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Oxygen supply to tissues: The Krogh model and its assumptions

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The human organism can survive anoxia for only a few minutes. Its regular energy requirements are met predominantly by oxidations; this is not surprising since anaerobic glycolysis is about 20 times less efficient in energy supply than oxidation. The basic functions of ventilation, circulation, blood carriage of gases and gas exchange in the lungs and in the tissues serve to supply the tissues with oxygen from the ambient air. Enough oxygen must be transferred per unit of time to ensure a proper function of the terminal oxidases in the cells. Thus, during steady state conditions, the amount of oxygen taken up by the lungs and conveyed along the sequential steps of oxygen transport must equal the amount of oxygen used by the tissue (Kreuzer[29]).

All movement of substance is governed by the general law of transport which states that the flux or flow is proportional to a force, with a proportionality constant having the dimension of conductivity or the reciprocal of resistance. The transfer of oxygen from the air to the tissues may thus be represented in terms of resistances to the flux where the total resistance equals the sum of all individual resistances in series. These specific resistances include those involved in

pulmonary ventilation, simultaneous diffusion and chemical reaction in the lung, carriage of oxygen in the blood and distribution by the circulation, simultaneous diffusion and chemical reaction in the tissue capillaries and in the tissues with their mitochondria. During this transfer along the 'cascade' of oxygen, the driving force of the oxygen partial pressure difference is gradually used up along these resistances in series to probably less than 1 mm Hg at the site of consumption in the mitochondria. This means that the system is very efficient with respect to oxygen extraction and does not leave any appreciable reserve of oxygen at the end of the chain.

A consideration of the oxygen transfer system leads to the following important findings:

1. A certain minimum value of the oxygen pressure is required at the starting point of the path of oxygen (ambient air) in order to overcome these resistances along the 'cascade' and to ensure an oxygen supply sufficient to satisfy the oxygen needs of even the most remote cells in the tissues. The question arises whether this initial value is sufficient also in situations deviating from the normal level of normoxia or involving pathological processes somewhere along the line.

2. Derangements of various kinds can occur at the site of the specific resistances along the 'cascade', possibly leading to an increase of resistance to the oxygen transfer and to inadequate oxygen supply of the tissues. Clinical medicine knows numerous cases of such impairments involving hypoxia, and pathophysiology is particularly interested in the consequences of a lowering of the oxygen pressure in the inspired air (hypoxic hypoxia).

3. In the case of disturbances in the course of the oxygen transfer regulating or compensating adaptation mechanisms are needed and called upon in order to diminish the increased resistances and thus to ensure an appropriate oxygen supply. In the case of hypoxia a lowering of the resistances is indispensable in view of the decreased overall driving force, that is to say reduced oxygen pressure. These adaptation mechanisms in response to various hypoxic 'stresses' are of vital importance for the survival of the organism in situations adverse to the supply of oxygen to the cells maintaining the metabolic functions.

The uptake of oxygen occurs in one particular organ, the lung, and the oxygen is carried by the arterial blood from the site of uptake to the site of consumption, the tissues. The situation concerning the release of oxygen to and its consumption in the tissues is much more complicated in so far as there are many kinds of tissue with widely different characteristics. Experimental studies of tissue oxygen supply are numerous but have met with many methodological difficulties and are often not easy to interpret. This is the reason why numerous investigators have taken recourse to modeling and mathematical analysis of tissue oxygen supply. The decisive breakthrough for a theoretical approach is credited to August Krogh who, in 1919, devized his famous model which still is the basis of all such studies.

The arterial blood supplies the tissues with oxygen, the flux of which is divided into two fractions along the oxygen-supplying capillaries: part of it diffuses into the tissue cells to be consumed and another part leaves the capillaries in the venous blood. The diffusion of oxygen from the capillaries into the tissues is coupled with chemical reactions, i.e., reversible chemical reactions between oxygen and hemoglobin in the capillary blood (oxygen release from hemoglobin) and irreversible chemical reactions in the mitochondria of the tissues (oxygen consumption). In heart and skeletal muscle there is a further reversible chemical reaction between oxygen and myoglobin. Krogh[34] idealized the situation in the tissues by assuming that the oxygen diffuses from a cylindrical capillary into a concentric cylindrical tissue portion (Krogh model, fig. 1). The Danish mathematician Erlang derived for him an equation based on the first law of Fick holding for steady-state conditions, i.e., time-independent conditions, equating the oxygen extracted from the capillary to that supplied to the tissue:

$$\Delta P = P_c - P_x = \frac{M}{K}\left(\frac{R^2}{2}\ln\frac{x}{r} - \frac{x^2 - r^2}{4}\right) \qquad (1)$$

where P_c = oxygen pressure in capillary in mm Hg, P_x = oxygen pressure at point x in the tissue in mm Hg, M = oxygen consumption in ml oxygen per ml tissue per time, K = Krogh's diffusion coefficient or oxygen conductivity in ml O_2/cm sec mm Hg ($K = \alpha D$ with α = oxygen solubility and D = physical

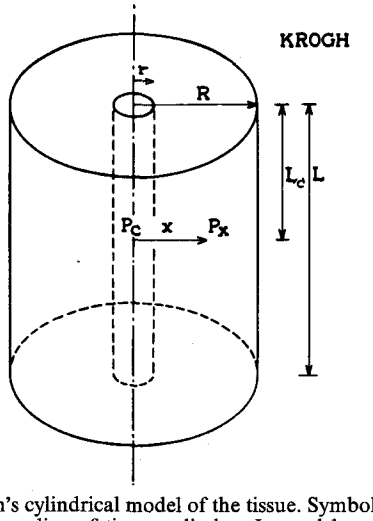

Figure 1. Krogh's cylindrical model of the tissue. Symbols: r, radius of capillary; R, radius of tissue cylinder; L, total length of capillary; L_c, any fractional length of capillary; P_c, capillary oxygen pressure; P_x, tissue oxygen pressure at any distance x from the capillary. (From Turek and Kreuzer[56], fig. 1, p. 76, with permission.)

diffusion coefficient or diffusivity in cm^2/sec), R = radius of tissue cylinder, r = radius of capillary, x = distance from capillary to any point in the tissue.

This Krogh-Erlang equation is based on a number of simplifying and often unrealistic assumptions (Kreuzer[30]; Kreuzer and Turek[31]) such as:

1. There is only radial but no longitudinal or axial diffusion.
2. The intracapillary chemical reactions in the blood are neglected, i.e., the oxygen concentration is the same over the capillary cross section, and chemical equilibrium is assumed between oxygen and hemoglobin.
3. The oxygen consumption in the tissue does not depend on the local oxygen pressure (zero-order reaction).
4. The cells may be represented as an homogeneous volume distribution of minute sinks of oxygen independent of time and position.
5. The capillaries are straight, run parallel, have a unidirectional blood flow, and are homogeneously distributed.
6. Capillary radius and length are constant, implying, with constant blood flow, a constant transit time.
7. The capillary wall does not present any resistance to oxygen diffusion.
8. The capillary blood flow is constant. With unchanging oxygen consumption this implies the same venous oxygen concentration in all capillaries (Fick principle).
9. The flow of oxygen from the capillary is cylindrically symmetric.
10. The oxygen exchange occurs only in the capillary, not in arterioles and venules.
11. The oxygen does not diffuse out of the tissue cylinder.
12. The diffusion coefficient is the same throughout the tissue.
13. There is no facilitated diffusion of oxygen, e.g., by myoglobin in muscle.
14. The whole configuration is independent of time (steady state).
15. The transfer is by diffusion only (no stirring).

This is an impressive list of assumptions, which in turn raises the question as to how realistic and meaningful the calculations according to the Krogh model might be. Hess[21] was fully aware of this problem. When discussing Krogh's model and calculations, he wrote (p. 12): 'Allerdings können die Unterlagen für eine solche Rechnung nicht mit der wünschbaren Schärfe zahlenmässig gefasst werden. Man muss eine Fehlerbreite gelten lassen, welche es nicht gestattet, die Mitwirkung anderer Kräfte mit Sicherheit auszuschliessen; für andere Stoffe (als Sauerstoff) bleibt die Frage ohnehin offen. Bei der ausserordentlichen Schwierigkeit, in die im Innersten der Gewebe sich abspielenden Vorgänge zuverlässigen Einblick zu erhalten, müssen wir uns immer der Tatsache bewusst bleiben, dass lebende Zellen erwiesenermassen aktiv in Austauschvorgänge eingreifen können... Neben einer aktiven Beförderung bestimmter Austauschstoffe muss auch die Möglichkeit ins Auge gefasst werden, dass der Stoffwanderung durch die lebenden Zellen Hemmungen in den Weg gelegt werden. Dabei ist es durchaus möglich, dass allfällige Austauschwiderstände sich nur in *einer* Richtung geltend machen, während gleichzeitig in der andern Richtung Stosskräfte wirksam sind'.

(In translation: 'However, the basis for such a calculation cannot be defined numerically with desirable accuracy. One must admit a range of error which does not permit the exclusion of the intervention of other forces with certainty; for substances other than oxygen the question remains open anyhow. In view of the extraordinary difficulties of reliably assessing the processes occurring in the innermost parts of the tissue we must always be aware of the fact that living cells demonstrably may participate actively in the exchange processes... Apart from an active transport of certain exchanging substances the possibility must be considered that the migration of substances across the living cells may encounter impediments on their path. Hereby it is quite possible that certain exchange resistances show only in one particular direction whereas promoting forces act simultaneously in the other direction'.) It is not quite clear what Hess meant by 'active processes'. At any rate, after having considered the capillaries as purely passive structures for many years, their active regulation has once more gained increasing attention in recent times (see below).

Before embarking on a more detailed discussion of some of the assumptions listed above, the effects of the most important determinants of tissue oxygen pressure must be reviewed briefly in order to appreciate the impact of possible deviations from the assumptions. Rakušan[48] has developed a computer program to evaluate the changes in myocardial oxygen pressure at the periphery of the tissue cylinder due to deviations from the initial conditions of the most important oxygen determinants: myocardial oxygen consumption, myocardial blood flow, diffusion distance, capillary radius, oxygen content of the arterial blood and Krogh's diffusion coefficient. Figure 2 presents direct computer drawings of changes of myocardial oxygen pressure caused by variations in these major determinants; each individual curve represents the changes in oxygen pressure due to a variation in any one determinant both above and below the initial conditions while keeping the remaining determinants constant. The point of their intersection indicates the oxygen pressure in the heart muscle under normal conditions (36 mm Hg). The most relevant results may be summarized as follows.

The most important determinant of oxygen pressure is the myocardial oxygen consumption (curve M). Myocardial blood flow and arterial oxygen content (curves F and C, respectively, coinciding) are also important and of equal significance. The radius of the tissue cylinder (curve R) is important only where it increases, e.g., in hypertrophy; note that R occurs squared in equation 1. Capillary radius and oxygen conductivity (curves r and K respectively) are similar, and both would become important only in those cases where they attain values lower than in fact could ever occur.

We will now turn to the main topic of this paper, an investigation of some of the assumptions listed above, based on a purview of the literature and recent findings obtained in our laboratory. Space does not permit a discussion of the mathematical methods used by the various workers; preferably numerical methods were used - these were greatly facilitated by progress in computer technology. Not all assumptions could be included in this survey due to missing data and lack for space (see also reviews by Middleman[43]; Leonard and Jørgensen[35]; Fletcher[15]).

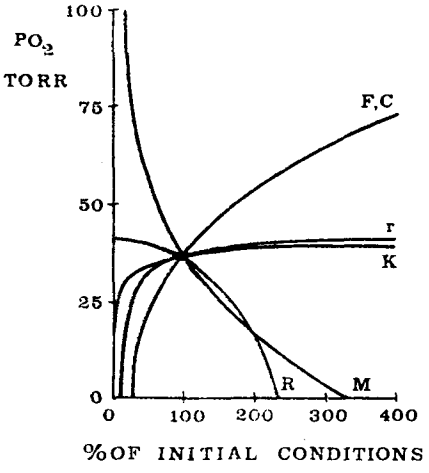

Figure 2. Changes in myocardial oxygen pressure as a result of changes in individual oxygen determinants. M, myocardial oxygen consumption; F, myocardial blood flow; C, oxygen content of arterial blood; R, tissue cylinder radius; r, capillary radius; K, Krogh's diffusion coefficient. (From Rakušan[48], fig. 4, p. 39, with permission.)

1. Assumption of radial oxygen diffusion only, i.e., neglect of axial or longitudinal diffusion in capillary and tissue. Thews[53] was the first to consider the effect of axial diffusion. He calculated that it was not important in the capillary, but was able to improve the oxygen supply somewhat, particularly at the lethal corner of the tissue cylinder (region at the venous end of the capillary most distant from the capillary). Reneau et al.[49] found axial diffusion to be effective in the tissue mostly in venous hypoxia due to the steepened gradient in axial direction. It lowers the oxygen pressure in the normoxic tissue particularly at the arterial end and at the periphery of the cylinder, and slightly increases the oxygen pressure at the venous end, i.e., renders the axial gradient somewhat less steep (fig. 3). Axial diffusion in an isotropic tissue plays a role only when diffusion prevails over convection in the capillary (Blum[4]). Fletcher[15] further elucidated the influence of capillary flow on axial diffusion. The decrease of oxygen pressure at the arterial end and its increase at the venous end due to axial diffusion are minimized by increasing capillary flow velocity, the contribution of axial diffusion becoming important at both ends only when flow velocity falls below 200 μm/sec (fig. 4). Similar concusions were reached by Salathé et al.[52] who added that a decrease of arterial oxygen concentration and the nonlinearity of the oxygen dissociation curve involve a diminution of the effect of axial diffusion in the tissue.

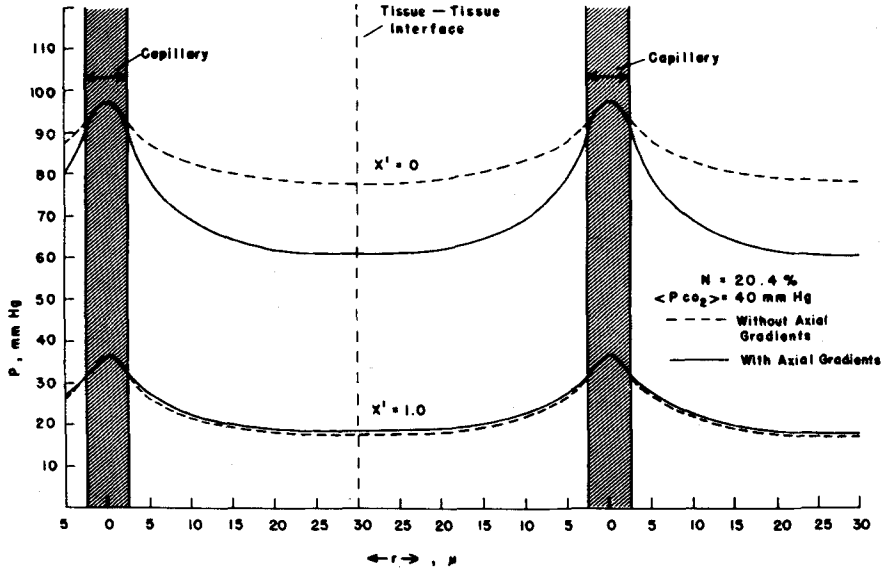

Figure 3. Effect of axial gradients on radial oxygen pressure profiles for a normal human under normal conditions. Arterial end above, venous end below. (From Reneau et al.[49], fig. 16, p. 218, with permission.)

2. Neglect of intracapillary chemical reactions, i.e., assumption of chemical equilibrium between oxygen and hemoglobin according to the oxygen dissociation curve. Thews[54] pointed out that the oxygen pressure cannot be constant over the entire capillary cross section because otherwise there would not be any driving oxygen pressure gradient within the blood. He therefore took into account the influence of the oxygen release from the capillary blood when studying the oxygen diffusion in the brain (using a hexagonal rather than a cylindrical pattern for the tissue), as an example of the oxygen supply to organs. Figure 5 from Fletcher[15] shows the dependence of lethal corner O_2 concentration on the release kinetics value β, a measure of the speed of release of oxygen from hemoglobin, in a plot of concentration against flow velocity. The oxygen concentration is larger as the flow velocity increases (as in fig. 2) and as the speed of release increases. However, since the influence of the chemical reactions of oxygen in the blood is not very marked (see also Metzger[39]), assumption of chemical equilibrium may often be justified. This raises the question how the nonlinear oxygen dissociation curve affects the tissue oxygen concentration. Turek et al.[55] have shown that a shift of the position of the oxygen dissociation curve has a different effect on mixed-venous oxygen pressure depending on the level of oxygenation. Low oxygen affinity of hemoglobin (high P_{50}, P_{50} being the oxygen pressure for half oxygen saturation) increases and high oxygen affinity (low P_{50}) decreases venous oxygen pressure at conditions of normoxia and moderate hypoxia, whereas the reverse holds true for severe hypoxia. Thus there is a point of inversion at a certain value of arterial oxygen pressure. This was again confirmed by Fletcher[15] for the Krogh tissue cylinder. It is the steepness of the oxygen dissociation curve which determines this pattern. When the slope of this curve is plotted against the arterial oxygen pressure for different values of P_{50} it appears that the slope has a maximum at a certain arterial oxygen pressure and that this maximum is higher and moves to lower values of arterial oxygen pressure as the P_{50} is lowered (oxygen affinity increased). This is shown in figure 6 from Turek et al.[58] where the slope is expressed in terms of the capacitance coefficient defined as the straight line connection between the arterial and venous points on the 'physiological' (actual) oxygen dissociation curve (see also Fletcher[14]). Experimental data agree with these calculations (Kreuzer and Turek[32]). Thus a left shift of the oxygen dissociation curve is favorable for tissue oxygenation at high altitude (Turek et al.[55]). Fletcher[14] found for the Krogh tissue cylinder that

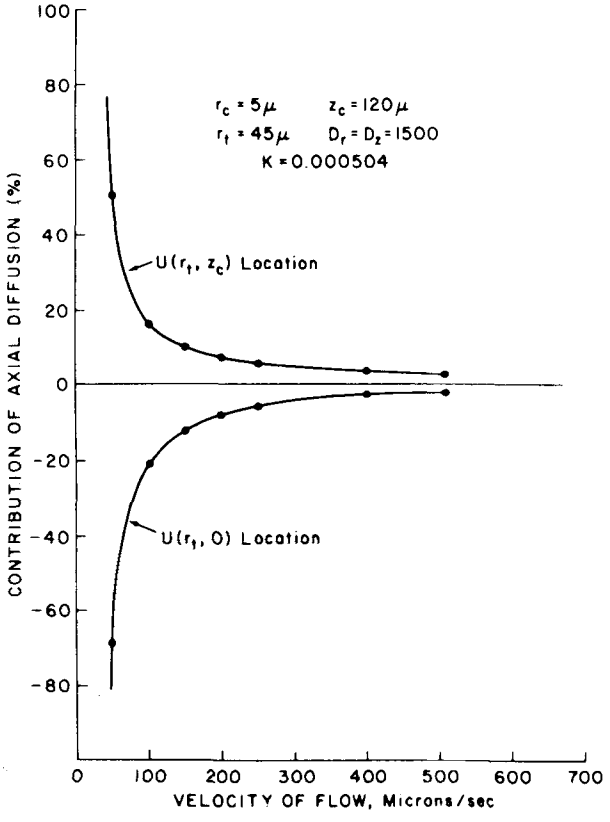

Figure 4. Contribution of axial diffusion at the arterial and venous ends of the Krogh cylinder as a function of flow velocity. Venous end above, arterial end below. Symbols: U, relative oxygen concentration; r_c, capillary radius; z_c, capillary length; r_t, tissue radius; D_r and D_z, diffusion coefficient in radial (r) and axial (z) direction respectively; K, constant oxygen consumption. (From Fletcher[15], fig. 6, p. 176, with permission.)

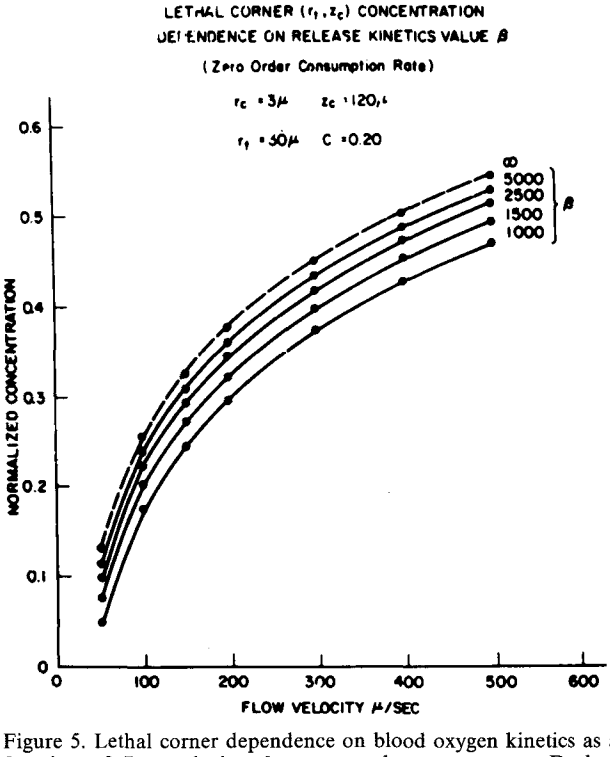

Figure 5. Lethal corner dependence on blood oxygen kinetics as a function of flow velocity. β, oxygen release parameter. Dashed curve, kinetic equilibrium case with $\beta = \infty$. C, blood oxygen capacity. (From Fletcher[15], fig. 8, p. 178, with permission.)

high oxygen affinity steepens the axial capillary oxygen pressure gradient, resulting in a lower oxygen pressure at the venous end under high altitude conditions, i.e., more oxygen is released to the tissue. So the position (P_{50}) and steepness of the oxygen dissociation curve play an important role for tissue oxygenation in conditions of hypoxic hypoxia. It is interesting to note that Hess[22] remarked, when discussing the active secretion of oxygen in the lungs (p. 17): 'Bei der Anpassung an das Leben in grossen Höhen spielt eher eine Änderung in den Bindungseigenschaften des Hämoglobins für Sauerstoff eine Rolle und nicht ein aktiver Sauerstofftransport aus der Alveole ins Blut' (in translation: 'In the adaptation to the life at high altitudes it is more the change in the binding properties of hemoglobin with oxygen that plays a role, rather than an active oxygen transport from the alveolus into the blood').

Hellums[20] also treated the blood as a continuum and calculated that the resistance to oxygen transfer in the capillaries is of approximately equal importance as the resistance in the surrounding tissue.

A recent study by Homer et al.[23] has focused attention on some other aspects of intracapillary blood. Klitzman and Duling[26] suggested that, in vivo, a considerable part of the capillary radius may be occupied by an unstirred layer of plasma at the periphery of the flowing stream of cells and plasma, reducing the 'effective' capillary radius to less than the anatomical radius. Low hematocrits in the capillaries were found by Klitzman and Duling[26]. Substantial differences between the oxygen pressure of cells and that of plasma probably exist in capillaries in the presence of severe acute anemias due to the increase in distance between the cells. The presence of plasma hemoglobin between the cells at low hematocrits might improve oxygen transport and oxygen extraction. Regulation of the variation in intercell distances or intercapillary inhomogeneity in red cell density provides a possible mechanism for the adjustment of functional arteriovenous oxygen shunting through peripheral capillary beds (Homer et al.[23]).

3. Assumption of zero-order oxygen consumption in tissue. A comparison of oxygen consumption following zero-order, first-order or Michaelis-Menten kinetics in a plot of the peripheral tissue oxygen pressure against capillary length shows that zero-order kinetics provides the lowest values, whereas Michaelis-Menten and particularly first-oder kinetics result in higher values of oxygen pressure (fig. 7; Fletcher[15]).

4. Assumption of homogeneous oxygen consumption. On the microscopic level there are always discontinuities in the tissue in that the mitochondria are the discrete oxygen sinks. This assumption implies that these minute sinks are evenly distributed in the volume of the tissue. However, the mitochondria must also be viewed in their relationship to the capillaries. Mainwood and Rakušan[37] showed that when the mitochondria are clustered around the capillaries, the Krogh cylinder radius shrinks from the anatomical value to that of the cluster. These authors assumed a lattice of 30-μm cells with a 1:1 cell to capillary ratio and a mitochondrial aggregation within 3 μm from the capillaries. They calculated a necessary oxygen pressure gradient of 24.0 mm Hg for an homogeneous

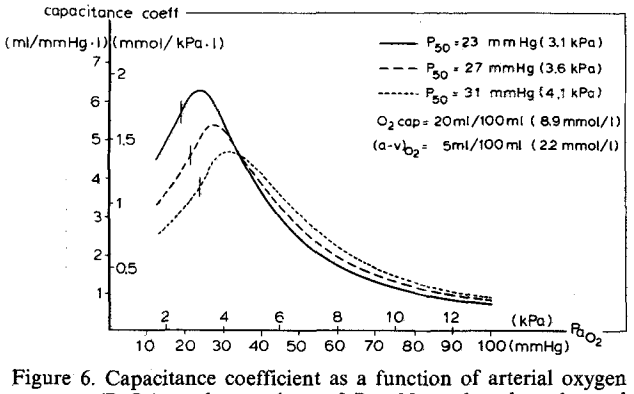

Figure 6. Capacitance coefficient as a function of arterial oxygen pressure (PaO_2) at three values of P_{50}. Normal and unchanged values of blood oxygen capacity (O_2 cap) and arterio-venous oxygen difference ($(a-v)O_2$). (From Turek et al.[58], fig. 1).

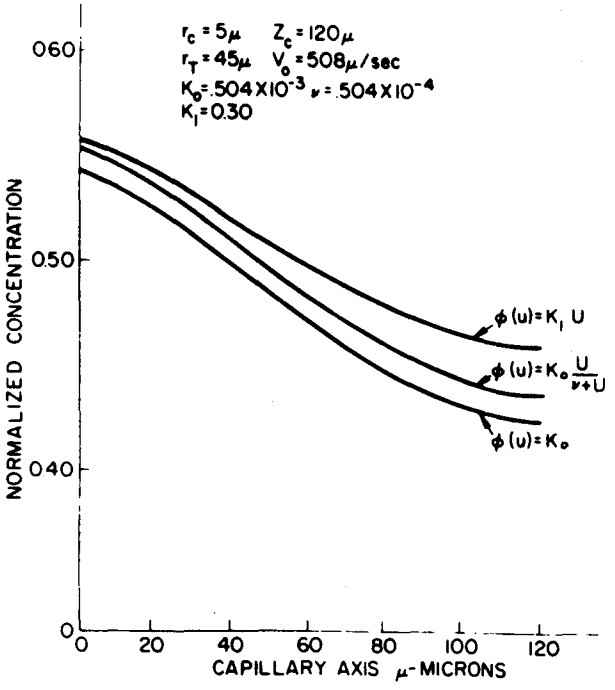

Figure 7. Effect of three different metabolic rate reaction orders on the outermost tissue substrate concentration as plotted against capillary axis. First curve from above for first order reaction, second curve for Michaelis-Menten kinetics, third curve for zero order. Symbols: r_c, capillary radius, Z_c, capillary length; r_T, tissue radius; V_o, flow velocity; K_o and K_1, metabolic rates of zero and first order respectively; ν, Michaelis-Menten constant; U, concentration. (From Fletcher[15], fig. 14, p. 183, with permission.)

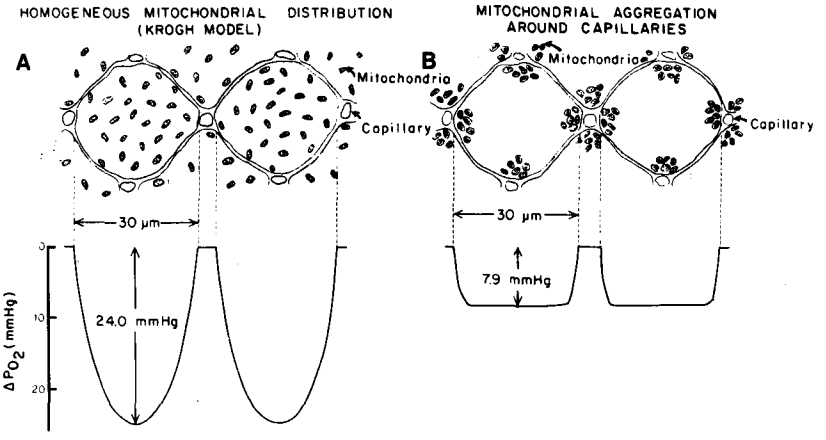

Figure 8. Diffusion profile of oxygen pressure (PO_2) in a lattice of 30-µm cells and a 1:1 cell to capillary ratio. *A* With homogeneous mitochondrial distribution; *B* with mitochondria clustered within 3 µm of capillaries. Oxygen pressure gradients ΔPO_2 in mm Hg indicated in figure. (From Mainwood and Rakušan[37], fig. 2, p. 100, with permission.)

mitochondrial distribution as against 7.9 mm Hg in the presence of mitochondrial aggregation (fig. 8). Thus in the latter case the capillary oxygen pressure required for an adequate oxygen supply to the tissue was reduced to one third of that in the homogeneous situation.

5. Assumption of homogeneous distribution of capillaries. Turek and Rakušan[57] considered the effect of a distribution of intercapillary distances approximated by a lognormal distribution on the oxygen supply to normal and hypertrophic rat hearts at normoxia and hypoxia, the spread being characterized by a single parameter, the log standard deviation. Bourdeau-Martini et al.[5], using a microcinematographic method, observed that capillary spacing is not uniform on the heart surface (confirmed by Feldstein et al.[12]). Mean tissue oxygen pressure and the percentage of anoxic tissue at the venous end of the tissue cylinder were calculated using Krogh's model. Two boundary situations were considered. The end-capillary oxygen pressure was assumed to be equal in all capillaries due to compensatory adjustment in blood flow, or the same flow in all capillaries was assumed to result in varying end-capillary oxygen pressure values. An actual situation is expected to lie between these two limiting conditions. An increase in the variability of the intercapillary distance (increase in log standard deviation) impaired tissue oxygenation, particularly in terms of an increased percentage of anoxic tissue, which turned out to be a better index of tissue oxygenation than the mean oxygen pressure, particularly at hypoxia (fig. 9). The effects on mean tissue oxygen pressure are minor in hypoxia. The situation with adaptation of blood flow with respect to the width of the tissue cylinder is more favorable, particularly during normoxia. The impairment is further aggravated by hypertrophy with or without hypoxia.

Whereas heterogeneous capillary spacing leads to variable radii of the tissue cylinders, variability of the capillary transit times results in differing oxygen pressure patterns in the various tissue cylinders. Tran-

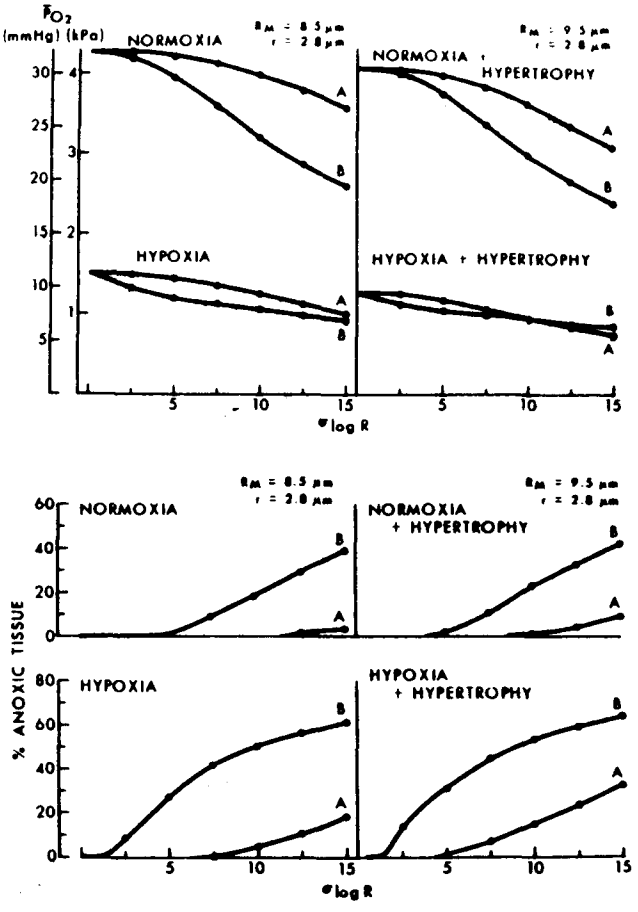

Figure 9. Above: Mean tissue oxygen pressure PO_2 as a function of log standard deviation $\sigma_{\log R}$ (in percent of the mean on logarithmic scale) in normal (tissue cylinder $R_M = 8.5$ µm) and hypertrophic ($R_M = 9.5$ µm) hearts at normoxia and hypoxia. Capillary radius = 2.8 µm in both groups. Situation A calculates the mean tissue PO_2 assuming the same end-capillary PO_2 in all tissue cylinders (i.e., a change of flow compensates for differences in the radius of the tissue cylinder). Situation B calculates the mean tissue PO_2 assuming the same flow in all capillaries (i.e., a higher end-capillary PO_2 in thin and a lower end-capillary PO_2 in thick cylinders).

Below: Percentage of anoxic tissue (i.e., tissue $PO_2 \leq O$) as a function of $\sigma_{\log R}$(in percent of the mean on logarithmic scale) in normal ($R_M = 8.5$ µm) and hypertrophic ($R_M = 9.5$ µm) hearts. Situations A and B as above. Note that at normoxia in normal hearts the percentage of anoxic tissue in situation A is not distinguishable from zero. (From Turek and Rakušan[57], figs 3 and 4, p. 20, with permission.)

sit time is determined by blood volume/blood flow, where capillary volume = length times cross section. Honig et al.[25] found variable capillary lengths and computed a heterogeneity of transit times which should profoundly affect the calculations of oxygen transport.

6. Assumption of straight, parallel and concurrent capillaries. The assumption of straight and parallel capillaries with concurrent and steady flow in the Krogh model undoubtedly is an extreme idealization – even in the case of skeletal muscle where the ideal situation is most closely approached. Therefore a number of alternative geometries have been proposed which, however, cannot be discussed in detail here (please refer to review by Leonard and Jørgensen[35]). Such alternatives include a spherical model for subcutaneous tissue (Caligara and Rooth[6]), countercurrent flow and conical tissue for human brain (Diemer[8]; Reneau and Knisely[51]), countercurrent flow and parallel layers of blood and tissue (Bailey[3]), rectangular capillary net and cubic tissue regions (Metzger[42]), three-dimensional multicapillary model with interaction for skeletal muscle (Akmal et al.[2]), and rectangular tissue regions supplied by parallel capillaries with concurrent, countercurrent or asymmetric flow (Grunewald[18]; Grunewald and Sowa[19]). Figure 10 (adopted from Grunewald[18]) compares the capillary blood oxygen extraction along a capillary with concurrent, countercurrent or asymmetric blood flow. The oxygen extraction is most efficient with countercurrent and least efficient with concurrent flow, although there is no difference at the venous end of the capillary. Metzger[40,41], however, found for a two-dimensional tissue model that a capillary network is least favorable and a countercurrent system most favorable. It may be mentioned in passing that the type of flow profiles in the capillary (parabolic vs plug flow) does not seem to have much effect on oxygenation (Reneau et al.[49]; Davis et al.[7]). Capillary diameter barely changes along a capillary segment length in muscle (Klitzman and Johnson[27]).

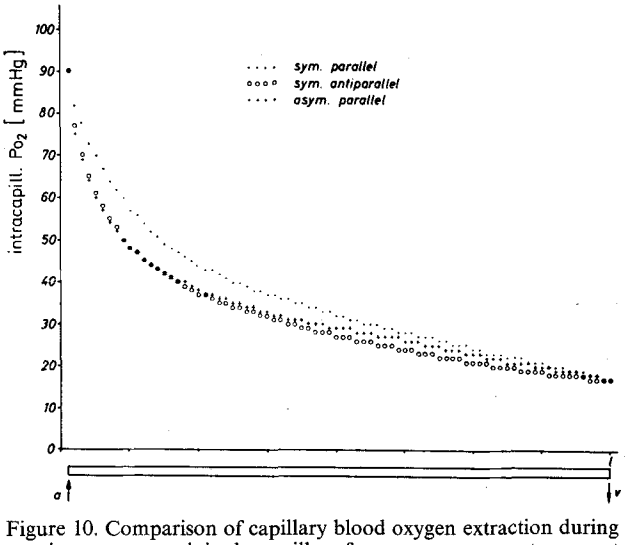

Figure 10. Comparison of capillary blood oxygen extraction during arterio-venous transit in the capillary for concurrent, countercurrent and asymmetric perfusion in the supplying capillaries. (From Grunewald[18], fig. 9, p. 11, with permission.) Curves from above to below; ...., sym. parallel = concurrent; + + + +, asym. parallel = asymmetric; oooo, sym. antiparallel = countercurrent.

Popel[46] applied his analytical solution (Popel[44]) to a simple case of heterogeneous capillary flow represented by alternating layers of capillaries with cocurrent flow. Asymmetry in oxygen distribution was introduced by considering different velocities of blood in the alternate capillary layers, different inlet capillary oxygen tensions, and different capillary hematocrits. Symmetric and asymmetric distributions of oxygen concentration between the layers were compared. Solutions for the symmetric case were very close to the corresponding solutions of the Krogh cylinder model, but increase in the degree of asymmetry led to diminution of the mean oxygen tension.

Another aspect of capillary perfusion has gained increasing importance in modern concepts of microcirculation. Contrary to the purely passive behavior subsumed in the Krogh model, the possibility of control of local blood flow, local metabolism and even capillary radius and wall permeability by as yet unknown mechanisms is drawing mounting attention. This is a revival of old ideas which were extensively discussed, e.g., by Hess[21] (p. 10–20). Mechanisms considered at present include diffusional bypass, the activity of arteriolar and precapillary sphincters (myogenic control), temporal and spatial interactions and changing activities, feedback and autoregulation. The importance of these effects may be variable and specific in the microcirculations of various organs.

The group of Honig has investigated the phenomenon of autoregulation, i.e., the relationship between intercapillary distance or capillary density and arterial oxygen pressure. The capillary regions are supposed to be in a dynamic condition, alternating between open and closed capillaries. The arteriolar sphincters would be closed or opened depending on capillary flow, oxygen level and local ATP concentration. In this way the oxygen diffusion from the capillary could be manipulated. For instance, with open capillaries the oxygen would have to reach only 6 μm in the tissue, whereas with closed capillaries it would have to cover 16 μm from the arteriole. That precapillary and postcapillary oxygen exchange is possible has been shown repeatedly, more recently by Duling and Berne[10] (see also Popel and Gross[45]). Figure 11 (Martini and Honig[38]; Middleman[43]) shows that intercapillary distance increases and capillary density decreases as arterial oxygen pressure increases, demonstrating a strong coupling between oxygen supply and control of capillary density. This autoregulation may be a self-protection against anoxia in the tissue.

A lack of oxygen may be met by an adaptive increase in capillary flow rate and vice versa (Duvelleroy et al.[11]). In the Krogh model the tissue cylinder is supposed to have an impermeable peripheral boundary, and the value the oxygen pressure will assume there under specific conditions is computed. Garby and Meldon[17] adopted another approach. They evaluated the maximum possible tissue volume supplied by an individual capillary, i.e., they assumed an oxygen flux equal to zero as well as oxygen pressure = 0 at the periphery of the tissue cylinder. This results in a cone rather than in a cylinder for the tissue, similar to a countercurrent pattern (see above). The authors calculated the required blood flow rate per unit mass of muscle tissue vs capillary density or average radius of tissue oxygenated by the vessel at various metabolic rates corresponding to rest and several levels of work (fig. 12). The curves show below which capillary density the minimum flow rate has to be increased and what is the minimum capillarization required at high flow. The 45° lines are loci of the time the blood stays in the capillaries.

7. Assumption of no facilitation of oxygen diffusion (e.g., by myoglobin in muscle). Several mechanisms for the facilitation of oxygen diffusion have been suggested for various tissues, but some are rather controversial and not readily amenable to analysis in terms of the Krogh model (for a review see Kreuzer and Hoofd[33], in press). For myoglobin-facilitated oxygen diffusion in muscle, however, Fletcher[16] has published a thorough analysis based on steady state conditions. Since deviations from chemical equilibrium of the reaction myoglobin + oxygen were minor only, equilibrium was assumed. A maximum diffusion coefficient of myoglobin was derived from the Stokes-Einstein formula for a 18 g% protein solution at 37 °C and used for the calculations in skeletal muscle at rest and normoxia. It was found that facilitation raises the tissue oxygen pressure particularly at the venous end of the capillary and at the periphery of the tissue cylinder. Figure 13 shows percent facilitation along the radius of the tissue cylinder and as related to the position in the capillary. Increase of oxygen pressure by facilitation depends on myoglobin concentration as expected. Thus, myoglobin in muscle acts as a safety or buffering mechanism against local hypoxia. A high or even almost complete average oxygen saturation of the muscle need not preclude a local facilitating effect. The mitochondria as small local regions with high oxygen pressure gradients may create local oxymyoglobin disequilibrium with partial deoxygenation conducive to local oxymyoglobin gradients as a basis for the facilitation of oxygen diffusion in these regions (see also de Koning et al.[28]).

8. Assumption of steady state vs transient changes. Not much attention has been paid so far to the effect of non-steady-state conditions on the calculations according to the Krogh model. The relaxation time of transients is increased during the passage from entrance to exit of the capillary, possibly by more than two orders of magnitude (Reneau et al.[50]). Fletcher[15] calculated the response of the substrate concentration at the lethal corner to step changes in flow at normox-

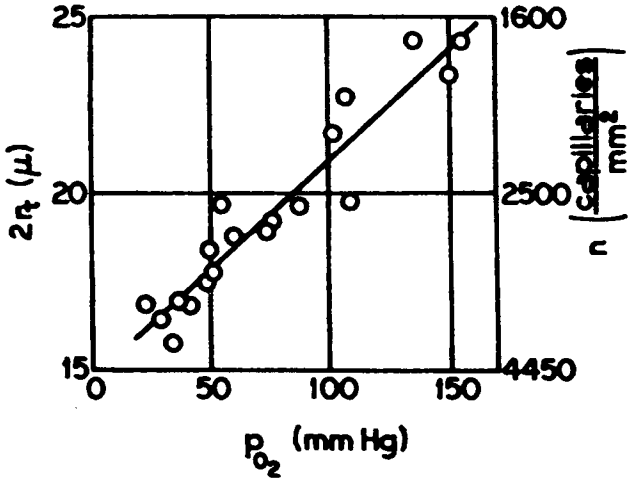

Figure 11. Relationship between intercapillary distance (or capillary density) and arterial oxygen pressure P_{O_2}. (From Middleman[43], fig. 3.13, p. 138, based on Martini and Honig[38], with permission.)

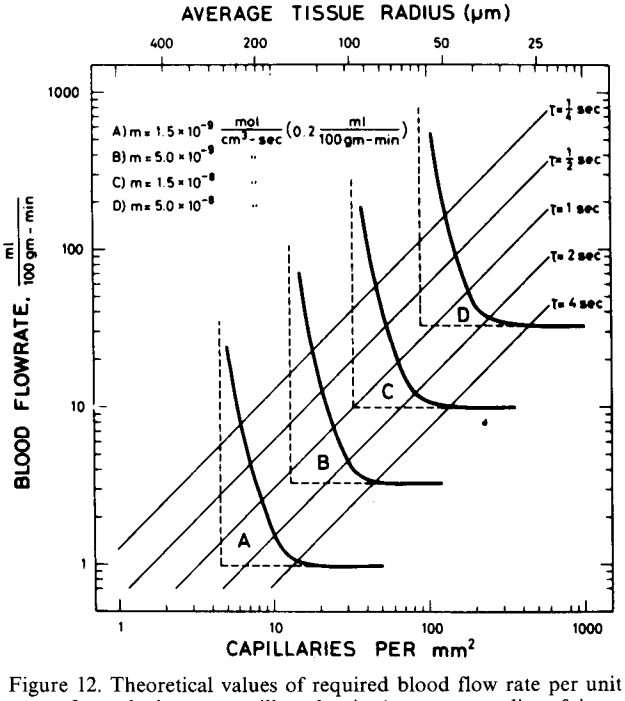

Figure 12. Theoretical values of required blood flow rate per unit mass of muscle tissue vs capillary density (or average radius of tissue oxygenated by a representative vessel), at metabolic rates corresponding to (A) rest and (B) lightly, (C) moderately, and (D) heavily working muscle. Vertical broken lines denote high-flow, minimum capillarization flow rate asymptotes. Horizontal broken lines denote high O_2 extraction, minimum flow rate asymptotes. 45-degree lines are loci of constant blood residence time in the microcirculation. (From Garby and Meldon[17], fig. 40, p. 176, with permission.)

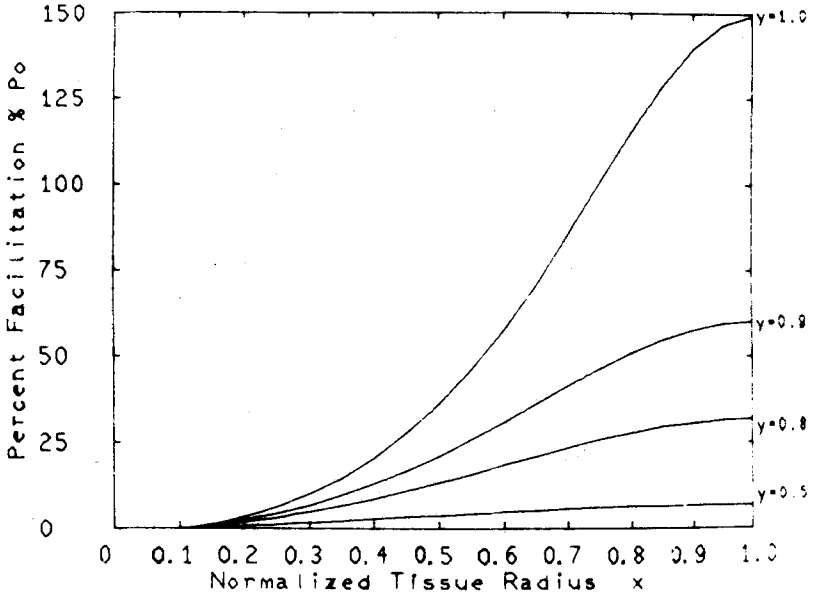

Figure 13. Percent facilitation of oxygen diffusion by myoglobin along the tissue radius and at four different positions along the capillary axis (parameter). y = 1.0 = venous end. Diffusion coefficient of myoglobin = 0.7×10^{-6} cm^2/sec. (From Fletcher[16], fig. 8, p. 452, with permission.)

ia and hypoxia, and with infinite and finite capillary wall permeability. A steady value was reached after about 6 sec at normoxia and a little earlier at hypoxia. A similar value was obtained with a step change in arterial oxygen saturation (fig. 14). Periodic flow impairs tissue diffusion only slightly (Fletcher[13]). When changing the distance between the red cells along the capillary, the oxygen pressure differences with time at the cylinder wall calculated from the transient solution are within 15% of those calculated from the steady-state solution. Longer transit times, shorter distances, and small oxygen extractions all bring the transient solution closer to the steady-state solution (Homer et al.[23]). Thus, on the whole, periodic phenomena may be of limited effect, and transients will usually be of short duration and lead to a new steady-state situation.

9. Assumption of absence of stirring. The problem of stirring and its effect on oxygen exchange in tissue is a largely virgin field. Recently, stirring in blood has been shown to enhance oxygen transfer (Diller et al.[9]), but its effect on calculations from the Krogh model has not been demonstrated as yet. For tissues some possible mechanisms have been suggested; these include protoplasmic streaming, water movement between mitochondria and their surroundings, interference by the fluxes of other substances, and mechanical movement in muscle during contraction and relaxation. There are, however, no quantitative data available, and experimental investigation as well as theoretical extension of the Krogh model are clearly called for.

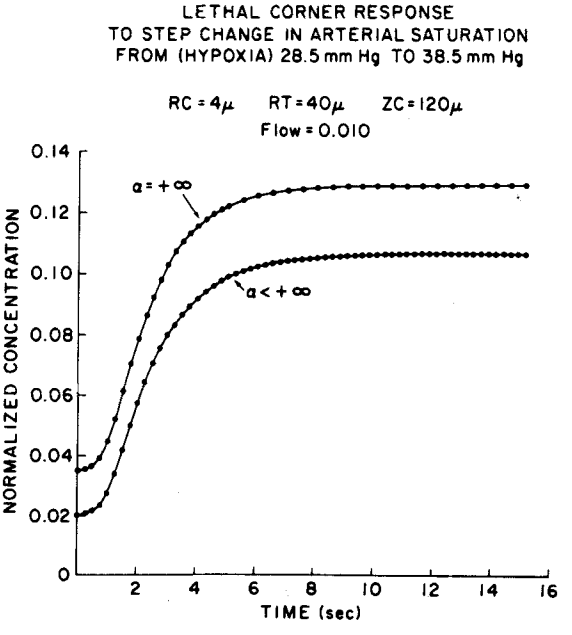

Figure 14. Lethal corner response to step changes in inflow arterial oxygen saturation for semipermeable ($\alpha < \infty$) and infinitely permeable capillary wall ($\alpha = \infty$). RC, capillary radius; RT, tissue cylinder radius; ZC, capillary length. (From Fletcher[15], fig. 10, p. 179, with permission.)

Conclusion

Mathematical modeling of microcirculation and tissue oxygen supply provides the only predicting tools at the moment, and stochastic models may be superior to deterministic models, according to Fletcher[15]. Numerous theoretical studies and experimental investigations have been performed during the past two decades, but these two approaches were often separate without an attempt at a linkage. After having arrived at a remarkable sophistication in both mathematical analysis and experimental methods, there is now an urgent need for a comparison between modeling and experimental studies involving refined histo-

logical data and improved measuring techniques. Experimental investigations using the platinum microelectrode or oxygen indicators often provide valuable information concerning the distribution of oxygen concentration in the tissue, i.e., an oxygen pressure field or oxygen pressure histogram (Lübbers[36]; Quistorff et al.[47]). Honig et al.[24] obtained data on blood flow and oxygen extraction in resting muscle, but attempted in vain to explain their data using the Krogh-Erlang equation. They concluded that this equation cannot be used for quantitative evaluation of oxygen transport in tissue. It appeared that the principal obstacle was a detailed knowledge of the three-dimensional arrangement of capillaries in vivo (Leonard and Jørgensen[35]). Analysis of the assumptions in the Krogh model uncovers some interesting effects which, however, are often of minor consequence and have not been studied so far in combination. Fletcher[15] concludes that after balancing all the various factors and complications the simple Krogh model may still be the most effective approach, also considering the fact that unidirectional structures are most frequent.

1 Acknowledgments. I am grateful to Dr Z. Turek for discussion of the manuscript.

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A modern neurobiological concept of vigilance

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In 1924/25, W.R. Hess in one of his easily most cogent and far-reaching papers – a programmatic treatise on the interrelation between psychic and vegetative functions – hypothesized that the reactivity of the cerebral cortical networks, and, for that matter, of all central nervous networks involved in the organization of (animalic) sensory-motor as well as psychic activities, is under the double – antagonistic – controlling influence of vegetative information channels arising in the brain stem. With this hypothesis Hess anticipated practically everything which later experimentors, through 'dry' and 'wet' – biophysical, biochemical and pharmacological – methodology would prove to constitute the various ascending regulatory systems, including the now modern neurotransmitter channels, that impinge on what is usually referred to as 'higher centers'. And still more importantly, with his notion of an ascending vegetative control, Hess provided the very basic neurophysiological foundation necessary for the eventual development functionally well-defined *concept of vigilance.*

1. Introduction – the problem

The term vigilance was introduced into psychophysiology by Head[22]. For Head, 'vigilance' constituted a neurodynamic variable, a scale, indicating the level of ability of the organism to adapt to changes in environmental conditions. For many later investigators Head's original definition was apparently either too strict or too loose and they chose to deviate, often considerably, from the original concept. Some