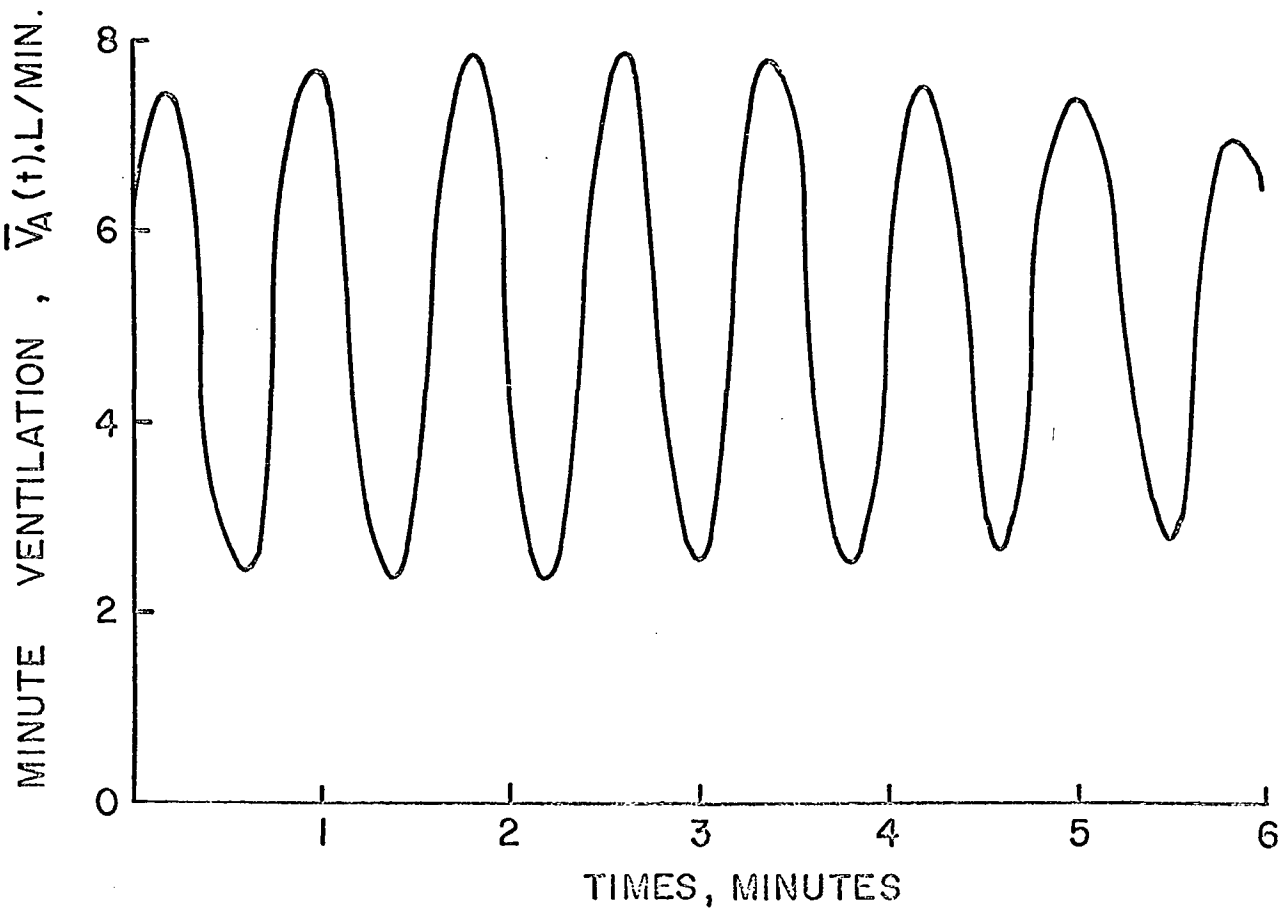


Figure 48. Oscillatory minute ventilation

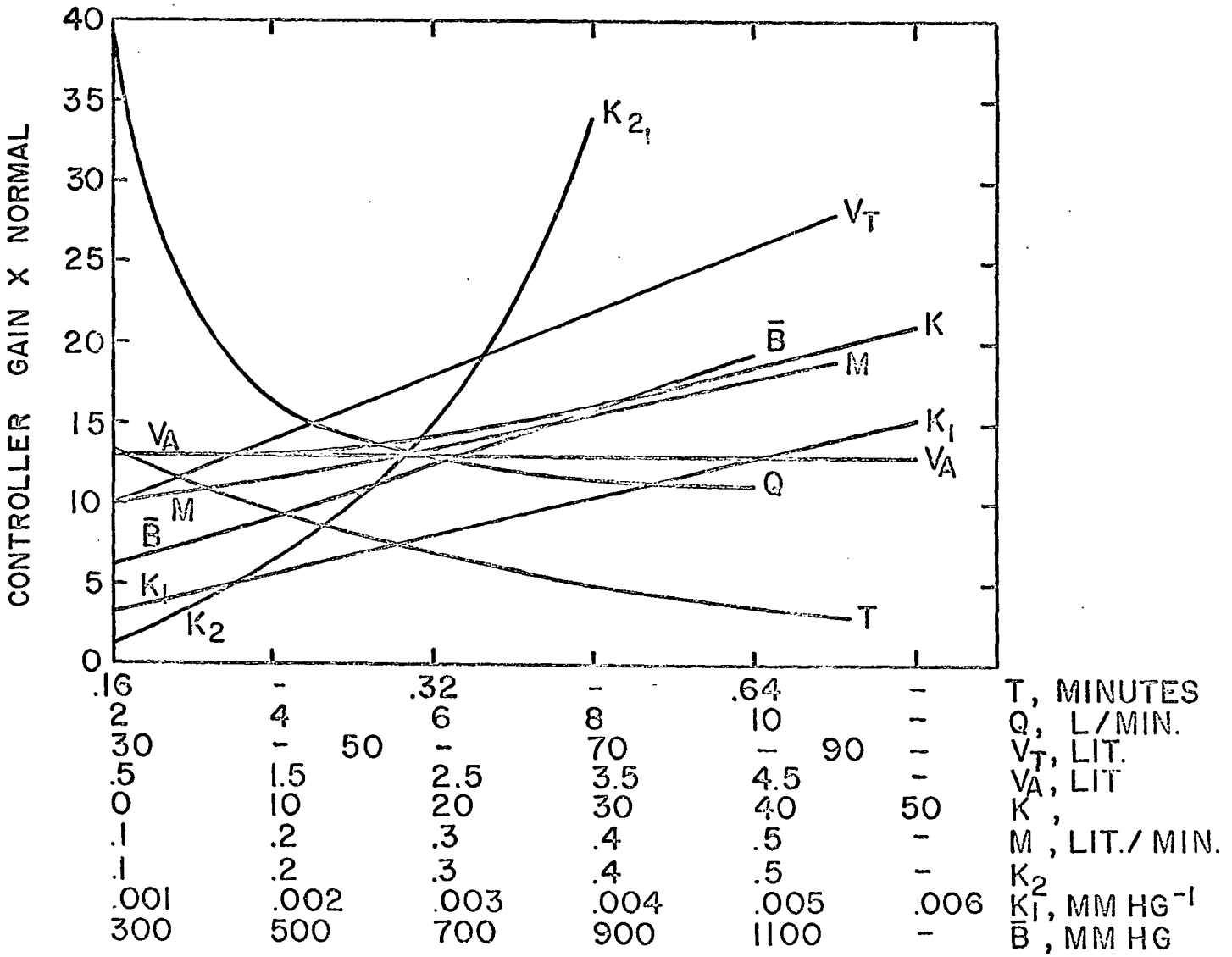
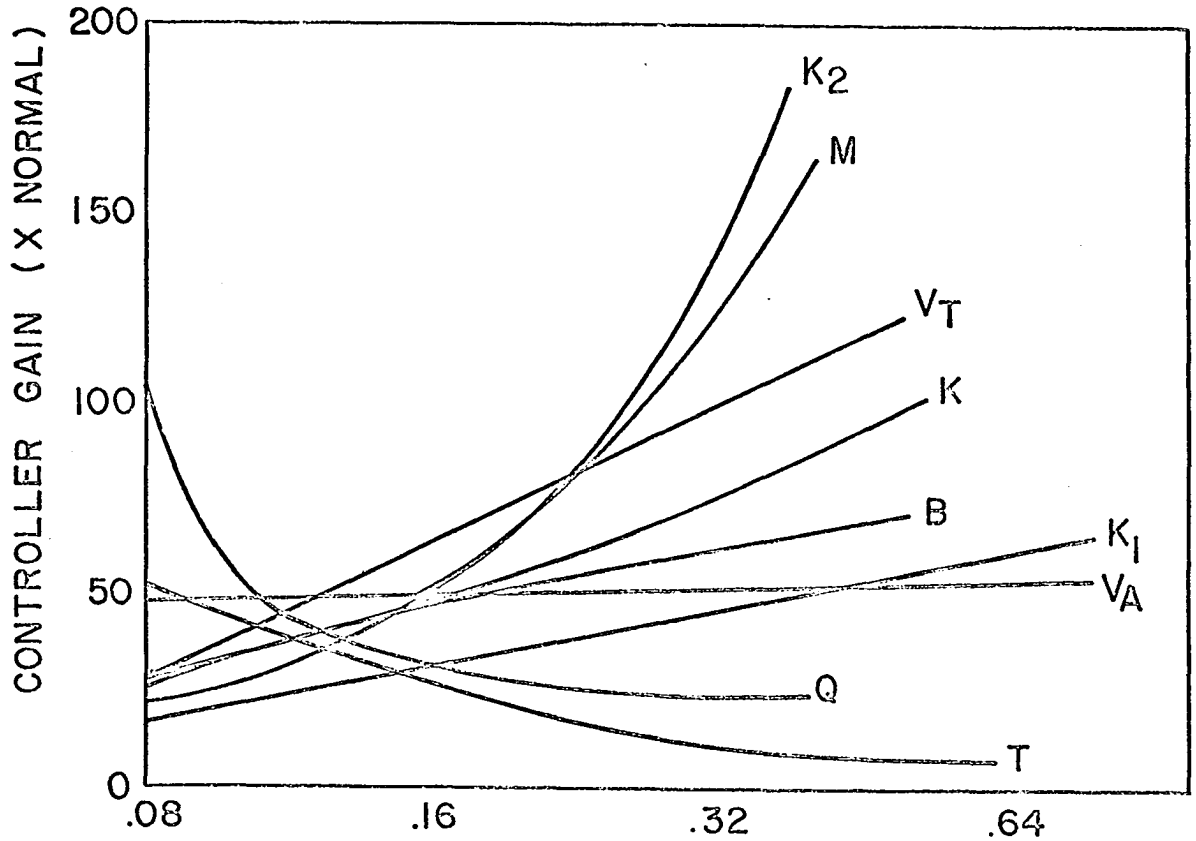


Figure 49. Adult stability boundaries



.2	.4	.6	.8	1.0	1.2	T, MIN.
1	2	3	4	5	6	Q, LIT/MIN.
.2	–	.4	–	.6	–	V_T, LIT.
.1	.2	.3	.4	.5	.6	V_A, LIT.
.005	.015	.03	.045	.06	.075	K
.05	.15	.25	.35	.45	.55	M, LIT/MIN
.001	.002	.003	.004	.005	.006	K_2,
300	500	700	900	1100	1300	K, MM ITG^{-1}
						B, MM ITG

Figure 50. Infant stability boundaries

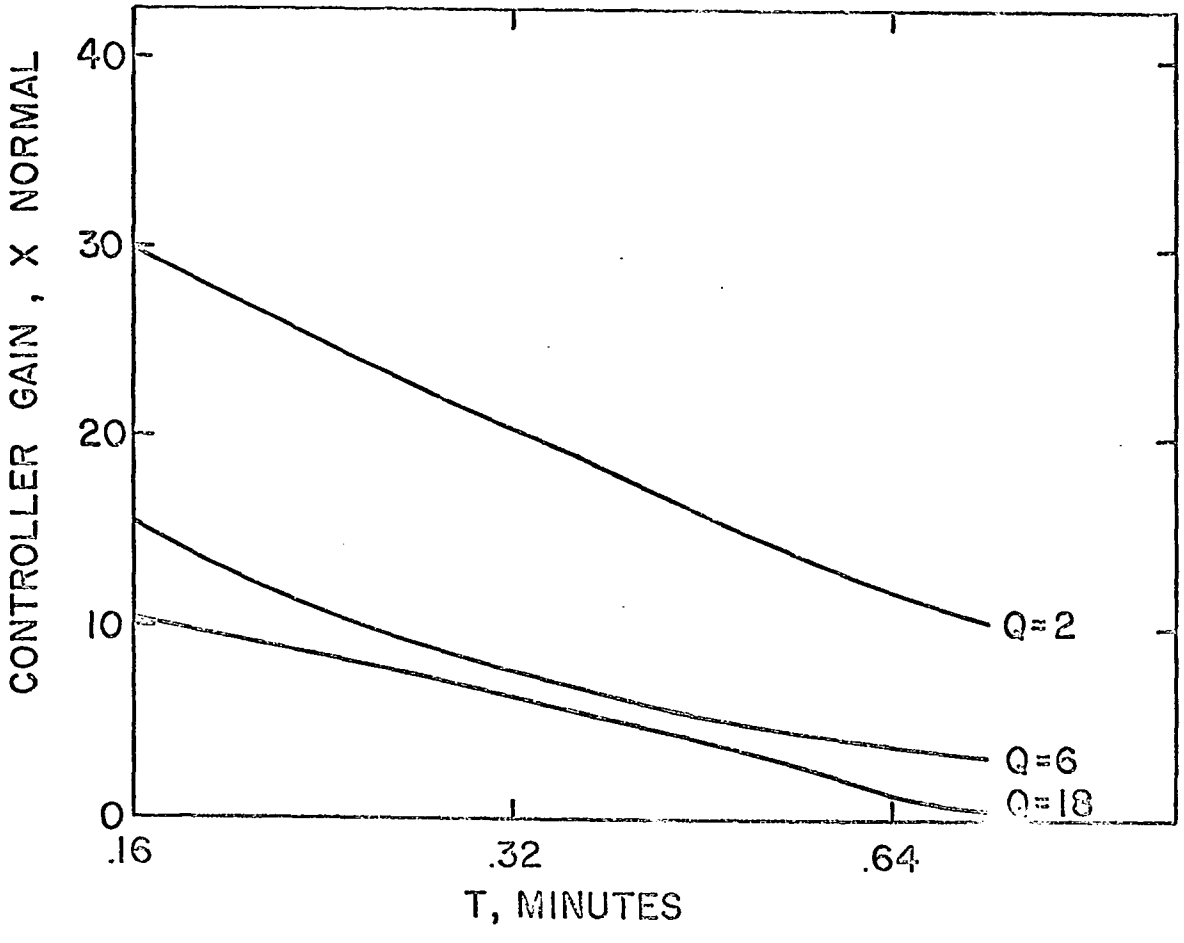


Figure 51. Adult stability boundaries for T as a function of cardiac output

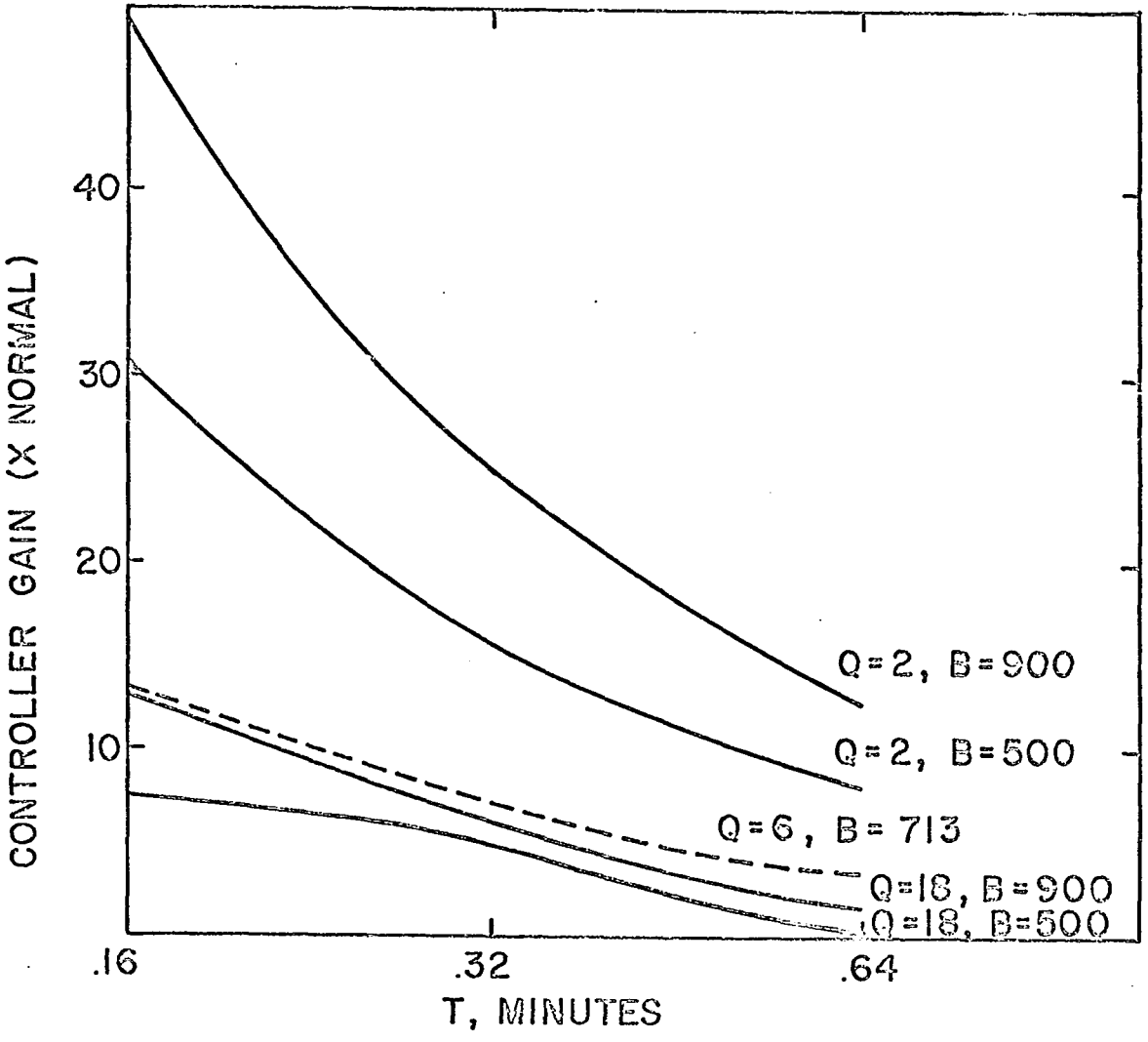


Figure 52. Adult stability boundary for T as a function of cardiac output and barometric pressure

TABLES

Table 1. Respiratory nomenclature used in Figure 3

Parameter	Symbol	Units
Alveolar CO_2 concentration	$C_A(t)$	Liters/Liter
Arterial-alveolar CO_2 concentration	$C_{Aa}(t)$	Liters/Liter
Venous pulmonary CO_2 concentration	$C_{pv}(t)$	Liters/Liter
Arterial-tissue CO_2 concentration	$C_{aT}(t)$	Liters/Liter
Tissue CO_2 concentration	$C_T(t)$	Liters/Liter
Tissue-venous CO_2 concentration	$C_{Tv}(t)$	Liters/Liter
Venous-alveolar CO_2 concentration	$C_{vA}(t)$	Liters/Liter
Alveolar compartment volume	V_A	Liters
Tissue compartment volume	V_T	Liters
Inspired fractional CO_2 concentration	$C_1(t)$	Unitless
Effective alveolar ventilation	$V_A(t)$	Liters/Minute
Cardiac output	Q	Liters/Minute
Shunted cardiac output	Q_s	Liters/Minute
Pulmonary blooc flow	Q_a	Liters/Minute
Metabolic rate of CO_2 production	M	Liters/Minute
Volume of CO_2 in the alveoli	$v_A(t)$	Liters
Volume of CO_2 in the tissues	$v_T(t)$	Liters
Arterial circulation time	T_a	Minutes
Venous circulation time	T_v	Minutes
Ventilation controller slope	a	Liters/Minute
Ventilation controller intercept	b	Liters/Minute

Table 2. Respiratory parameter values for 'normal' individuals

Parameter	Adult value[a]	Neonatal value[b]
Cardiac output, Q	6 liters/min.	0.30 liters/min.
Cardiac shunting fraction, k	2.5%	25%
Metabolic CO_2 production, M	0.2805 lit./min.*	0.0269 lit./min.*
Minute ventilation, $\overline{V}_A$	5 liters/min.	0.60 liters/min.
CO_2 dissociation curve slope, k_1	0.005[c] mm. Hg.$^{-1}$	0.0044[d] mm. Hg.$^{-1}$
CO_2 diss. curve intercept, k_2	0.28 lit./min.[c]	0.18 lit./min.[d]
Ventilation controller gain, a	448 lit./min.*	21.8 lit./min.*
Vent. controller intercept, b	231.52 lit./min.*	8.997 lit./min.*
Barometric pressure, $\overline{B}$	713 mm. Hg.	713 mm. Hg.
Tissue volume, V_T	40. liters	2.0 liters
Alveolar volume, V_A	3.0 liters	0.80 liters
Circulation time, T	1/6 minute	1/12 minute
Alveolar pCO_2, $(pCO_2)_A$	40 mm. Hg.	32 mm. Hg.
Tissure pCO_2, $(pCO_2)_T$	49.6 mm. Hg.*	59 mm. Hg.*
Alveolar CO_2 concentration, $\overline{C}_A$	0.0561*	0.04488*
Tissure CO_2 concentration, $\overline{C}_T$	0.5279	0.4402
Weight	70 kg.	3 kg.

[a]From References 13 and 31

*A calculated value

[b]From References 3 and 40

[c]From Figure 5

[d]From Figure 6

Table 3. Initial and 20 minute values of the sensitivity coefficients for the open loop adult respiratory system

Sensitivity	Value at t = 0	Value at t = 20 minutes
$S^{C_T}_{V_A}$	0	-10.1×10^{-6}
$S^{C_T}_{Q}$	-474×10^{-6}	$-11{,}910 \times 10^{-6}$
$S^{C_T}_{k_2}$	2800×10^{-6}	2800×10^{-6}
$S^{C_T}_{k}$	0.3×10^{-6}	152×10^{-6}
$S^{C_T}_{T}$	0	18×10^{-6}
$S^{C_T}_{M}$	2479×10^{-6}	2471×10^{-6}
$S^{C_T}_{B}$	2060×10^{-6}	2279×10^{-6}

Table 4. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to V_A, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	0	-5.0	-4.2	-2.5	-1.1	- .48	- .23	+6.9	+3.3	-1.0	-.32
V_A=1.5	0	-2.5	-2.1	-1.2	- .50	- .24	- .11	+3.1	+1.4	- .50	-.15
Q=2	0	-8.4	-8.4	-6.7	-4.9	-3.6	-2.8	+2.6	+2.3	+1.5	+.33
Q=18	0	-2.1	-1.9	-1.4	- .56	- .20	- .07	+2.5	+ .87	- .07	-.01
T=0.8	0	-4.9	-4.2	-2.7	- .92	- .60	-0.3	+8.9	+4.7	-1.3	-.4
k=.25	0	-6.1	-5.2	-3.2	-1.6	- .80	- .40	7.2	4.4	- .67	-.22
a=224	0	-5.3	-5.0	-4.1	-2.6	-1.6	- .96	6.7	4.8	1.3	-.26
a=896	0	-4.5	-3.0	-1.1	- .2	- .04	-0.00	5.4	- .4	- .6	
k_2=0.32	0	-6.0	-5.7	-4.5	-2.7	-1.5	- .8	6.8	4.4	- .07	-.67
$\bar{B}$=350	0	-4.0	- .9	+ .48	+ .06	+ .00	+ .00	+5.4	- .87	- .17	+.00
$\bar{B}$=1400	0	-6.0	-7.2	-8.9	-7.8	-5.6	-3.6	4.2	3.2	.9	-.4

Table 5. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to Q, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	- 25.	- 23.	- 28.2	- 52.6	-103.	-145.	-174.	-191.	-179.	- 86.	- 30.7
V_A=1.5	- 23.7	- 25.1	- 30.	- 53.7	-103.	-145.	-174.	-190.	-176.	- 85.	
Q=2	-214.7	-214.4	-214.	-230.	-301.	-391.	-486.	-526.	-589.	-719.	-760.
Q=18	- 4.	- 7.	- 10.1	- 20.5	- 34.9	- 42.3	- 45.4	- 41.9	- 28.9	- 10.3	- 6.6
T=.8	- 16	- 19	- 28.5	- 57	-105	-144	-171	-206	-201	- 93	
k=.25	- 39.	- 35	- 40	- 68	-129	-188	-234	-261	-265	-169	- 57
a=224	- 48	- 45.2	- 48.3	- 63.2	- 99	-137	-170	-190	-196	-163	- 95
a=896	- 13.00	- 11.5	- 19.7	- 55.1	-112	-148	-167	-176	-120	- 17.2	
k_2=.32	- 37	- 34	- 38	- 59	-113	-171	-218	-260	-274	-191	- 68
$\bar{B}$=350	- 14.	- 11.4	- 18.6	- 33	- 39	- 39	- 39	- 41	- 26	- 13	
$\bar{B}$=1400	- 41	- 40.2	- 38.7	- 19.4	3.0	- 31.4	-103	-250	-363	-427	-230

Table 6. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to k, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	.65	.55	.64	1.2	2.5	3.6	4.4	5.0	4.7	2.3	.8
V_A=1.5	.62	.60	.69	1.2	2.5	3.6	4.4	4.9	4.6	2.3	
Q=2	5.5	5.5	5.4	5.8	7.4	9.6	12.1	13.1	14.8	18.4	19.6
T=.8	.70	.40	.45	.87	2.1	3.2	4.1	5.3	5.7	2.9	
Q=18	.06	.14	.19	.43	.84	1.16	1.16	1.15	.83	.29	.17
k=.25	1.3	1.1	1.2	2.1	4.1	6.1	7.7	8.8	9.0	5.8	1.9
a=224	1.25	1.1	1.2	1.5	2.3	3.4	4.2	4.9	5.1	4.3	2.5
a=896	.41	.26	.43	1.3	2.8	3.8	4.3	4.6	3.2	.4	
k_2=.32	.95	.83	.88	1.3	2.7	4.2	5.5	6.7	7.1	5.1	1.8
$\bar{B}$=350	.41	.28	.46	.85	.99	1.0	1.0	1.1	.68	.35	
$\bar{B}$=1400	1.1	.95	.79	- .04	- .91	- .02	1.9	6.1	9.3	11.4	6.0

Table 7. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to T, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	0	- 818	- 683	- 404	- 170	- 76	- 33	1538	750	- 133	- 46
V_A=1.5	0	- 403	- 337	- 201	- 88	- 39	- 17	729	360	60	
Q=2	0	-2661	-2440	-1923	-1378	-1019	- 763	3194	2911	2112	984
Q=18	0	- 300	- 285	- 201	- 84	- 31	- 11	383	136	- 6.8	- 1.4
T=.8	0	-3784	-3255	-2079	- 989	- 472	- 226	8258	3992	- 972	
k=.25	0	- 835	- 702	- 433	- 205.	- 100	- 49	1600	994	- 14.8	-86
a=224	0	- 889	- 841	- 687	- 452	- 283	- 172	1427	1023	300	-20
a=896	0	- 686	- 446	- 138	- 13.	5.6	5.6	1212	- 25	- 83	- .21
k_2=.32	0	-1058	-1004	- 800	- 491	- 286	- 162	2001	1317	130	-96
$\bar{B}$=350	0	- 246	- 6.	43	4.6	.3	0	273	155	- 6	
$\bar{B}$=1400	0	-2083	-2487	-3166	-2974	-2219	-1506	3812	2996	1210	21

Table 8. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to 'a', x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	-5000	-4924	-4807	-4420	-3881	-3537	-3338	-3578	-3900	-4644	-4970
V_A=1.5	-5000	-4917	-4797	-4408	-3868	-3521	-3317	-3570	-3892	-4628	
Q=2	-4600	-4519	-4433	-4135	-3623	-3160	-2765	-2730	-2714	-2732	-2981
Q=18	-5050	-4954	-4829	-4465	-4091	-3940	-3887	-4320	-4631	-4982	-5049
T=.8	-5050	-4998	-4912	-4567	-4015	-3635	-3403	-3411	-3706	4579	
k=.25	-5100	-5069	-4963	-4610	-4096	-3741	-3514	-3692	-3949	-4672	-5089
a=224	-4780	-4679	-4580	-4262	-3790	-3446	-3219	-3370	-3561	-4045	-4505
a=896	-5140	-5055	-4914	-4458	-3914	-3629	-3494	-3887	-4436	-5109	-5136
k_2=.32	-4900	-4788	-4630	-4102	-3330	-2808	-2487	-2715	-3030	-3957	-4721
$\bar{B}$=350	-5077	-5043	-4989	-4880	-4841	-4838	-4838	-4911	-5004	-5077	-5077
$\bar{B}$=1400	-4895	-4745	-4523	-3728	-2510	-1716	-1267	-1542	-1878	-2853	-3890

Table 9. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to 'b', x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	4900	4820	4700	4292	3714	3341	3125	3342	3659	4464	4856
V_A=1.5	4900	4811	4689	4279	3700	3326	3104	3333	3651	4448	
Q=2	4430	4353	4269	3974	3461	2996	2598	2556	2530	2523	2747
Q=18	4950	4860	4729	4333	3912	3739	3676	4100	4438	4863	4955
T=.8	4940	4895	4811	4451	3862	3449	3196	3184	3449	4380	
k=.25	5050	4964	4856	4483	3932	3549	3306	3464	3713	4483	4971
a=224	4600	4481	4382	4059	3559	3186	2934	3057	3228	3713	4236
a=896	5090	5000	4852	4367	3787	3483	3339	3716	4287	5049	5081
k_2=.32	4770	4664	4507	3973	3178	2632	2292	2486	2776	3712	4561
$\bar{B}$=350	5022	4988	4927	4797	4751	4747	4747	4820	4927	5022	5022
$\bar{B}$=1400	4740	4561	4355	3624	2471	1676	1196	1375	1621	2453	3513

Table 10. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to k_2, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	135	188	253	474	788	989	1107	989	818	381	169
V_A=1.5	139	193	260	481	795	998	1118	994	822	390	
Q=2	435	442	487	647	925	1177	1392	1416	1429	1432	1312
Q=18	90	167	238	452	680	774	808	578	396	165	
T=.8	123	148	193	388	708	931	1068	1074	931	427	
k=.25	157	208	270	486	812	1048	1204	1125	1000	574	229
a=224	2720	318	373	552	829	1036	1175	1107	1013	744	454
a=896	65	119	199	459	770	933	1010	808	502	94	76
k_2=.32	200	312	409	740	1232	1570	1781	1660	1481	902	376
$\bar{B}$=350	75	97	130	201	226	228	228	188	130	79	
$\bar{B}$=1400	200	329	440	837	1460	1892	2152	2055	1922	1471	783

Table 11. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to M, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	122	164	204	291	372	412	430	382	322	193	136
V_A=1.5	123	168	207	294	377	418	438	387	327	198	
Q=2	360	406	446	559	724	858	966	973	975	965	888
Q=18	90	138	171	228	258	262	263	193	149	106	
T=.8	95	140	180	272	361	405	427	418	358	203	
k=.25	140	183	223	319	422	481	515	476	426	278	169
a=224	240	281	319	409	496	539	559	520	476	375	290
a=896	62	101	139	220	291	322	336	270	182	72	67
k_2=.32	160	203	249	355	454	500	521	480	430	296	189
$\bar{B}$=350	62	83	99	122	129	130	130	108	85	68	
$\bar{B}$=1400	220	300	378	567	717	747	734	685	632	495	337

Table 12. The effects of abnormal adult respiratory parameter values on the sensitivity of $C_T(t)$ with respect to $\bar{B}$, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	95	145	201	388	650	817	914	778	615	270	120
V_A=1.5	97	147	204	392	654	822	921	778	616	275	
Q=2	135	190	235	375	603	801	966	960	916	791	601
Q=18	80	142	205	398	606	693	725	503	338	137	
T=.8	84	110	150	314	582	767	881	857	700	299	
k=.25	100	152	205	385	651	840	964	857	723	380	149
a=224	190	239	287	448	697	886	1014	923	819	564	328
a=896	43	96	161	370	614	739	798	593	350	66	54
k_2=.32	112	173	237	459	794	1027	1174	1039	875	479	190
$\bar{B}$=350	50	74	96	144	160	162	162	124	88	55	
$\bar{B}$=1400	150	265	378	819	1617	2243	2661	2408	2116	1398	646

Table 13. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to V_A, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	0	-20.8	-34.1	-24.9	-11.9	- 6.0	- 3.1	26.0	29.1	10.2	-4.1
V_A=.4	0	-18.3	-18.8	-11.6	- 5.7	- 2.9	- 1.5	16.4	13.2	3.9	-1.9
Q=.1	0	-10.6	-11.7	-10.4	- 8.6	- 7.1	- 5.8	2.5	2.7	2.4	2.0
Q=.9	0	-18.4	-18.0	- 8.6	- 2.3	- .57	- .14	28.1	13.9	-2.2	- .2
T=.4	0	-13.4	-32.5	-26.0	-12.8	- 6.6	- 3.4	21.5	30.0	12.0	-4.1
k=.5	0	-20.2	-33.5	-28.7	-18.3	-12.0	- 7.9	14.1	16.7	11.3	4.1
a=10.9	0	-20.9	-36.1	-32.6	-19.7	-11.7	- 6.9	21.6	31.0	18.7	4.6
a=45.6	0	-23.3	-34.0	-22.2	-11.0	- 5.8	- 3.1	21.8	19.1	4.7	-6.1
k_2=.25	0	-26.7	-38.7	-31.8	-19.2	-11.4	- 6.7	21.0	21.1	12.4	3.2
$\bar{B}$=350	0	- 8.5	-19.1	-11.3	- 1.6	1.2	.51	11.7	23.8	3.1	-6.4
$\bar{B}$=1400	0	-36.2	-45.2	-42.0	-29.8	-19.5	-12.4	22.3	19.7	11.0	1.7

Table 14. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to Q, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	- 195	- 190	- 191	- 243	- 379	- 507	- 605	- 645	- 688	- 660	- 397
V_A=.4	- 195	- 190	- 196	- 253	- 389	- 514	- 610	- 658	- 692	- 647	- 391
Q=.1	-3070	-3065	-3028	-2928	-2819	-2763	-2745	-2764	-2809	-2933	-3087
Q=.9	-10.2	-20.6	-30.4	-70.7	- 116	- 135	- 141	- 157	- 122	- 46	- 32
T=.4	- 198	- 192	- 191	- 240	- 372	- 498	- 596	- 624	- 675	- 416	
k=.5	- 542	- 549	- 550	- 569	- 672	- 807	- 937	- 989	-1062	-1195	-1188
a=10.9	- 336	- 327	- 322	- 340	- 420	- 515	- 601	- 641	- 687	- 728	- 631
a=45.7	- 150	- 148	- 156	- 235	- 416	- 577	- 699	- 761	- 828	- 779	- 318
k_2=.25	- 401	- 397	- 389	- 395	- 480	- 598	- 709	- 776	- 857	- 962	- 869
$\bar{B}$=350	- 124	- 123	- 126	- 181	- 288	- 339	- 359	- 358	- 351	- 253	- 114
$\bar{B}$=1400	- 275	- 255	- 243	- 227	- 276	- 396	- 537	- 674	- 819	-1014	- 887

Table 15. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to k, x 10^{-6}

Time (MINS.)	0	1	2	5	10	15	20	21	22	25	30
Normal	65	63	63	80	124	168	201	215	230	221	133
V_A=.4	69	63	65	83	127	170	202	219	232	217	131
Q=.1	1023	1022	1009	975	937	918	911	917	933	975	1028
Q=.9	3.5	6.6	9.5	22.8	38.4	44.9	47.0	52.9	41.7	15.8	10.7
T=.4	66.	63.	60.7	73.	116	159	193	205	226	231	143
k=.5	542	547	547	563	665	799	930	983	1058	1197	1192
a=21.8	112	109	106	112	140	170	199	213	229	243	212
a=45.6	50	49	51.2	76	136	191	231	253	277	262	107
k_2=.25	134	132	129	129	157	197	234	258	286	322	292
$\bar{B}$=350	42	41	42	60	96	113	120	120	117	85	38
$\bar{B}$=1400	92	84	79	72	86	127	175	222	272	340	299

Table 16. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to T, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	0	- 8.1	- 8.9	- 6.9	- 4.4	- 2.7	- 1.7	12.4	11.2	5.6	.65
V_A=.4	0	- 4.9	- 4.9	- 4.3	- 3.1	- 2.1	- 1.4	6.3	5.7	3.5	.89
Q=.1	0	-20.4	-20.2	-18.9	-16.8	-14.9	-13.1	8.3	8.1	7.7	6.9
Q=.9	0	- 3.2	- 3.3	- 2.3	- .87	- .27	- .08	5.0	2.9	.31	.00
T=.4	0	-38.	-42.7	-33.9	-22.1	-14.0	- 9.0	61.3	55.1	28.9	3.7
k=.5	0	- 8.2	- 9.7	- 9.5	- 8.3	- 6.9	- 5.6	6.8	7.3	6.9	5.2
a=10.9	0	- 8.1	- 9.5	- 8.9	- 6.9	- 4.9	- 3.4	9.5	9.7	7.0	3.5
a=45.7	0	- 7.8	- 7.8	- 4.5	- 2.4	- 1.3	- .75	14.5	11.5	1.9	- .45
k_2=.25	0	-11.3	-12.4	-11.4	- 8.5	- 5.9	- 4.0	12.9	12.1	8.9	4.6
$\bar{B}$=350	0	- 2.8	- 3.3	- 1.0	+ .07	+ .06	.03	4.4	4.3	- .09	- .3
$\bar{B}$=1400	0	-18.5	-20.9	-22.5	-19.4	-14.8	-10.6	21.6	20.0	14.9	7.6

Table 17. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to 'a', x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	-3690	-3607	-3487	-3134	-2622	-2264	-2033	-2143	-2250	-2613	-3263
V_A=.4	-3700	-3588	-3469	-3105	-2595	-2245	-2021	-2123	-2226	-2632	-3279
Q=.1	- 840	- 776	- 761	- 730	- 679	- 630	- 586	- 602	- 600	- 595	- 590
Q=.9	-3965	-3875	-3745	-3393	-3082	-2978	-2947	-3223	-3495	-3881	-3963
T=.4	-3690	-3646	-3535	-3200	-2687	-2317	-2073	-2127	-2229	-2550	-3210
k=.5	-3180	-3078	-2969	-2699	-2281	-1941	-1682	-1725	-1742	-1808	-2055
a=10.9	-3170	-3102	-3002	-2736	-2368	-2105	-1928	-1999	-2084	-2293	-2628
a=45.7	-4030	-3943	-3803	-3345	-2694	-2269	-2009	-2172	-2319	-3079	-3994
k_2=.25	-3040	-2905	-2746	-2350	-1833	-1486	-1264	-1357	-1418	-1622	-2061
$\bar{B}$=350	-3840	-3800	-3740	-3537	-3261	-3129	-3079	-3141	-3250	-3553	-3843
$\bar{B}$-1400	-3560	-3406	-3215	-2676	-1978	-1526	-1245	-1377	-1484	-1834	-2459

Table 18. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to 'b', x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	3460	3381	3267	2910	2377	2002	1759	1840	1927	2270	2967
V_A=.4	3450	3363	3247	2877	2347	1981	1746	1822	1908	2295	2986
Q=.1	610	568	557	533	493	454	419	426	424	417	411
Q=.9	3800	3709	3573	3179	2814	2689	2651	2905	3186	3672	3792
T=.4	3466	3418	3314	2980	2447	2058	1801	1835	1911	2205	2906
k=.5	2900	2800	2700	2441	2031	1696	1438	1461	1465	1507	1732
a=10.9	2780	2715	2626	2378	2011	1738	1551	1594	1652	1820	2151
a=45.7	3910	3824	3684	3205	2526	2084	1815	1952	2085	2860	3868
k_2=.25	2750	2624	2478	2109	1609	1266	1043	1104	1145	1309	1723
$\bar{B}$=350	3700	3668	3608	3388	3079	2933	2880	2936	3041	3371	3714
$\bar{B}$=1400	3210	3056	2885	2399	1744	1298	1009	1077	1138	1388	1959

Table 19. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to k_2, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	270	325	375	531	763	927	1033	997	960	810	505
V_A=.4	280	330	383	545	776	936	1038	1051	968	799	498
Q=.1	1540	1552	1557	1568	1585	1602	1617	1614	1615	1618	1620
Q=.9	122	182	241	412	572	627	643	532	409	198	146
T=.4	259	309	355	500	733	902	1014	995	966	839	533
k=.5	528	578	623	735	914	1060	1172	1163	1161	1142	1045
a=10.9	490	532	573	690	861	989	1076	1056	1029	950	796
a=45.7	126	188	247	449	735	922	1035	977	922	594	170
k_2=.25	820	910	998	1222	1525	1733	1868	1831	1807	1707	1456
$\bar{B}$=350	170	199	227	322	457	520	544	519	473	330	180
$\bar{B}$=1400	370	467	541	753	1039	1234	1360	1330	1303	1195	945

Table 20. The effects of abnormal infant respirator parameter values on the sensitivity of $C_T(t)$ with respect to M, x 10^{-6}

Time (mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	410	470	534	682	849	949	1008	967	928	806	583
V_A=.4	420	480	540	687	853	952	1009	972	935	799	576
Q=.1	3310	3313	3323	3343	3374	3401	3425	3416	3416	3418	3418
Q=.9	200	240	302	389	432	441	442	369	302	218	201
T=.4	390	448	512	663	833	937	1000	977	939	827	602
k=.5	860	880	943	1078	1257	1388	1483	1462	1453	1423	1320
a=10.5	719	769	825	948	1073	1142	1181	1150	1114	1034	917
a=45.6	210	270	341	512	714	835	904	850	803	560	236
k_2=.25	690	753	820	952	1080	1149	1187	1156	1135	1076	961
$\bar{B}$=350	244	274	308	398	498	545	562	536	490	372	253
$\bar{B}$=1400	625	725	826	1039	1223	1302	1334	1291	1255	1150	974

Figure 21. The effects of abnormal infant respiratory parameter values on the sensitivity of $C_T(t)$ with respect to $\bar{B}$, x 10^{-6}

Time (Mins.)	0	1	2	5	10	15	20	21	22	25	30
Normal	210	281	358	564	846	1036	1156	1059	946	682	386
V_A=.4	215	292	366	577	858	1044	1161	1059	952	677	382
Q=.1	200	250	298	436	635	801	939	930	902	824	713
Q=.9	160	240	320	547	760	834	856	661	490	234	171
T=.4	190	256	330	526	809	1006	1134	1085	972	712	405
k=.5	270	332	403	585	840	1031	1171	1114	1045	870	649
a=10.6	380	443	515	699	954	1138	1263	1196	1104	900	668
a=45.6	90	174	255	485	787	977	1089	958	822	445	132
k_2=.25	280	358	447	680	987	1193	1326	1231	1125	874	598
$\bar{B}$=350	110	152	188	276	371	415	431	396	334	210	132
$\bar{B}$=1400	335	475	614	1039	1666	2122	2429	2244	2049	1563	1002

Table 22. Summary of adult sensitivity data of Tables 4 - 12

	V_A=1.5	Q=2	Q=18	T=.8	k=.25	a=224	a=896	k_2= .32	$\bar{B}$=350	$\bar{B}$=1400
$S_{V_A}^{C_T}$	0.5	1.2	0.4	1.3	1.0	1.0	0.8	1.0	0.8	1.3
$S_{Q}^{C_T}$	1.0	4.0	0.2	1.1	1.4	1.0	0.9	1.4	0.2	2.2
$S_{k}^{C_T}$	1.0	4.0	0.2	1.1	1.8	1.0	0.9	1.4	0.2	2.3
$S_{T}^{C_T}$	0.5	2.1	0.3	5.4	1.0	1.0	0.8	1.3	0.2	2.5
$S_{a}^{C_T}$	1.0	0.8	1.2	1.0	1.1	1.0	1.0	0.7	1.5	0.4
$S_{b}^{C_T}$	1.0	0.8	1.2	1.0	1.1	0.9	1.1	0.7	1.5	0.4
$S_{k_2}^{C_T}$	1.0	1.3	0.7	1.0	1.1	1.1	0.9	1.6	0.2	2.0
$S_{M}^{C_T}$	1.0	2.3	0.6	1.0	1.2	1.3	0.8	1.2	0.3	1.7
$S_{\bar{B}}^{C_T}$	1.0	1.1	0.8	1.0	1.1	1.1	0.9	1.3	0.2	2.9

Table 23. Summary of infant sensitivity data of Tables 13-21

	V_A=.4	Q=.1	Q=.9	T=.4	k=.5	a=10.9	a=45.6	k_2=.25	$\bar{B}$=350	$\bar{B}$=1400
$S_{V_A}^{C_T}$	0.6	0.3	0.8	0.9	1.0	1.1	1.0	1.1	0.7	1.3
$S_Q^{C_T}$	1.0	4.5	0.2	1.0	1.7	1.1	1.2	1.4	0.5	1.5
$S_k^{C_T}$	1.0	4.5	0.2	1.0	5.2	1.1	1.2	1.3	0.5	1.5
$S_T^{C_T}$	0.5	1.6	0.4	5.0	0.8	0.8	1.2	1.0	0.4	1.7
$S_a^{C_T}$	1.0	0.3	1.5	1.0	0.8	1.0	1.0	0.6	1.5	0.6
$S_b^{C_T}$	1.0	0.2	1.5	1.0	0.8	0.9	1.0	0.6	1.6	0.6
$S_{k_2}^{C_T}$	1.0	1.5	0.5	1.0	1.1	1.0	1.0	1.8	0.5	1.3
$S_M^{C_T}$	1.0	3.4	0.4	1.0	1.5	1.2	0.9	1.2	0.6	1.3
$S_{\bar{B}}^{C_T}$	1.0	0.8	0.6	1.0	1.0	1.1	1.0	1.1	0.4	2.1