CHAPTER 142

Oxygen Transfer from Blood to Mitochondria

Louis Hoofd and F. Kreuzer

One of the central tasks of the microcirculation is to deliver an adequate amount of O\textsubscript{2} to ensure a proper function of the terminal oxidase of the respiratory chain in the mitochondria. Thus, during steady state, the amount of O\textsubscript{2} released from the microvasculature must equal the amount of O\textsubscript{2} consumed by the mitochondria. This O\textsubscript{2} delivery or supply is essential because more than 95% of the energy generated by the body normally originates via aerobic pathways, and it is urgent because the entire O\textsubscript{2} store of the body would support resting needs for less than 5 min. In this chapter we describe the pathway of O\textsubscript{2} from its delivery by the microvasculature to its consumption in the mitochondria for skeletal and cardiac muscle. In view of the limited space available, the coverage must be restricted to the essential points and the references must be condensed to the most central and recent papers, other references often being subsumed in citing review articles.

MICROVASCULAR ARCHITECTURE

Microvascular arrangement varies according to structure and function of an organ or tissue. Terminal arterioles empty directly into capillaries, which run parallel to the muscle fibers and often cross-connect with one another, thus forming a network. Precapillary sphincters are the final smooth muscle cells guarding the entrance to the capillary network and functionally represent the local control site for blood flow into the exchange area (1). Microcirculation may be arranged in repeating modules or units consisting of approximately 15 capillaries supplied by a common arteriole. Capillary blood flow is intermittent, while all or not all capillaries may be perfused at rest. There are no anatomic arteriovenous anastomoses, but there may be preferential channels across large capillaries. The most important morphological data for skeletal and cardiac muscles are summarized in Weibel (2) and Rakusan (3).

EXPERIMENTAL ASSESSMENT OF OXYGEN PARTIAL PRESSURE (P\textsubscript{O\textsubscript{2}}) OF STRIATED MUSCULAR TISSUE

The propagation of O\textsubscript{2} from the capillaries into the tissue must result in an O\textsubscript{2} field in the tissue. Silver (4), using his P\textsubscript{O\textsubscript{2}} microelectrode, mapped this field on and in rat cerebral cortex and found a P\textsubscript{O\textsubscript{2}} distribution as expected from the histological electrode track in relation to the microvascular pattern. Numerous subsequent studies with various kinds of electrode, however, failed to provide such rather regular P\textsubscript{O\textsubscript{2}} profiles. When the tissue is penetrated stepwise or measured along the surface, very irregular P\textsubscript{O\textsubscript{2}} profiles are usually obtained. The various P\textsubscript{O\textsubscript{2}} values then are plotted as percentages of their frequencies, providing a P\textsubscript{O\textsubscript{2}} histogram or, when being summed up, a cumulative P\textsubscript{O\textsubscript{2}} histogram, indicating the range and the peak P\textsubscript{O\textsubscript{2}} values in the tissue (5,6). Figure 1 shows the P\textsubscript{O\textsubscript{2}} histograms of six organs, including skeletal and cardiac muscles (6). Numerous other P\textsubscript{O\textsubscript{2}} histograms have been obtained with surface or needle P\textsubscript{O\textsubscript{2}} electrodes. The P\textsubscript{O\textsubscript{2}} profiles measured in tissue are the result of the interference of the P\textsubscript{O\textsubscript{2}} field in the tissue and the electrode diffusion field and are affected by the local consequences of pressure and impalement in the tissue (see review of P\textsubscript{O\textsubscript{2}} electrodes in refs. 5, 7, and 8). Some representative P\textsubscript{O\textsubscript{2}} values, obtained with surface or needle microelectrodes, for skeletal and cardiac muscles are listed in Table 1 (9-16). Knowledge of the order of magnitude of these “normal” normoxic P\textsubscript{O\textsubscript{2}} values will be important for a subsequent evaluation of various models of O\textsubscript{2} transport in tissue.

A promising new method to measure tissue O\textsubscript{2} is with O\textsubscript{2}-dependent fluorescent probes in the tissue (17).

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MODELING APPROACH TO O₂ TRANSPORT TO TISSUE

The Krogh Model

Thinking about O₂ supply to tissues started long before a realistic experimental approach as described earlier became possible. The decisive breakthrough for a theoretical approach is due to Krogh (18) with his model of a tissue cylinder around a central capillary running parallel to resting muscle fibers (centrifugal divergent model), assuming no O₂ flux at the periphery of the cylinder. The mathematical relationships developed by Krogh’s mathematician Erlang and later by Kety (19) permit the calculation of the P₀₂ field in this tissue (5,20). Despite its oversimplifications (numerous assumptions; see ref. 21), the Krogh model remains a valuable approach to assess the general properties of O₂ transport. The most critical location in the tissue cylinder with respect to O₂ supply is at the periphery of the venous end of the cylinder (lethal corner). The Krogh model allows for differentiating between diffusive and perfusive (convective) O₂ transfer resistances (22) but does not account for steep pericapillary gradients (see later).

Effect of Axial Diffusion

Axial diffusion, which is neglected in the Krogh model, lowers the P₀₂ in normoxic tissue, particularly at the arterial end of the cylinder, and increases it at the venous end; that is, it renders the axial gradient in the tissue somewhat less steep. The effect is minimized by increasing capillary flow velocity (see the review in ref. 21).

### TABLE 1. Experimental striated muscle tissue P₀₂ (in torr) obtained from P₀₂ electrode measurements

<table>
<thead>
<tr>
<th>Method</th>
<th>Heart Range</th>
<th>Heart Mean</th>
<th>Skeletal muscle Rasting Range</th>
<th>Skeletal muscle Rasting Mean</th>
<th>Skeletal muscle Working Range</th>
<th>Skeletal muscle Working Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface P₀₂ electrodes</td>
<td>20–70 (6)</td>
<td>45.1 (9)</td>
<td>2–65 (12)</td>
<td>16–39 (12)</td>
<td>20–45 (14)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>Needle P₀₂ electrodes</td>
<td>0–90 (10)</td>
<td>15–20 (10)</td>
<td>0–110 (13)</td>
<td>20–39 (13)</td>
<td>15–30 (15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–13 (11)</td>
<td>6.9 (11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5–10 (18)</td>
<td>5 (16)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Po₂ from cryomicrospectroscopic O₂Mb (PₐPo₂: for comparison)
Krogh’s O₂ Diffusion Coefficient K

The coefficient K is the product of O₂ diffusion coefficient D and O₂ solubility α and equals the O₂ permeability coefficient P. It is assumed homogeneous and isotropic in the Krogh model, although its effective value may be influenced by several factors and there must be local differences according to structure and components of the tissue. There is much confusion about these quantities in tissue, starting with the terminology. Reported values for D, α, and K(ρ) may differ quite considerably; even recent reported values range from twice as large (23) to much lower (24) than the commonly used values. Moreover, in highly structured tissue, such as muscle tissue, these may depend on orientation (25,26), that is, have different values in different directions. K might even be regulated; Popel et al. (27) noted an increase of 10 times in hamster retractor muscle when changing tissue status from imperfused to perfused.

Effect of Facilitated O₂ Diffusion

A complicating factor in determining K(ρ) or D for tissue is that these should be separated from augmentation of O₂ diffusional transport by O₂ binding proteins (facilitated diffusion). In particular, hemoglobin (Hb) and red muscle tissue myoglobin (Mb) can play such a role. The possible physiological significance of facilitated O₂ diffusion has been reviewed by Kreuzer and Hoofd (28); see also ref. 29. The maximum effect on O₂ diffusional driving force can be quantified as facilitation pressure P_f (30). Oxymyoglobin (O₂Mb) diffusion in muscle flattens both axial and radial O₂ profiles at low P_O₂; that is, it raises tissue P_O₂, particularly at the venous end of the capillary and at the periphery of the tissue cylinder.

Resistances Concerning Capillary and Red Blood Cell (RBC)

It is widely accepted that the membranes of capillary and RBC do not offer any appreciable extra resistance to O₂ diffusion (for RBC membrane see ref. 31). The capillary wall accordingly is mostly included in the tissue mass and RBC membrane in the RBC interior—for red muscle, the capillary wall may be discerned from the tissue because it does not contain Mb [Carrier Free Region (32)]. However, since virtually all the oxygen has to be drawn from the red blood cell, local O₂ fluxes are high, leading to steep gradients, where small alterations in permeability immediately show up in the large local P_O₂ drops. Several authors have modeled this phenomenon, giving rise to the term capillary barrier for this functional restraint of O₂ distribution. It causes the actual drop in P_O₂ close to the capillary to be up to much larger than predicted from the simple Krogh model; the additional P_O₂ drop can be quantified as extraction pressure (EP) (30). EP strongly depends on hematocrit and blood flow (32,33) and can be larger than the Krogh P_O₂ drop from capillary to cylinder periphery (30,34,35).

The Determinants of Tissue P_O₂

Kety (19) and Rakusan (3) examined how the determinants of O₂ supply to tissue affect tissue P_O₂ in the Krogh model when they are manipulated independently. Figure 2 is an analog of the figures in ref. 3, where a representative “tissue” P_O₂ was calculated for human heart at the periphery of a Krogh cylinder halfway along its length. In Fig. 2, the effects of facilitation (P_f) and of pericapillary gradients (EP) are incorporated (30). Most factors show a strong effect on P_O₂, where K becomes influential only when it decreases to quite low values. Note that facilitation by Mb is not effective at these high P_O₂ (28); P_f has no influence. Any influence of capillary radius cannot be quantified accurately, but it is effectively counteracted by a changing EP and will have little net influence. Without EP the lines for Hct and flow F would coincide (3,33).

![FIG. 2. Changes in myocardial oxygen pressure as a result of changes in individual oxygen determinants. M, myocardial O₂ consumption; F, Hct, capillary blood flow and hematocrit, respectively; R, L, tissue cylinder radius and length, respectively; K, Krogh’s O₂ diffusion coefficient (O₂ permeability coefficient); Pr, facilitation pressure accounting for facilitated diffusion exerted by myoglobin.](image-url)
Other Models with Idealized Geometry

Whereas the centrifugal divergent Krogh model deals with a tissue cylinder around a single capillary, in the centripetal convergent models the \( \text{O}_2 \) is supplied to a solid cylinder from a homogeneous peripheral sheet of blood (36) or, more realistically, from a certain number of peripheral capillaries (solid cylinder model). In comparison with the Krogh model, from the Hill model higher \( \text{Po}_2 \) values often are inferred. However, Rakusan et al. (37) compared the Krogh model with various symmetric solid cylinders and found the differences mainly to be due to different parameter choices; in particular, for similar capillary densities the \( \text{Po}_2 \) profiles were similar. This view was confirmed by Piiper and Scheid (38), who found that the differences indeed largely reside in the respective geometries. Groom et al. (39) suggested that for the maximally contracted muscle the Hill model would be more applicable to represent the dense network of folded capillaries around the individual muscle fiber, but they did not indicate how to keep the capillary volume density unchanged.

All these models agree in that they assume an idealized (mostly cylindrical) geometry and, with the exception of the original Hill model, the origination of \( \text{O}_2 \) from uniform sources, the capillaries. However, whereas in the Krogh cylinder mostly a single cylinder and capillary are considered (presuming homogeneity), the solid cylinder model admits the possibility of a differing number, distribution, and nature of capillaries (including interactions) and could be considered as a first step toward multicapillary models, also three-dimensional models. As long as these are regular, the findings do not differ much from the Krogh approach (29,32).

Incorporating Capillary Distribution

In view of the constraints (including a great number of assumptions; see ref. 12) in these idealized models, it may be preferable to adopt an approach that starts from the actual capillary locations and their respective supply areas. Two approaches are possible here. The first involves an ensemble of circular Krogh cylinders, either a full distribution (40) or selected values (41); these, however, cannot fill the tissue. In the method of capillary domains developed by Hoofd et al. (42), such domains, geographic areas around the capillaries, cover the entire tissue surface area of a histological section, resulting in irregular polygonal areas. So a second approach is to model a whole histological section covering several capillaries by superposition of source terms (43,44), taking into account the actual capillary locations. This method also permits calculation of the actual capillary \( \text{O}_2 \) supply areas, which coincide with the morphological domains remarkably well for identical capillary \( \text{Po}_2 \). Both model-

\[ \text{O}_2 \] Diffusion Versus \( \text{O}_2 \) Supply

We have seen earlier that the \( \text{Po}_2 \) gradient from capillary blood to tissue depends on the sum of diffusive and perfusive resistances to \( \text{O}_2 \) transport. The question is which of these two resistances is mainly limiting. The Krogh and Hill models stipulate a limitation by diffusion, whereas data from \( ^{16} \text{O}^{18} \text{O} \) wash-out experiments are more in favor of a limitation by perfusion (46). Cain (47), comparing anemic and hypoxic hypoxia in the dog, concluded that \( \text{M} \) was not limited by diffusion but by \( \text{O}_2 \) supply (= \( \text{Ca}_\text{O}_2 \times \text{flow} \)), where \( \text{Ca}_\text{O}_2 \) is the arterial oxygen concentration) and that therefore the validity of mixed venous oxygen pressure \( \text{Pv}_\text{O}_2 \) as a measure of tissue \( \text{O}_2 \) supply is open to question.

According to Schumacker and Samsel (48), the Krogh model fails to fully predict \( \text{O}_2 \) supply dependency because of its basic limitations or assumptions. The \( \text{D/M} \) relationship, where \( \text{D} \) is the oxygen delivery, was similar for anemic, hypoxic, and stagnant hypoxia as long as the intercapillary distance (ICD, taken as twice the Krogh radius \( \mathcal{R} \)) was below 80 \( \mu \text{m} \), but \( \text{O}_2 \) extraction was unrealistically high. This may come down to the same argument that was given earlier, where the Krogh model fails to predict tissue \( \text{Po}_2 \). Piiper and Haab (49) incorporated heterogeneous compartmentation and found much better agreement. Experimental results coinciding with Krogh calculations may be misinterpreted with regard to what happens in the tissue, especially concerning venous (\( \text{P}_\text{O}_2 \)) or capillary oxygen pressure (\( \text{P}_\text{cO}_2 \)) (50–52). The authors in refs. 50–52 found in isolated canine gastrocnemius muscle in situ that normoxic maximal \( \text{M} \) is limited by \( \text{O}_2 \) diffusion in the peripheral tissue. It is, however, impossible to ascertain the location of this diffusive resistance from these experiments.

Myoglobin Oxygen Saturation

Honig et al. (53) measured local \( \text{O}_2 \text{Mb} \) saturation by cryomicrospectroscopy in maximally contracting dog gracilis muscle and deduced the corresponding \( \text{Po}_2 \) values from the \( \text{O}_2 \text{Mb} \) dissociation curve (\( \text{P}_m \text{O}_2 \)); their measurements with a spatial resolution of 4 \( \mu \text{m} \) covered the intracellular regions beyond a distance of 3–5 \( \mu \text{m} \) from the capillary. In this and much subsequent work, this group found that intracellular \( \text{P}_m \text{O}_2 \) was only a few torr and evenly distributed, which they ascribed to \text{Mb}-facilitated \( \text{O}_2 \) diffusion. An apparent \( \text{K}_m \) (\( \text{Po}_2 \) for half-maximal
O₂ consumption) of 0.06 torr was similar to that in mitochondrial suspensions, and the perimitochondrial O₂ gradient was very low. There are almost no radial or axial tissue gradients.

This view is consistent with models of high-pericapillary gradients ("capillary barrier") and facilitation of O₂ transport in the tissue at low Pₒ₂ (34,54,55) or with extreme clustering of mitochondria with high O₂ consumption (56). (See later for more about this.) Tamura et al. (57) showed that the curve of a plot of oxidized cytochrome aa₃ versus % O₂Mb ("coherence diagram") moves to the right (higher half-maximum value) as M increases. The corresponding Pₒ₂ gradient between cytosol and mitochondria ("gradient coherence") therefore also increases with M from small values at low M to more than 10 torr at high M. The dependence on M might lead to discrepant results, particularly in vitro because of different viability of the cell preparations.

There is a striking difference between the cumulative myocardial Pₒ₂ histograms obtained experimentally from Pₒ₂ electrode studies and the Pₒ₂ histograms derived by Honig's group. Turek et al. (40) tried to find the changes in various factors necessary to approach the Pₒ₂ histograms of Honig and Gayeski (16) and found that manipulation of the input data can provide Pₒ₂ profiles or Pₒ₂ histograms more similar to either of these, but only when including Michaelis-Menten kinetics of M (not considered in other models) for quite peculiar input data of Km and Mₘₙₐₓ of several times larger than obtained experimentally. Otherwise, the experimentally found heterogeneity of capillary spacing prevented tissue Pₒ₂ from being homogeneously low; this was shown not only for rat heart but also for dog gracilis muscle (45). Recent direct tissue determination of the diffusion coefficient of Mb (58) led to a low-muscle tissue value and consequently low facilitation of O₂ transport, to which Honig's group attached a key role in maintaining low tissue Pₒ₂. As a consequence, Hoofd and Turek (45) suggested that the equilibrium between Pₒ₂ and O₂Mb might be uncoupled, so that P_mO₂ would only reflect Mb saturation S but not tissue Pₒ₂. Conversely, Severinghaus (59,60) reported a discrepancy between S derived from modeling tissue Pₒ₂ and the actually observed values. Wittenberg and Wittenberg (61) found Mb to play a role in O₂ utilization of the mitochondria, which they termed myoglobin-mediated oxidative phosphorylation. If Mb is involved in multiple chemical reactions, this might indeed cause disequilibrium between oxygen pressure and saturation.

Possible Effects of Stirring in Blood and Tissue

Stirring plasma, RBC contents, and tissue might greatly enhance O₂ transport, but no quantitative data amenable to a realistic estimation of these effects are available (28,62,63). For plasma, circulating flow patterns between the RBCs (eddies) can be calculated (64), but the effect on O₂ delivery is not yet settled (65).

MITOCHONDRIAL AND CAPILLARY DISTRIBUTION AND FLOW

Capillary Distribution

That precapillary O₂ loss is possible has been shown repeatedly, but its estimates vary widely and are controversial. O₂ loss from arterioles will increase local tissue Pₒ₂ but will decrease blood Pₒ₂ at the entrance of the capillary and consequently decrease tissue Pₒ₂ around that capillary. Capillaries traversing an arteriole will "pick up" O₂, either directly by shunting or indirectly, since some of the surrounding tissue is already supplied with O₂ by the arteriole, which will increase capillary Pₒ₂ at its distal end (66). This effect will be largest for resting muscle; in the model of Secomb and Hsu (67) up to 85% of the tissue supply is estimated to be directly from arterioles, but these authors use the high K value mentioned earlier (23).

Practically all variables in muscle may be heterogeneously distributed: intercapillary distance, capillary length and diameter, blood flow, transit time, M, and oxyhemoglobin (O₂Hb) and O₂Mb saturations and their respective Pₒ₂ values. Resulting heterogeneities in, for example, NADH (68) and recently also O₂ itself (17) can be visualized through fluorescent probes and are consistent with the idea of "O₂ supply units" with typical dimensions of some hundreds of micrometers, including several capillaries. Such units were suggested from both experimental (69) and theoretical work (43).

Apart from technical, geometric, and histological problems, counting capillaries to obtain capillary density (CD) is subject to at least two more problems: (a) open versus closed or functional versus nonfunctional capillaries; capillaries with or without RBC or with moving versus stationary RBC (70); (b) neglect, of capillary length, cross section and volume.

Capillary density is, when considering only the open capillaries, a particularly important determinant of tissue Pₒ₂ (Fig. 2). There is a distinct effect of the capillary-to-fiber ratio on tissue Pₒ₂ only when it increases from 1 to 2 (normal range in skeletal muscle); an increase of capillary-to-fiber ratio above 2 has a minimal effect (71). Thus, it may not be surprising that there is no agreement about a possible increase and effect of CD in hypoxia and exercise.

Capillary density may increase toward the venous side of the capillary, thus shortening R in the region where P_mO₂ is lowest. The Krogh cylinder therefore should be tapering toward the venule in the form of a cone (2,72). The calculated effect on tissue Pₒ₂, however, is mostly insignificant (32,73). More important, increased hetero-
geneity of R lowers mean tissue PO2 (particularly at normoxia) and increases the percentage of anoxic tissue (particularly at hypoxia) (30,74). In the presence of an unequal distribution of the local capillary-to-fiber ratio, the ensuing interaction between capillaries can decrease the heterogeneity of tissue O2 supply (75).

Mitochondrial Distribution

Muscular mitochondria occur preferentially subsarcolemmal and interfibrillar (76). Their density decreases with increasing distance from the capillary, rendering the PO2 profile flatter and penetrating deeper into the cell (2). CD in general correlates well with mitochondrial density and M, an important adjustment, since the PO2 gradient in the tissue is proportional to M according to the Krogh–Erlang equation (63). Capillary length and blood volume are proportional to the O2 flux necessary for maximal M (2).

Mainwood and Rakusan (77) showed that when the mitochondria are clustered around the capillaries, R shrinks from the anatomic value to that of the cluster, and the required PO2 gradient decreases accordingly. It should be noted, however, that their situation is an extreme case. On the other hand, Jones (78) found that mitochondrial clustering results in a marked decrease of O2 permeability.

Capillary Blood Flow

In addition to the other determinants in Fig. 2, flow also can be zero, for unperfused capillaries, or negative, for countercurrent flow. The Krogh model assumes straight, parallel, and concurrent capillaries. Reeves and Rakusan (79) found 93% of cardiac capillaries to have concurrent flow. A number of alternative geometries have been proposed (see reviews in refs. 21, 29, 80, and 81). Countercurrent flow results in conical tissue regions or even shunting from one capillary to another. The same might be true for heterogeneous flow distribution in adjacent capillaries, but the differences between various models in terms of tissue PO2 are often surprisingly small or contradictory.

A large fraction of the total number of capillaries is perfused in resting skeletal muscle, and blood flow rates in individual capillaries are very inhomogeneous (70,82), are often intermittent, and can be PO2 dependent (83). This allows for a capillary reserve where blood flow becomes a regulatory factor to maintain tissue PO2 over a wide range of changes in O2 supply and/or M (84). Increase of overall flow will raise PO2 and tissue PO2, but the effects of increase in flow inhomogeneity are not clear-cut. Piiper et al. (85) noted that resting skeletal muscle perfusion inhomogeneity was even increased during contraction and relaxation; Renkin (86) and Tyml (87), however, found all capillaries open and a decreased flow heterogeneity during exercise. Duling (88) pointed out that heterogeneity during exercise may decrease, or increase at very high workload. Local flow redistributions seem to affect tissue PO2 only when flow increases or decreases simultaneously in multiple adjacent capillaries (89), possibly the size of the oxygen supply units mentioned earlier (43,69). Otherwise, there is no appreciable effect on tissue PO2 (30,45), even though capillary values can be affected (90).

Capillary Transit Time and O2 Shunting

Shunting is transport directly from a supplying vessel into a draining vessel. Shunting from arterioles to venules, through anastomoses or through tissue, elevates PO2 while bypassing the tissue. Capillaries can pick up O2 from arterioles, as discussed earlier, or from an adjacent capillary. This results in an elevated end-capillary PO2, which, however, also results from conical O2 supply regions, since the smaller tissue portion at the outflow side leads to a diminished capillary PO2 loss. The expected arteriovenous O2 diffusion shunting with countercurrent flow has been found to be minimal or negligible (91). If present (92), the concomitant venoarterial back diffusion of CO2 with resulting drop in pH may increase PO2 (Bohr effect), particularly in hypoxia: in hyperoxia, PO2 would be decreased by the O2 diffusion shunt (93).

Whereas heterogeneous capillary spacing leads to variable radii of the tissue cylinders, variability of capillary transit time results in differing PO2 patterns in various tissue cylinders. Capillaries with very long transit time imply almost stagnant blood with fast exhaustion of its O2; capillaries with very short transit time lead to some form of O2 shunting. Sarelius (94) observed that mean flow path length in different networks is twice anatomic capillary length; that is, actual transit time is longer than expected from anatomic measurements.

Capillary Hematocrit and Venular PO2

The role of the capillary hematocrit in capillary gas exchange remains poorly understood, also because practically nothing is known about the capillary hematocrit in resting and working muscles. It is generally accepted, however, that capillary hematocrit bears little relation to arterial hematocrit and is certainly much lower (down to 10%). It fluctuates in parallel with M and the contractile state of the arterioles, which suggests that it is a controlled variable in the regulation of tissue oxygenation (95). A decreased capillary hematocrit not only implies a decreased O2 content but also a steeper PO2 gradient along the capillary (96)—that is, a higher extraction pressure leading to impaired tissue delivery. (See the
deviation between Hct and F in Fig. 2.) Preferential flow channels with increased hematocrit and flow in skeletal muscle (to compensate for low capillary hematocrit) might result in functional arteriovenous O\textsubscript{2} shunting and in a higher P\textsubscript{vO2} (97). Misleadingly high venous P\textsubscript{O2} values occur particularly in the presence of functional arteriovenous O\textsubscript{2} shunting as a result of countercurrent flow, too short transit time or preferential flow channels, or shock (98).

In view of all these inhomogeneities, it is obvious that there will be no clear relationship between venous P\textsubscript{O2} and tissue P\textsubscript{O2}, as already suggested from Fig. 1. This makes judgment of tissue oxygenation from blood O\textsubscript{2} measurements of questionable value (51).

Capillary Regulation

There seems to be a common regulatory mechanism for functional hyperemia, hypoxic vasodilation, flow autoregulation, reactive hyperemia after vascular occlusion, and regulation of CD in skeletal muscle (99). The arterioles, innervated by the sympathetic nervous system, control the resistance and thus the flow, whereas the functional precapillary sphincters metabolically regulate the exchange by the capillaries, with a feedback from the more sensitive precapillary sphincters to the arterioles. The decreased P\textsubscript{O2} acts directly or indirectly by vasodilating metabolites on the smooth muscles of the sphincters. ICD decreases or CD increases in a linear fashion as P\textsubscript{O2} decreases from 120 to 20 torr. This autoregulation may be a self-protection against anoxia in the tissue (100). Capillary recruitment is due to increased RBC velocity and a more homogeneous flow rather than to opening of unperfused capillaries (101) and to a denser RBC spacing and path length recruitment. It leads to (a) decreased diffusion distance or increased interaction between diffusion fields; (b) decreased linear blood velocity resulting from increased total capillary surface area with increased transit time; (c) often decreased heterogeneity of CD and transit times with removal of the longest diffusion pathways and of the shortest and longest transit times (prevention of O\textsubscript{2} shunting and excessive O\textsubscript{2} extraction, respectively); and (d) an increased transcapillary O\textsubscript{2} conductance (100).

CAPILLARY BLOOD

Effect of Chemical Reactions Between Hb and O\textsubscript{2}

Some authors found a moderate influence of a slowed release of O\textsubscript{2} from Hb on plasma or tissue P\textsubscript{O2} (see ref. 65). Increase in M enhances the P\textsubscript{O2} gradient between RBC and plasma (102). Other workers concluded that the contribution of chemical reactions is minor (103); O\textsubscript{2} diffusion within the RBC mainly is rate limiting for O\textsubscript{2} transfer. Gutierrez (104) suggested that nonequilibrium O\textsubscript{2} release from capillaries might lead to a (venular) P\textsubscript{vO2} greater than end-capillary P\textsubscript{cO2}—that is, mimicking shunting (29).

Effect of O\textsubscript{2} Dissociation Curve

Turek et al. (105) have shown that the effect of a shift of the oxygen dissociation curve (ODC) depends on the level of oxygenation. High P\textsubscript{50} (P\textsubscript{O2} for 50\% saturation) increases and low P\textsubscript{50} decreases P\textsubscript{vO2} in normoxia and mild hypoxia, whereas the opposite holds in severe hypoxia. It is the local steepness of the ODC that determines this difference. A P\textsubscript{50} inadequate for a particular oxygenation level can be compensated for by an increase in blood flow (106). The effect of a shift of the ODC on tissue oxygenation has been confirmed in many studies, though not always, but the effect of moderate shifts may often be of questionable practical significance (48,107). At normoxia, an increase in P\textsubscript{50} (e.g., because of the Bohr effect) makes the capillary blood maintain a higher P\textsubscript{O2} toward the venous end of the capillary and renders the axial P\textsubscript{O2} profile flatter after the first third of capillary length (2).

OXYGEN CONSUMPTION

Critical P\textsubscript{O2} and Apparent K\textsubscript{m}

One of the many assumptions of the Krogh model is that M is of zero-order kinetics, that is, independent of P\textsubscript{O2} throughout. It is generally accepted that K\textsubscript{m} is very low in well-stirred mitochondrial suspensions (order of 0.05 torr). Longmuir (108) showed that M of cells depends on P\textsubscript{O2} up to considerably higher values than expected from zero-order kinetics; he ascribed this to intracellular diffusion resistance. Liver slices in vitro follow Michaelis–Menten kinetics rather than zero-order kinetics (109), K\textsubscript{m} being about 100 times higher than in mitochondrial suspensions (110). Thus, one has to distinguish between “true” mitochondrial K\textsubscript{m} and “apparent” K\textsubscript{m} in tissues. The notion of an apparent K\textsubscript{m} is well established in the kinetics of immobilized enzymes, which are analogous to the situation of the enzymes in the mitochondria (e.g., ref. 111).

Wilson et al. (112) found that mitochondrial oxidative phosphorylation depends on P\textsubscript{O2} over the entire physiological range of P\textsubscript{O2}, but metabolic adjustments ensure a constant adenosine triphosphate (ATP) synthesis and M with decreasing P\textsubscript{O2}; that is, there are no critical P\textsubscript{O2}, no difference between isolated mitochondria and intact cells (113), and thus no appreciable effect of O\textsubscript{2} gradients. O\textsubscript{2}
Physiological O₂ Supply Dependency

Isolated small muscles and muscle slices in vitro show O₂ supply dependency, presumably because of subcritical Po₂ values in the core (115). For a muscle in situ, Stainsby and Otis (116) found the same in the absence of flow autoregulation but a supercritical plateau with flow autoregulation. Autoregulation is very sensitive to experimental manipulations (117), which may explain some discrepant results; for a recent review see Cain (118). Physiological O₂ supply dependency means a condition where organ or even whole body O₂ consumption VO₂ decreases with O₂ supply below a low critical threshold and there is a horizontal plateau above that critical threshold; the subcritical slope indicates optimal O₂ extraction (119). (See solid lines in Fig. 3.) The plateau region might imply an optimum regulation of O₂ consumption and/or O₂ extraction; however, when O₂ supply is reduced below the critical threshold, O₂ extraction no longer increases proportionately to compensate for the reduction in O₂ supply. In Fig. 3 this is shown as a plateau for O₂ extraction; other models still allow for a moderate increase.

Pathological O₂ Supply Dependency

Powers et al. (120) found O₂ supply dependency of M over a wide range of O₂ supplies in adult respiratory distress syndrome (ARDS) patients during positive end-expiratory pressure (PEEP) and O₂ breathing. Pathological O₂ supply dependency is characterized by a lower subcritical slope, a higher critical O₂ supply, a higher supercritical plateau (which may be slightly sloping) (121), or no plateau at all (118). The lower slope indicates a deficiency in O₂ extraction from the blood with ensuing increase in mixed-venous Po₂. The underlying mechanisms for this deficiency are vascular microembolization, disruption of endothelial function resulting in a protein-rich permeability edema, and microvascular dysregulation by loss of autoregulation. Its consequences are a decrease in capillary reserve, an increase in capillary distances (loss of open capillaries and edema), a massive increase in heterogeneity of capillary distribution and flow, and an increase in capillary shunts. The increase in VO₂ above the physiological plateau value is not yet understood. The dashed lines in Fig. 3 are for pathological O₂ supply dependency as modeled by Cain (118), in his Fig. 5.

All this results in a derangement of the microvascular adaptability and in an impaired O₂ extraction from the blood with a consequent deficiency of O₂ supply to the tissue.

GENERAL CONCLUSION

Experimental determinations of tissue Po₂ are afflicted by great scattering of the results and remain controversial among various investigators. Modeling attempts have led to divergent conclusions that are difficult to reconcile and sometimes deviate greatly from experimental results. A systematic comparison between experiments and modeling is still lacking (see also ref. 29), and several aspects are in dispute. Although many single aspects of this problem have been investigated, the need for an integrative concept remains.

![Figure 3](attachment:image.png)

**FIG. 3.** O₂ consumption (top panel) and O₂ extraction ratio (bottom panel) versus O₂ delivery, for whole body or an isolated organ, in relative units. In physiological O₂ supply dependency (solid lines), O₂ consumption remains virtually constant at normal or high delivery but becomes extraction-limited below a critical threshold. In pathological O₂ supply dependency (dashed lines), O₂ consumption is limited earlier, at a higher level of delivery; on the other hand, it can increase above the physiological maximum.
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