

A COMPUTER MODEL OF HYPOXIC MAN

A Thesis Presented

by

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to

The Faculty of the Graduate College

of

The University of Vermont

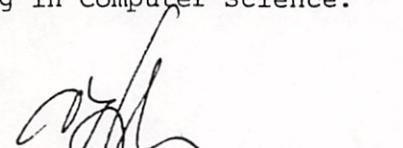
In Partial Fulfillment of the Requirements  
for the Degree of Master of Science

May, 1980

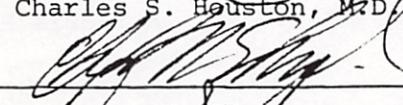
Accepted by the Faculty of the Graduate College, the University of Vermont, in partial fulfillment of the requirements for the degree of Master of Science, specializing in Computer Science.

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Date: March 14, 1980

8/17/77

## ABSTRACT

Acute or chronic hypoxia can be caused by a number of factors, among them air pollution, high altitude and diseases of the cardiopulmonary system. Despite the varying causes, however, all adversely affect the amount of oxygen getting to the cells, and all cause a series of physiologic changes in response to the impaired oxygen supply.

This paper describes a computer program developed to examine the physiologic changes with which man responds to hypoxia. The program uses 66 parameters defining the circulatory and pulmonary systems and blood gases, and equations describing their inter-relationships. A modification of the Krogh-Erlang model is used to estimate the oxygenation of an "ideal" cell. This allows compensation for variable capillary volume and changing metabolic rates. We can examine chronic hypoxia, as well as transient effects during the unsteady state adjustment to acute hypoxia.

The purpose of this computer model is to provide a tool for the study and clinical management of several forms of hypoxia. We can study the physiologic changes comprising adaptation and acclimatization to high altitude and help identify and isolate the causes behind favorable and unfavorable responses to hypoxia. This may also aid in evaluating prevention, treatment and management of high altitude diseases, as well as the more common cardio-pulmonary diseases.

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## CHAPTER 1

### INTRODUCTION

This paper will describe a computer program designed to model the steady-state physiologic changes that occur in man due to hypoxia. One purpose of this program is to use data normally available in a hospital intensive care unit to quantify a patient's level of tissue oxygenation. Information about the clinical state of a patient supplied by any machine, such as a monitor or a computer, may not be definitive but will yield an additional assessment for use by the patient's physician. Furthermore, we wish to estimate how various physiologic changes alter tissue oxygenation. In addition, this program can aid in the evaluation of different methods to prevent and treat high altitude illnesses and other diseases causing hypoxia.

The author's interest in hypoxia arises from an interest in mountaineering and emergency medicine; hence one of the main thrusts of this study has been to examine medical problems at high altitude. While this was the original impetus, the program is by no means limited to problems of altitude; it is an attempt to study any hypoxic disorder. However, since altitude sickness was among man's earliest encounters with hypoxia, the remainder of this section will present a brief history of man's journeys into the mountains and his experiences there, before more fully defining 'hypoxia.'

Chapter 2 of this paper will present some of the physiologic functions of the oxygen transport system, and the changes that occur with hypoxia. It will describe these functions in terms of the model, and will help to explain the equations which will be presented in

Chapter 3. The final chapter will summarize this type of study, and indicate some extensions for the future.

Throughout time, man has looked upwards into the mountains. The Gods lived there, they were mysterious and unknown, and they were beautiful. So as time progressed, man's curiosity overcame his fears, and he travelled into the higher elevations.

People had already suspected dangers in mountain travel. They believed in dragons and ghosts, as well as the possibility of the atmosphere coming to an abrupt end at some unknown altitude, just as one might fall off the edges of the seas. They were not, however, aware of the sickness which might be associated with high altitude.

Father Jose Acosta, a Jesuit missionary travelling in the Andes Mountains in Peru in 1540-45, was one of the first to describe high altitude illnesses. He suffered from nausea, vomiting and other symptoms of what we now recognize as acute mountain sickness. He suspected a relationship between his symptoms and the "thin air" he was breathing. He seems to have recognized that the rate of ascent was an important factor. He noted that the chances of experiencing mountain sickness (then called "puna" or "soroche") were greater if one ascended from the west of the Andes as opposed to ascending from the east, presumably because the western ascent is more abrupt than the eastern one, thereby allowing less time to acclimatize (Acosta, 1590). However, in his belief the causes of altitude discomforts were also associated with other things, such as poisonous shrubs or antimony fumes; in fact, "soroche" is Spanish for "antimony."

It is interesting to note that the Incas were apparently aware of the dangers of rapid ascents to altitude, as they maintained separate high and low altitude armies. Unfortunately, this lesson seemed to be lost in history; during the Sino-Indian War in 1962, large numbers of Indian troops were taken from sea level to 4000-5000m in the Himalayas, with a very high incidence of acute mountain sickness and pulmonary edema (Singh, et. al., 1965; Singh, et. al., 1969).

Edward Whymper, leader of the first successful, but tragic, ascent of the Matterhorn in 1865, concluded that the thin air at high altitudes would impose limitations on man. Writing about climbs in the Andes, he described headache, rapid pulse, general malaise and being "preoccupied by the paramount necessity of obtaining air." But he also made one of the first references to the ability of low-land dwellers to acclimatize to altitude, by noting that he "became somewhat habituated to low pressure" (Whymper, 1892).

The advent of the hot air balloon in the late 1700s, gave man the chance to experience both higher altitudes and quicker rates of ascent than had been previously possible. Furthermore, balloons provided a stable platform on which to carry out a variety of experiments. From early balloonists came several graphic descriptions of illnesses brought on by high altitude. One of the best known accounts is that by the crew of the balloon Zenith, which in 1875 carried Theodore Sivel, Joseph Croce-Spinelli and Gaston Tissandier to 8600 meters, a record altitude for that time. All lost consciousness, and only Tissandier survived the journey - they had failed to use the oxygen which they had brought aboard in time. It was only then that balloonists, and other visitors

to high places, began to realize the medical hazards of thin air and the benefits of oxygen.

Paul Bert was one of the great pioneers in the study of the physiologic deterioration due to high altitudes. He studied low barometric pressures in a decompression chamber, and was the first to show that the changes brought on were due to low oxygen partial pressure (hypoxia) at altitude, and were relieved by breathing oxygen. It was he who advised the crew of the tragic Zenith flight to carry oxygen, which he supplied (Bert, 1878; Hitchcock, 1964).

The first major study of high altitude effects actually made at high altitude, was by Angelo Mosso, in the 1890s. He built a small laboratory on Punta Gnifetti, one of the summits of Monta Rosa (4560m). Mosso found that normal people developed periodic breathing (Cheyne-Stokes) syndrome at altitude. But he concluded that high altitude illnesses were brought on by low carbon dioxide pressure (hypocapnia), not by low oxygen partial pressure.

In 1910, Mosso led the first international expedition to study high altitude physiology on Tenerife in the Canary Islands. They noted that one member of the expedition, Joseph Barcroft, did not hyperventilate at altitude. He had a normal alveolar  $P_{CO_2}$ , low alveolar  $P_{O_2}$ , and became very mountain sick. (See Appendix A for explanation of symbols.) Another expedition member, however, J.S. Haldane, did hyperventilate. His alveolar  $P_{CO_2}$  was low, alveolar  $P_{O_2}$  normal, and he did not get sick. This appeared to be in agreement with Bert's theory that low  $P_{O_2}$  was the main cause of high altitude illness, and this is still the prevailing thought today.

As the desire to go to higher altitudes continued, much more research was devoted to this "new" (to the medical community) field. In 1922, Barcroft travelled to 4330m at Cerro de Pasco, Peru, and showed that arterial  $P_{O_2}$  was less than alveolar  $P_{O_2}$ . This break-thru discovery proved that pulmonary arterial  $P_{O_2}$  was not higher than alveolar  $P_{O_2}$ , thus disproving Haldane's theory that oxygen was secreted into the blood. David Bruce Dill, in 1935, led a party to the Bolivian Andes to make the first analysis of resident miners' blood at 5240m, about the highest elevation where permanent residents live. This was the beginning of the study of true "high altitude" man, continued by people such as Carlos Monge and Alberto Hurtado, who have done extensive research in Peru, comparing permanent dwellers of high altitude and lowlanders (Hurtado, 1964; Monge & Monge, 1966; West, 1978).

In 1913, Dr. T.H. Ravenhill, a physician working for a mining company in the Peruvian Andes, wrote one of the earliest and clearest accounts of acute mountain sickness. He regularly observed people who were mountain sick after being brought quickly (and effortlessly) from sea level to 4900m by rail, thereby avoiding exercise, fatigue, insufficient food and other problems which plague mountaineers. He found that symptoms of acute mountain sickness did not appear at once. They did subside, however, with rest, and after 3-4 days usually disappeared. Ravenhill called this "puna", characterized by poor sleep, headache, vomiting, dizziness, tachycardia and possible fever, among other symptoms.

Ravenhill also noted two other high altitude diseases, variations of regular "puna." His "cardiac puna" is what we now know to be pulmonary edema. It is not surprising that he thought this to be a cardiac problem,

since pulmonary edema is usually caused by congestive heart failure.

However, it was quite some time before it was generally recognized that "cardiac puna" was due to fluid in the lungs despite a normally functioning heart. Ravenhill also discussed "nervous puna" which we today recognize as cerebral (brain) edema.

It was not until 1960 that a clear description of a case of pulmonary edema appeared in the English medical literature. A paper by Dr. Charles Houston (1960) described five cases, and led to many subsequent reports by other colleagues, thus starting a base of information in English.

Another manifestation of high altitude hypoxia is retinal hemorrhage. These were first discovered by a group of scientists under the direction of Dr. Houston, at a high altitude laboratory on Mt. Logan at 5000m, in the late 1960s (Gray, 1976).

While air at all altitudes contains 21% oxygen, the partial pressure of the oxygen decreases as altitude increases due to decreased barometric pressure. As early balloonists discovered, the magnitude and rate of the physiologic changes which the body undergoes in response to high altitude depend upon the altitude reached and the rate of ascent. These physiologic changes effect and can cause problems to climbers and hikers, who usually maintain a relatively slow rate of ascent, as well as to pilots, who may experience a sudden, rapid loss of air pressure (Denison, 1979; Milledge, 1975). Hypoxia at altitude may cause relatively minor discomfort, such as nausea, headaches, dizziness or other symptoms of acute mountain sickness (AMS), or very serious illnesses, such as

high altitude pulmonary edema (HAPE) or cerebral edema (CE) (Rennie, 1975). Although enough is known to prevent and treat these illnesses, as many as 100-200 persons still die each year because of them; one recent near-fatality occurred in a climber who experienced severe HAPE at only 2450m (Houston, 1975; Smutek, 1978). HAPE may also affect high altitude residents upon re-ascent to their native elevations after a stay at low altitude (Hurtado, 1964). Furthermore, some types of hypoxic cardiopulmonary diseases, such as emphysema, smoke inhalation and bronchitis, cause symptoms similar to hypoxic "high altitude" diseases (Heath & Williams, 1977; Jackson, 1975). Appendix B contains a list of some of these similarities.

The body responds to hypoxia with a number of physiologic adaptions, designed to return the body to a state of normalcy. These adaptations taken together comprise acclimatization (Houston, 1947). However, processes of acclimatization are not immediate, nor are they always sufficient to return the body to its normal state (Lenfant & Sullivan, 1971).

Hypoxia can be classified in a number of ways. A functional classification which differs only slightly from the typical medical scheme would be as environmental, pulmonary, circulatory or histotoxic. Environmental hypoxia refers to low oxygen partial pressure in the surrounding air, such as at high altitudes or in a room filled with noxious fumes. Pulmonary hypoxia refers to an impairment in the gas exchange process (emphysema, bronchitis), decreased available alveolar area (pneumonia) or impeded alveolar-arterial oxygen-carbon dioxide flow

(pulmonary edema). In circulatory hypoxia, either the heart is not functioning at full capacity (heart failure, myocardial infarction), or there is an inadequate vascular bed (arteriosclerosis, high arterio-venous shunt), or else the blood cannot carry its full quota of oxygen (anemia, carbon monoxide poisoning). In rare instances, histotoxic hypoxia occurs because of the inability of the cells to utilize the available oxygen (cyanide poisoning, some vitamin deficiencies). Regardless of cause, however, all refer to a breakdown somewhere in the cardio-pulmonary system, whose primary purpose is to supply the tissues with oxygen from the environment.

The term 'hypoxia' is used to describe an inadequate supply of oxygen to the tissues. This may occur in hypoxic (less than normal amounts of oxygen), normoxic (normal amounts of  $O_2$ ) or even hyperoxic (above normal amounts of  $O_2$ ) states. Dr. Eugene Robin (1979) has used the term 'dysoxia' to refer to the metabolic changes due to oxygen lack. This paper will deal only with problems of hypoxic hypoxia, as classified above.

## CHAPTER 2

### PHYSIOLOGY AND ETIOLOGY

For normal function, man requires a constant flow of oxygen to the tissues. The General Law of Transport, which mathematically describes this flow, states that the flow is proportional to the concentration or pressure difference between source and destination. In the human organism, the gas transport system is comprised of four components, from the atmosphere which represents a relatively inexhaustible source of oxygen, to the mitochondria which uses the oxygen. These transport mechanisms, each of which are in themselves expressions in the transport equation, are ventilation ( $\dot{V}_A$ ), pulmonary diffusion ( $D_L$ ), circulation ( $Q$ ) and tissue diffusion ( $D_t$ ). They are related mathematically by:

$$(1) \dot{V}O_2 = \dot{V}_A (\Delta P_1) k_1 + D_L (\Delta P_2) k_2 + Q (\Delta P_3) k_3 + D_t (\Delta P_4) k_4$$

where  $\Delta P_{1,2,3,4}$  are pressure gradients  
and  $k_{1,2,3,4}$  are proportionality factors.

Graphically, the body's general oxygen pathway is shown in Figure 2.1. Air enters the body through the mouth and nose (pharynx), travels down the trachea, through the bronchi and into the alveoli. This pathway comprises the ventilation component of the equation. The lung diffusion portion comes from the membrane gradient as oxygen travels from the alveoli to the pulmonary capillary blood. Oxygen is then transported through the circulatory system, where the amount of blood and the rate at which it is pumped (cardiac output) comprises the circulatory component. Finally, the tissue diffusion component comes from the oxygen gradient between systemic capillaries to the cells in the tissue (Lenfant & Sullivan, 1971).

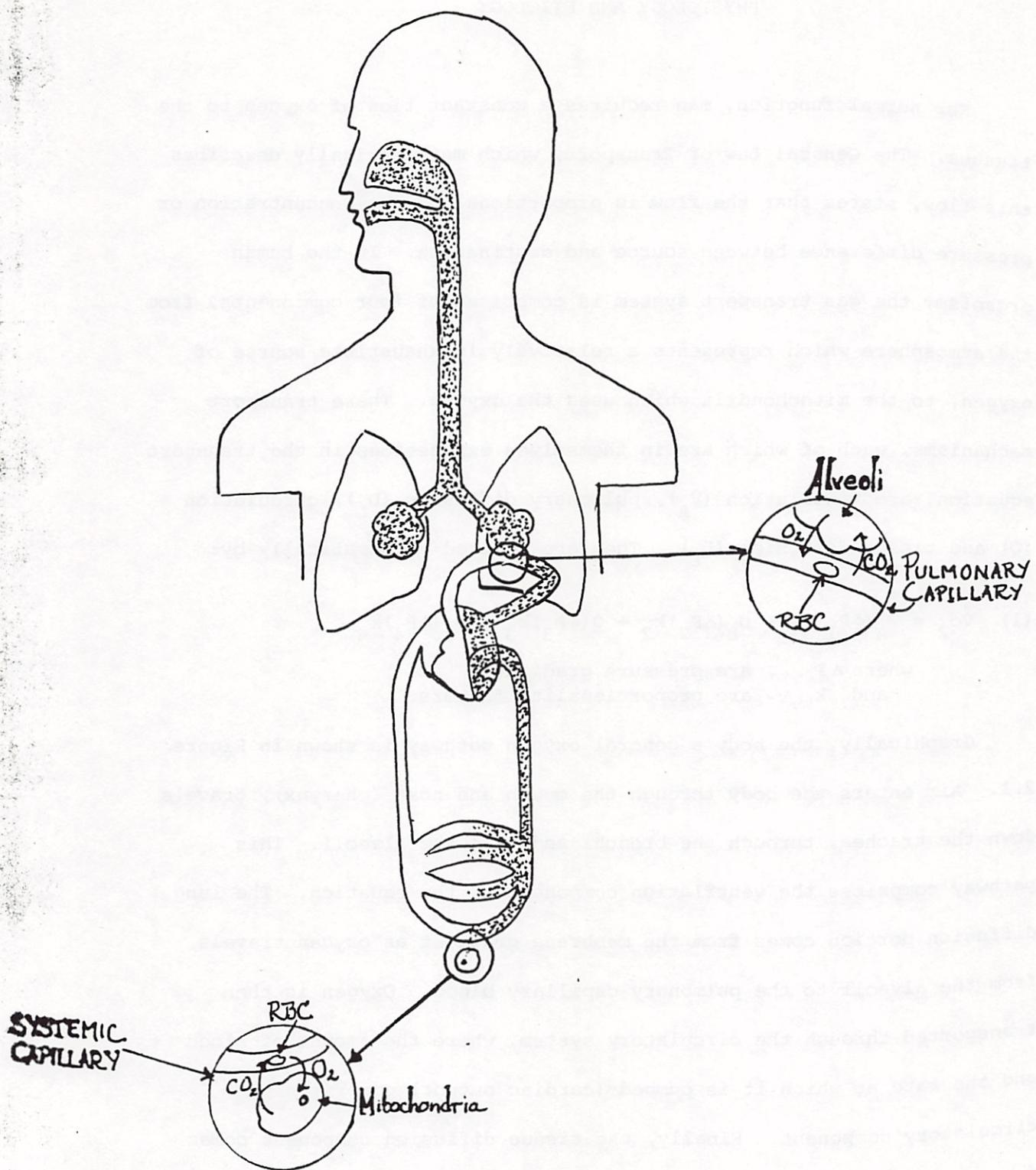


Figure 2.1. "Generalized" diagram of oxygen pathway, showing "ideal" cell.

Another way of viewing this pathway is shown in Figure 2.2. Oxygen enters the body at some partial pressure depending upon altitude and the percent of  $O_2$  in the air. Some oxygen is lost at various boundaries within the cardio-pulmonary system, until it reaches the cells and is used by the mitochondria. These drops in the  $Po_2$  comprise the 'oxygen cascade.'

Figure 2.3 shows in greater detail the flow of oxygen into the red blood cells in the pulmonary capillaries by passive diffusion and from the red blood cells in the systemic capillaries to tissue. The cardio-pulmonary system transports not only oxygen and nutrients to the tissues, but also removes carbon dioxide and waste materials from the tissues. Inspired air is comprised of 21% oxygen, while expired air is approximately 15% oxygen and 6%  $CO_2$ . Oxygen consumption ( $\dot{V}O_2$ ) is the measure of the amount of oxygen being used by the body. Basal (resting)  $\dot{V}O_2$  is that minimum required to produce adequate body heat and maintain the work of breathing, heart beat and all functions of living tissues. This is usually about 250-300 cc/min STPD. The basal  $\dot{V}O_2$  usually does not change appreciably from sea level ( $P_B = 760$  mmHg) to the summit of Mt. Everest (8484m,  $P_B = 240$  mmHg).

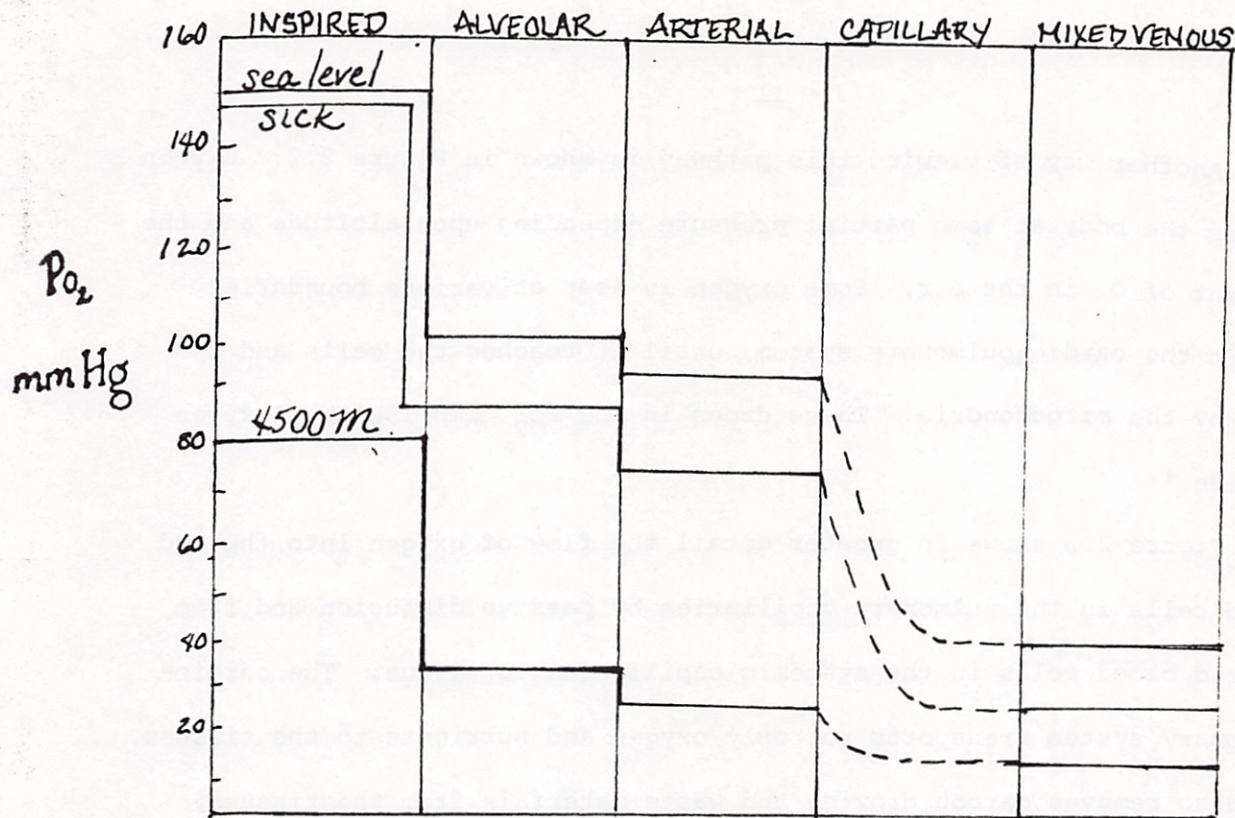


Figure 2.2. Typical oxygen cascade in normal people at sea level (S.L.) and at 4500m. Note that although the ambient (inspired)  $Po_2$  is much lower at altitude, the effects of the cascade diminish slightly, so that final  $Po_2$  is not that greatly decreased. Also shown is a "sick" person at S.L., to compare with normals, at the various steps of the cascade.

During strenuous work,  $\dot{V}O_2$  may actually rise to as high as 4 liters/min. At low altitudes, this rate of exertion may be sustained for an hour or more. As people ascend to above 2000m or so, the low  $Po_2$  in the air becomes a dramatic limiting factor in the vigor and duration of physical work. For example, at 5000m, an unacclimatized person may be able to perform at only 50% of his sea level maximum work capacity. After two months acclimatization, he may be able to maintain 68% of his work capacity; while natives living at 3800m and working at 5000m can maintain 87% of their maximum (Guyton, 1977; Henderson, 1939).

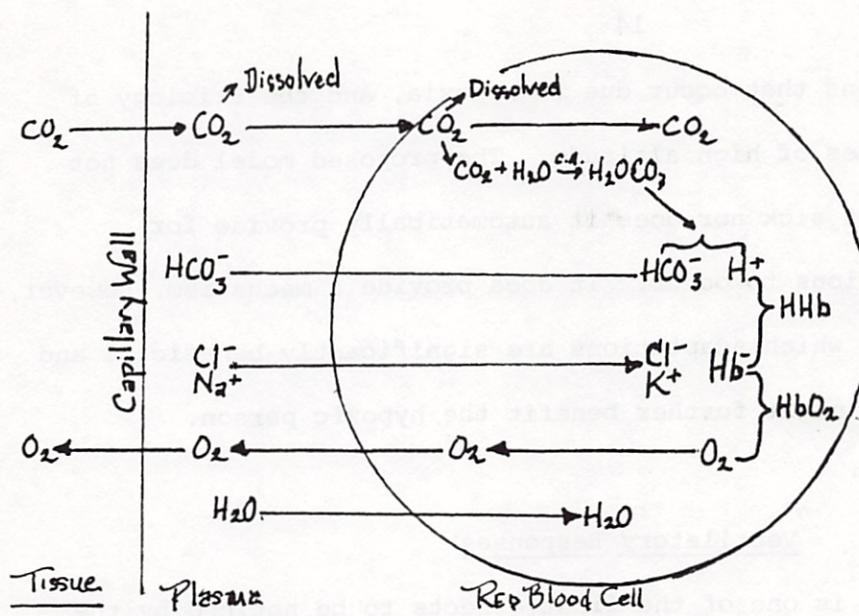


Figure 2.3. Scheme of the uptake of  $\text{CO}_2$  and liberation of  $\text{O}_2$  in systemic capillaries. Exactly opposite events occur in the pulmonary capillaries.

For purposes of this model, we assume that all effects of hypoxia are sudden and acute, as might happen in an aircraft suddenly losing cabin pressure. Figure 2.4 shows graphically the effects on man of sudden exposure to an hypoxic environment.

The function most sensitive to oxygen lack is night vision, which may be noticeably affected at altitudes as low as 1220m ( $P_B = 656 \text{ mmHg}$ ). Slight breathlessness and dyspnea with exercise may be detected at 2000m ( $P_B = 590 \text{ mmHg}$ ). At about 5200m, tingling, lightheadedness or dizziness may be felt; barometric pressure here is approximately half of the sea level value and this is the highest elevation known to have permanent, year-round human residents. Above 6100m or so, unconsciousness may occur (Milledge, 1975).

The following paragraphs will briefly discuss some of the short and

long term adaptations that occur due to hypoxia, and the etiology of some of the illnesses of high altitude. The proposed model does not predict who will get sick nor does it automatically provide for physiologic adaptations to occur. It does provide a mechanism, however, with which to study which adaptations are significantly beneficial and which interventions might further benefit the hypoxic person.

#### Ventilatory Responses

Breathlessness is one of the first effects to be noticed by the traveller to altitude. At sea level, ventilation is controlled primarily by the level of carbon dioxide in the arterial blood. If  $P_aCO_2$  increases, the brain realizes the need to rid itself of the excess carbon dioxide and hyperventilation occurs, resulting in a normalization of the  $CO_2$  level. In unacclimatized individuals at altitude hyperventilation lowers normal  $Pco_2$ , blunting the drive to breathe as  $CO_2$  is "washed out" by the over-breathing. As ventilation decreases, the hypoxic drive takes over, and causes over-breathing again. Fluctuations in carbon dioxide level may be the cause of periodic breathing - periods of apnea, followed by normal breathing, increasing to hyperventilation, slowing down to normal again, and returning to apnea - called Cheyne-Stokes (Guyton, 1977).

It has been found that persons with chronic obstructive pulmonary disease (COPD) actually breathe a little easier at moderate altitudes. This is due, in part, to a decrease in air density. However, another explanation may lie with the chemoreceptors. Patients with emphysema and COPD have dulled carbon dioxide receptors so that their breathing

is normally controlled by hypoxia rather than by hypercapnia; that is, they are chronically hypoxic. The level of  $\text{PCO}_2$  is not as important for breathing to these patients, nor to permanent high altitude dwellers, yet it may be one of the causes of periodic breathing observed in lowlanders at altitude (Graham & Houston, 1978; Lenfant & Sullivan, 1971).

#### Pulmonary Gas Exchange

One of the important factors in determining tissue oxygenation is the alveolar capillary gas exchange. A gradient exists between the alveoli and the pulmonary capillaries, in most part due to the diffusion coefficient of the lung membrane, called the A-a gradient. This gradient may be affected by many things. For example, hyperventilation generally reduces the gradient, while pulmonary edema, pneumonia or emphysema tend to increase it.

Carbon dioxide and carbon monoxide also travel across the membrane and are carried in the blood. Alveolar and arterial  $\text{PCO}_2$  are nearly the same, since the gradient for  $\text{CO}_2$  is very small, both at sea level and high altitude. The gradient for CO, however, decreases in a fashion similar to that for oxygen, hence carbon monoxide has no trouble getting to the blood. Furthermore, CO is picked up by the blood so much quicker than  $\text{O}_2$  that a little carbon monoxide can cause worse problems at altitude than at sea level. (This will be shown mathematically in Chapter 3.) Carbon monoxide is a major by-product of automobiles and industry. Hence, there is a very real question at "high altitude" cities, such as mile high Denver (1700m), as to which presents the greater problem - the carbon monoxide in the air or the decreased oxygen (Root, 1965; Roughton, 1965).

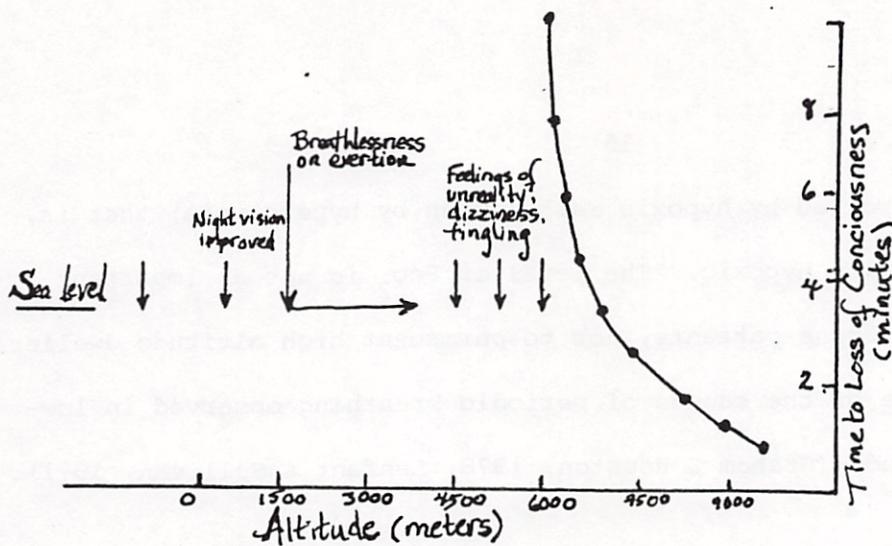


Figure 2.4. Effects of sudden exposure to increasing altitude (hypoxia).

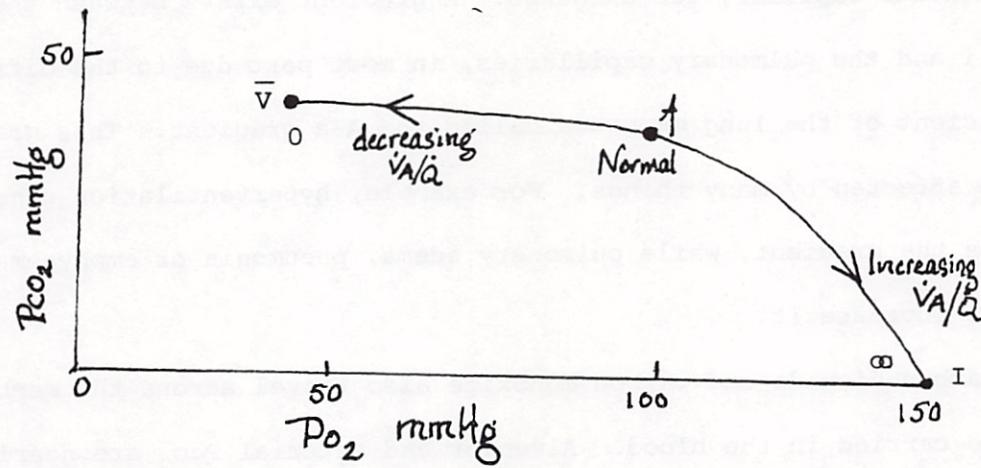


Figure 2.5.  $O_2$ - $CO_2$  diagram showing a  $\dot{V}_A/\dot{Q}$  ratio line. The  $Po_2$  and  $Pco_2$  of a lung unit move along this line from the mixed venous point,  $V$ , to the inspired gas point,  $I$ , as the  $\dot{V}_A/\dot{Q}$  ratio moves from 0 to infinity.

Gas exchange in the lungs occurs due to passive diffusion, and the efficiency is dependent upon the ratio of the alveolar ventilation ( $\dot{V}_A$ ) to the blood flow in the lungs ( $\dot{Q}$ ). The significance of the ventilation-perfusion ratio ( $\dot{V}_A/\dot{Q}$ ) can be seen graphically in Figure 2.5. With a normal  $\dot{V}_A/\dot{Q}$  ratio, the drop in  $Po_2$  from alveoli to blood is dependent almost entirely upon the diffusion variables across the lung membrane.

However, if ventilation is obstructed, the  $\dot{V}_A/\dot{Q}$  is reduced. Hence, the  $O_2$  in the lung will fall and the  $CO_2$  will rise, eventually reaching the same levels as in the mixed venous blood as the  $\dot{V}_A/\dot{Q}$  goes toward zero. Similarly, if the pulmonary blood flow is obstructed, the  $\dot{V}_A/\dot{Q}$  increases. Now, the  $O_2$  level rises and the  $CO_2$  falls, eventually reaching the same levels as in the inspired air, as the  $\dot{V}_A/\dot{Q}$  ratio goes to infinity (West, 1974).

Another reason that arterial  $Po_2$  is less than alveolar  $Po_2$  is shunting of blood; that is, blood that gets into the arterial circulation without going through a ventilated portion of the lung. This occurs in the normal lung since some of the bronchial artery blood is collected by the pulmonary veins after it has perfused the bronchi and its oxygen has been depleted (West, 1974).

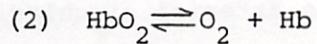
#### Circulatory Changes

During acute exposure to altitude, cardiac output increases. This increase is temporary, lasting only 3-4 days, and is due to an increase in heart rate. However, the subsequent return to normal of cardiac output is due to a decreased stroke volume. This may be due to a direct hypoxic effect on the myocardium (Lefant & Sullivan, 1971).

The distribution of the blood flow at altitude is modified to better supply the tissues most likely to suffer from hypoxia. The organs in the body have a 'pecking order,' to determine the order in which the organs get the available oxygen. The brain is at the top of this order, followed by the heart, lungs, liver, kidneys, gut and, finally, the skin. In hypoxia, since the brain is the organ most sensitive to oxygen

lack, cerebral blood flow increases, drawing blood away from the skin and other organs low on the 'pecking order.' After eating, the body must find blood for the digestive tract without decreasing cerebral blood, and this, too, usually is shunted from skin and other tissues (Lenfant & Sullivan, 1971; Siesjo, et. al., 1974).

The factor determining the volume of  $O_2$  carried by the blood is the relationship between oxygen and hemoglobin. Oxygen combines with hemoglobin (Hb) and is released by it, according to:



The ease with which the reversible reaction occurs is dependent upon the shape of the oxygen dissociation curve (Figure 2.6). This curve shows the relationship of  $P_{O_2}$  to oxygen saturation of the blood, which describes the percent of hemoglobin combined with  $O_2$  molecules.

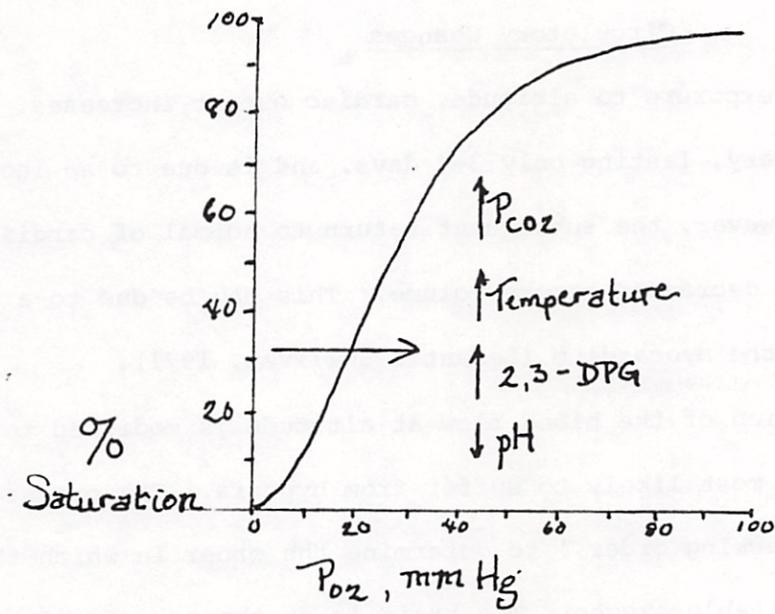


Figure 2.6. Position of the standard oxygen dissociation curve, and effects on its position by temperature, pH,  $P_{CO_2}$  and 2,3-DPG.

Heme picks up oxygen in the lungs to form oxyhemoglobin ( $\text{HbO}_2$ ), and drops off the  $\text{O}_2$  in the capillaries, where some of the  $\text{CO}_2$  joins with heme to form carbaminohemoglobin ( $\text{HbCO}_2$ ). Since  $\text{O}_2$  will flow by passive diffusion to areas of lower  $\text{P}_{\text{O}_2}$ , it "pushes" the  $\text{CO}_2$  out of the way in the tissues (Figure 2.3).

As Figure 2.6 shows,  $\text{P}_{\text{CO}_2}$ , temperature and pH are major factors in determining the position of the oxygen dissociation curve. As the  $\text{HbO}_2$  dissociation curve shifts to the right, it becomes easier for the heme to unload  $\text{O}_2$  and more difficult to pick it up. Conversely, as the curve shifts to the left, it becomes easier to pick-up  $\text{O}_2$ . For example, hypothermia will shift the curve to the left, making it easier to pick up available oxygen at low  $\text{P}_{\text{O}_2}$ ; thus, a hypothermic person can tolerate hypoxia longer than a normothermic person. Hypercapnia on the other hand, shifts the curve to the right. These right and left shifting factors, called the Bohr effects, are additive, and can therefore offset each other (Bunn, et. al., 1977). Temperature,  $\text{P}_{\text{O}_2}$  and pH have similar effects on the  $\text{CO}_2$  dissociation curve.

Another factor in determining the shape and position of the oxygen dissociation curve is the amount of 2,3-diphosphoglycerate (2,3-DPG), one of the major organic phosphates in the red blood cells. 2,3-DPG plays an important role in regulating the oxygen affinity of the hemoglobin. In hypoxia, the 2,3-DPG concentration is greater than normal, shifting the curve to the right thereby increasing the blood's ability to release oxygen to the tissues. Similar increases are found in persons with chronic lung disease, cyanotic heart disease, various forms of anemia, and are seen in persons living at high altitudes

(Benesch & Benesch, 1967; Chanutin & Curnish, 1967; Davenport, 1974; Heath & Williams, 1977; Perutz, 1978). The benefits of this DPG shift are questionable at high altitudes, since the oxygen loading in the lung is actually impaired by the shift; hence, increased oxygen release is offset by the initial decrease in oxygen pick-up. Below 3500m, this shift does show definite advantages towards adaptation, which is especially enhanced by the increased alveolar  $Po_2$  generally experienced by newcomers to altitude due to increased ventilation (hyperventilation) (Lenfant & Sullivan, 1971).

Another change which occurs with chronic hypoxia is polycythemia, an increase in red blood cell (RBC) mass. This raises the hemoglobin and hematocrit levels, and thus the blood's oxygen carrying capacity. Hence, polycytemia would appear to be a beneficial adaptation. However, increases in hematocrit increase blood viscosity, thus creating more work for the heart, decreasing cardiac output and actually placing individual RBCs farther from the tissues towards which the oxygen is being carried. To combat this, some authorities recommend hemodilution of climbers at altitude, fearing that the adverse effects of 'over-viscous' blood far outweigh the benefits (Smutek, 1979; Zink, 1979).

#### Tissue Adaptations

The final step in the oxygen transport system is delivery of oxygen to the tissues, and within the tissues to the mitochondria, where the consumption of oxygen occurs.

The basic process by which oxygen "flows" from capillary to mitochondria is passive diffusion (Figure 2.3). The rate at which

diffusion will take place depends upon several things, notably the difference in oxygen pressure between capillary blood and the mitochondria, the capillary/mitochondria ratio and the specific tissue's oxygen diffusion coefficient.

Normally, the  $Po_2$  in the mitochondria is nearly zero, therefore the pressure difference between capillary blood and mitochondria will depend almost entirely upon capillary blood  $Po_2$ .

Mitochondrial  $Po_2$  will also depend upon the distance between the capillary and the cells containing mitochondria. The further apart two

Figure 2.7.  $O_2$  delivery between adjacent cells.

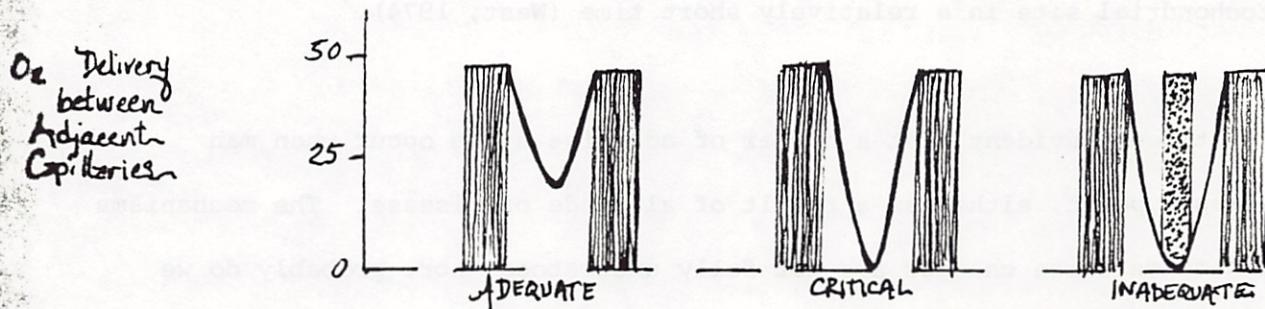
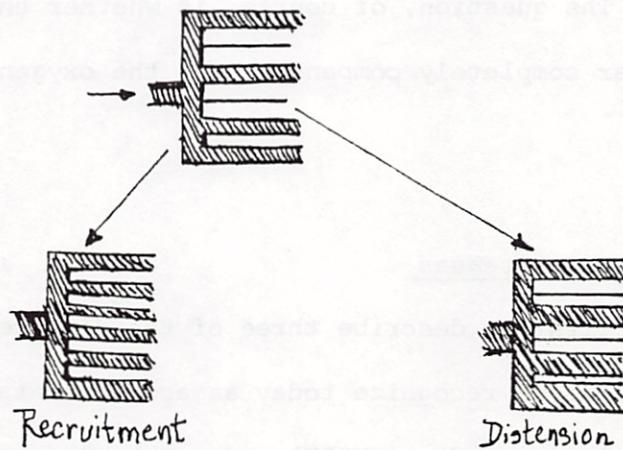


Figure 2.8. RECRUITMENT and DISTENSION are mechanisms which will increase the number and size of capillaries. Recruitment opens previously closed capillaries, and distension increases diameter of existing ones.



capillaries are, the lower will be the  $Po_2$  midway between these two capillaries. Hence, there is probably a "critical" distance between any two capillaries for a given  $PcO_2$ , at which an inadequate amount of oxygen is available (Figure 2.7). Capillaries respond to hypoxia by two mechanisms; distension and recruitment (Figure 2.8). With distension, existing capillaries dilate; with recruitment, new capillaries form and others normally shut are opened. Both of these mechanisms increase the capillary/cell ratio, so that there may be fewer "critical" portions of the tissue (Lenfant & Sullivan, 1971; West, 1974). It has also been demonstrated that mitochondrial density increases with hypoxia, thereby increasing the probability that an  $O_2$  molecule will find a suitable mitochondrial site in a relatively short time (West, 1974).

It seems evident that a number of adaptive steps occur when man becomes hypoxic, either as a result of altitude or disease. The mechanisms which cause these changes are not fully understood, nor, probably do we yet recognize all of them. However, it is likely that persons with any cardiopulmonary disease affecting oxygen transport undergo some form of adaptation to chronic hypoxia. The question, of course, is whether these acute or chronic changes can ever completely compensate for the oxygen lack.

#### High Altitude Diseases

Dr. T.H. Ravenhill was the first to describe three of the different forms of high altitude disease that we recognize today as acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and cerebral (brain)

edema (CE or HACE). In addition, we know that retinal hemorrhages (RH) also occur at altitude. While the interrelationships between these forms of high altitude illness are not clearly identified, it is felt that they are not separate entities, but rather clinical manifestations in a continuum of illness.

Acute mountain sickness is common among travellers to the mountains, occurring at altitudes as low as 1600m. It is evidenced by headache, dizziness, anxiety, ataxia, nausea, disturbed sleep and a general feeling of being unwell (malaise). AMS is rarely serious, feeling much like a bad hangover. The treatment is usually a day or two of rest.

High altitude pulmonary edema is less common than AMS, normally occurring above 2700m, although occasionally lower. This is usually brought on by a too rapid ascent, and is characterized by shortness of breath, dyspnea, weakness, coughing frothy, pink sputum and, not rarely, death. Because of these symptoms, HAPE is often confused with pneumonia. When first described by Ravenhill in 1913, it was attributed to heart failure, since pulmonary edema accompanies heart failure, until it was discovered upon autopsy that the hearts of "cardiac puna" victims were normal. Today, it is strongly suspected that fluid buildup in the lungs is caused by the large increase in mean pulmonary arterial pressure, causing leaks into the alveoli from the pulmonary capillaries.

Cerebral edema is rare and much more serious than either AMS or HAPE, usually occurring above 2600m. It is characterized by headache, vomiting, lethargy, ataxia, stupor and, eventually, coma and death. Brain edema is thought to be caused by a failure in the cells' sodium pump, which takes water out of cells. When this "water removal"

mechanism breaks down, the cells act like sponges, causing severe brain swelling.

Retinal hemorrhages, like AMS, are very common among mountain travellers. However, they are rarely symptomatic, and therefore require no medical treatment. They usually disappear upon descent to lower altitudes (Wilkerson, 1975; Houston, 1979).

Lack of oxygen is the precipitating factor which causes these illnesses. As the body becomes hypoxic, it attempts to adapt to the low oxygen pressure, but the adaptations may not be successful; especially if ascent is too rapid. Obviously, once HAPE or CE have begun, the effects of hypoxia will become more and more severe.

Physical conditioning does not seem to prevent illness or improve adaptation to high altitude. As early as 1590, Acosta noted that alcohol is not as relaxing at 2000m as it is at sea level; and most other vitamins, stimulants, depressant and hallucinogens do not seem to make man better able to handle the stress of high altitude, nor to have better endurance there (Jokl, 1966).

Man has evolved from each generation to better adapt to the environment in which he lives, be it heat, cold or altitude. This can be seen to some degree in athletes, who are constantly breaking old records. Man can adapt to environmental hypoxia and we know that he can adapt to hypoxia brought on by disease. Hence, by studying the physiologic changes that the body undergoes to adapt to the environment, can we learn something of how it adapts to disease?

There are still many unanswered questions regarding the cause and

treatment of high altitude diseases. Earlier, we mentioned that the  $\dot{V}O_2$  does not change appreciably from sea level to very high altitudes. How, then, can we speak about oxygen lack when oxygen consumption does not decrease?! Furthermore, the maximal  $\dot{V}O_2$  (exercise) is not significantly different between acclimatized low altitude dwellers and permanent inhabitants of altitude. What does this say about "adaptation" (Houston, 1979)? The exact etiology of high altitude disease is not known; we do not know if these are diseases of oxygen deprivation or "diseases" caused by the body's attempts to compensate for the oxygen lack! We do not know if a person once stricken is more immune upon subsequent ascents or more susceptible to getting sick again. But the important question, in terms of the model, is what lessons can we gain from the study of healthy man at altitude to help the sick at sea level (Grover, 1975; Houston, 1979)?

## CHAPTER 3

### COMPUTER MODEL AND EQUATIONS

The previous section has described the physiologic aspects of the oxygen transport system from the environment to the tissues, and the changes that occur with hypoxia. Utilizing equations that model this system, a computer program called HYPOXIA has been developed.

The purpose of this work is to obtain a closer approximation of tissue oxygenation in man in the physiologic steady-state. A steady state model is used for simplicity, as a first approximation. A mathematical model is being used rather than a statistical one, since statistical models are more useful for verifying results than for understanding the mechanisms involved. Use of algebraic equations allows us to describe individual phenomena, and may help in defining which changes are useful as compensation, and which are not. Mathematical models are also easier to modify than are statistical ones as new information is uncovered. It is hoped that the insights gained will have practical and useful clinical application, in addition to contributing to theory.

Most persons going to high altitudes, especially climbers and hikers who travel under their own power, are physically healthy. It is useful to study normal people at altitude, since many people with chronic lung conditions at sea level are as hypoxic as a climber high in the mountains; i.e., a person with emphysema at sea level may be getting as little oxygen as a climber at 5000m.

Modeling a complex system, such as the human body, requires that a

certain number of simplifying assumptions be made (Milhorn, et. al., 1965). This analysis makes the following assumptions:

- 1) All measured changes occur in the physiologic steady-state.
- 2) The  $Po_2$  of the 'ideal' cell is being calculated; i.e., this is the oxygenation that would prevail throughout the body if this  $Po_2$  were the average. Consequently, the system consists of only two oxygen reservoirs, the lungs and the tissues.
- 3) The shape of the oxygen dissociation curve is the same for arterial and venous blood at constant pH, temperature and  $Pco_2$ .
- 4) The shape of the carbon dioxide dissociation curve is the same for arterial and venous blood at constant pH, temperature and  $Po_2$ .
- 5) Arterial  $Pco_2$  is equal to alveolar  $Pco_2$ .
- 6) The rapid changes in alveolar and arterial gas concentrations with each respiratory cycle are ignored.

A number of computer models of the respiratory system have been described: Farrell & Siegel, 1973; Grodins, et. al., 1967; Jackson & Milhorn, 1973; Milhorn, et. al., 1965; Trueb, et. al., 1971. However, these models have been designed primarily as research tools and are complete only as to details of the ventilatory system; thus, they do not describe cellular or tissue oxygenation. Furthermore, as they are tools for research, they require in-depth information describing the ventilatory system, such as airway resistance, lung wall compliance, acid-base balance, etc. This information is generally not available in the clinical setting, however, and therefore these models have limited use in applications to patient care.

#### Equations

The following discussion will present the equations used by the program, in the general order in which they are computed. Upon entry to

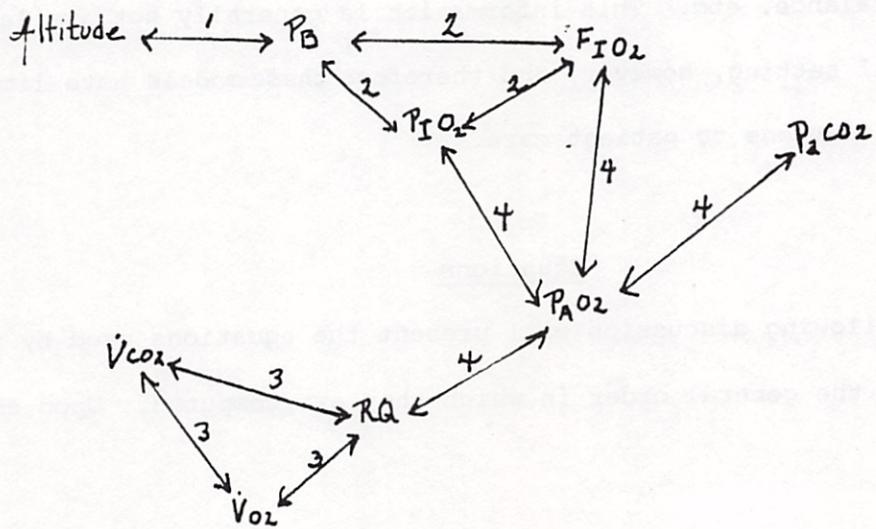
HYPOXIA, the user supplies all known information to the program. Appendix C gives a list of the parameters that the program utilizes. Based upon the available information, all equations are computed in a sequential fashion until, finally, no further information can be generated. Figure 3.1 (a-d) shows the organization and sequence of the equations.

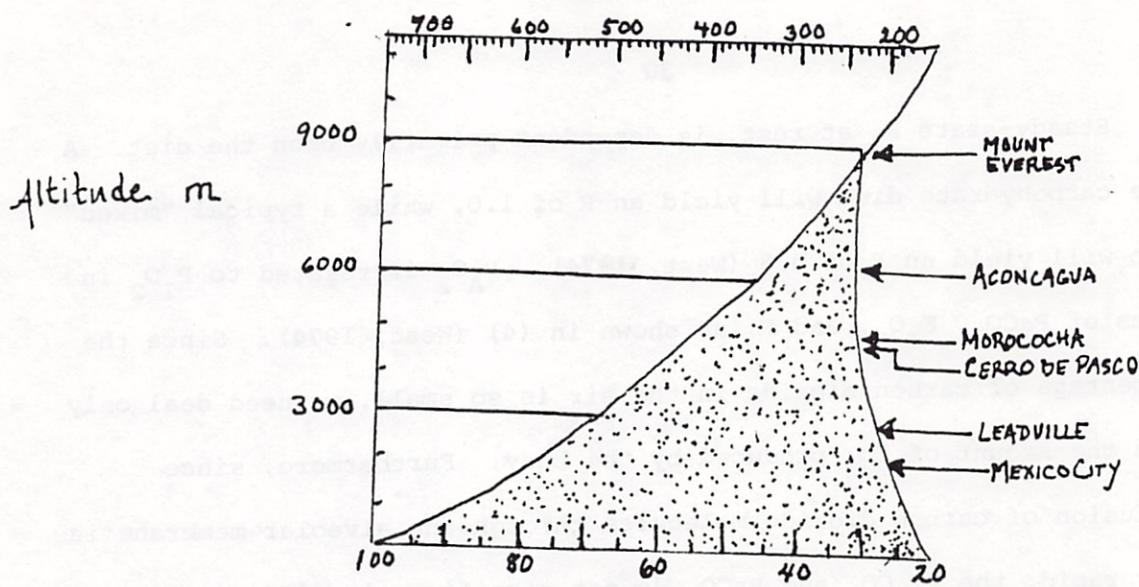
#### Environment to Alveoli

The barometric pressure at sea level is normally 760 mmHg; this value fluctuates slightly due to high and low pressure weather systems and at high and low latitudes, but these effects can be ignored. Oxygen comprises 20.93% of atmospheric air, nitrogen 78%, and other trace elements comprise the remaining 1%.

Equation (1) (Erb, 1978) describes the relationship between altitude and barometric pressure, also shown in Figure 3.2. The atmosphere also contains carbon dioxide which has been produced by green plants

Figure 3.1a. Environment to Alveoli (Equations 1-4).





AIR (AND O<sub>2</sub>) PRESSURE IS % OF THAT AT SEA LEVEL

Figure 3.2. The relationship between altitude, barometric pressure and air (and oxygen) pressure as percent of sea level values.

and carbon monoxide produced by industrial pollution and tobacco smoke.

$$(1) \text{ Altitude} = 44364.236 \times 1 - (P_B / 760)^{1/5.256}$$

Since  $P_B$  is a function of altitude, so must be inspired  $P_{O_2}$ . As soon as it enters the body, inspired air is saturated with water vapor at a partial pressure of 47 mmHg and heated (or cooled) to body temperature of 37°C before entering the lungs, so that the sum of the partial pressures of all inspired gases equals ( $P_B - 47$ ). This relationship is shown in (2) (Houston, 1947):

$$(2) P_{I O_2} = F_{I O_2} \times (P_B - 47)$$

The next drop in oxygen cascade occurs in the alveoli. Here, the relationship between oxygen consumption and carbon dioxide production is very important. The respiratory quotient, or respiratory exchange ratio (R), is defined as:

$$(3) R = (\text{CO}_2 \text{ production}) / (\text{O}_2 \text{ uptake}) = \dot{V}\text{CO}_2 / \dot{V}\text{O}_2$$

Steady-state R, at rest, is dependent primarily upon the diet. A pure carbohydrate diet will yield an R of 1.0, while a typical "mixed" diet will yield an R of 0.8 (West, 1974).  $P_{A\text{O}_2}$  is related to  $P_{I\text{O}_2}$  in terms of  $Pa\text{CO}_2$ ,  $F_{I\text{O}_2}$ , and R, as shown in (4) (West, 1974). Since the percentage of carbon dioxide in the air is so small, we need deal only with the amount of  $\text{CO}_2$  produced by the body. Furthermore, since diffusion of carbon dioxide molecules through the alveolar membrane is very rapid, the  $P_{A\text{CO}_2}$  and  $Pa\text{CO}_2$  do not significantly differ, and are therefore generally used interchangeably.

$$(4) \quad P_{A\text{O}_2} = P_{I\text{O}_2} - Pa\text{CO}_2 \times [1 - F_{I\text{O}_2} \times (1-R)] / R$$

#### Alveoli to Arterial Blood

Oxygen partial pressure falls again as oxygen moves across the alveolar-capillary membrane in the lungs, leaving the alveoli to be picked up by pulmonary capillary blood. The diffusion resistance of these membranes is a significant barrier and contributes largely to the alveolar-arterial gradient ( $D_{O_2} (A-a)$ ), which is normally less than 10 mmHg.

The relationship of alveolar to arterial  $P_{O_2}$  is shown in (5). There are two other phenomena which affect this fall; namely, the arterio-venous anatomic shunt (venous admixture) and a "shunt" caused by ventilation/perfusion inequality ( $\dot{V}_A/\dot{Q}$ ) (6)-(7) (Mithoefer, 1968; Tenney, 1968; West, 1974):

$$(5) \quad Pa\text{O}_2 = P_{A\text{O}_2} - D_{O_2} (A-a)$$

$$(6) \quad \text{Shunt} = (C_{A\text{O}_2} - Ca\text{O}_2) / (C_{A\text{O}_2} - Cv\text{O}_2)$$

$$(7) \quad \dot{V}_A/\dot{Q} = R \times (Ca\text{O}_2 - Cv\text{O}_2) / P_{A\text{CO}_2}$$

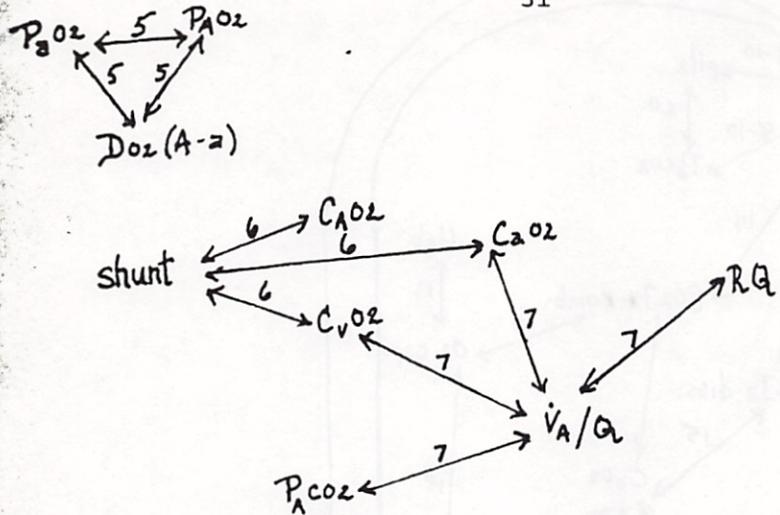


Figure 3.1b. Alveoli to Arterial Blood (Equations 5-7).

#### Arterial to Venous Blood

The "circulatory" gradient is determined by the relationship between the metabolic rate of the tissues and the rate of blood flow, according to the Fick principle. We begin to study this gradient by determining oxygen saturation (Figure 2.6), which can be calculated in two steps.

First, since the standard oxygen dissociation curve is based upon a temperature of  $37^{\circ}\text{C}$ , pH of 7.4 and  $P_{CO_2}$  of 40 mmHg, any measured  $Po_2$  must be corrected to a "virtual"  $Po_2$ ; i.e., corrected to standard temperature, pH and  $P_{CO_2}$ , as in (8) Kelman, 1966b; Severinghaus, 1966; West & Wagner, 1977):

$$(8) P' = Po_2 \times 10^{[0.024(36-\text{temp}) + 0.4(\text{pH}-7.4) + 0.06(\log(40) - \log(P_{CO_2}))]}$$

The second step is to calculate oxygen saturation from the new  $Po_2$  and the standard curve. Two different equations are used for this, for accuracy, since the curve is exponential. For the main body of the curve, (9) is used; for the tail end, ( $Po_2 < 10$  mmHg) (10) is used (Kelman, 1968; Olszowka & Farhi, 1968; West & Wagner, 1977).

$$(9) S_o_2 = u / (1+u)$$

$$\text{where } u = 0.00925XP' + 0.00028XP'^2 + 0.0000306XP'^3$$

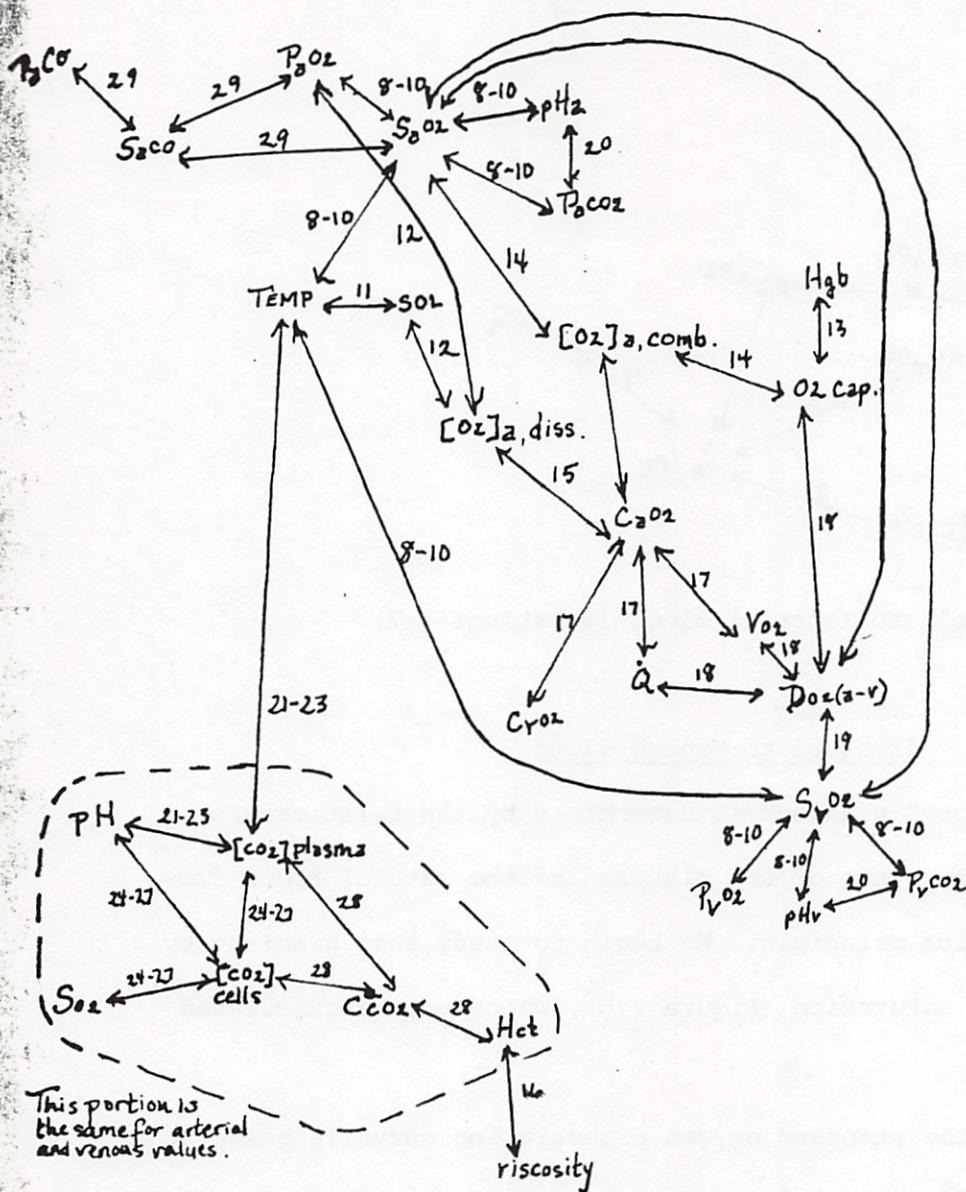


Figure 3.1c. Arterial to Venous Blood (Equations 8-29).

and  $P'$  = "virtual"  $P_{O_2}$

$$(10) \quad S_{O_2} = 0.003683XP' + 0.000584Xp'^2$$

where  $P'$  is "virtual"  $P_{O_2}$ ; and  $P' < 10$  mmHg.

Oxygen content describes the volume of oxygen actually being carried in the blood. It, too, is calculated in two steps.

First, solubility is calculated (11), then the volume of oxygen dissolved in the blood (12) (Kelman, 1966a; West, 1974; West & Wagner, 1977):

$$(11) \text{ SOL} = 0.0059519 - 0.0001266x\text{TEMP} + 0.0000013x\text{TEMP}^2$$

$$(12) [\text{O}_2]_{\text{diss}} = \text{SOL} \times \text{Po}_2$$

Only a very small amount of oxygen is carried in solution in the blood, most being combined with hemoglobin, as oxyhemoglobin ( $\text{HbO}_2$ ). The value of 1.34 cc. is the theoretical volume of oxygen which will combine with 1 gram of hemoglobin at full saturation, although some experiments indicate that the true value may be nearer to 1.39. Total volume of oxygen carried in the blood, then, is the sum of the oxygen dissolved in the blood and the amount combined with hemoglobin.

Equations (13)-(15) describe these relationships (Kelman, 1966a; West, 1974; West & Wagner, 1977):

$$(13) \text{O}_2 \text{ CAP} = 1.39 \times \text{Hgb}$$

$$(14) [\text{O}_2]_{\text{comb}} = \text{O}_2 \text{ CAP} \times \text{So}_2$$

$$(15) \text{Co}_2 = [\text{O}_2]_{\text{comb}} + [\text{O}_2]_{\text{diss}}$$

Previous discussion shows how to calculate  $\text{So}_2$  and  $\text{Co}_2$  from  $\text{Po}_2$ , which is the usual case for calculating arterial values. Later discussion will show that it is possible to calculate venous  $\text{So}_2$  and  $\text{Co}_2$  directly from the arterial  $\text{So}_2$  and  $\text{Co}_2$ . Hence, it is necessary to be able to calculate  $\text{Po}_2$  from  $\text{So}_2$  and  $\text{Co}_2$ . Since the saturation equations are polynomials, calculating  $\text{Po}_2$  from  $\text{So}_2$  is a straight-forward procedure. With oxygen content, however, it is not so simple, since there are two parts to the equation, one depending upon  $\text{Po}_2$  and the other on  $\text{So}_2$ . To calculate  $\text{Po}_2$  from  $\text{Co}_2$ , make a first approximation that dissolved  $[\text{O}_2]$  is zero. This is reasonable since it is in reality very low. Now,  $\text{Co}_2$  depends only upon  $\text{So}_2$ , and a good approximation for  $\text{Po}_2$  can be obtained. This new  $\text{Po}_2$  can be used in the equation, and a

new approximation found. In general, this second iteration will yield a  $Po_2$  within 1% or so of the correct value. At high  $Co_2$ 's, where the dissolved  $O_2$  content is larger, several iterations are required to produce a valid  $Po_2$  estimate. Hence, the program described here uses five iterations for all values of  $Co_2$ . The  $Po_2$  found in this way will be at standard temperature, pH and  $Pco_2$ ; the true value is obtained by using the inverse of the correction equation, (8).

Earlier discussion indicated that polycythemia occurs at altitude, increasing hematocrit and, therefore, viscosity of the blood ( $\eta$ ). This relationship is seen in (16) (Zingg, et. al., 1970):

$$(16) \eta = 1.24 \times e^{0.02471 \times Hct}$$

At this point in our calculations, we know the  $PaO_2$  and can calculate the  $SaO_2$  and  $CaO_2$ . We can determine venous blood gas values using the Fick Principle as follows:

The oxygen consumption ( $\dot{V}o_2$ ) is the amount of oxygen taken up by the tissues. That amount is the difference between arterial and venous concentrations of oxygen in the blood, multiplied by the cardiac output ( $\dot{Q}$ ) (Mithoefer, 1968; West, 1974). This is shown algebraically by the Fick Principle:

$$(17) \dot{V}o_2 = \dot{Q} \times (CaO_2 - CvO_2)$$

We can use this information to find the arterio-venous saturation difference ( $Do_2 (a-v)$ ), by noting that the  $[O_2]_{comb}$  divided by oxygen carrying capacity is the  $So_2$ , from (14). Assuming the  $[O_2]_{diss}$  to be very close to zero, then the concentration difference divided by oxygen carrying capacity is the saturation difference, as in (18) (Houston, 1947; West, 1974):

$$(18) \text{Do}_2 \text{ (a-v)} = (\text{CaO}_2 - \text{CvO}_2) / \text{O}_2 \text{ CAP} = \dot{V}\text{O}_2 / \dot{Q}/\text{O}_2 \text{ CAP}$$

From this, we find:

$$(19) \text{SvO}_2 = \text{SaO}_2 - \text{Do}_2 \text{ (a-v)}$$

From the venous saturation, we can calculate  $\text{PvO}_2$  and  $\text{CvO}_2$ , by using the inverse functions described previously for calculating saturation and concentration from  $\text{Po}_2$ .

Blood transports two other gases besides oxygen, namely, carbon dioxide and carbon monoxide.

Approximately 23% of the  $\text{CO}_2$  transported in the blood joins with hemoglobin to form carbaminohemoglobin ( $\text{HbCO}_2$ ). Dissolved carbon dioxide accounts for 7%, and the remaining 70% is carried as bicarbonate ion ( $\text{HCO}_3^-$ ).

The relationship between carbon dioxide and bicarbonate is given by the Henderson-Hasselbalch equation (20) (West, 1974):

$$(20) \text{pH} = \text{pK}' + \log \left( \frac{[\text{HCO}_3^-]}{[\text{CO}_2]} \right)$$

where  $\text{pK}' = 6.1$   
and  $[\text{CO}_2] = 0.03 \times \text{Pco}_2$

Total blood  $\text{CO}_2$  content can be determined from the  $\text{Pco}_2$ , plasma pH,  $\text{SO}_2$ , hematocrit (Hct) and temperature (Kelman, 1967; West & Wagner, 1977). First, plasma  $\text{Cco}_2$  can be calculated from pK and solubility, as shown in (21)-(23).

$$(21) \text{pK} = 6.086 + 0.042x(7.4-\text{pH}) + (38-\text{TEMP}) \times [0.0047 - 0.0014x(7.4-\text{pH})]$$

$$(22) \text{SOL} = 0.0307 + 0.00057 \times (37-\text{TEMP}) + 0.00002 \times (37-\text{TEMP})^2$$

$$(23) [\text{CO}_2]_{\text{plasma}} = \text{SOL} \times \text{Pco}_2 \times [1 + 10^{(\text{pH}-\text{pK})}]$$

The ratio of cellular  $\text{CO}_2$  concentration to plasma  $\text{CO}_2$  concentration is an experimentally determined function. This ratio (CPRAT) is obtained

by linear interpolation between the ratio of fully oxygenated (FOB) and fully reduced blood (FRB), as in (24)-(27):

$$(24) \text{FOB} = 0.590 + 0.2913 \times (7.4-\text{pH}) - 0.0844 \times (7.4-\text{pH})^2$$

$$(25) \text{FRB} = 0.664 + 0.2275 \times (7.4-\text{pH}) - 0.0938 \times (7.4-\text{pH})^2$$

$$(26) \text{CPRAT} = \text{FOB} + (\text{FRB} - \text{FOB}) + (1 - \text{SO}_2/100)$$

$$(27) [\text{CO}_2]_{\text{cells}} = \text{CPRAT} \times [\text{CO}_2]_{\text{plasma}}$$

From this we find:

$$(28) \text{Cco}_2 = [\text{CO}_2] = \text{Hct} \times [\text{CO}_2]_{\text{cells}} + (1 - \text{Hct}) \times [\text{CO}_2]_{\text{plasma}}$$

Carbon monoxide is also transported by the blood, as carboxyhemoglobin (HbCO). While little CO occurs naturally in the atmosphere, it is becoming more abundant as a pollutant of industrialization. The danger of CO is due to its very high affinity for hemoglobin, thus excluding oxygen. For example, a  $P_{\text{O}_2}$  of 84 mmHg will saturate 75% of

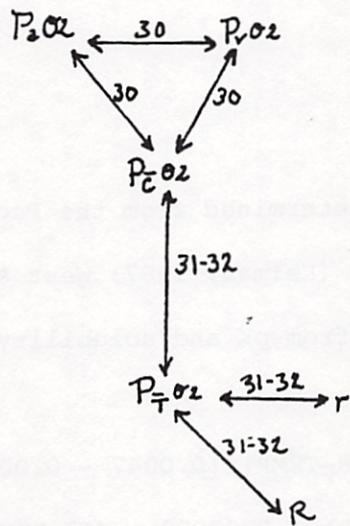


Figure 3.1d. Venous Blood to Cells (Equations 30-32).

the hemoglobin; a  $P_{CO}$  of 0.16 will also saturate 75% (Root, 1965; Roughton, 1965)! The dissociation curves of  $O_2$  and CO are similar, and are related using a form of the Haldane equation (Goldsmith & Friberg, 1977):

$$(29) \quad S_{CO}/S_{O_2} = 245 \times P_{CO}/P_{O_2}$$

#### Capillaries to Cells

Everything else being equal, the  $P_{O_2}$  for any individual cell will depend upon its distance from its nearest nutrient capillary. For the body as a whole, the oxygenation of the 'average' cell will depend upon the capillary/cell ratio. That is, the greater this ratio, the closer cells are to their nutrient capillary.

Barcroft (1938) first proposed the concept of the mean capillary  $P_{O_2}$  as an approximation to the oxygenation of an 'ideal' cell, shown algebraically by:

$$(30) \quad P_{CO_2} = P_{VO_2} + (P_{AO_2} - P_{VO_2})/3$$

This 'ideal' cell does not really exist, but the  $P_{CO_2}$  can be taken as a measure of the body's oxygenation if this  $P_{O_2}$  were to prevail throughout the body (Houston, 1947). Other references suggest use of the  $P_{VO_2}$  as a guide to true capillary  $P_{O_2}$  (Tenney, 1974; West & Wagner, 1977), but clearly  $P_{VO_2}$  should be the lower bound on capillary  $P_{O_2}$ , and the relation  $P_{VO_2} \leq P_{CO_2} \leq P_{AO_2}$  must hold.

Outside of the capillary, there is another set of oxygen gradients, each causing a further drop in the  $P_{O_2}$ . The final  $P_{O_2}$  value may be very close to zero, and, in fact, the critical  $P_{O_2}$  for the mitochondria is thought to be as low as 1-3 mmHg (Guyton, 1977; Heath & Williams, 1977).

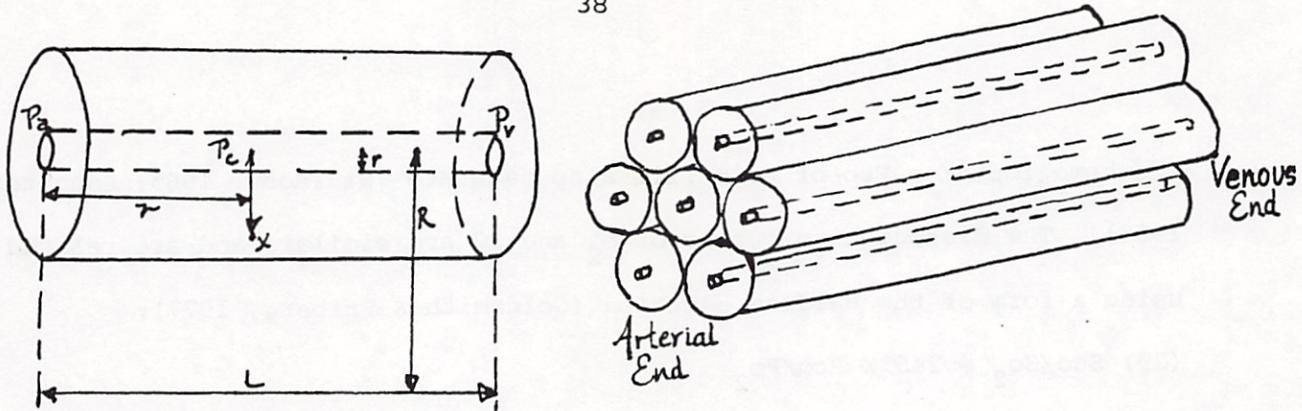


Figure 3.3. a) Krogh tissue cylinder. Capillary radius  $r$ , cylinder radius  $R$ , capillary length  $L$ . b) Krogh tissue cylinder arrangement; all cylinders equidistant and same length.

A number of models attempt to describe the movement of  $O_2$  to the cells. This program uses the Krogh model (1919), with modifications by Kety (1957), Tenney (1974) and Denison (1979).

The original Krogh model assumes a cylindrical capillary, with radius  $r$ , which must supply oxygen to a cylinder of tissue around that capillary, of radius  $R$  (Figure 3.3a). It assumes, furthermore, that this is but one capillary in a group, which is assembled in a parallel array, where all capillaries are equidistant, start and end at the same level, and have concurrent flow (Figure 3.3b).

The Kety-Tenney-Denison modifications to Krogh's model are significant because they allow for the fact that radial diffusion is not completely uniform from the arterial end of the capillary to the venous end. The diffusion distance will be a function of the  $Po_2$ , and as we progress down the capillary  $Po_2$  must decrease, hence so will the diffusion radius. This changes the cylindrical model into a conical section, with hyperbolic-shaped walls, where the diffusion radius at the arterial end is denoted  $R_a$ , and at the venous end  $R_v$  (Figure 3.4).

The Krogh model, using equations supplied by the Danish mathematician Erlang, showed the oxygenation of a tissue a distance  $x$  from the center

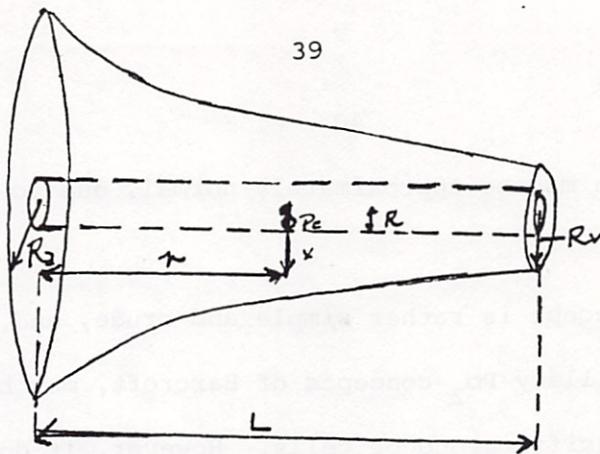


Figure 3.4. Modification of Krogh model by Kety and Tenney. The "cylinder" of tissue oxygenation is replaced by a "hyperbolic cone," with radius  $R_a$  at the arterial end and  $R_v$  at the venous end.

of the capillary, by equation (31) (Krogh, 1919):

$$(31) P_T O_2 (x) = P_{CO_2} - M x [R x \ln (x/r) - (x^2 - r^2)/2]$$

where  $r$  and  $R$  are as above,

and  $M = (\text{tissue } \dot{V}O_2) / (O_2 \text{ diffusion coeff. of tissue})$

This takes into account radial diffusion only, and ignores longitudinal effects. To find the mean tissue  $P_O_2$  in any of the radial planes, we must integrate (Kety, 1957; Tenney, 1974):

$$(32) P_{TO_2} = \frac{2 \int_r^R P_T O_2 (x) dx}{2 \int_r^R x dx} = \dots = P_{CO_2} + M \left( \frac{3(R^2 - r^2)}{8} - \frac{R^4}{2(R^2 - r^2)} \ln \frac{R}{r} \right)$$

The possible radius of oxygenation will depend directly upon  $P_O_2$ . Capillaries respond to low oxygen pressure by distension and recruitment (Figure 2.8). Distension increases  $r$ , which, in turn, also increases the maximum possible  $R$ . Recruitment puts the capillaries closer together, thus decreasing the  $R$  necessary to maintain adequate  $O_2$  levels.

For example, at sea level a typical capillary has a radius  $r = 0.0005$  cm., and  $R = 0.004$  cm. In slight hypoxia, capillary radius may increase to 0.0008 cm. and  $R$  decrease to 0.003 cm. In the latter case, the  $P_{CO_2}$  will be significantly lower than in the former case, yet the

tissue oxygenation may be approximately normal, due to these compensations.

The Krogh concept is rather simple and crude, and, like the "ideal" cell and mean capillary  $Po_2$  concepts of Barcroft, may be misleading when referring to a specific group of cells. However, it does provide a useful tool with which to explore the general problem.

#### Computer Program

The computer program HYPOXIA is written in XEROX Extended FORTRAN IV, to be run on the XEROX Sigma 6 at the University of Vermont Academic Computer Center (ACC). Another program called HYPLOT controls HYPOXIA's plot output, directed to a CALCOMP 656 plotter, also at ACC. (See Appendix D for a User's Guide to HYPOXIA and HYPLOT, and Appendix E for the source code.)

HYPOXIA uses only two major implementation-dependent features that would need to be revised for transportability. First, input and output uses indexed files, a local feature not commonly available on most FORTRAN systems. Each study uses two consecutive records for storage of data, where the key of the first record is the study number multiplied by 10. Second the XEROX FORTRAN logical-IF structure allows multiple statement execution if the logical expression is true. Both of these features can be easily avoided at any installation desiring to implement this program. (Troublesome IF-statements can be removed by placing all 'true' statements directly after the IF. Then, use the opposite logical test and a GO TO to jump around them.) Other language-dependent features are the use of labelled COMMON, the IMPLICIT type statement, variable

names with more than 6 characters, and I/O unit device designations.

HYPOXIA is comprised of a main program with 36 subprograms, and fits in less than 20K of memory (1K = 1,024 32-bit words).

HYPOXIA is designed to accomodate up to 75 parameters and 35 equations, although it currently only uses 66 parameters and 25 equations. The COMMON block VARIABLE (in the main program) keeps track of the names of the variables.

Upon entry to HYPOXIA, the user is asked to input new patient data or else retrieve an old patient's data from the data base file. Each parameter has a value and a flag associated with it. The flag is initially set to 0; it is set to 1 or 2 if its value is input as experimentally determined or assumed, respectively; flag is set to 3 if the parameter's value is calculated. Each value is initially set to -1.0.

Certain parameters have default values, if the user fails to over-ride them on input. For example, body temperature defaults to 37° C., tissue diffusion radius defaults to 0.002 cm., and capillary radius defaults to 0.0005 cm. These values are assigned by the subroutine DEFAULTS.

After inputting the data, the user then chooses from four running options. The first option allows the user to input a set of data, perform all possible calculations, then to output the data to the line printer and save the values in the data base file. The second option allows the user to merely retrieve an old set of data from the data file and print out the values. The third option allows the user to generate a table of output where at least one parameter is allowed to vary over some range of values. The fourth option is similar to the third, except

that it generates a family of curves, which are plotted by HYPLOT.

CHARTOK and GETCHARTS are the two subroutines that control which equations are called and in what order. The array LIST (in the main program) keeps the list of which parameters are required for each equation. The array IPARM (in the main program) provides a pointer into LIST, telling the program where in LIST to look. Each equation is classified as to whether or not it is a function. 'Function' equations have a list of parameters associated with them and are called only if exactly one parameter value is missing. When called, it calculates this missing value. Non-'function' equations are called only if their entire parameter list has known values. Each equation is called by GETCHARTS in the order specified by the array ORDER (in GETCHARTS). The array FUNC (in GETCHARTS) indicates if the equation is a function or not. CHARTOK determines if enough information is known to call the equation or not, and if it is safe to call the equations GETCHARTS does so. Each equation is attempted, in order, until finally no new information can be calculated.

It is fairly easy to add a new equation to the program. To do so, a new subroutine must be written for the equation, and the parameters that are required must be listed in the available space in LIST. IPARM must be set to point to the appropriate place in LIST, and the ORDER and FUNC arrays must define the order and type of equation. Lastly, the variables NVAR and NTABLES (both in the main program) refer to the total number of parameters and equations, respectively, and must be appropriately adjusted. To delete an equation, merely remove all references to them in the above pointers.

Parameter inputs to the program describe a person's known physiologic condition. By setting parameters appropriately, such conditions as a change of diet, breathing 100% oxygen, anemia, distention and recruitment of capillaries, emphysema, etc. can be simulated. Varying different parameters simultaneously allows the user the opportunity to study a variety of physiologically possible situations.

Output from HYPOXIA can be directed to the line printer or plotter. Line printer output deals with a specific set of data regarding a patient. Plotter output is useful when an entire family of curves is required, to "fill in" missing data. The plot output allows the user to visualize a large set of data with greater understanding than is possible with huge amounts of printed output.

Figure 3.5 shows a sample of the entire set of data available on print output as called by options 1 or 2. Both pages indicate the data that is assumed by the user and that which is experimentally determined; the remainder is calculated by the program. The first page deals mostly with blood gas values and the second page with other cardio-pulmonary system indicators. The second page also has the  $P_{CO_2}$  value, as well as four different  $P_{T O_2}$  values, assuming a range of different diffusion cylinder radii, R. By varying r and R, the user can simulate distension and recruitment.

Figure 3.6 shows a sample plot. The family of curves generated describes the effect on  $P_{CO_2}$  over a physiologically possible range of oxygen carrying capacities and a range of  $\dot{V}O_2$ . For example, the curve where  $\dot{V}O_2 = 800 \text{ ml/min}$ , or heavy work, indicates that the oxygen capacity

must be greater than 19 vols % to support this level of work.

## HYPOXIA ANALYSIS STUDY

PAGE 1

MEL D.C. KUMQUAT

STUDY #

1

DATE 6/19/79

NORMAL MALE AT SEA LEVEL

MALE	AGE: 25	HT: 170 CM	WT: 60.0 KG	BSA: 1.69 SQ M
ALTITUDE	•0 METERS	PRESSURE 760.0 MM HG		
TEMPERATURE	37.0 C.			HOURS AT ALTITUDE: 0
<hr/>				
INSPIRED F <sub>O2</sub>	20.93 %			
INSPIRED P <sub>O2</sub>	149.2 MM HG			
ALVEOLAR P <sub>O2</sub>	105.7 MM HG			
A-A GRADIENT	10.0 MM HG			
<hr/>				
ARTERIAL	VENOUS			
pH	7.40	7.10		
P <sub>O2</sub>	55.7	58.5 MM HG		
PC <sub>O2</sub>	40.0	80.6 MM HG		
PCO <sub>2</sub>	•0	MM HG		
<hr/>				
DISSOLVED O <sub>2</sub>	.29	.18 ML/100 ML BLOOD		
O <sub>2</sub> WITH HB	20.14	15.97 ML/100 ML BLOOD		
TOTAL O <sub>2</sub>	20.43	16.15 ML/100 ML BLOOD		
TOTAL CO <sub>2</sub>	47.63	51.38 ML/100 ML BLOOD		
TOTAL CO <sub>2</sub>	.00	ML/100 ML BLOOD		
HbO <sub>2</sub> SATIN	26.8	76.8 %		
HbC <sub>02</sub> SATIN	.5	%		
HbC <sub>02</sub> SATIN	•0	%		
<hr/>				
MIXED VENOUS P <sub>O2</sub>	81.3 MM HG			
PHYSIOLOGIC SHUNT	4.4 %			
<hr/>				
DATA - EXPERIMENTAL				
NONE				
<hr/>				
DATA - ASSUMED				
ALTITUDE TEMP	DURATION	F <sub>I</sub> O <sub>2</sub>	A-A GRAD	ART PH
ART PC <sub>O2</sub>	ART PCO <sub>2</sub>			VEN PCO <sub>2</sub>

Figure 3.5. Sample output from HYPOXIA.

## HYPOXIA ANALYSIS STUDY

PAGE 2

MEL D.C., KUMQUAT

STUDY #

1 DATE 6/19/79

NORMAL MALE AT SEA LEVEL

RESPIRATORY QUOTIENT	.800
CHEFF. OF O <sub>2</sub> DELIVERY	4.902
VENT.-PERF. RATIO	.809 ML/ML BLOOD

CO<sub>2</sub> RELEASE 225.0 ML/MIN STPD

O <sub>2</sub> CONSUMPTION	250.0 ML/MIN STPD
OXYGEN DELIVERY	1225.6 ML/MIN

ALVEOLAR VENTILATION 4.9 ML/MIN

MAX. BREATHING CAP.	124.5 L/MIN
TIDAL VOLUME	1000.0 ML
RESPIRATORY RATE	15/MIN
MINUTE VENTILATION	15000.0 ML/MIN

A-V O<sub>2</sub> DIFF 20.0 % SATIN

CARDIAC OUTPUT	6.0 L/MIN	CARDIAC INDEX	3.5 L/MIN/SQ M
CEREBRAL BLOOD FLOW	903.6 ML/MIN		
TISSUE BLOOD FLOW	5.1 L/MIN		
STROKE VOLUME	100.0 ML		
HEART RATE	60/MIN	MAXIMUM HR	193/MIN

O <sub>2</sub> CAPACITY	20.8 VOL %
HEMOGLOBIN	15.0 GM/100 ML BLOOD
HEMATOCRIT	44.9 ML/100 ML BLOOD

HCO<sub>3</sub> CONCENTRATION 46.4 VOL %MEAN CAPILLARY P<sub>O</sub>2 70.9 MM HG

CAPILLARY RADIUS .0005 CM.

TISSUE DIFFUSION	.002	.003	.004	.005 CM.
TISSUE P <sub>O</sub> 2	69.77	67.30	63.03	56.74 MM HG

DATA - EXPERIMENTAL  
NONE

DATA - ASSUMED  
R.G. O<sub>2</sub> CONS TIDL VOL RESP RT. CARD OUT HEART RT O<sub>2</sub> CAP  
CAP RAD

Figure 3.5. (con't.).

R.L. PATIENT 1, II

STUDY # 502

CARD OUT 4.3	L/MIN			
ART PCO2 117.0	MM HG	ART PH	7.5	
R.Q. .9	METERS	FIO2	25.0	%
ALTITUDE .0		ART PCO2	24.0	MM HG

Z = 02 CONS ML/MIN

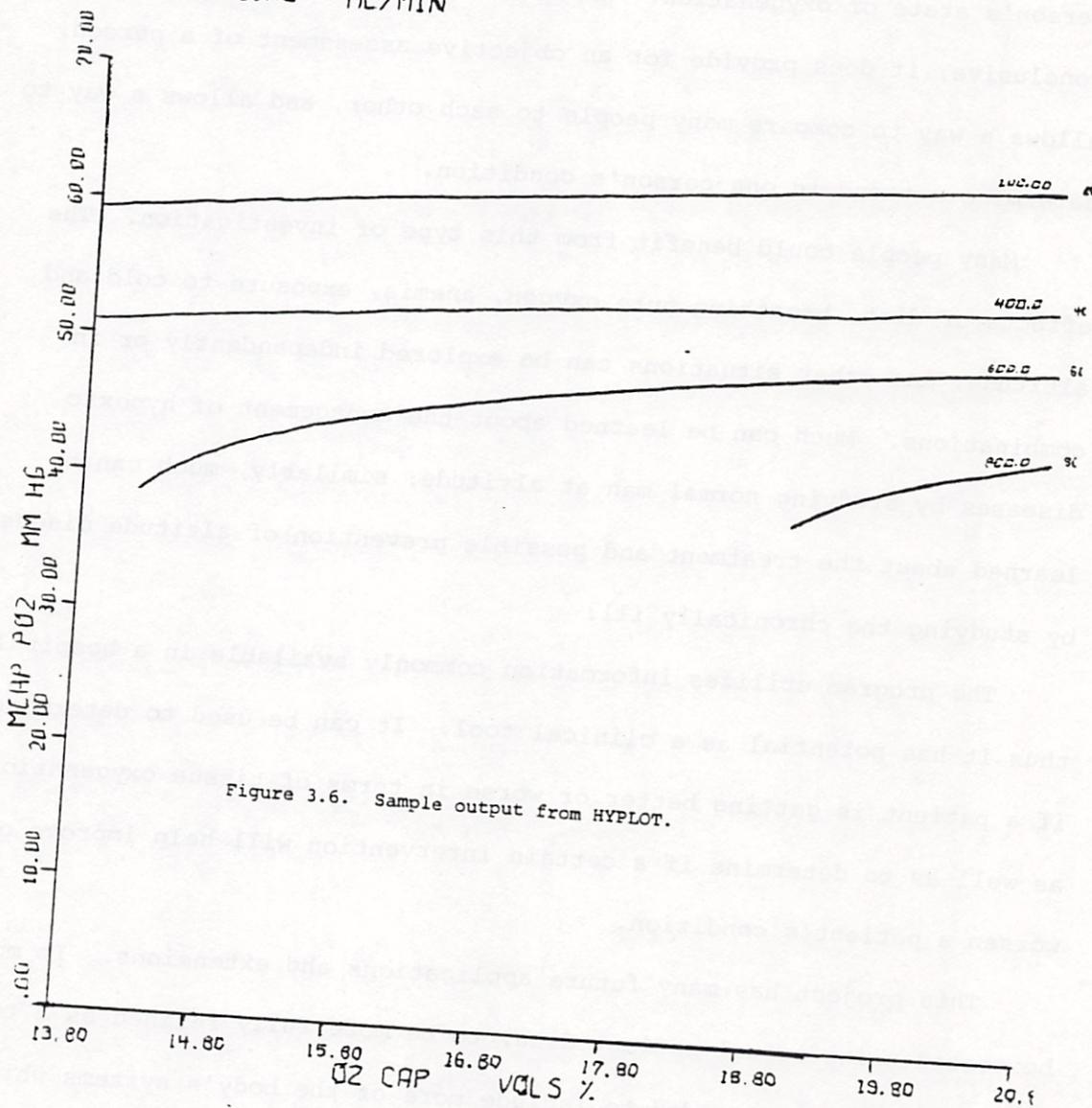


Figure 3.6. Sample output from HYPLOT.

## CHAPTER 4

### SUMMARY

This computer program, especially in conjunction with the plotter outputs, allows the user to analyze a large body of information at one time, and to yield some sort of numerical quantification as to a person's state of oxygenation. While this quantification is not conclusive, it does provide for an objective assessment of a person, allows a way to compare many people to each other, and allows a way to determine a trend in one person's condition.

Many people could benefit from this type of investigation. The effects of diet, breathing pure oxygen, anemia, exposure to cold and altitude, and other situations can be explored independently or in combinations. Much can be learned about the management of hypoxic diseases by studying normal man at altitude; similarly, much can be learned about the treatment and possible prevention of altitude disease by studying the chronically ill.

The program utilizes information commonly available in a hospital, thus it has potential as a clinical tool. It can be used to determine if a patient is getting better or worse in terms of tissue oxygenation, as well as to determine if a certain intervention will help improve or worsen a patient's condition.

This project has many future applications and extensions. It must be tested using actual patient data, to be more fully refined as a tool. It can be further extended to include more of the body's systems which are affected by hypoxia, as well as to further modify the capillary model. With further refinement, this program may become an important

tool in the study and clinical management of hypoxia. As we study the physiologic changes comprising adaptation to several forms of hypoxia we can identify and isolate favorable and unfavorable responses to oxygen lack.

This research has given the author the opportunity to learn much in the way of physiology as well as computing techniques. The excitement of this work comes with the possible clinical applications. Future work still needs to be done in that area, but a fairly firm groundwork has been placed.

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## APPENDIX A

### SYMBOLS

#### Primary

- C Concentration of gas in blood (Also denoted with  $[ ]$ )
- F Fractional concentration in dry gas
- P Pressure or partial pressure
- S Saturation of hemoglobin with gas

#### Secondary Symbols for Gas Phase

- A Alveolar
- B Barometric
- I Inspired
- T Tissue

#### Secondary Symbols for Blood Phase

- a arterial
- c mean capillary
- i ideal
- v venous

#### Examples

- $C_aO_2$  - Arterial  $O_2$  concentration (vols %) (or:  $[O_2]_a$ )
- $P_A CO_2$  - Alveolar  $CO_2$  partial pressure (mmHg)
- $S_v CO$  - Venous  $CO$  saturation (%)
- $F_I O_2$  - Fraction of  $O_2$  in inspired air (%)

#### Miscellaneous

STPD - Standard temperature and pressure in dry air  
BTPS - Body temperature and pressure, saturated with water vapor

$\dot{V}$  - Change in ventilation over time ( $dV/dt$ )  
 $\dot{Q}$  - Change in blood flow over time ( $dQ/dt$ )  
R - Respiratory quotient or exchange ratio

## APPENDIX B

### SOME ANALOGIES BETWEEN HIGH ALTITUDE HYPOXIA AND SEA LEVEL ILLNESSES

Acute Mountain Sickness. Headache, nausea, vomiting, malaise. These are symptoms of hypoxia from many causes.

Changes in Mean Corpuscular Hemoglobin Concentration and in Red Cell Water Content. Seen in acute and chronic hypoxia from many causes, such as chronic uremia and cirrhosis of the liver.

Cheyne-Stokes Respiration. Common in persons above 3300 meters. Also seen in various types of cardiac failure, thickening of cerebral arteries, pulmonary disease and agonal hypoxia.

Decreased Plasma Volume and Increased Renin and Angiotensin Secretion in the Presence of Decreased Aldosterone. Common in many acute and chronic conditions which cause a fall in the plasma volume.

Edema of the Optic Nerve. Seen in chronic respiratory insufficiency, inflammation of the brain and cystic fibrosis of the pancreas.

Increased Erythropoietin and Red Blood Cell Production. Seen in many illnesses and congenital defects causing hypoxemia.

Increase in 2,3-Diphosphoglycerate levels and Shift of HbO<sub>2</sub> Curve. Shifts of the HbO<sub>2</sub> curve are eliminated when arterial pH is stabilized. In patients with renal failure, shifts in the HbO<sub>2</sub> curve due to phosphate depletion can worsen the clinical condition. The low 2,3-DPG levels in stored blood can reduce oxygen delivery by up to 30%.

Pulmonary Artery Hypertension. Common in long-term residents at high altitudes. Also common in hypoxia caused by many types of pulmonary or cyanotic cardiac diseases. Rapidly reversed by oxygen therapy.

Pulmonary Edema. Symptomatic of rapid ascent to high altitudes, with exertion during or after ascent. Common in left ventricular failure, valvular heart disease and often after exertion where oxygen demand exceeds oxygen supply. Seen also in alkalosis and in the apnea following prolonged hyperventilation. Also occurs after some types of brain damage, burns, anemia, traumatic shock, as well as acute hypoxia caused by drug overdose, asphyxia and drowning.

Retinal Vasodilation and Retinal Hemorrhage. Usually asymptomatic. Observed in diabetes, neonates and altitude hypoxia.

## Appendix B (con't.)

Shifts in Water Between Body Compartments. Occurs in variable degree to different individuals at different altitudes. Common in diseases such as cirrhosis, chronic congestive heart failure, diabetic coma, etc. - i.e., wherever there is decreased arterial  $Po_2$ . Also, traumatic shock, burns and acute brain damage.

## APPENDIX C

### LIST OF PARAMETERS

- 1: Altitude, meters
- 2: Barometric Pressure, mmHg
- 3: Inspired Po<sub>2</sub>, mmHg
- 4: Arterial PCO<sub>2</sub>, mmHg
- 5: Respiratory Quotient
- 6: FIO<sub>2</sub>, mmHg
- 7: Alveolar Po<sub>2</sub>, mmHg
- 8: A-a Gradient, mmHg
- 9: Arterial Po<sub>2</sub>, mmHg
- 10: Arterial pH
- 11: Arterial So<sub>2</sub>, %
- 12: A-V Diff, %
- 13: O<sub>2</sub> Capacity, vols %
- 14: (unused)
- 15: O<sub>2</sub> Consumption, ml/min STPD
- 16: Cardiac Output, l/min
- 17: Venous So<sub>2</sub>, mmHg
- 18: Venous pH
- 19: Venous Po<sub>2</sub>, mmHg
- 20: Mean Capillary Po<sub>2</sub>, mmHg
- 21: Body Temperature, Degrees Centigrade
- 22: Duration of Exposure to altitude, Hours
- 23: HCO<sub>3</sub> Ion Concentration, mM/l
- 24: Tidal Volume, ml
- 25: Respiratory Rate, breaths/min
- 26: Respiratory Minute Volume, ml/min
- 27: Arterial PCO<sub>2</sub>, mmHg
- 28: Arterial Sco, %
- 29: Arterial Sco<sub>2</sub>, %
- 30: Hematocrit, Vols %
- 31: Stroke Volume, ml
- 32: Heart Rate, beats/min
- 33: Hemoglobin, gm/100 ml blood
- 34: Arterial Dissolved O<sub>2</sub>, vols %
- 35: Arterial O<sub>2</sub> Combined with Hb, vols %
- 36: Arterial Total O<sub>2</sub> Content, vols %
- 37: Venous Dissolved O<sub>2</sub>, vols %
- 38: Venous O<sub>2</sub> Combined with Hb, vols %
- 39: Venous Total O<sub>2</sub> Content, vols %
- 40: Age, Years
- 41: Sex
- 42: Height, cm
- 43: Weight, kg
- 44: Body Surface Area, square meters
- 45: Maximum Breathing Capacity, l/min
- 46: Cardiac Index, l/min/sq m
- 47: Arterial CO Concentration, vols %

## Appendix C (Con't.)

- 48: Brain Blood Flow, ml/min
- 49: Tissue Blood Flow, l/min
- 50: Mixed Venous Po<sub>2</sub>, mmHg
- 51: Oxygen Delivery, ml/min
- 52: Coefficient of Oxygen Delivery
- 53: CO<sub>2</sub> Release, ml/min STPD
- 54: Maximum Heart Rate, beats/min
- 55: Alveolar Ventilation, ml.min
- 56: Ventilation-Perfusion Ratio, l/l blood
- 57: Physiologic Shunt, %
- 58: Arterial CO<sub>2</sub> Content, vols %
- 59: Mixed Venous CO<sub>2</sub> Content, vols %
- 60: Venous Pco<sub>2</sub>, mmHg
- 61: Tissue diffusion radius, cm
- 62: Tissue Po<sub>2</sub> for given diff. radius, mmHg
- 63: Tissue Po<sub>2</sub> for given diff. radius + 0.001 cm, mmHg
- 64: Tissue Po<sub>2</sub> for given diff. radius + 0.002 cm, mmHg
- 65: Tissue Po<sub>2</sub> for given diff. radius + 0.003 cm, mmHg
- 66: Capillary radius, cm

## APPENDIX D

### USERS' GUIDE TO HYPOXIA AND HYPLOT

GENERAL NOTES: All underlined CAPITAL items are printed on the terminal by the program. All other CAPITAL items are to be typed in by the user exactly as written. All 'lower case' items are to be substituted with the appropriate value by the user. All user entries are to be followed by a Carraige Return (<CR>).

#### Users' Guide to HYPOXIA (Version 6.63)

1. Log-on or sign-on to your computer account.
2. Call up the HYPOXIA program.
3. INPUT FROM 'CRT' OR 'FILE'?  
If input is coming from the data base file, type FILE <CR> and continue at step 8. If new data is being input from the terminal, type CRT<CR> and continue at the next step.
4. INPUT NAME (< 28 CHARACTERS)?  
Type in a name with which to identify this study.
5. INPUT STUDY NUMBER?  
Enter a number with which to identify this study.
6. INPUT DATE (MMDDYY)?  
Enter the date, using 2 digits for the month, day and year. If this is a change in the study identification (i.e., if you were sent to this step from step 10), continue at step 11.
7. INPUT DATA: PARAMETER #', ' VALUE  
ENTER ',' WHEN DONE  
When prompted, enter the data in the form: parameter #, value <CR>  
Continue until all data is entered, then enter: ,<CR>  
If a parameter is entered with a wrong value, merely re-enter it with the correct value. If a parameter is given a value accidentally, remove it by re-entering the parameter with a value of -1.0.
8. INPUT STUDY # ?  
Enter the i.d. number of the study to restore from the data base file.  
If an invalid study number is requested, the program will respond NON-EXISTANT STUDY # and then the program will stop.

## Appendix D (con't.)

9. RESTORING. RETAIN ONLY ORIGINAL DATA (YES/NO)?  
If you want to retain the entire data set as is, enter NO <CR> and continue at step 13. If you wish to retain only the original experimental and assumed data, enter YES<CR>.
10. CHANGE STUDY NAME (YES/NO)?  
If you want to use this data and give it a new study identification, type YES <CR> and continue with step 4. Otherwise type NO <CR>.
11. LIST DATA (YES/NO)?  
If you want the current data set displayed on the terminal, type YES <CR>. Otherwise type NO <CR>.
12. CHANGE ANY DATA (YES/NO)?  
If you want to change any of the parameter values, type YES <CR> and continue with step 7. Otherwise type NO <CR>.
13. INPUT TITLE (< 72 CHARACTERS)?  
Type in a title to label the output.
14. LIST OPTIONS (YES/NO)?  
Type YES <CR> to get the following list:  
1: CALCULATIONS, 2: FORMAT ONLY, 3: VARY PARAMETERS, 1 STEP  
4: PLOT, 99: STOP  
Type NO <CR> to suppress this list.
15. ENTER OPTION?  
Enter desired option.  
If option = 1 or 2, continue at step 16.  
If option = 3, continue at step 17.  
If option = 4, continue at step 19.  
If option = 99, continue at step 23.
16. OUTPUT RAW INFO TO DATABASE (YES/NO)?  
If this information was input from the CRT or updated from the data base file and you wish to save it, type YES <CR>. If the study number is a duplicate number, you will be asked to enter a new study i.d. or else to enter 0 to delete the old data.  
If you don't want to save it, type NO <CR>. Continue at step 23.
17. INPUT: 'PARAMETER #, START, END, STEP'. MAXIMUM OF 15.  
ENTER ',,,' WHEN DONE  
Up to 15 parameters can be given initial, final and increment values.  
Enter these in form: parameter #, initial value, final value, increment <CR>  
When done with list, enter: ,,, <CR>

## Appendix D (con't.)

18. INPUT 'PARAMETER #'S TO OUTPUT', MAX. OF 15.  
ENTER <CR> WHEN DONE.

Up to 15 parameters can be listed in the output table. Enter each desired parameter number, followed by <CR>. When done, hit <CR>. Continue at step 23.

19. INPUT: 'PARA # OF LABELS'. <CR> WHEN DONE.

Input up to 16 parameter numbers to be printed at the top of the plot. Follow each number by <CR>. When done, hit <CR>.

20. ENTER X-AXIS: 'PARA #,MIN,MAX'

Enter the parameter number to be plotted on the x-axis, as well as the minimum and maximum values of x. Enter these three values on one line, separated by commas.

21. ENTER Y-AXIS: 'PARA #' ?

Enter the parameter number to be plotted on the y-axis.

22. ENTER Z-AXIS: 'PARA #,MIN,MAX,(# CURVES)' ?

Enter the parameter number to be plotted on the z-axis, as well as the minimum and maximum values of z. In addition, supply the number of curves that you wish to be plotted. If no value is given for the number of curves, it will default to 5. Input all four values on one line, separated by commas.

23. NEW CASE STUDY (YES/NO) ?

If you have another set of data to examine, type YES <CR> and continue at step 3. Otherwise, type NO <CR>.

24. The program will stop with the message \*\*\*\*HYPOXIA STUDY COMPLETED\*\*\*\*.  
The program is now terminated.

To get the plot output, see Users' Guide to HYPLOT.

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## Users' Guide to HYPLOT

1. Call up the HYPLOT program.
2. SCALING: 0 = STANDARD, 1 = DATA MAX/MIN:  
Enter a 0 <CR> if you want the scaling of the y-axis to be based upon a uniform set of minimum and maximum values, based only upon the y parameter. Enter a 1 <CR> if you want scaling based upon the actual minimum and maximum values of the current data set.  
If you select option 0 and see the message:  
Y-AXIS PARAMETER nn HAS NO ESTABLISHED MIN/MAX VALUES.  
PLOT ACTION CANCELLED  
it means that uniform scaling for parameter nn has not been established. Either modify HYPLOT to include this parameter or select option 1.

To get the output generated by HYPLOT, type the appropriate plot command(s) for your system.

## APPENDIX E

## SOURCE CODE

The source code for HYPOXIA and HYPLOT is contained in 11 source files, comprising the 2 main programs and 36 subprograms.

<u>PROGRAM</u>	<u>SOURCE FILE*</u>	<u>PROGRAM UNITS</u>			
HYPOXIA	HMAIN:SI	F:main	SETNGO		
	HCHART:SI	BICARB	MINVOL	CARDIACOUT	HEMO
		PBALT	COHALDANE	BSAMBC	CARDINDEX
		CO2GUYTON			
	HCHART2:SI	BLOODFLOW	FICK	HBHCT	CO2
	HCSH:SI	CHART1	CHART2	CHART3	CHARTS47
		CHART5	CHART6B	CHART8	
	HDIFF:SI	TISSUE			
	HGET:SI	CHARTOK	GETCHARTS		
	HMIT:SI	OXYDEL	RQO2CO2	VENTILATION	
HREAD:SI	READINFO	DEFAULTS			
	HSPEC:SI	O2DISS	BLOODO2	ROOT	BLOODCO2
	HWRITE:SI	WRITEINFO	LISTLABEL	ERRLABEL	
HYPLOT	HYPLOT:SI	F:main			

\* Source file name refers to the following listings.

Appendix E (con't.)

Subprogram Flow Diagram for HYPOXIA

