OPTIMIZATION OF THE OXYGEN TRANSPORT SYSTEM

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ABSTRACT Emphasizing the over-all performance of the O_2 transport system, as well as the interactions between its various subsystems, a method for a parametric performance analysis has been developed. The purpose of such an analysis is threefold: 1. It permits an evaluation of those parameters which are critical for the performance of the system under conditions of stress. 2. It leads to an assessment of the ranking of individual members within the hierarchy of biological control systems. 3. It permits an objective assessment of the severity and prognosis of cardiovascular and respiratory diseases and of the degree of disability resulting therefrom. Starting with the principle of conservation of mass, two equations are derived which express the balance of oxygen in terms of supply, consumption, and waste. These equations are then developed in terms of the parameters of the system; namely, ventilation, inspired O_2 concentration, cardiac output, O_2 capacity of the blood, energy requirements of the two pumps, fractional extraction of O_2 from alveolar air (ventilation-perfusion ratio), and the oxygen utilization fraction in the periphery. The results indicate that the normal system attempts to maximize the oxygen utilization fraction while minimizing ventilatory and cardiac energy requirements. Changes in the ventilation-perfusion ratio are relatively less important. Possible extensions of the model are discussed.

INTRODUCTION

For the last two decades, systems engineering has provided considerable insight and understanding into the behavior and the control of living systems. However, it is becoming increasingly apparent that biological systems are much more complex than the technological systems usually considered by the control engineer. These differences in complexity are closely related to the origin of the two types of systems. A technological system is usually designed on the basis of predesignated criteria of stability and response which are expressed in some analytical form. Physiological systems, on the other hand, have evolved slowly, continuously adapting the performance of specific tasks to a wide variety of conditions. In this process, the criteria of stability, response, and optimization came about by natural selection (evolution). The performance of even a simple task depends upon the coordination and integra-

tion of a number of biological systems (for example: cardiovascular, respiratory, and neurohumoral) and involves a hierarchy of control systems, as well as adaptability and redundancy in design. While an engineering design evolves from a narrow selection of workable systems, natural selection is not saddled with an expediency demand. The evolution of physiological control systems might, therefore, be expected to result in optimal systems chosen from a large population of possible systems with complexity of description not at all entering as a limiting factor (1).

The complexities of biological systems and the unknown ranking of the individual subsystems with respect to over-all performance are not easily analyzed by the classical scientific method that concentrates on the description of isolated components and deliberately ignores the fact that in real life all these components interact. To understand biological systems, we must focus our attention on the behavior of the over-all system and the interaction between its individual parts. The oxygen transport system and its adaptation to stresses, such as exercise and hypoxia was among the first biological systems where such interactions between subsystems was clearly recognized (10, 18, 19). The observation that the failure of one key step in the adaptation process may be associated with an overreaction of the other members of the adaptation chain has led to the concept of excess response or hyperexis (18). Such failures in homeostatic processes are closely linked to the development of chronic disease although the limits where such mechanisms become pathological are not well defined.

A parametric performance analysis appears to be more promising in this respect than an approach based on classical control theory. From the evaluation of the factors which determine optimal performance, one may eventually be able to derive an assessment of the hierarchies of biological control systems. At present we know little about the individual members of this hierarchy and their rank, we have problems in identifying controlled and controlling variables and we have only fragmentary information about feedback pathways, sensors and signal sources (2, 10). One would expect that those parameters whose changes influence systems performance most strongly would be the primary targets of a biological control system. In this paper a parametric performance analysis has been carried out for the normal O_2 transport system whose performance limits are given by the physical properties of the cardiovascular and respiratory systems.

First we must decide which aspect of performance should be optimized. Among the choices to be considered for the O_2 transport system are the following: (*a*) The minimization of O_2 and/or CO_2 transport time between the lungs and the site of tissue exchange. (*b*) The efficiency of the supply of O_2 and/or the elimination of CO_2 (amount of O_2 or CO_2 transported per unit work performed by the pumps). (*c*) The flexibility of the amount of oxygen supplied to the periphery and the limits of supply under conditions of stress.

We concentrated the analysis on the third item because this seems to us to be the most important criterion for the successful functioning of a living organism under

conditions of stress. At rest, an adult uses about 0.25 liters of oxygen per min. During maximal exertion, the oxygen requirements increase by a factor of 15 or more. Since the body carries no appreciable reserves of oxygen, intake and distribution to the tissues must be adjusted within seconds. This represents a marked contrast to other biological carrier systems where transport can be interrupted *for hours* without producing irreversible damage. The adaptation to the requirements is brought about by an amazing cooperation of individual organs which restrict their needs in favor of more essential functions. The limitations for the performance of the organism are given by the critical intracellular oxygen tension (saturation of oxidative enzymes, particularly in the most vulnerable organs such as the brain) for the aerobic metabolism and by the lowest tolerable pH (integrity of cell function) for the anaerobic supply of energy. If the system is to perform satisfactorily under a wide range of conditions, integrated control of respiration and circulation is of the essence.

Admittedly, our analysis represents only a first crude approximation. Considerable sophistication will be necessary before the full potential of the method can be exploited (2). Some of this sophistication is not possible at present because the pertinent experimental data are not available. One of the advantages of such an approach, therefore, lies in the possibility that it points out disparities between the relative importance of parameters indicated by the analysis and the scarcity of empirical data with regard to changes in these parameters under conditions of stress, thus pointing to areas of research which should be given high priority (3).

Our approach is similar to that of the systems analyst in that we are first constructing a model of the system and then examining its over-all performance for several possible behaviors of the different parts of the model system. The model differs from that of the systems engineer in that it treats only over-all averaged performance and not transient behavior. This treatment is in accordance with our interest in performance and output as opposed to mechanism and/or response times. We expect then to be able to identify optimum system performance in terms of component performance. Specifically, we are interested in the flexibility and limits of the amount of oxygen supplied to the body tissues under conditions of stress as a function of: 1. The ventilation-perfusion ratio. 2. The fraction of utilization of circulating oxygen. 3. Ventilatory volume. 4. Cardiac output. 5. Oxygen carrying capacity of the blood.

THE MODEL SYSTEM

The model O_2 transport system used for the analysis is shown in Fig. 1. A single tissue bed consumes oxygen at a rate of $\dot{V}_{O_2}^{T}$. This oxygen is suppled by the circulating blood, but its availability is modified by the amount of blood shunting ($\dot{Q}_{TS}$) and the fraction of oxygen (α) extracted from tissue blood flow ($\dot{Q}_T$). The combined effects of shunting and fractional extraction can be represented by a fraction α',

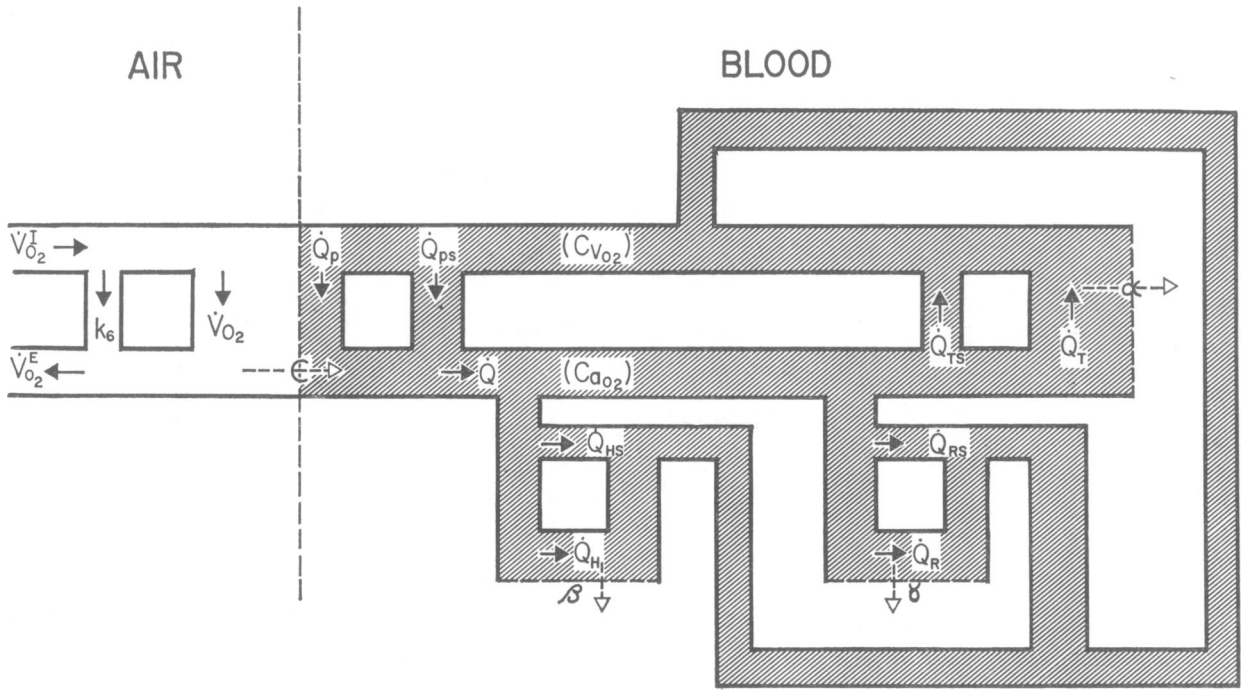

FIGURE 1 Model of the oxygen transport system. The circulation to the periphery is in parallel with that supplying the heart and the respiratory pump. The blood flow to each bed is divided into tissue flow and shunt flow. Oxygen is only extracted from the former. The Greek symbols indicate fractional oxygen extraction (see text).

which may be called the oxygen utilization fraction. The blood supply to the heart and the respiratory muscles is in parallel with the blood supply to the tissue bed. The amount of oxygen consumed by these pumps is determined by the work required to supply the tissue bed. Similar to the organization of the latter, the circulation of the respiratory muscles and the heart are also characterized by blood shunts ($\dot{Q}_{RS}$, $\dot{Q}_{HS}$) and fractional extractions (γ, β).

Using the principle of conservation of mass, this respiratory-circulatory system can be described by the equations:

$$\dot{V}^I_{O_2} = \dot{V}^T_{O_2} + \dot{V}^H_{O_2} + \dot{V}^R_{O_2} + \dot{V}^E_{O_2} \tag{1}$$

and

$$\dot{Q} = \frac{\epsilon \dot{V}^A_{O_2} + \dot{Q}_p c_{v_{O_2}} + \dot{Q}_{ps} c_{v_{O_2}}}{c_{a_{O_2}}} \tag{2}$$

where the super(sub)scripts represent:

I = inspired	E = expired
T = tissue	a = arterial
A = alveolar	v = venous
H = heart	p = pulmonary
R = respiratory muscles	s = shunt

and ϵ = fractional extraction of O_2 from alveolar air ($\epsilon = \dot{V}_{O_2}/\dot{V}^A_{O_2}$), $\dot{V} = dV/dt$ (V = gas volume), $\dot{Q}$ = blood flow, and c = concentration (ml O_2/ml blood).

Equation 1 states that the inspired oxygen is equal to the sum of the oxygen consumed by the tissues, heart and respiratory muscles plus the amount of oxygen expired. Equation 2 states that the arterial oxygen content is equal to the sum of the oxygen extracted from the alveolar air and the oxygen returning in the venous blood.

Equations 1 and 2 must now be expressed in terms of the variables $\dot{V}^I_{O_2}$ and $\dot{Q}$ and the pertinent system parameters. From Fig. 1, we see that:

$$\dot{V}^E_{O_2} = k_6 \dot{V}^I_{O_2} + (1 - \epsilon)\dot{V}^A_{O_2}$$

where k_6 represents the fractional dead space (dead space ventilation/total ventilation).

The oxygen supply required by the two pumps must be a function of their output. Initially, we assume that these functions may be expressed by linear relationships. Thus:

$$\dot{V}^H_{O_2} = k_1 \dot{Q}$$

and

$$\dot{V}^R_{O_2} = k_2 \dot{V}^I_{O_2} .$$

Later, nonlinear relationships will be considered where k_1 and k_2 are treated as variable parameters.

Equation 1 can now be written:

$$\dot{V}^I_{O_2} = \dot{V}^T_{O_2} + k_1 \dot{Q} + k_2 \dot{V}^I_{O_2} + k_6 \dot{V}^I_{O_2} + (1 - \epsilon)(1 - k_6)\dot{V}^I_{O_2}$$

$$\dot{V}^I_{O_2}[1 - k_2 - k_6 - (1 - \epsilon)(1 - k_6)] - k_1 \dot{Q} = \dot{V}^T_{O_2}$$

$$\dot{V}^I_{O_2}[\epsilon(1 - k_6) - k_2] - k_1 \dot{Q} = \dot{V}^T_{O_2} . \tag{3}$$

Similarly, equation 2 can be reduced by noticing from Fig. 1 that:

$$c_{\bar{v}O_2} = \frac{[\dot{Q}_T(1 - \alpha) + \dot{Q}_{TS} + \dot{Q}_H(1 - \beta) + \dot{Q}_{HS} + \dot{Q}_R(1 - \gamma) + \dot{Q}_{RS}]c_{aO_2}}{\dot{Q}} .$$

We also assume that the shunt flow is proportional to the tissue flow. A constant ratio of shunt to tissue flow implies a fixed relation (e.g. geometric) between shunt and tissue resistances. However, since this ratio enters into the analytical expressions only in combination with the variable fractional oxygen extraction as the oxygen utilization fraction α', the exact form of the relationship is not important as far as the analysis of the over-all performance is concerned.

We thus have:

$$\dot{Q}_{TS} = k_3 \dot{Q}_T$$

$$\dot{Q}_{HS} = k_4 \dot{Q}_H$$

$$\dot{Q}_{RS} = k_5 \dot{Q}_R .$$

This leads to:

$$c_{\bar{v}O_2} = \frac{[\dot{Q}_T(1 - \alpha + k_3) + \dot{Q}_H(1 - \beta + k_4) + \dot{Q}_R(1 - \gamma + k_5)]c_{aO_2}}{\dot{Q}}$$

or

$$c_{\bar{v}O_2} = \frac{\left[\dot{V}^T_{O_2}\frac{(1 - \alpha + k_3)}{\alpha} + \dot{V}^H_{O_2}\frac{(1 - \beta + k_4)}{\beta} + \dot{V}^R_{O_2}\frac{(1 - \gamma + k_5)}{\gamma}\right]}{\dot{Q}} .$$

Equation 2 can now be rewritten:

$$\dot{Q}c_{a_{O_2}} = \epsilon(1 - k_6)\dot{V}^I_{O_2} + \frac{(\dot{Q}_p + \dot{Q}_{ps})}{\dot{Q}} \cdot \left[\dot{V}^T_{O_2}\frac{(1 - \alpha + k_3)}{\alpha} + \frac{k_1\dot{Q}(1 - \beta + k_4)}{\beta} + \frac{k_2\dot{V}^I_{O_2}(1 - \gamma + k_5)}{\gamma}\right]$$

$$\dot{Q}\left[c_{a_{O_2}} - \frac{k_1(1 - \beta + k_4)}{\beta}\right] - \dot{V}^I_{O_2}\left[\epsilon(1 - k_6) + \frac{k_2(1 - \gamma + k_5)}{\gamma}\right] = \frac{1 - \alpha + k_3}{\alpha}\dot{V}^T_{O_2}. \quad (4)$$

Equations 3 and 4 are simultaneous equations in $\dot{V}^I_{O_2}$ and $\dot{Q}$ expressed in terms of $\dot{V}^T_{O_2}$ and the parameters of the model system. Solving for $\dot{V}^I_{O_2}$ and $\dot{Q}$ one gets:

$$\dot{V}^I_{O_2} = \frac{\dot{V}^T_{O_2}}{[\epsilon(1 - k_6)]} \frac{[c_{a_{O_2}} - k_1(B - A)]}{c_{a_{O_2}}\left[1 - \frac{k_2}{\epsilon(1 - k_6)}\right] - k_1\left[1 + B - \frac{(B + C)k_2}{\epsilon(1 - k_6)}\right]} \quad (5)$$

and

$$\dot{Q} = \frac{\dot{V}^T_{O_2}}{c_{a_{O_2}}\frac{1 - \frac{k_2}{\epsilon(1 - k_6)}}{1 + A - \frac{k_2(A + C)}{\epsilon(1 - k_6)}} - k_1\frac{1 + B - \frac{k_2(B + C)}{\epsilon(1 - k_6)}}{1 + A - \frac{k_2(A + C)}{\epsilon(1 - k_6)}}} \quad (6)$$

where

$$A = \frac{1 - \alpha + k_3}{\alpha}; \qquad B = \frac{1 - \beta + k_4}{\beta}; \qquad C = \frac{1 - \gamma + k_5}{\gamma}.$$

The two equations (5 and 6) express the rate of O_2 inspired ($\dot{V}^I_{O_2}$) and cardiac output ($\dot{Q}$) each as a function of tissue oxygen supply ($\dot{V}^T_{O_2}$). Thus, presumably, knowing the model parameters and the tissue oxygen demand, we could calculate $\dot{V}^I_{O_2}$ from equation 5 and $\dot{Q}$ from equation 6. However, normally k_1 and k_2 are not constants but are functions of $\dot{Q}$ and $\dot{V}^I_{O_2}$, respectively. Thus we have not, in fact, yet solved the simultaneous equations although we have expressed them in a convenient form.

PARAMETERS OF THE MODEL SYSTEM

If we can assign values or ranges of values for the parameters of equations 5 and 6 (i.e., mathematically characterize the component parts of the model system), we

may then generate the behavior of the respiratory and cardiac pumps with relation to tissue oxygen demand.

Dead Space Fraction, k_6

We will assume that dead space ventilation represents one-fourth of the total ventilation ($k_6 = 0.25$) (17). Similarly to the parameters k_3, k_4, and k_5, which characterize the ratio of shunt and tissue flow and appear in all equations combined with the fractional oxygen extraction, k_6 is always associated with ϵ, the fractional oxygen extraction from alveolar air. Changes in k_6 can thus be taken into account for computational purposes by altering the value of ϵ.

Oxygen Utilization Fraction, α'

The fractional extractions, α, β, and γ, and the functional blood shunts, k_3, k_4, and k_5, determine the amount of oxygen which can be removed from the circulating blood. This joint effect is expressed in equation 6 by the fraction:

$$\alpha' = \frac{1}{1 + A} = \frac{\alpha}{1 + k_3}$$

which we will call the oxygen utilization fraction (α'). This fraction describes the amount of oxygen removed from the arterial blood by the metabolizing tissue bed. The normal a–v oxygen difference ranges from about 4 ml O_2/100 ml blood at rest to a maximum of 16 during heavy exercise (12). This corresponds to values for α' from about 0.2 to 0.8 and represents the maximal possible physiological range of this parameter. All calculations were carried out for several values of α'.

The fraction, $1/1 + C$, representing the oxygen utilization fraction for the respiratory muscles is assumed equal to α'. The fraction, $1/1 + B$, representing the oxygen utilization fraction for the heart, is taken as constant and equal to 0.8. This is in agreement with the experimental finding that coronary venous pO_2 is nearly constant and that an increase in cardiac oxygen consumption is achieved almost exclusively by an augmentation of coronary blood flow (5, 9).

Oxygen Extraction from Alveolar Air (ϵ) and Arterial Oxygen Concentration ($c_{a_{O_2}}$)

The alveolar oxygen extraction fraction and the arterial oxygen concentration are coupled via the partial pressure of O_2 in the lungs. While k_6 characterizes primarily the difference in oxygen tension between inspired and alveolar air, ϵ is a measure of the transfer of oxygen across the alveolocapillary membrane. If this transfer is not diffusion limited, ϵ is only a function of the alveolocapillary oxygen gradient and, thus, of the ventilation-perfusion ratio.

The alveolar pO_2 is determined by the input of $O_2(\dot{V}^I_{O_2})$ and k_6 while the venous

oxygen concentration is dependent on α'. Under normal conditions, the value of ϵ is between 0.4 and 0.5 (12, 17). If we let $\epsilon = \alpha'$, then the ventilation-perfusion remains constant and $c_{a_{O_2}}$ varies according to $P^A_{O_2}$ and the hemoglobin saturation curve. On the other hand, if ϵ is maintained constant, then the ventilation-perfusion ratio is variable and $c_{a_{O_2}}$ remains constant. Solutions for equations 5 and 6 were obtained for both behaviors of ϵ (i.e. $\epsilon = \alpha'$ or ϵ = constant). The hemoglobin saturation curve used for the calculations is shown in Fig. 2 (20).

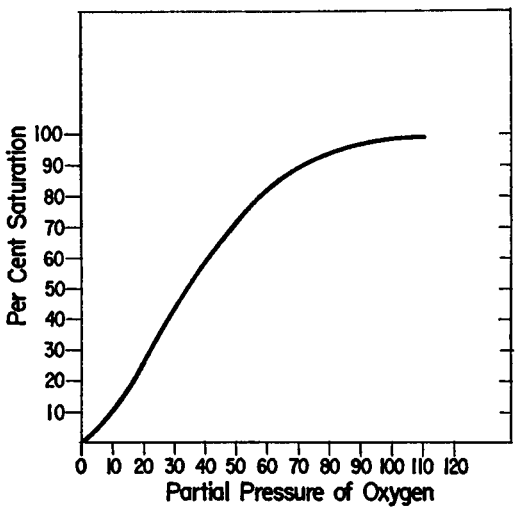

FIGURE 2 The oxygen saturation curve used for the calculations (from Roughton, reference 20).

Ratio of Cardiac Oxygen Consumption to Cardiac Output, $k_1 = \dot{V}^H_{O_2}/\dot{Q}$

In the intact, innervated heart, the oxygen consumption is a function of cardiac output that probably depends both on how the output increases (whether by a change in frequency or in stroke volume) and on the external load of the heart. Present experimental data do not yet permit the inclusion of these additional parameters into the model. Since no data are available on the oxygen consumption of the human heart during stress and exercise, we based our calculations on the following considerations:

(*a*) During heavy work loads, the increment of energy required for a fixed incremental increase of work becomes progressively larger as the level of effort rises. Thus, it becomes increasingly difficult to augment the work output at high work loads. If we consider the work of the heart to be characterized by cardiac output and the energy requirements of the heart by cardiac oxygen consumption, then we might reasonably expect that the incremental change in oxygen consumption with respect to cardiac output be proportional to the level of oxygen consumption (i.e. $d\dot{V}^H_{O_2}/d\dot{Q} = c_1\dot{V}^H_{O_2}$). Such a behavior is described by the exponential relation: $\dot{V}^H_{O_2} = c_2 e^{-c_1\dot{Q}}$.

(*b*) Khouri et al. (11) have measured both cardiac oxygen consumption and output in dogs using chronically implanted flowmeters. Their results are shown as a semilogarithmic plot in Fig. 3 and agree with the predicted exponential behavior thus permitting the determination of c_1 and c_2 for the dog heart.

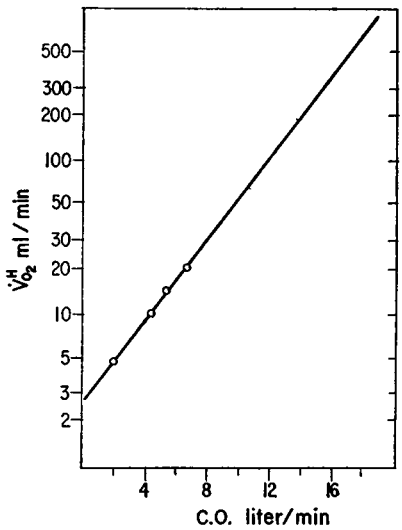

FIGURE 3 The relation between cardiac oxygen consumption and cardiac output obtained from the data of Khouri et al. (11).

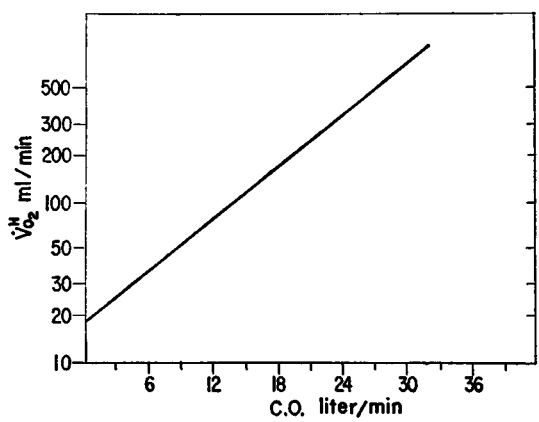

FIGURE 4 Extrapolation of Khouri's data to normal man.

(*c*) If we accept the exponential relationship described above, we are now left with the task of finding the constants c_1 and c_2 for a description of the behavior of the human heart. These values can be estimated from the resting values for man ($\dot{V}_{O_2}^H$ = 32 ml O_2/min) at a cardiac output of 6 liter/min (4, 5, 9, 23) and from the rate of increase in cardiac O_2 consumption with a rise in cardiac output for the dog.

(An increase of $\dot{Q}$ from the resting value by a factor of three leads to a fourfold augmentation in cardiac oxygen consumption, Fig. 3.)

The resulting curve of $\dot{V}^H_{O_2}$ vs. $\dot{Q}$ for a normal human heart, shown in Fig. 4, permits the calculation of k_1 at any level of $\dot{Q}$.

Ratio of Oxygen Consumption of the Respiratory Muscles to Rate of Inspiration of Oxygen, $k_2 = \dot{V}^R_{O_2}/\dot{V}^I_{O_2}$

The relation between oxygen consumption of the respiratory muscles and the rate of ventilation has been measured (7, 15) and is shown plotted semilogarithmically in Fig. 5. We can see that the points fit the straight line of an exponential response very well. The value of k_2 can be calculated by taking the ratio $\dot{V}^R_{O_2}/\dot{V}^I F_{I_{O_2}}$ at any level of ventilation.

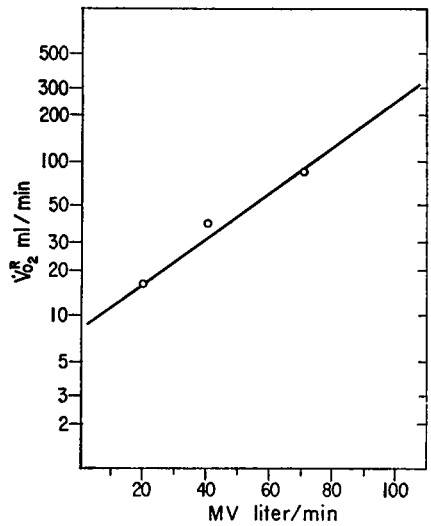

FIGURE 5 The relation between oxygen consumption of the respiratory muscles and ventilation for normal man (data from Cherniak, reference 7).

USE OF THE EQUATIONS OF THE MODEL SYSTEM

Results

Equations 5 and 6 together with the parameters just described have been used to calculate the amount of oxygen that can be delivered to the peripheral tissues as a function of cardiac output and ventilation. This relationship has been explored for a combination of environmental and physiological variations as shown in Fig. 6.

The effects of variations in environment are demonstrated by a comparison of the results at two altitudes (sea level and 6000 ft). The results for the several values of ϵ_{max} (the maximal possible extraction of oxygen from alveolar air) illustrate the effect of a trade-off between $c_{a_{O_2}}$ and $\dot{V}^A_{O_2}$ (or expressed differently, the results of changes in the ventilation-perfusion ratio). Finally, a variation in α' shows the

performance limits within the total range of adaptability of the system. It is assumed that in a normal individual the limit of fractional oxygen utilization from the blood is 0.8 (at high work) whereas the resting value of α' is close to 0.2, corresponding to arteriovenous oxygen differences of 16 and 4 volumes per cent, respectively.

The results of the calculations described above are shown in Figs. 7 (sea level) and 8 (6000 ft) as plots of tissue oxygen supply vs. cardiac output. There are three sets of curves on each figure representing the three assumed values of ϵ_{max}. Each of these sets, in turn, is made up of three curves representing different values of α'. For each curve the numbers indicate the minute ventilation required to provide the tissue oxygen consumption at the cardiac output specified for the operating point

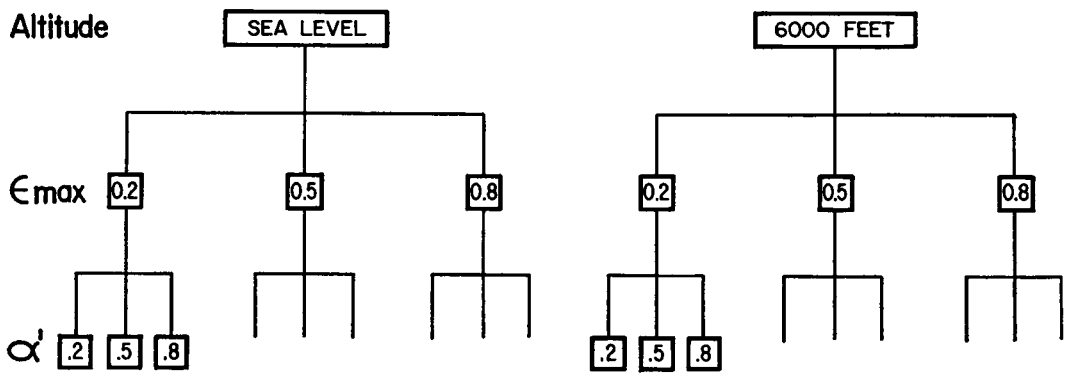

FIGURE 6 The combination of environmental and physiological variation of the model parameters used in the analysis. For each level of altitude, three values for ϵ_{max} were assumed and each value of ϵ_{max} was associated with three different values of α'. ϵ_{max} is the maximum allowed fractional extraction of oxygen from the alveoli. α' is the fractional utilization of oyxgen from the circulating blood.

marked by an arrow. Experimental values at various levels of exercise (23) are also indicated in Fig. 7 by crosses for total oxygen uptake and by full circles for the amount of oxygen available to the periphery.

Discussion

Character of a Single Curve. The curves of tissue oxygen supply vs. cardiac output (Figs. 7 and 8) are characterized by a peak in the amount of oxygen which may be delivered to the tissues. Although an increased output of the two pumps is associated with a rise of the total amount of oxygen transported by the system, the oxygen requirements of the two pumps increase progressively faster than the increments in the amount of oxygen transported. Because of the rising energy requirements of the two pumps, an increase of the pumping activity beyond the level at

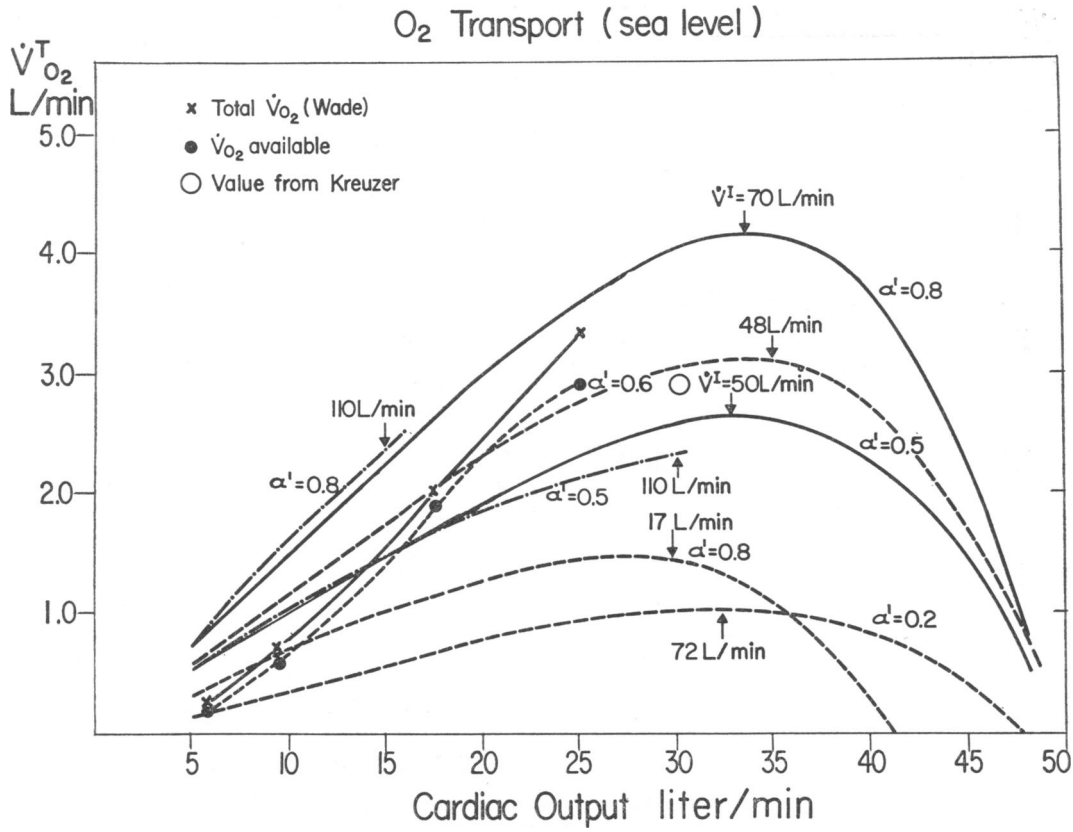

FIGURE 7 Results of a parametric performance analysis of the normal oxygen transport system at sea level for different values of ϵ and α'. ϵ represents the fractional extraction of O_2 from alveolar air and is, thus, a measure of the ventilation-perfusion ratio. α' represents the oxygen utilization in the periphery and depends both on the oxygen extraction from the blood and the amount of shunt flow. The oxygen available to the periphery is plotted as a function of cardiac output. The required ventilation rates at the points of peak delivery of oxygen are also indicated. The model parameters were changed according to the scheme shown in Fig. 6: $\epsilon = 0.2$, dashed-dot lines; $\epsilon = 0.5$, solid lines; $\epsilon = 0.8$, dashed lines. The values for α' are shown on the individual curves. For $\alpha' = 0.2$, the curves for the three values of ϵ are superimposed. The crosses indicate experimental values from Wade (23), the full dots represent the same values after subtraction of the oxygen costs of the two pumps, according to the relations shown in Figs. 4 and 5. The open circle is an exercise value given by Kreuzer (12).

which the peak occurs results actually in a decrease in the amount of oxygen available to the periphery.

Character of a Set of Three Curves for a Fixed ϵ_{max}. For any assumed ϵ_{max}, we can calculate a family of curves for which α', the oxygen utilization, represents the variable parameter. ϵ_{max} is defined as the maximal fractional extraction of

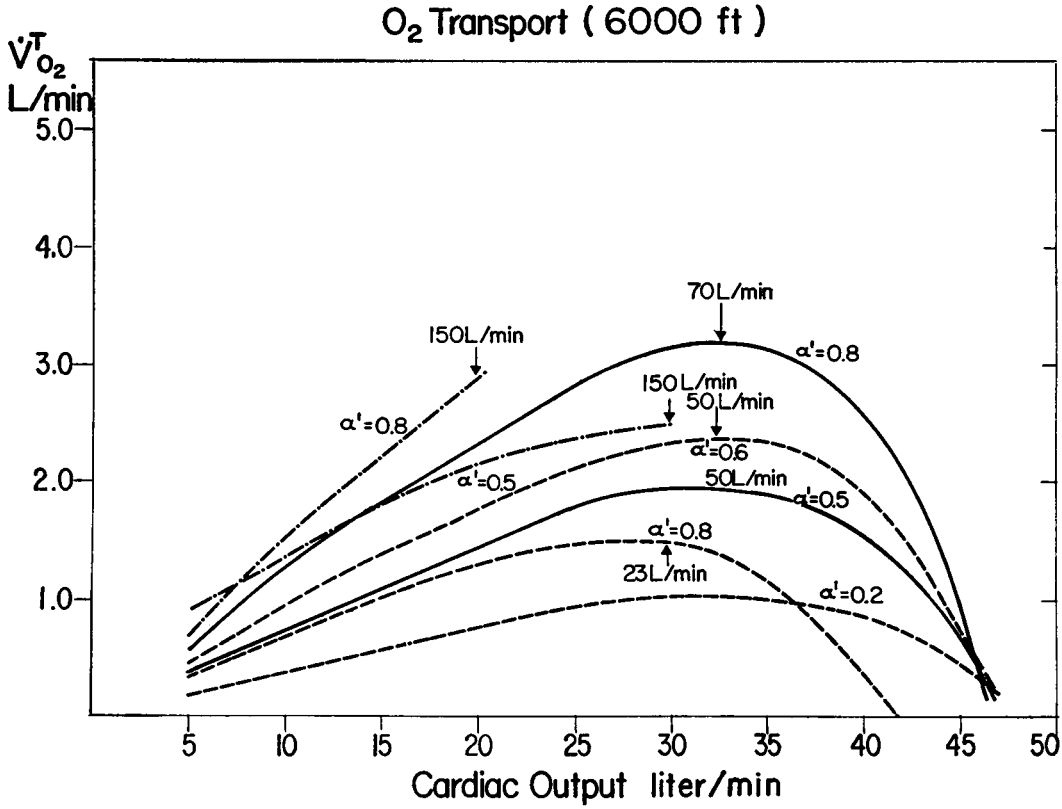

FIGURE 8 Results of a parametric performance analysis of the normal oxygen transport system at high altitude, according to the scheme outlined in Fig. 6. Symbols as in Fig. 7.

oxygen from the alveolar air. For a healthy subject, the values of ϵ range from about 0.4 at rest to 0.25 during heavy exercise (12). Note that for $\alpha' = 0.2$, changes in ϵ have no effect on the relation between $\dot{V}_{O_2}^T$ and $\dot{Q}$, which indicates the reserve potential of the system at rest.

$\epsilon_{max} = 0.2$ (*dashed-dot lines in Figs. 7 and 8*). This value for ϵ represents a lower limit for the oxygen extraction of the lungs and implies a ventilation-perfusion ratio which is much greater than one. The restriction imposes a high demand on the ventilatory system while slightly decreasing cardiac work for maintaining a normal arterial oxygen saturation. Except for $\alpha' = 0.2$, the performance of the system is limited by the maximal ventilatory rate (indicated by the termination of the curves at a ventilatory rate of 110 liter/min) rather than by a peak in the $\dot{V}_{O_2}^T$ vs. $\dot{Q}$ curve. Nevertheless, an increase in α' from 0.5 to 0.8 decreases the cardiac work more than twofold with a corresponding gain in the amount of oxygen available to the periphery.

$\epsilon_{max} = 0.8$ (*dashed lines in Figs. 7 and 8*). This value for ϵ characterizes the other end of the performance range, with a ventilation-perfusion ratio much smaller

than one. Although the fractional extraction of oxygen from the lungs is large and the demands on the respiratory system are minimized, great demands are imposed on cardiac performance at high work levels. The dashed curves in Fig. 7 indicate that the maximal amount of oxygen available to the periphery increases from a minimum of 0.9 liter/min ($\alpha' = 0.2$, $\dot{V}^I = 72$ liter/min, $\dot{Q} = 32$ liter/min) to 3.1 liter/min ($\alpha' = 0.6$, $\dot{V}^I = 48$ liter/min, $\dot{Q} = 36$ liter/min) and decreases thereafter to 1.4 liter/min ($\alpha' = 0.8$, $\dot{V}^I = 17$ liter/min, $\dot{Q} = 29$ liter/min).

$\epsilon_{max} = 0.5$ (*solid lines in Figs. 7 and 8*). Maintaining the fractional oxygen utilization at normal levels below 0.5 keeps the arterial oxygen saturation near maximum. The ventilation-perfusion ratio increases at high performance levels but to a smaller degree than in the first case ($\epsilon_{max} = 0.2$). Fig. 7 indicates that the amount of oxygen delivered to the periphery is greater than in either case 1 or 2 and, in fact, is near the optimum. The maximum amount available is about 4.2 liter/min and requires a ventilation rate of 70 liter/min and a cardiac output of 33 liter/min with $\alpha' = 0.8$. From these results, one would predict that the body optimizes oxygen supply during exercise by increasing α' (represented by a vertical movement through the curves) in such a way that the energy requirements of the heart and the respiratory muscles are minimized. Once the maximal possible value of α' is obtained, further increases in the peripheral oxygen supply are achieved by changes in ϵ and the outputs of the two pumps. The experimental data plotted in Fig. 7 are in agreement with such a prediction.

Comparison of Oxygen Transport at Sea Level and at High Altitude. It is to be expected that the decreased oxygen tension of the ambient air at high altitude lowers the maximal amount of oxygen which can be supplied to the periphery. This is, in fact, apparent from the decreased height of the peaks in the $\dot{V}^T_{O_2} - \dot{Q}$ curves calculated for conditions at an altitude of 6000 ft (Fig. 8). A comparison of the results illustrated in Figs. 7 and 8 further reveals that at high altitudes an increase of the ventilation-perfusion ratio (lower ϵ_{max}) is of greater benefit in terms of oxygen available to the periphery for submaximal oxygen requirements. This is in contrast to the condition at sea level where there is no appreciable benefit derived from an increased ventilation-perfusion ratio at performance levels which correspond to less than maximal effort.

Conclusions

The proposed model represents an attempt to analyze the over-all performance of the oxygen transport system within the limits set by the physicochemical properties of the individual subsystems. The amount of oxygen available to the periphery is evaluated as a function of ventilation, inspired O_2 concentration, cardiac output, oxygen capacity of the blood, the oxygen requirements of the two pumps, ϵ (a function of the ventilation-perfusion ratio) and α' (a function of tissue blood flow,

local shunts, and local metabolism). These parameters may assume quite different values depending on the physicochemical characteristics of the system and the demands which are put on it. In contrast to previous studies on the optimization of biological systems, where the efficiency of an individual subsystem was considered (6, 8, 13, 14, 16, 22, 24) we focused our attention on the over-all performance as affected by the interactions between the various subsystems and optimized with respect to flexibility and maximal limits of performance. While other carrier functions of biological systems, such as heat transport or the transport of nongaseous metabolites, may tolerate an interruption for hours without irreversible damage, a failure in the oxygen transport system can only be compensated for a few minutes. The control systems which maintain homeostasis and provide the possibility for adaptation to stress and disease must, therefore, affect not only the performance of the individual subsystems but also provide mechanisms by which the interaction of the various subsystems are matched to the existing needs.

The presented analysis is based on the behavior of the normal system during exercise at sea level and at high altitude. The only parameters which were varied were ϵ and α'. In such a system, a change in α' is considerably more effective than a change in ϵ. α' may be altered by either changing the ratio between shunt and tissue flow or by changing the extraction rate. The latter depends primarily on the gradient in O_2 tension between arterial blood and cell interior. Stainsby (21) has shown that the density of capillaries increases considerably during exercise thus providing additional evidence for the importance of tissue flow vs. shunt flow. Adequate data for a further exploration of this problem are not available at present. In obstructive respiratory disease, the oxygen requirements of the respiratory pump increase manyfold, thus shifting the peak of the amount of oxygen available to the periphery toward the left and downward. Similar changes are to be expected if cardiac oxygen consumption is greater than that indicated in Fig. 4. In our analysis, we have assumed an oxygen carrying capacity of 20 volumes per cent for the blood. Preliminary data for anemias (arterial oxygen content 15%) indicate that a lowering of the oxygen carrying capacity not only limits cardiac output and changes in the ventilation-perfusion ratio but also reduces the maximal amount of oxygen available to the periphery by some 25%.

Once appropriate experimental data are available, the model and the underlying equations can be applied to a wide variety of conditions. These can be investigated by merely inserting appropriate parameter values for a particular condition into the equations. Wider use of the system, however, awaits the measurement of such parameters as the efficiency of the normal and pathological cardiac and respiratory pumps and the fractional oxygen extraction in normal and pathological tissue beds under conditions of stress. Based on such data, the analysis permits an objective evaluation of the system's performance and of the relative importance of individual components and interphases (3). It, thus, provides a potentially powerful tool for the assessment of the severity and prognosis of cardiovascular and respiratory

diseases and the degree of disability resulting therefrom. For example, the maximal oxygen uptake is now often used as a performance index for exercise capacity. But when disabilities exist in terms of cardiovascular or respiratory pathophysiology, a large fraction of the total oxygen uptake may be required to provide for the metabolic needs of the cardiac and respiratory muscles. Cherniak's (7) data for exercise indicate that for a ventilation of 30 liter/min the total O_2 uptake is reduced from 1.2 liter/min in the normal condition to 1.15 liter/min in acute hypoxia, 1 liter/min in chronic hypoxia to 0.75 liter/min in heart disease, but remains unaltered in obesity. Under these conditions, the oxygen requirements of the respiratory muscles represent approximately the following fractions of the total O_2 uptake: 0.06 for the normal, 0.15 in acute hypoxia, 0.16 in heart disease, 0.20 in obesity and 0.42 in chronic hypoxia. These are dramatic changes in terms of the over-all performance of the system. Other parameter changes associated with these pathological states may have additional deleterious effects, which also may not be appropriately reflected in the results of conventional fitness tests, such as the maximal oxygen uptake. Because the presently available methodological tools are inadequate to quantitatively assess the amount of oxygen delivered to the periphery under conditions of stress, the practicing physician is yet unable to quantitate disabilities due to malfunctions of the oxygen transport system.

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